### List of Abstracts

To view an abstract simply click on the link in the last column.

<table>
<thead>
<tr>
<th>Number</th>
<th>Abstract Title</th>
<th>Author(s)</th>
<th>Group(s)</th>
<th>Presentation Type</th>
<th>Link to Abstract</th>
</tr>
</thead>
</table>
** Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, Ghent, Belgium  
*** Department of Pharmaceutical Technology, Complutense University, Plaza de Ramón y Cajal, Madrid, Spain | Oral               | Click here |
<p>| 2      | Fluid bed coating with extremely high drug load                                | F. Priese, B.Wolf                                                        | Department of Applied Biosciences and Process Engineering, Anhalt University of Applied Sciences, Strenzfelder Allee 28, D-06406 Bernburg, Germany | Oral               | Click here |
| 3      | Dynamic behaviour of continuous fluidized bed plants – CFD-simulation and experimental investigations | M. Jacob                                                                 | Glatt Ingenieurtechnik GmbH, Nordstrasse 12, 99427 Weimar, Germany                       | Oral               | Click here |</p>
<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Authors</th>
<th>Institution</th>
<th>Type</th>
<th>Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>A general framework for modelling the deformation of a body subject to a large number of random impacts during spheronisation</td>
<td>I.C. Sinka</td>
<td>Department of Engineering, University of Leicester, Leicester LE1 7RH, UK</td>
<td>Oral</td>
<td><a href="#">Click here</a></td>
</tr>
<tr>
<td>5</td>
<td>Optimisation of high shear granulation of multicomponent fertiliser</td>
<td>C. Mangwandi, S.J. Allen, G.M. Walker</td>
<td>School of Chemistry and Chemical Engineering, Queen’s University Belfast, Belfast BT9 5AG, Northern Ireland UK</td>
<td>Oral</td>
<td><a href="#">Click here</a></td>
</tr>
<tr>
<td>6</td>
<td>Friability of fluid bed coated pellets</td>
<td>B. Wolf</td>
<td>Hochschule Anhalt (FH) Fachbereich 7 Neues Laborgebäude Strenzfelder Allee 28 D-06406 Bernburg BRD</td>
<td>Poster paper</td>
<td><a href="#">Click here</a></td>
</tr>
<tr>
<td>7</td>
<td>Spheronisation mechanism of MCC II-based pellets</td>
<td>C. Krüger, M. Thommes, P. Kleinebudde</td>
<td>Institut für Pharmazeutische Technologie und Biopharmazie Heinrich-Heine-Universität Universitätsstr. 1 / Geb. 26.22, Raum 00.24 40225 Düsseldorf, Germany</td>
<td>Oral</td>
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</tr>
<tr>
<td>8</td>
<td>Physical properties of pharmaceutical pellets</td>
<td>R. Sibanc, R. Dreu, T. Kitak, B. Govedarica, S. Srčič</td>
<td>Department of Pharmaceutical technology, Faculty of Pharmacy, University of Ljubljana, Askercea 7, 1000 Ljubljana, Slovenia</td>
<td>Oral</td>
<td>[Click here]</td>
</tr>
<tr>
<td>9</td>
<td>Model-based measurement and control of fluidised bed layering granulation processes</td>
<td>A. Bück*, M. Peglow*, E. Tsotsas*, M. Mangold**, A. Kienle***</td>
<td>* Chair of Thermal Process Engineering, Otto von Guericke University Magdeburg, Germany, ** Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany, *** Chair of Automation and Modelling, Otto von Guericke University Magdeburg, Germany</td>
<td>Oral</td>
<td>[Click here]</td>
</tr>
<tr>
<td>10</td>
<td>Fluidised bed agglomeration of skim milk powder: follow-up of agglomerates growth</td>
<td>C. Turchiuli***, R. Smail*, E. Dumoulin*</td>
<td>*Agroparistech, UMR GENIAL 1145, 1 Avenue des Olympiades, Massy, 91744, F, **Univ Paris-sud, Orsay, 91400, F</td>
<td>Oral</td>
<td>[Click here]</td>
</tr>
<tr>
<td>11</td>
<td>Continuous pellet coating for the pharmaceutical industry</td>
<td>N. Ivanova, A. Buck, M. Peglow, E. Tsotsas</td>
<td>Otto-von-Guericke-Universität Magdeburg, Fakultät für Verfahrens- und Systemtechnik, Institut für Verfahrenstechnik, Universitätsplatz 2, 39106 Magdeburg</td>
<td>Oral</td>
<td>[Click here]</td>
</tr>
<tr>
<td>12</td>
<td>Twin screw wet granulation: Effects of liquid properties</td>
<td>R.M. Dhenge*, Z.A. Mirza*, J.J. Cartwright**, M.J. Hounslow*, A.D. Salman*</td>
<td>*Department of Chemical and Biological Engineering, University of Sheffield, Newcastle Street, Sheffield, S1 3JD, UK ** Product Development, GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK</td>
<td>Oral</td>
<td>[Click here]</td>
</tr>
<tr>
<td>13</td>
<td>Impact of particle shape on solid lipid extrusion</td>
<td>P. Kleinebudde*, R. Witzleb*, V-R. Kanikanti**, H-J. Hamann**</td>
<td>*Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany, **Bayer Animal Health GmbH, Leverkusen, Germany</td>
<td>Poster (Competition)</td>
<td>[Click here]</td>
</tr>
<tr>
<td>14</td>
<td>DEM-simulation of impact behaviour of granules</td>
<td>P. Müller, J. Tomas</td>
<td>Otto-von-Guericke University Mechanical Process Engineering Universitätsplatz 2 39106 Magdeburg Germany</td>
<td>Oral</td>
<td>[Click here]</td>
</tr>
<tr>
<td>15</td>
<td>A nuclei size distribution model including nuclei breakage in drum granulation process</td>
<td>L.X.Liu*, L. Zhou**, J. Addai-Mensah**, A. Nosrati**</td>
<td>*School of Chemical Engineering, University of Queensland, St Lucia, Qld., 4072, Australia **Ian Wark Research Institute, University of South Australia, Mawson Lakes, Adelaide, SA. 5095 Australia</td>
<td>Poster paper</td>
<td>[Click here]</td>
</tr>
<tr>
<td>16</td>
<td>Understanding the variables controlling HSMG of detergent Powders</td>
<td>J.M. Bonsall*, P.R. Moore*, P.T. McGuire**, I. Hussain**, G. Leslie**</td>
<td>*Unilever R&amp;D Port Sunlight, Bebington, Wirral CH64 9UT ** University of Strathclyde, Department of Chemical and Process Engineering,75, Montrose Street, Glasgow, Scotland, G1 1XJ</td>
<td>Oral</td>
<td>[Click here]</td>
</tr>
<tr>
<td>17</td>
<td>Quantification of mass transfer during spheronisation</td>
<td>M. Koester, M. Thommes</td>
<td>Institut für Pharmazeutische Technologie und Biopharmazie Heinrich-Heine-Universität Universitätsstrasse 1 40225 Düsseldorf</td>
<td>Poster paper (competition)</td>
<td>[Click here]</td>
</tr>
<tr>
<td>19</td>
<td>Unified compaction curve: A potential link between the wet granulation and tableting processes</td>
<td>T.H. Nguyen*, D. Morton**, K. Hapgood*</td>
<td>*Monash Advanced Particle Engineering Laboratory, Department of Chemical Engineering, Monash University, Clayton 3800 **Monash Institute of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville 3052</td>
<td>Oral</td>
<td>[Click here]</td>
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<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
<td>Affiliations</td>
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<td>--------------------</td>
<td>-------</td>
</tr>
</tbody>
</table>
| 22   | Parameter study of an Eulerian-Eulerian CFD model in high-shear granulation | P.J. Abrahamsson*, I. Niklasson Björn**, A. Rasmuson*                   | *Department of Chemical Engineering, Chalmers University of Technology, SE-412 96, Göteborg, Sweden  
**Astra Zeneca Pharmaceutical Development R&D Mölndal, SE-431 83, Mölndal, Sweden | Oral                | [Click here] |
| 24   | Effect of disintegrants on the properties of multiparticulate tablets comprising starch pellets and excipient granules | S. Mehta*, T. De Beer**, J.P. Remon*, C. Vervaet*                       | *Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium.  
**Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Ghent, Belgium. | Oral                | [Click here] |
| 25   | Effect of mixing parameters of a solvent based granulation process   | P.R. Bolton*, M.K. Hopkins Till*, S.E. Gaulter**                        | * AWE, Aldermaston, Reading, Berkshire. RG7 4PR, UK.  
** Department of Applied Science, Security and Resilience, Shriverham Campus, Cranfield University, Shriverham, Swindon, SN6 8LA, UK. | Poster paper (competition) | [Click here] |
<p>| 26   | Dynamic optimization of a urea granulation circuit                   | I. Cotabarren, D. Bertín, V. Bucalá, J. Piña                           | Planta Piloto de Ingeniería Química (UNS - CONICET), Camino La Carrindanga Km.7 (8000), Bahía Blanca, Argentina. | Oral                | [Click here] |
| 27   | Process analysis: A fluidizing granulation industrial case study     | T.A. Nagy                                                               | Gedeon Richter Plc., 19-21 Gyomroi Street, Budapest, H-1104, Hungary          | Oral                | [Click here] |</p>
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
<th>Institution</th>
<th>Oral Status</th>
<th>Click Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>A CFD-DEM study of the complex granular flow in a fluid-bed rotor processor</td>
<td>J. Neuwirth*, S. Antonyuk*, S. Heinrich*, M. Jacob**</td>
<td>Institute of Solids Process Engineering and Particle Technology, Hamburg University of Technology, Denickestraße 15, 21073 Hamburg, Germany</td>
<td>Oral</td>
<td>Click here</td>
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<td>**Glatt Ingenieurtechnik GmbH, Nordstrasse 12, 99427 Weimar, Germany</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 29   | Experimental and numerical study on the effect of an elevated spout on spout fluidized bed dynamics | N.G. Deen, M.S. van Buijtenen, J.A.M. Kuipers                         | Dept. Chemical Engineering and Chemistry (ST) 
Multiphase Reactors (SMR) 
Multi-scale Modeling of Multiphase Flows (SMM) 
P.O. Box 513, STW 0.45 5600 MB Eindhoven 
The Netherlands | Oral        | Click here |
| 30   | High shear mixer granulation experiments using binders for food industry | E. Franceschinis*, A. Trotter*, A. Santomaso**, M. Cavinato**, D. Voinovich***, B. Perissutti***, N. Realdon* | *Department of Pharmaceutical Science, University of Padua, via Marzolo 5, 35131 Padova, Italy  
**DIPIC, Dept. of Chemical Engineering, University of Padua, via Marzolo 9, 35131 Padova, Italy  
***Department of Pharmaceutical Science, University of Trieste, P.le Europa 1, 34100 Trieste, Italy | Oral        | Click here |
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
<th>Affiliations</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Developing better process understanding; the role of the granulation process, materials properties and storage environment on drug release from a matrix tablet</td>
<td>D.T. Ring*, J.C. Oliveira*, A.Crean**</td>
<td>*Department of Process &amp; Chemical Engineering, University College Cork, **School of Pharmacy, University College Cork,</td>
<td>Oral</td>
</tr>
<tr>
<td>32</td>
<td>Twin screw wet granulation: Influence of formulation parameters</td>
<td>A. S. El Hagrasy*, J. D. Litster* **</td>
<td>*School of Chemical Engineering, Purdue University, West Lafayette, IN 47906 **Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN 47906</td>
<td>Oral</td>
</tr>
<tr>
<td>33</td>
<td>Tests for multiple compression of solids</td>
<td>R. Heinz, S. Bensmann, D. Barrera Medrano, R. Wengeler, H. Feise</td>
<td>BASF SE, 67056 Ludwigshafen, Germany</td>
<td>Oral</td>
</tr>
<tr>
<td>34</td>
<td>An experimental design methodology to evaluate the importance of different parameters on flocculation by polyelectrolytes</td>
<td>I. Pinheiro **, P. Ferreira **, F. A. García **, M.S. Reis **, C. Wandrey **, L. Amaral **, D. Hunkeler **, M. G. Rasteiro **</td>
<td>Research Centre for Chemical Processes Engineering and Forest Products, Coimbra Univ, PORTUGAL **Chemical Engineering Department, Coimbra University, PORTUGAL **École Polytechnique Fédérale de Lausanne, SWITZERLAND **RAIZ - Institute of Forest and Paper Research, PORTUGAL **Aqua+ tech, SWITZERLAND</td>
<td>Oral</td>
</tr>
<tr>
<td>35</td>
<td>Modifications of fluid-bed coater and study of their influence on the coating uniformity, yield and degree of agglomeration</td>
<td>M. Luštrik*, R.Dreu**, M. Perpar***, I. Zun***, S. Srčič**</td>
<td>*Brinox d.o.o. process systems, Sora 21, 1215 Mevode, Slovenia **Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia *** Faculty of Mechanical Engineering, University of Ljubljana, Aškerčeva 6, 1000 Ljubljana, Slovenia</td>
<td>Oral</td>
</tr>
<tr>
<td>37</td>
<td>A multi-scale modeling approach to batch/continuous multi-component wet granulation processes</td>
<td>R. Ramachandran</td>
<td>Department of Chemical and Biochemical Engineering, Rutgers University, 98 Brett Road, Piscataway, NJ 08854, USA</td>
<td>Oral</td>
</tr>
<tr>
<td>38</td>
<td>Scale-up of the wet agglomeration process.</td>
<td>H. Leuenberger, M. Puchkov</td>
<td>Institute for innovation in industrial pharmacy, Ifiip GmbH and Center for innovation in computer-aided pharmaceutics, CINCAP GmbH Kreuzackerweg 12, CH-4148 Pf effingen, Switzerland</td>
<td>Oral</td>
</tr>
<tr>
<td>39</td>
<td>Solution of multi-component population balance models for wet granulation via Monte Carlo</td>
<td>T. Matsoukas*, C.L. Marshall, Jr.*, P. Rajniak**</td>
<td>*Department of Chemical Engineering, The Pennsylvania State University, University Park, PA, 16802 **Pharmaceutical Commercialization Technology, Merck &amp; Co., Inc., West Point, PA 19486</td>
<td>Oral</td>
</tr>
<tr>
<td>40</td>
<td>Analysis of aerodynamic dispersion of cohesive clusters</td>
<td>G. Calvert, A. Hassanpour, M. Ghadiri</td>
<td>Institute of Particle Science and Engineering, School of Process, Environmental and Materials Engineering, University of Leeds, Leeds, LS2 9JT, UK</td>
<td>Oral</td>
</tr>
<tr>
<td>41</td>
<td>Discrete element modelling of seeded granulation in high shear granulators</td>
<td>A. Hassanpour*, L. Susana**, M. Pasha*, A.C. Santomaso**, M. Ghadiri*</td>
<td>*Institute of Particle Science and Engineering, University of Leeds, LS2 9JT, UK ** DIPIC - Department of Chemical Engineering, University of Padua, Italy</td>
<td>Oral</td>
</tr>
<tr>
<td>42</td>
<td>The effects of lubrication on roll compaction, ribbon milling and tabletting</td>
<td>S. Yu*, M. Adams*, B. Gururajan**, G. Reynolds**, R. Roberts**, C-Y Wu*</td>
<td>* School of Chemical Engineering, University of Birmingham, Edgbaston, Birmingham, B15 2TT ** Pharmaceutical Development, AstraZeneca, Macclesfield, Cheshire, SK10 2NA</td>
<td>Oral</td>
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<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
<td>Institution/Location</td>
<td>Type</td>
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<td>------</td>
<td>-----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>43</td>
<td>Monitoring and controlling product and process performance in pharmaceutical production using multivariate tools</td>
<td>M. Machin, L. Liesum</td>
<td>Novartis Pharma AG, Switzerland</td>
<td>Oral</td>
</tr>
<tr>
<td>44</td>
<td>Influence of initial mixing on granule properties</td>
<td>A. Alkhatib, L. Briens</td>
<td>Department of Chemical and Biochemical Engineering, The University of Western Ontario, London, Ontario, Canada N6A 5B9</td>
<td>Oral</td>
</tr>
<tr>
<td>45</td>
<td>A novel oral dissolving multi-functional excipient composed of crystalline mannitol and α-chitin</td>
<td>N. Daraghmeh**, M. M. H. Al Omari*, I. Rashid*, S. A. Leharme**, B. Z. Chowdhry**, A. Badwan*</td>
<td>* The Jordanian Pharmaceutical Manufacturing Co., PO Box 94, Naor 11710, Jordan. ** School of Science, University of Greenwich at Medway, Chatham Maritime, Kent ME44TB, UK.</td>
<td>Poster (competition)</td>
</tr>
<tr>
<td>46</td>
<td>Mechanisms of continuous granulation of pharmaceutical powder using a twin screw compounding</td>
<td>K. T. Lee, A. Ingram, N. A. Rowson</td>
<td>School of Chemical Engineering, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK</td>
<td>Oral</td>
</tr>
<tr>
<td>47</td>
<td>Granulation of lactic acid bacteria using fluidized bed technology</td>
<td>M. Wassermann*, S. Weinholz**, N. Ivanova***, C. Cordes**, M. Peglow***, W. Pergande*</td>
<td>*VTA GmbH Gölzau, Wilfried-Pergande-Platz 1, 06369 Weißandt-Gölzau, Germany  ** Institute of Molecular Biology, Anhalt University of Applied Sciences, Bernburg, Germany  *** Institute Process Engineering, Otto-von-Guericke-University, Magdeburg, Germany</td>
<td>Oral</td>
</tr>
<tr>
<td>48</td>
<td>Behavior of wetted insoluble granular materials: effect of particle shape</td>
<td>D. Oulahna, R. Collet, A. Michrafy, A. DeRyck</td>
<td>Université de Toulouse, Mines Albi, CNRS FRE 3213, RAPSODEE, Laboratory for Particulate Solids, Energy and Environment Campus Jarlard, 81013 Albi, France</td>
<td>Oral</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
<td>Affiliations</td>
<td>Type</td>
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<tr>
<td>------</td>
<td>-----------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>49</td>
<td>Simulation and experimental investigation of product moisture distribution in a continuous fluidised bed dryer</td>
<td>I. Alaathar, E-U Hartge, S. Heinrich, J. Werther</td>
<td>Hamburg University of Technology, Hamburg, Germany</td>
<td>Oral</td>
</tr>
<tr>
<td>50</td>
<td>Application of the flux number approach for the simulation of granulation processes by use of flowsheeting tools</td>
<td>R. Boerefijn*, M. Orlovic*, C. Reimers**, M. Pogodda**, M.Jacob***</td>
<td>*PURAC Biochem b.v., P.O. Box 21, 4206 AC Gorinchem, The Netherlands **SolidSim Engineering GmbH, Harburger Schloßstrasse 6-12, 21079 Hamburg, Germany ***Glatt Ingenieuretechnik GmbH, Nordstrasse 12, Weimar, D-99427, Germany</td>
<td>Oral</td>
</tr>
<tr>
<td>51</td>
<td>Multi-holed die extrusion for assessing paste formulations for granulation by extrusion-spheronisation</td>
<td>M. Zhang*, S.L. Rough*, C. Seiler**, R. Ward**, D.I. Wilson*</td>
<td>*Department of Chemical Engineering &amp; Biotechnology, New Museums Site, Pembroke Street, Cambridge, CB2 3RA, UK **MSD Devlab, Hertford Road, Hoddesdon, Herts, EN11 9BU, UK</td>
<td>Oral</td>
</tr>
<tr>
<td>52</td>
<td>The future of food agglomeration - Needs, trends and technological solutions-</td>
<td>S. Palzer</td>
<td>Nestle Product technology Centre York, Haxby Road, York YO91 1XY, United Kingdom</td>
<td>Oral</td>
</tr>
<tr>
<td>53</td>
<td>From colloidal aggregation to wet agglomeration: a fractal growth whatever the scale</td>
<td>M. Delalonde*, E. Rondet*, T., Ruiz**</td>
<td>**UMR 95 Qualisud - Université Montpellier 1, Faculté de Pharmacie, Laboratoire de Physique Moléculaire et Structurale, 15 avenue Charles Flahaut, BP 14491, 34093 Montpellier cedex 5, France. *UMR IATE 1208 CIRAD/INRA/Montpellier SupAgro/Université Montpellier 2 – place Eugène Bataillon,</td>
<td>Poster</td>
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<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
<td>Affiliations</td>
<td>Type</td>
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<td>------</td>
<td>----------------------------------------------------------------------</td>
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<td>--------------------------------------------------------------------------------</td>
<td>-------</td>
</tr>
</tbody>
</table>
| 54   | Simulation of Liquid binder distribution in fluidised bed granulation using the single particle spray flux | R. Smith*, G. Calvert**, A. Hassanpour**, C. Hare**, Y. Feng***, M. Rhodes****, K. Hapgood*, M. Ghadiri** | * Monash Advanced Particle Engineering Laboratory, Dept Chemical Engineering, Monash University, Melbourne, Australia  
** Institute of Particle Science & Engineering, University of Leeds, Leeds, LS2 9JT, UK  
*** CSIRO Mathematics, Informatics & Statistics, CSIRO, Clayton, Australia  
**** School of Engineering, Monash University, Malaysia | Oral  |
** Hamburg University of Technology, Hamburg, Germany  
*** Nestle Research Centre Lausanne, Switzerland  
**** The University of Sheffield, Sheffield, United Kingdom | Oral  |
| 56   | Pharmaceutical application of the segregation tester                | B. Moroney*, N. Sewell**, V. Revens**, A. Brookes**, D. Brooks**, B. Gururajan**          | *Department of Chemical Engineering and Biotechnology, University of Cambridge, CB2 3RA, UK  
**AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, LE11 5RH, UK | Oral  |
<p>| 58   | Application of microbial carbonation to agglomeration in suspension-flocculation | M. Fukue, S. Ono, Y. Sato, R. Takahashi                                                    | Tokai University Japan                                                        | Oral  |</p>
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
<th>Institution</th>
<th>Type</th>
<th>Click Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>Prevention of segregation of pore former by granulating with MOX powder in low density pellet fabrication for fast breeder reactors</td>
<td>T. Murakami, S. Aono</td>
<td>Japan Atomic Energy Agency (JAEA)</td>
<td>Oral</td>
<td>[Click here]</td>
</tr>
<tr>
<td>63</td>
<td>Palygorskite strengthens ammonium sulphate granules</td>
<td>A. J. Saunders*, R. J. Gilkes</td>
<td>Product Development CSBP Limited PO Box 345, Kwinana 6966 Western Australia</td>
<td>Oral</td>
<td>[Click here]</td>
</tr>
<tr>
<td>65</td>
<td>An experimental evaluation of the accuracy to simulate granule compression using the discrete element method</td>
<td>A. Persson, G. Frenning</td>
<td>Uppsala University, Department of Pharmacy, Uppsala Biomedical Centre P.O. Box 580, SE-751 23 Uppsala, Sweden.</td>
<td>Oral</td>
<td>[Click here]</td>
</tr>
<tr>
<td>66</td>
<td>Meso-scale coupling model of DEM and CIP for nucleation processes in wet granulation</td>
<td>K. Washino*, H.S. Tan**, M.J. Hounslow*, A.D. Salman</td>
<td>*Department of Chemical and Biological Engineering, University of Sheffield, Newcastle Street, Sheffield, S1 3JD, UK **P&amp;G Technical Centres Ltd, Whitley Road, Longbenton, Newcastle upon Tyne, NE12 9TS, UK</td>
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<tr>
<td>68</td>
<td>New method for measuring tensile, shear and torsional strength of solid bridges between particles</td>
<td>R. Kirsch, U. Bröckel, L. Brendel, J. Torok</td>
<td>Institute for Micro-Process-Engineering and Particle Technology, Umwelt-Campus Birkenfeld, P.O. Box 1380, 55761 Birkenfeld, Germany Faculty of Physics, University of Duisburg-Essen, 47048 Duisburg, Germany</td>
<td>Oral</td>
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</tr>
<tr>
<td>69</td>
<td>Coating of fertilizer granules with biodegradable materials as a preparation method of controlled release fertilizer</td>
<td>K. Lubkowski, B. Kic, B. Grzmil,</td>
<td>Institute of Chemical and Environment Engineering, West Pomeranian University of Technology, Pułaskiego 10, 70-322 Szczecin, Poland</td>
<td>Oral</td>
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</tr>
<tr>
<td>71</td>
<td>An experimental evaluation of an effective medium based compaction equation</td>
<td>F. Mahmoodi, G. Alderborn, G. Frenning</td>
<td>Department of Pharmacy, Uppsala University, Uppsala Biomedical Center, P.O. Box 580, SE-751 23 Uppsala, Sweden</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>72</td>
<td>Characterisation of granulated and sintered chromium oxide</td>
<td>U.Kanerva*, T.Suhonen*, X. Liu**, E.M. Garcia*, O. Söderberg**, S-P. Hannula**, E. Turunen*</td>
<td>*VTT Technical Research Centre of Finland, P.O.BOX 1300, FI-33101 Tampere, Finland **Aalto University, Department of Materials Science and Engineering, POB 16200, FI-00076, Aalto, Espoo, Finland</td>
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| 73   | Influence of binder liquid viscosity and superficial tension on granule properties in high shear granulation process | V. Falk*, A. Martin*, Y. Boudiaf*, N. Smirani-Khayati**                                                            | * LRGP, ENSIC- INPL Nancy-Université, 1 rue Grandville, Nancy, 54000, France  
** Laboratoire d'Ecologie et de Technologie Microbiologique, Institut National des Sciences Appliquées de Tunis, Université 7 Nov, Carthage, Tunisie | Oral        | [Click here] |
| 74   | Measurement of cross sectional area of powder profile and its effect on drop behaviour | V.A. Chouk,*, K. Washino*, P. Avontuur,**, M.J. Hounslow*, A.D. Salman*                                               | * Department of chemical and biological engineering, Mappin st., the University of Sheffield, S1 3 JD  
**Pharmaceutical Development, GlaxoSmithKline research & development limited, new frontier Science Park, 3rd avenue, Harlow, Essex, CM19 5AW | Oral        | [Click here] |
| 78   | Characterization and in vitro release of acetaminophen loaded hard gelatin capsules coated by spouted bed | W.P. Oliveira, G.Z. Martins, C.R.F. Souza,                                                                                       | Faculdade de Ciências Farmacêuticas de Ribeirão Preto/USP                                                                                                                | Oral        | [Click here] |
| 79   | Influence of the installed in-line spatial filter velocimetry (SFV) probe on the fluidized bed stability | K.Germer*, B.Wolf*, G. Eckardt**                                                                                         | *Department of Applied Biosciences and Process Engineering, Anhalt University of Applied Sciences, Strenzfelder Allee 28, D-06406 Bernburg, Germany,  
** Parsum GmbH, D-Chemnitz                                                                                     | Poster paper (competition) | [Click here] |
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<th>Institution</th>
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<tbody>
<tr>
<td>80</td>
<td>Characterisation and modelling of layered powder compacts</td>
<td>C. Shang, S. Lawes, J. Pan, I.C. Sinka*</td>
<td>Department of Engineering University of Leicester University Road Leicester LE1 7RH United Kingdom</td>
<td>Poster</td>
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<td>***Department of Pharmaceutics and Biopharmaceutics, Martin-Luther-University, Wolfgang-Langenbeck-Straße 4, 06120 Halle-Wittenberg, Germany</td>
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<tr>
<td>82</td>
<td>Simulation of fluidized bed spray agglomeration focussing on the pre-drying of droplets</td>
<td>M. Dernedde, M. Peglow, E. Tsotsas</td>
<td>Institute for Process Technology Young Researchers Group “Fluid Bed Technology” - NaWiTec Otto-von-Guericke University Magdeburg Universitätsplatz 2 39106 Magdeburg</td>
<td>Poster paper (competition)</td>
<td>[Click here]</td>
</tr>
<tr>
<td>83</td>
<td>Investigation of growth kinetics in fluidised bed spray granulation</td>
<td>T. Hoffman, P. Bachmann, M. Peglow, E. Tsotsas</td>
<td>Wissenschaftlicher Mitarbeiter NaWiTec Fakultät für Verfahrens- und Systemtechnik Institut für Verfahrenstechnik Otto-von-Guericke-Universität Magdeburg Universitätsplatz 2</td>
<td>Poster paper</td>
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<tr>
<td>84</td>
<td>Twin screw granulation: Velocity of material</td>
<td>R.M. Dhenge*, K. Washino*, J.J. Cartwright**, M.J. Hounslow*, A.D. Salman*</td>
<td>*Department of Chemical and Biological Engineering, University of Sheffield, Newcastle Street, Sheffield, S1 3JD, UK  ** Pharmaceutical Development, GlaxoSmithKline, Third Avenue, Harlow, Essex, CM19 5AW, UK</td>
<td>Poster paper (competition)</td>
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<tr>
<td>85</td>
<td>Influence of punch deformation on models describing compressibility of powders during tableting</td>
<td>I. Ilic, B. Govedarica, R. Dreu, S. Srčič</td>
<td>asist. Ilija Ilč, mag. farm. Katedra za farmaceutsko tehnologijo UL – Fakulteta za farmacijo Aškerčeva 7 1000 Ljubljana, Slovenija</td>
<td>Poster paper (competition)</td>
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<tr>
<td>86</td>
<td>The characterisation of granulation wet masses using powder rheometry</td>
<td>T. Freeman, B. Armstrong</td>
<td>Freeman Technology Boulters Farm Centre, Castlemorton Common, Welland, Malvern, Worcestershire, WR13 6LE, UK</td>
<td>Poster paper (competition)</td>
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</tr>
<tr>
<td>87</td>
<td>Modeling of particle formation from a single nano suspension droplet</td>
<td>M. Naumann*, M. Peglow*, A. Bück*, D.L. Marchisio**, E. Tsotsas*</td>
<td>* Otto-von-Guericke University, Chair of Thermal Process Engineering, 39106 Magdeburg, Germany  ** Politecnico di Torino, Departement of Material Science and Chemical Engineering, 10129 Torino, Italy</td>
<td>Poster paper</td>
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<td>89</td>
<td>Pellet layering: Scale-up considerations using different kinds of processing equipment</td>
<td>L. Suhrenbrock***, G. Radtke*, K. Knop**, P. Kleinebudde**</td>
<td>* Boehringer Ingelheim Pharma GmbH &amp; Co KG, Binger Str. 173, 55216 Ingelheim, Germany ** Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, Germany</td>
<td>Poster paper</td>
<td>Click here</td>
</tr>
<tr>
<td>90</td>
<td>Twin screw granulation: influence of process and formulation variables on granule quality</td>
<td>J. Vercruysse*, D. Córdoba Díaz**, M. Fonteyne***, T. De Beer***, J.P. Remon*, C. Vervaet*</td>
<td>* Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, Ghent, Belgium ** Department of Pharmaceutical Technology, Complutense University, Plaza de Ramón y Cajal, Madrid, Spain *** Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Harelbekestraat 72, Ghent, Belgium</td>
<td>Poster (Competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>91</td>
<td>Real-time particle size measurement for granulation optimization</td>
<td>B. Looser*, S. Dietrich**</td>
<td>*Malvern Instruments Ltd, Enigma Business Park, Grovewood Road, Malvern, WR14 1XZ, UK **Parsum GmbH, Reichenhainer Straße 34-36, 09126 Chemnitz, Germany</td>
<td>Poster</td>
<td>Click here</td>
</tr>
<tr>
<td>92</td>
<td>Energetical approach of wet agglomeration process: methodology and measurements</td>
<td>E. Rondet*, M. Denavaut**, S. Mandato**, A. Duri**, B. Cuq**</td>
<td>*UMR 95 Qualisud - Université Montpellier 1, 15 avenue Charles Flahault, BP 14491, 34093 Montpellier cedex 5, France. **UMR IATE 1208 CIRAD/INRA/Montpellier SupAgro/Université Montpellier 2 – 2 place Viala, 34060 Montpellier cedex 2, France.</td>
<td>Poster paper</td>
<td>Click here</td>
</tr>
<tr>
<td>93</td>
<td>Effect of binder on the friability of highly filled composites</td>
<td>A.C. Glauser*, S.E. Gaulter**.</td>
<td>* AWE, Aldermaston, Reading, Berkshire, RG7 4PR, UK. ** Department of Applied Science, Security and Resilience, Shrivenham Campus, Cranfield University, Shrivenham, Swindon, SN6 8LA, UK.</td>
<td>Poster paper</td>
<td>[Click here]</td>
</tr>
<tr>
<td>94</td>
<td>Investigation into particle size effects on the processability of highly filled compacts</td>
<td>P.R. Bolton, A.C. Glauser,</td>
<td>AWE, Aldermaston, Reading, RG7 4PR</td>
<td>Poster paper (competition)</td>
<td>[Click here]</td>
</tr>
<tr>
<td>95</td>
<td>Prediction of particle liquid coverage in fluid bed granulation</td>
<td>W. I. J. Kariuki*, R. M. Smith*, M. Rhodes**, K. P. Hapgood*</td>
<td>* Monash Advanced Particle Engineering Laboratory (MAPEL), Department of Chemical Engineering, Monash University, Clayton, Vic 3800, Australia. ** Department of Chemical Engineering, Monash University, Malaysia</td>
<td>Poster paper (competition)</td>
<td>[Click here]</td>
</tr>
<tr>
<td>96</td>
<td>Application of experimental parameters in an extended PBM of a Wurster fluidized bed granulation</td>
<td>M. Börner, M. Peglow, E. Tsotsas</td>
<td>NaWiTec, Thermal Process Engineering, Otto-von-Guericke-University of Magdeburg, Universitätsplatz 2, 39106 Magdeburg, Germany</td>
<td>Poster paper</td>
<td>[Click here]</td>
</tr>
<tr>
<td>97</td>
<td>Fundamentals of product makeup in high shear mixer</td>
<td>J. Fu, M. Dodd, H.S. Tan</td>
<td>P&amp;G Technical Centres Ltd, Whitley Road, Longbenton, Newcastle upon Tyne, NE 12, 9TS, UK</td>
<td>Poster paper</td>
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<tr>
<td>98</td>
<td>Predicting scale-up effects on flow pattern in high shear mixing of cohesive powders</td>
<td>M. Cavinato*, R. Artoni*, M. Bresciani**, P. Canu*, A.C. Santomaso*</td>
<td>*DIPIC, Dept. of Chemical Engineering, University of Padova, via Marzolo 9, 35131 Padova, Italy **former GlaxoSmithKline R&amp;D, via Fleming 4, 37135 Verona, Italy</td>
<td>Poster paper (competition)</td>
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<tr>
<td>99</td>
<td>Agglomeration of pharmaceutical drugs in high shear mixers: effects of formulation and operative variables on the granule growth kinetics</td>
<td>M. Cavinato*, E. Andreato**, M. Bresciani***, I. Pignatone***, G. Bellazzi***, E. Franceschinis**, N. Realdon**, P. Canu*, A. Santomaso*</td>
<td>*DIPIC, Dept. of Chemical Engineering, University of Padova, via Marzolo 9, 35131 Padova, Italy **Department of Pharmaceutical Science, University of Padova, via Marzolo 5, 35131 Padova, Italy ***former GlaxoSmithKline R&amp;D, via Fleming 4, 37135 Verona, Italy</td>
<td>Poster paper (competition)</td>
<td></td>
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<tr>
<td>100</td>
<td>Investigation of the influence of different organics combination on processing properties of spray dried ceramic granules</td>
<td>S. Eckhard*, M. Fries*, H. Svoboda**, M. Nebelung*</td>
<td>*Fraunhofer-Institut für Keramische Technologien und Systeme, IKTS Dresden Pulvertechnologie / Powder Technology Winterbergstraße 28, 01277 Dresden, Germany **Dresden University of Technology, Institute of Material Science, 01062 Dresden, Germany</td>
<td>Oral</td>
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</tr>
<tr>
<td>101</td>
<td>Accounting for pharmaceutical excipient variability in high shear wet granulation</td>
<td>S. Dale*, J. D. Litster**, C. Wassgren***</td>
<td>*Department of Industrial and Physical Phamacy, Purdue University, West Lafayette, IN, 47907, USA **School of Chemical Engineering, Purdue University, West Lafayette, IN,47907, USA ***School of Mechanical Engineering, Purdue University, West Lafayette, IN,47907, USA</td>
<td>Poster paper</td>
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<tr>
<td>103</td>
<td>Relationships between mechanical strength and binder properties for agglomerates</td>
<td>A. Tita, D. Campos, C. Vallières, V. Sadtler, P. Marchal, V. Falk,</td>
<td>LRGP (Laboratoire Réactions et Génie des Procédés) ENSIC (Ecole Nationale Supérieure des Industries Chimiques) 1, rue Grandville, B.P 20451, 54001 Nancy Cedex, France</td>
<td>Poster paper (competition)</td>
<td>[Click here]</td>
</tr>
<tr>
<td>104</td>
<td>Characterization of the particle dynamics in a prismatic spouted bed apparatus</td>
<td>V. Salikov*, S. Antonyuk*, S. Heinrich*, V.S. Sutkar**, N.G. Deen**, J.A.M. Kuipers**</td>
<td>*Institute of Solids Process Engineering and Particles Technology, 21073 Hamburg, Germany **Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands</td>
<td>Poster paper</td>
<td>[Click here]</td>
</tr>
<tr>
<td>106</td>
<td>Hierarchical control of multi-component high-shear granulation processes</td>
<td>R. Ramachandran</td>
<td>Department of Chemical and Biochemical Engineering, Rutgers University, 98 Brett Road, Piscataway, NJ 08854, USA</td>
<td>Poster</td>
<td>[Click here]</td>
</tr>
<tr>
<td>107</td>
<td>Nucleation mechanisms in melt granulation</td>
<td>R. Artoni*, M. Cavinato*, E. Franceschinis**, P. Canu*, A. Santomaso*</td>
<td>*DIPIC, Dept. of Chemical Engineering, University of Padova, via Marzolo 9, 35131 Padova, Italy **Department of Pharmaceutical Science, University of Padova, via Marzolo 5, 35131 Padova, Italy</td>
<td>Poster</td>
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<tr>
<td>108</td>
<td>What is Janssen's length doing in an agglomerator?</td>
<td>S. Mandato*, B. Cuq*, T. Ruiz**</td>
<td>U.M.R. IATE – Montpellier SupAgro INRA, 2 place Pierre Viala, 34060 Montpellier, France</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>112</td>
<td>Influence of physicochemical binder properties on fractal agglomeration of wheat powder in low shear mixer</td>
<td>A. Barkouti*, E. Rondet**, M. Delalonde**, T. Ruiz*</td>
<td>UMR IATE 1208 CIRAD/INRA/Montpellier SupAgro/Université Montpellier 2 – place Eugène Bataillon, 34950 Montpellier cedex, France.</td>
<td>Oral</td>
<td>Click here</td>
</tr>
<tr>
<td>113</td>
<td>Characterization of the impact of magnesium stearate lubrication on the tableting properties of chitin-Mg silicate as a superdisintegrating binder when</td>
<td>I. Rashid*, N. Daraghmeh**, M. Al-Remawi*, S. A. Leharne**, B. Z. Chowdhry**, A. Badwan*</td>
<td>The Jordanian Pharmaceutical Manufacturing Co., PO Box 94, Naor 11710, Jordan</td>
<td>Poster (competition)</td>
<td>Click here</td>
</tr>
</tbody>
</table>
| 114 | A novel multifunctional pharmaceutical excipient: modification of the permeability of starch by processing with magnesium silicate | *The Jordanian Pharmaceutical Manufacturing Co., PO Box 94, Naor 11710, Jordan*  
**School of Science, University of Greenwich at Medway, Chatham Maritime, Kent ME4 4TB, UK | Poster (competition) | Click here |
| 115 | Twin screw wet granulation: Development of a Modified Release Formulation. | *Pharmaceutical Development, GlaxoSmithKline, Third Avenue, Harlow, Essex, CM19 5AW, UK | Poster | Click here |
| 116 | Experiment and simulation of the dry particle coating | *ENSME, LPMG-UMR 5148, 158 cours Faubriel, 42023 Saint-Etienne, France*  
**EMAC, Rapsodee, FRE CNRS 3213, université de Toulouse, Campus Jarlard, 81013 Albi, France | Poster paper | Click here |
<p>| 117 | Granule attrition by coupled particle impact and shearing | Institute of Particle Science and Engineering, School of Process, Environmental and Materials Engineering, University of Leeds, Leeds, LS2 9JT, UK | Poster paper | Click here |
| 118 | Agglomeration of amorphous food powders in a fluidised bed: Comparison of different granulator configurations | *Institute of Solids Process Engineering and Particle Technology, Hamburg University of Technology.**Nestlé Research Center Vers-Chez-Les-Blanc, Lausanne, Switzerland.***Nestlé PTC York, UK. | Poster paper | Click here |
| 119 | Wet granulation of hydrophobic powders: drop penetration, drug | Monash Advanced Particle Engineering Laboratory (MAPEL), Department of Chemical Engineering, Monash University, Melbourne, | Poster paper | Click here |</p>
<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Authors</th>
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</thead>
<tbody>
<tr>
<td>120</td>
<td>Multiscale simulation of fluidised bed spray agglomeration</td>
<td>M. Dosta*, L. Fries*, S. Antonyuk*, S. Heinrich*, S. Palzer**</td>
<td>*Institute of Solids Process Engineering and Particle Technology, Hamburg University of Technology. **Nestlé PTC York, UK.</td>
<td>Poster paper</td>
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<tr>
<td>121</td>
<td>Assessment of the surface energy to characterize the surface modification of talc particles by dry coating with hydrophobic silica nano particles</td>
<td>G. Lefebvre*, L. Galet*, R. Calvet*, A. Chamayou*, S. Del Confetto*, F. Saito**</td>
<td>*EMAC, Rapsodee, FRE CNRS 3213, Université de Toulouse, Campus Jarlard, 81013 Albi, France ** Tohoku University, IMRAM Center, Sendai, Japan</td>
<td>Oral</td>
<td>Click</td>
</tr>
<tr>
<td>122</td>
<td>Experimental validation of a 2-D population balance model for spray coating processes</td>
<td>J. Li*, B. Freireich**, C. Wassgren**,*** (by courtesy), J. D. Litster*</td>
<td>*School of Chemical Engineering, Purdue University, West Lafayette, IN 47907 **School of Mechanical Engineering, Purdue University, West Lafayette, IN 47907 ***Department of Industrial Physical Pharmacy, Purdue University, West Lafayette, IN 47907</td>
<td>Oral</td>
<td>Click</td>
</tr>
<tr>
<td>123</td>
<td>Compartmental and multiscale design models of granulation processes</td>
<td>J.D. Litster*, C. Wassgren**, S. Beaudoin*, J. F. Li*, B. Freireich**, A. Muljadi*, T. Sinha**, R. McCann***, N. Zarate*</td>
<td>*School of Chemical Engineering, Purdue University, West Lafayette, IN 49707, USA ** School of Mechanical Engineering, Purdue University, West Lafayette, IN 49707, USA ***Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN 49707, USA</td>
<td>Oral Plenary</td>
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<tr>
<td>124</td>
<td>Investigation of spatial density distribution of roll-compacted powders: The influence of roll pressure, roll gap and formulations</td>
<td>N.V. Zarate*, A. Muljadi**, C. Wassgren**, S.P. Beaudoin*, J.D. Litster***</td>
<td>*School of Chemical Engineering, Purdue University, Stadium Mall Dr., West Lafayette, IN 47907, US **School of Mechanical Engineering, Purdue University, Purdue Mall, West Lafayette, IN 47907, US ***School of Industrial and Physical Pharmacy, Purdue University, Stadium Mall Dr., West Lafayette, IN 47907, US</td>
<td>Poster paper</td>
<td><a href="#">Click here</a></td>
</tr>
<tr>
<td>125</td>
<td>Analysis of liquid marble formulation using super-hydrophobic powders</td>
<td>G.M. Walker, P. McEleney, I.A. Larmour, C. Mangwandi, S.E.J. Bell,</td>
<td>*School of Chemistry and Chemical Engineering, Queen's University Belfast, David Keir Building, Stramillis Road, Belfast, BT9 5AG, UK</td>
<td>Poster paper</td>
<td><a href="#">Click here</a></td>
</tr>
<tr>
<td>126</td>
<td>Scaffolds made of nanostructured phosphates, collagen and chitosan for cell culture</td>
<td>G. Tomoaia*, O. Soritau**, M. Tomoaia-Colisel***, L-B. Pop***, A. Pop***, A. Mocanu***, O. Horovitz***, L-D Bobos***</td>
<td>*Iuliu Hatieganu University of Medicine and Pharmacy, Orthopaedics and Traumatology Department, 47 Traian Mosoiu Str., 400132 Cluj-Napoca, Romania; **Oncologic Institute of Cluj-Napoca, 34-36 Republicii Str., 400015 Cluj-Napoca, Romania ***Babes-Bolyai University, Faculty of Chemistry and Chemical Engineering, 11 Arany J. Str., 400028 Cluj-Napoca, Romania</td>
<td>Oral</td>
<td><a href="#">Click here</a></td>
</tr>
<tr>
<td>128</td>
<td>Roller compaction: Change in particle bonding mechanisms with temperature</td>
<td>J. Osborne*, L. Forny**, G. Niederreiter**, S. Palzer***, M. J. Hounslow*, A. D. Salman*</td>
<td>*Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield, S1 3JD, UK **Food Science and Technology Department, Nestlé Research Centre, Vers-Chez-Les-Blanc, CH-1000 Lausanne, Switzerland</td>
<td>Poster paper (competition)</td>
<td><a href="#">Click here</a></td>
</tr>
<tr>
<td><strong>129</strong></td>
<td>A novel method to quantify tablet disintegration</td>
<td>X. Mesnier*, L. Forny**, G. Niederreiter**, S. Palzer***, M.J. Hounslow*, A.D. Salman*.</td>
<td>Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield, S1 3JD, UK&lt;br&gt;** Food Science and Technology Department, Nestlé Research Centre, Vers-Chex-Les-Blanc CH-1000 Lausanne 26, Switzerland&lt;br&gt;*** Nestlé Product Technology Centre York, Haxby Road, York, YO91 1XY, UK</td>
<td>Oral</td>
<td><a href="#">Click here</a></td>
</tr>
<tr>
<td><strong>130</strong></td>
<td>Relationships between surface composition and functional properties of food powders</td>
<td>I. M. Pazos* <strong>, L. Galet</strong>, C. Gaiani* , A. Chamayou**, J. Scher*</td>
<td><em>Laboratory of Biomolecular Engineering, LiBio, Nancy University, 2 av de la Foret de Haye, 54505 Vandoeuvre lès Nancy, France&lt;br&gt;</em>* Université de Toulouse, Mines Albi, CNRS, Centre RAPSODEE, Campus Jarlard, F-81013 Albi cedex 09, France</td>
<td>Poster paper (competition)</td>
<td><a href="#">Click here</a></td>
</tr>
<tr>
<td><strong>131</strong></td>
<td>Blade-granular bed stress in cylindrical high shear granulator: Online measurement</td>
<td>E.L. Chan*, G.K. Reynolds**, B. Gururajan***, M.J. Hounslow*, A.D. Salman*</td>
<td>Department of Chemical and Biological Engineering, University of Sheffield, Mappin Street, Sheffield, UK&lt;br&gt;** AstraZeneca, Charter Way, Silk Road Business Park, Macclesfield, Cheshire, UK&lt;br&gt;*** AstraZeneca, Bakewell Road, Loughborough, Leicestershire, UK</td>
<td>Poster paper (competition)</td>
<td><a href="#">Click here</a></td>
</tr>
<tr>
<td><strong>132</strong></td>
<td>Origin of particle aggregation mechanisms in a pilot-scale counter</td>
<td>V. Francia* <strong>, L. Martin</strong>, A.E. Bayley**, M.J.H. Simmons*</td>
<td>*P&amp;G Technical Centres Ltd, Whitley Road, Longbenton, Newcastle upon Tyne, NE12 9TS, UK</td>
<td>Oral</td>
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<td>Subject</td>
<td>Authors</td>
<td>Institution</td>
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</tr>
<tr>
<td>134</td>
<td>Determination of the tensile strength of elongated tablets</td>
<td>K.G.Pitt*, M.G. Heasley**.</td>
<td>*Global Manufacturing &amp; Supply and **Research &amp; Development, GlaxoSmithKline, Ware, SG12 0DJ, UK.</td>
<td>Oral</td>
<td>Click here</td>
</tr>
<tr>
<td>136</td>
<td>Granule disruption in upflow anaerobic reactor</td>
<td>J. Wu*, L. Bi*, JB Zhang**, S Poncin**, HZ Li**, Y Jiang*</td>
<td>* State Key Joint Laboratoryof Environment Simulation and Pollution Control, Dept. of Envir. Sci &amp; Eng., Tsinghua University, Beijing 100084 P.R.China **Laboratory of Reactions and Process Engineering, Nancy-Universite, CNRS, 1, rue Grandville, BP20451, 54001 Nancy cedex, France</td>
<td>Poster (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>138</td>
<td>Particle-particle agglomeration and use of the hard-sphere model</td>
<td>P. Kosinski, A.C. Hoffmann</td>
<td>The University of Bergen Norway</td>
<td>Oral</td>
<td>Click here</td>
</tr>
<tr>
<td>140</td>
<td>Predicting granule size in nucleation only granulation for crater formation regime</td>
<td>D. Kayrak-Talay*, H. Emady*, W.C. Schwerin*** J.D. Litster* **.</td>
<td>*School of Chemical Engineering, Purdue University, West Lafayette, IN 47907, USA **School of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN 47907, USA *** Honeywell, Des Plaines, IL 60017,USA</td>
<td>Oral</td>
<td>Click here</td>
</tr>
<tr>
<td>141</td>
<td>DEM simulation of wet particles in a high shear mixer considering liquid bridge force</td>
<td>K. Washino*, H.S. Tan**, M.J. Hounslow*, A.D. Salman*</td>
<td>*Department of Chemical and Biological Engineering, University of Sheffield, Newcastle Street, Sheffield, S1 3JD, UK **P&amp;G Technical Centres Ltd, Whitley</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
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<td>------</td>
</tr>
<tr>
<td>142</td>
<td>DEM investigation of the traverse mixing of wet particles in a rotating drum</td>
<td>P.Y. Liu, R.Y. Yang, A.B. Yu</td>
<td>School of Materials Science and Engineering, The University of New South Wales</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>143</td>
<td>Numerical study of the agglomerate dispersion in dry powder inhaler</td>
<td>Z.B. Tong*, R.Y. Yang*, A.B. Yu*, S. Adi**, H.K. Chan**</td>
<td>*Laboratory for Simulation and Modelling of Particulate System, School of Materials Science and Engineering, University of New South Wales, Sydney, NSW 2052, Australia **Faculty of Pharmacy, University of Sydney, NSW 2006, Australia</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>144</td>
<td>Microencapsulation of active ingredients in solid particles</td>
<td>E. Heinrich*, S. Palzer**</td>
<td>*Nestlé Research Centre, Vers-Chez-Les-Blanc, Switzerland **Nestlé Confectionery Product Technology Centre, York, United Kingdom</td>
<td>Poster paper</td>
<td>Click here</td>
</tr>
<tr>
<td>146</td>
<td>Scale up of geometrically non-similar high shear granulators: A case study</td>
<td>M. Cavinato*, R. Artoni*, M. Bresciani**, P. Canu*, A.C. Santomaso*</td>
<td>*DIPIC, Department of Chemical Engineering, University of Padova, via Marzolo 9, 35131 Padova, Italy **former GlaxoSmithKline R&amp;D, via Fleming 4, 37135 Verona, Italy</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>147</td>
<td>Recent advances in fluid bed agglomeration of beverage powders</td>
<td>E. Chávez Montes*, M. Peglow**, R. Hampel***, J. Mariano*, C. Filiol*, J.-C. Gumy</td>
<td>* Nestlé PTC Orbe, CH-1350 Orbe, Switzerland ** NaWiTec, Institute for Process Engineering, Magdeburg University, Germany *** Process Development, AVA GmbH, Magdeburg, Germany</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>149</td>
<td>Kinetics of dry neutralization of dodecylbenzensulfonic acid</td>
<td>M. Schongut, F. Stepanek</td>
<td>Department of Chemical Engineering, Institute of Chemical Technology Prague,Technicka 3, 166 28 Prague 6, Czech Republic</td>
<td>Poster paper</td>
<td>Click here</td>
</tr>
<tr>
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<td>Institution</td>
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</tr>
<tr>
<td>150</td>
<td>Effect of powder bed inclination on binder drop behaviour</td>
<td>V.A. Chouk.<em>, P. Avontuur**, M.J. Hounslow.</em>, A.D. Salman*</td>
<td>* Department of Chemical and Biological engineering, Mappin st., University of Sheffield, S1 3 JD * **Pharmaceutical Development, GlaxoSmithKline research &amp; development limited, new frontier Science Park, 3rd avenue, Harlow, Essex, CM19 5AW</td>
<td>Poster paper</td>
<td>Click here</td>
</tr>
<tr>
<td>151</td>
<td>Simulation of in-line particle sizing techniques during agglomeration processes</td>
<td>C. Fischer, M. Peglow, E. Tsotsas</td>
<td>NaWiTec, Thermal Process Engineering, Otto-von-Guericke-University of Magdeburg, Universitätsplatz 2, Magdeburg, 39106, Germany</td>
<td>Poster paper</td>
<td>Click here</td>
</tr>
<tr>
<td>152</td>
<td>Coating of aerogel particles in spouted beds: Experimental study and DPM simulation</td>
<td>S. Antonyuk*, S. Heinrich*, I. Smirnova**</td>
<td>* Hamburg University of Technology, Denickestr. 15, 21071 Hamburg, Germany ** University of Technology, Eissendorferstr. 38, 21073 Hamburg, Germany</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>154</td>
<td>Monitoring aggregation and scaling of calcium carbonate in the presence of ultrasound irradiation using focused beam reflectance measurement</td>
<td>W. N. Al Nasser*, K. Pitt**, M. J. Hounslow**, A.D. Salman**</td>
<td>* Saudi Aramco Company, Dhahran 31311, Saudi Arabia, <a href="mailto:waleed.nasser@aramco.com">waleed.nasser@aramco.com</a> ** Department of Chemical and Process Engineering, University of Sheffield, Mappin Street, Sheffield – S1 3JD, UK</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>155</td>
<td>Determination of surface deposition and aggregation kinetics of calcium carbonate using</td>
<td>W. N. Al Nasser*, K. Pitt**, M. J. Hounslow**, A.D. Salman**</td>
<td>* Saudi Aramco Company, Dhahran 31311, Saudi Arabia, <a href="mailto:waleed.nasser@aramco.com">waleed.nasser@aramco.com</a> ** Department of Chemical and Process Engineering, University of Sheffield, Mappin Street, Sheffield – S1 3JD, UK</td>
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</tr>
<tr>
<td>156</td>
<td>Using DOE in Industrial Granulation</td>
<td>R. Shen, Y. Weng</td>
<td>Procter &amp; Gamble Technology (Beijing) Co., Ltd. No.35 Yu An Road, KongGang Development Area(Area B), ShunYi District, Beijing 101312 P.R.China</td>
<td>Poster</td>
<td>Click here</td>
</tr>
<tr>
<td>157</td>
<td>Moisture transfer with silica gel agglomerate coating</td>
<td>J.C. Bolster*, R.W. Evitts*, R.W. Besant**</td>
<td>*Department of Chemical Engineering, University of Saskatchewan, 57 Campus Drive, Saskatoon, SK, S7N 5A9, Canada ** Department of Mechanical Engineering, University of Saskatchewan, 57 Campus Drive, Saskatoon, SK, S7N 5A9, Canada</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>158</td>
<td>Modifications/ improvement of the Wurster process for drying or coating sensitive bioactive materials</td>
<td>S. El-Mafadi*, A Picot*, A. Maudhuit**, D. Poncelet**</td>
<td>* CAPSULAE, rue de la Géraudière, 44322 Nantes Cedex, France ** GEPEA UMR 6144-ONIRIS, rue de la Géraudière, 44322 Nantes Cedex, France</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>159</td>
<td>Design of Lansoprazole delayed release fast melt tablets using fluidised bed processor</td>
<td>S.Y. Bhagwate, M.S. Farooqui, N.J.Gaikwad</td>
<td>Department of Pharmaceutical Sciences Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur 440 033, India.</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>160</td>
<td>Hot-melt extruded complexes of basic polyelectrolyte and poorly water-soluble drugs</td>
<td>C. Kindermann*, F. Sievert**, J. Breitkreutz*</td>
<td>*Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Duesseldorf, Germany **ratiopharm GmbH, Ulm, Germany</td>
<td>Poster (competition)</td>
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</tr>
<tr>
<td>161</td>
<td>The sticking propensity of a dicalcium phosphate based roller compaction platform: an observational study</td>
<td>E.L. McConnell, M.J. Pollitt</td>
<td>Formulation Development, MSD, Hertford Road, Hoddesdon, UK, EN11 9BU</td>
<td>Poster (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>162</td>
<td>Anticipation of agglomeration in fluidized bed coating process by control system</td>
<td>A. Prada, A. Maudhuit, L. Boillereaux, D. Poncelet</td>
<td>* GEPEA UMR 6144-ONIRIS, rue de la Géraudière, 44322 Nantes Cedex, France</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>163</td>
<td>Salt deposit at particle contact points</td>
<td>X. Nie*, R. W. Evitts*, R. W. Besant**</td>
<td>*Department of Chemical and Biological Engineering, University of Saskatchewan, 57 Campus Drive, Saskatoon, SK S7N 5A9, Canada  **Department of Mechanical Engineering, University of Saskatchewan, 57 Campus Drive, Saskatoon, SK S7N 5A9, Canada</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>164</td>
<td>Experimental study on the hygroscopic relationship to fracture strength of potash particulate test specimens</td>
<td>S. Gao*, R. W. Besant*, R. W. Evitts**</td>
<td>*Department of Mechanical Engineering, University of Saskatchewan, 57 Campus Drive, Saskatoon, Saskatchewan, Canada, S7N 5A9  **Department of Chemical and Biological Engineering, University of Saskatchewan, 57 Campus Drive, Saskatoon, Saskatchewan, Canada,</td>
<td>Poster paper (competition)</td>
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<tr>
<td>166</td>
<td>Partial dissolution and recrystallization at controlled relative humidity to predict caking</td>
<td>M. Langlet*, M. Benali**, I. Pezron*, K.Saleh, L. Metlas-Komunjer</td>
<td>UTC Compiègne, Equipe d'Accueil &quot;Transformations Intégrées de la Matière Renouvelable&quot; (EA 4297), rue Personne de Roberval - 60200 Compiègne &quot;Ecole Supérieure de Chimie Organique et Minérale, 1 allée du réseau Jean-Marie Buckmaster - 60200 Compiègne</td>
<td>Poster paper (competition)</td>
<td>Click here</td>
</tr>
<tr>
<td>167</td>
<td>FBRM as a PAT tool for in-line monitoring of particle growth kinetics in wet granulation processes</td>
<td>F. Alshihabi*, T. Vandamme**, G. Betz*</td>
<td>*Industrial Pharmacy Lab, Dept. of Pharmaceutical Sciences, University of Basel, Basel, Switzerland **CNRS 7199, Université de Strasbourg, Faculté de Pharmacie, équipe de Pharmacie Biogalénique, 74 route du Rhin BP 60024 F-67401 Illkirch Cedex, France</td>
<td>Poster</td>
<td>Click here</td>
</tr>
<tr>
<td>168</td>
<td>High shear granulation with Starch 1500® - Evaluation of process parameters by design of experiments</td>
<td>K. Hughes*, G. LaBella**</td>
<td>*Colorcon Ltd, Dartford, DA2 6QD, U.K. **Colorcon Inc, West Point, PA19486-0024, USA</td>
<td>Poster</td>
<td>Click here</td>
</tr>
<tr>
<td>169</td>
<td>Mechanical material properties and their influence on particle deformation and the formation of particle-particle contact points in agglomeration processes</td>
<td>C. Haider*, T. Althaus**, D. Dopfer**, G. Niederreiter**, K. Sommer*** and S. Palzer****</td>
<td>* The University of Sheffield, Sheffield, United Kingdom ** Nestlé Research Centre, Lausanne, Switzerland *** Technische Universität München, Germany **** Nestlé Product Technology Centre, York, United Kingdom</td>
<td>Oral</td>
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<tr>
<td>170</td>
<td>In-line monitoring of a continuous pharmaceutical granulation and drying process</td>
<td>M. Fonteyne*, J. Vercruysse**, D. Córdoba Díaz***, J.P. Remon**, C. Vervaet**, T. De Beer*</td>
<td>* Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Harelbekestraat 72, Ghent, Belgium ** Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, Ghent, Belgium *** Department of Pharmaceutical Technology, Complutense University, Plaza de Ramón y Cajal, Madrid, Spain</td>
<td>Poster (competition)</td>
<td></td>
</tr>
<tr>
<td>171</td>
<td>Evolution of the structures and properties of microcrystalline cellulose granules during high shear wet granulation – implications for bulk powder compaction and flow performance</td>
<td>Y. Feng*, L. Shi**, C. C. Sun**</td>
<td>* Eli Lilly and Company, Indianapolis, IN 46285 ** Dept. of Pharmaceutics, College of Pharmacy, University of Minnesota, MN 55455</td>
<td>Poster (competition)</td>
<td></td>
</tr>
<tr>
<td>173</td>
<td>Laundry detergent build-up in auger fillers</td>
<td>C. Hewitt*, D. Smith**, M. Ridyard**, A. Ingram*, C. Wu*</td>
<td>*Department of Chemical Engineering, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK **P&amp;G Technical Centres Ltd, Whitley Road, Longbenton, Newcastle upon</td>
<td>Poster (competition)</td>
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</tr>
</tbody>
</table>
| 174| Influence of raw material particles size to properties of granulated fertilizers | A. M. Sviklas*, R. Paleckienė*, R. Šlinkšienė*, V. Štreimikis** | * Department of Physical Chemistry, Kaunas University of Technology, Radvilėnų pl. 19, Kaunas LT - 50254  
** UAB "Arvi fertis" P.Armino g. 65, Marijampolė, LT - 68127 | Poster      | Click here |
| 175| MicroCT analysis of migration effect on granule structure during fluidized bed and oven tray drying | S. Poutiainen, M. Honkanen, K. Järvinen, J. Ketolainen | School of Pharmacy, University of Eastern Finland, P.O. Box 1627 70211 KUOPIO, FINLAND | Poster (competition) | Click here |
| 176| Influence of initial mixing on granule properties | A. Alkhatib, L. Briens | Department of Chemical and Biochemical Engineering, The University of Western Ontario, London, Ontario, Canada N6A 5B9 | Poster (competition) | Click here |
| 177| On the capillary force/viscous force transition in pendular liquid bridges | J. Bowen*, D. Cheneler**, Z. Zhang*, M.C.L. Ward**, M.J. Adams | * School of Chemical Engineering, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK  
** School of Mechanical Engineering, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK | Oral       | Click here |
| 178| Influence of agglomeration process conditions on the sintering of amorphous model food particles | C. Haider*, D. Dopfer**, G. Niederreiter**, S. Palzer***, A.D. Salman*, M.J. Hounslow* | * The University of Sheffield, Sheffield, United Kingdom  
** Nestlé Research Centre, Lausanne, Switzerland  
*** Nestlé Product Technology Centre, York, United Kingdom | Poster (competition) | Click here |
<table>
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<th>Title</th>
<th>Authors</th>
<th>Affiliations</th>
<th>Type</th>
<th>Click Link</th>
</tr>
</thead>
</table>
| 179  | Drop penetration time: Effective drawing area and multicomponent mixtures | H.R. Charles-Williams*, R. Wengeler**, K. Flore**, H. Feise**, M.J. Hounslow*, A.D. Salman*        | *Department of Chemical and Process Engineering, University of Sheffield, Mappin Street, Sheffield, S1 3JD, UK  
**BASF SE, Chemical and Process Engineering, 67056 Ludwigshafen, Germany | Poster   | [Click here](#) |
| 180  | Granulation behaviour of increasingly hydrophobic mixtures            | H. Charles-Williams*, R. Wengeler**, K. Flore**, H. Feise**, M. J. Hounslow*, A.D. Salman*        | *Department of Chemical and Process Engineering, University of Sheffield, Mappin Street, Sheffield, S1 3JD, UK  
**BASF SE, Chemical and Process Engineering, 67056 Ludwigshafen, Germany | Poster   | [Click here](#) |
| 181  | Interactions of hydrophilic particles in hydrophobic media in presence of hydrophilic liquid - a preliminary study | A. Alves Negreiros*, T. Althaus**, G. Niederreiter**, S. Palzer***, M.J. Hounslow*, A.D. Salman* | *Department of Chemical and Biological Engineering, University of Sheffield, United Kingdom  
**Nestlé Research Centre Lausanne, Switzerland  
***Nestlé Product Technology Centre, York, United Kingdom | Poster   | [Click here](#) |
| 182  | EFFECT OF LUBRICANT ADDITION ON GRANULAR VELOCITY DURING EARLY STAGE OF TABLETTING | V.A. Chouk*, B. Gururajan**, G.K. Reynolds**, M.J. Hounslow*, A.D. Salman*                      | *Department of Chemical and Biological Engineering, The University of Sheffield, Sheffield, UK  
* AstraZeneca, Charter Way, Silk Road Business Park, Macclesfield, Cheshire, UK | Poster paper (competition) | [Click here](#) |
| 183  | Compact pore volume distribution and granular velocity during granular | V.A. Chouk*, B. Gururajan**, G.K. Reynolds**, C. Sinka***, M.J. Hounslow*, A.D. Salman*         | *Department of Chemical and Biological Engineering, The University of Sheffield, Sheffield, UK  
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1 - Implementing PAT-tools in a continuous pharmaceutical granulation process for the in-line monitoring of critical process and product quality attributes


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The Process Analytical Technology (PAT) initiative was launched by the FDA in 2004. The main idea behind it, is to ensure the safety of drugs by building quality into the products instead of testing quality after production. Therefore, it is important to obtain critical process and product information during processing by implementing process analytical tools. Granulation is a process in which solid-state transformations of drug products (API) and excipients can occur. Since the solid-state of the API and the excipients might have an influence on the properties of the final dosage form (stability, solubility, bioavailability, etc.), it is important to monitor and control the product solid-state during processing. Furthermore, the particle size distribution (PSD) of the wet granules is an important variable, since it has direct influence on the granule drying process and the dried granule properties. The aim of this work was to investigate if the PSD and product solid-state can be continuously monitored using a particle size analyzer, Raman- and NIR-spectroscopy during a continuous pharmaceutical granulation process.

An anhydrous theophylline/lactose/PVP (30-67.5-2.5%) formulation was continuously granulated using a twin-screw granulator, being part of a full continuous from powder-to-tablet production line. (Consigma™, GEA). A Design of Experiments was performed to study the influence of 4 factors (screw speed, powder feed rate, liquid concentration and barrel temperature) upon the in-line monitored critical product aspects (PSD and API solid state). Wikström et al. [1] detected an immediate and complete conversion from anhydrous theophylline to theophylline monohydrate during a batchwise high shear granulation process. For this continuous granulation process, both Raman and NIR spectroscopy revealed that a small amount of theophylline remained anhydrous. From the DOE experiments, it could be concluded that the barrel temperature, the liquid concentration and to a smaller extent the powder feed rate significantly influenced the product quality attributes. High barrel temperature, low liquid concentration and high barrel filling all resulted in an uncomplete theophylline monohydrate formation. This study shows the possibility of monitoring some critical product aspects using Raman- and NIR spectroscopy and a particle size analyzer during a continuous pharmaceutical twin-screw granulation process.

2 - Fluid bed coating with extremely high drug load

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Fluid bed coating plays a more and more important role in film coating. The bottom-spray method with Wurster equipment provides a controlled fluidization producing a very dense film. Furthermore, the film forming droplets can spread out at the lowest viscosity because premature droplet evaporation is almost absent [1].

In this work, coating processes with Wurster technique in laboratory scale were performed to find out possibilities and limits of the coating process for pellets with extreme large amounts of coating material on the pellets. Therefore, inert pellets (Celllets® 200, IPC, D-Dresden) were coated with a model drug (sodium benzoate) in a weight ratio of coating to core of 3:1 and further excipients in different concentrations. In the aqueous coating liquid the Polymers HPMC (Pharmacoat 606®, Syntapharm, D- Mülheim an der Ruhr) and polyvinylpyrrolidone PVP (Kollidon25, BASF, D-Ludwigshafen) were added as film forming agents to reduce drug abrasion and loss, talcum (Chemie Vertrieb, D-Magdeburg) as anti-sticking agent. Optimum of the fluid bed process parameters were evaluated in earlier investigations, here stability of the process and yield were regarded. Product quality was estimated by the amount of layer in relation to the pellet core, homogeneity of the layer, particle size and bulk and tap density of the product.

The process was performed in a laboratory fluidized bed coater GPCG 1.1. (Glatt, D-Binzen) equipped with a Wurster tube. Process air temperature was 90°C; air flow rate 45±5 m3/h, spraying rate 20 g/min, atomization air pressure 1.9 bar; nozzle diameter 1.0 mm, pellet batch size 150 g. The coating liquid consisted of water dissolved sodium benzoate (30% w/w), polymers in different concentrations and suspended talcum. Particle size of coated pellets was measured with digital image processing (Camsizer, Retsch, D-Haan), sodium benzoate content by UV spectroscopy (Spekol 1300, Analytik Jena, D-Jena), bulk and tap volume by tap volumeter (Retsch, D-Haan), film homogeneity was evaluated with a stereo light microscope (Stemi 2000-C, Carl-Zeiss, D-Jena).

The yield of coated pellets amounts about 90%. Sodium benzoate loss occur by abrasion at the wall of the granulator. The addition of PVP and HPMC results indeed in a better mechanical stability reducing abrasion, but also increases agglomeration of the pellets. Polymer concentrations above 2% lead to particle sticking and unstable fluid bed process. The addition of talcum (0,5-1,5%) reduces agglomeration and increased the yield and content amounts to more than 95%. The coated pellets have a narrow particle size distribution. Polymer concentration up 3% is possible. In further investigations the drug loaded pellets will be coated with film building polymers to provide retard dissolution.

To manufacture granulated products continuous fluidized bed processes are more than suitable. Based on known basic principles of fluidized bed processing different standard types of continuous fluidized bed plants were developed. One of the most used versions is a fluidized bed unit with rectangular design of bottom screen. The section below the bottom screen can be divided into several inlet air chambers to distribute the air flow to the different process steps and feed different air qualities to the fluidized bed. The main advantage of this equipment design is the possibility to carry out multi-step processes in one apparatus. For instance a combination of granulation processes with subsequent cooling are of industrial importance.

Different studies on particle movement are also shown which are simulated based on CFD using the Euler-granular approach. The studies discussed here were made with 3-dimensional model of an existing Glatt continuous GF pilot plant. All simulations were carried out using the commercially CFD software package Fluent 6.2. The simulations focus on differences in particle velocity distribution when e.g. process air velocity is changing (fig. 1). Practical experiments were carried out using the GF pilot plant to investigate the dynamic properties of the apparatus measured by its residence time distribution (fig. 2) and to compare simulated results with measurements. Additional the residence time distributions were compared with the CSTR-model.

![Figure 1. Contour plots of solid-phase volume fraction.](image1)

![Figure 2. Residence time measurements.](image2)
4 – A general framework for modelling the deformation of a body subject to a large number of random impacts during spheronisation

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In this paper we present a general mathematical framework for modelling the deformation of a deformable body when subject to a large number of successive random impacts. The key element of the proposed approach is a contact law which determines the deformation of a sphere impacting with a rigid surface. In order to capture the rounding of a body into the sphere, an equivalent sphere is generated, the contact law is applied and a rounding law is proposed to describe how the local contact flattening determines the evolution of the shape of the body during successive impacts. The feasibility of the model is proven and parametric show the effect of the key material and processing parameters. Finally the underlying assumptions are discussed to highlight the current limitations and possible extensions of the model as well as possibilities for exploitation in material and spheronisation process design.
5 - Optimisation of high shear granulation of multicomponent fertiliser


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Granulation is defined as a size enlargement process of the agglomeration of smaller particles together into larger, semi-permanent aggregates (granules) in which the original particles can still be distinguished [1]. High shear granulation is a unit operation, which is used to process powder material into a higher quality product with improvement in handling and flow properties. This paper describes a novel method of producing multi-component fertiliser granules using the high shear granulation process. The process was optimised using the response surface methodology technique. The variables used in the optimisation process include granulation time, batch size, impeller speed and binder concentration. The product yield, mean granule size and recycle ratio were the product parameters that were optimised. It was possible to produce high quality granules with properties comparable to typical commercial synthetic fertilizers. Product yield of around 60% could be obtained.


Figure 1. Schematic diagram showing the proposed process of production of organic fertiliser granules from AD liquor.
6 – Friability of fluid bed coated pellets

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In the application of pellets for drug formulation the drug substance is mostly incorporated into the pellets with the aim of drug protection, masking of bad taste or smell or controlled drug release. Otherwise, inert pellets as carrier may be coated with drug substances and excipients by the use of coating solutions or suspensions. Critical points seem to be the spraying process of suspensions, the risk of abrasion of the film and therefore of material loss during finally drying and insufficient mechanical stability of the drug coated pellets.

Pellets were coated in the fluid bed with different aqueous solutions and suspensions of model drug substances. Fluid bed process was evaluated due to stability, constant spraying rate and yield. Product quality was investigated due to friability with a modified method, homogeneous blue color by methylene blue added to the spraying liquid, particle size (sieve analysis), bulk volume and residual moisture.

Microcrystalline cellulose pellets (Cellets®200, IPC, D-Dresden) were used and as model drug substances the sugars mannitol and fructose, the film forming polymers methyl cellulose (MC) and hydroxypropylmethylcellulose (HPMC), urea as very good soluble substance and fine-grained zinc oxide, benzocaine and dimenhydrinate (both coarse-grained) as very poorly soluble substances. The coating process was performed in a batch laboratory fluid bed granulator GPCG 1.1 (Glatt, D-Binzen) with Wurster partition under constant process parameters except process air volume which was varied from 40-90 m3/h to maintain constant fluid bed at increasing pellet weight. Immediately after coating the products were dried in the fluid bed to a residual moisture below 1%.

The fluid bed coating process was stable for soluble substances (mannitol, urea) and low concentrated MC and HPMC solutions and also with fine-grained zinc oxide suspensions. The yield was in the range of 80-95% except for urea 25% lot. The amount of uncoated white pellets in the products was below 5% due to some dead space. HPMC 2.5% solution with suspended coarse-grained benzocaine 0.5% or with higher amount of dimenhydrinate (5%) led to blocking of the spray nozzle. Fructose 5% solution was not suitable, hygroscopicity of the substance caused sticking of the particles already during the process. Friability of all lots of coated pellets was below 0.2% confirming the demand of pharmacopoeia (<1% for tablets) and indicating sufficient hardness of the film and only low brittleness. Mean particle size was slightly increased (300-305 µm) in comparison to the uncoated Cellets (290 µm). Bulk volume varied without tendency for all lots in the range 1.13-1.32 ml/g. Coating with suspensions and film forming polymers is limited by concentration. With suspensions, additionally particle size of the dispersed substance should be regarded. Mechanical stability of the coated pellets was sufficient with as well as without film forming polymers.
7 - Spheronisation mechanism of MCC II-based pellets

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Microcrystalline cellulose II (MCC II) - a polymorph of commonly used MCC I – was introduced as new pelletisation aid in extrusion/spheronisation [1]. Preliminary investigations suggested that the spheronisation mechanism of MCC II-based pellets differs from the known mechanism of MCC I. Therefore the spheronisation mechanism of MCC II-based pellets was investigated and compared to that of MCC I.

Mixtures of 20% MCC I or MCC II and 80% lactose were processed at appropriate water contents in a twin-screw extruder and spheronised at 14m/s for time periods from 10s to 15min (13 steps) for MCC II and from 10s to 10min (16 steps) for MCC I. The pellets were sieved, the fraction passing the 0.63mm sieve was defined as fine fraction. The pellets were characterized by aspect ratio, equivalent diameter, 10%-interval (size distribution), weight and porosity.

The results are summarized in Figure 1. Aspect ratio and porosity decreased over the whole spheronisation period for both MCC types. The equivalent diameter developed differently: It increased for MCC II and decreased for MCC I-based pellets during spheronisation. The same applied to the pellet mass: The MCC II-based pellets showed a weight gain from 0.97mg to 1.89mg, the weight of the MCC I-based pellets remained nearly constant (~1mg) during spheronisation. The higher fine fraction of MCC II occurring during processing could partly explain this result as the fine fraction layered on the pellets. However, a fine fraction of maximal 17% could not explain the complete weight gain. Therefore, it was suspected that pellets bigger than 0.63mm abraded during processing and also layered on the other pellets. This presumption was supported by the high increase of the 10%-interval of the MCC II-based pellets (from 48 to 95%) indicating a narrowing of the size distribution; the improvement was less pronounced for the MCC I-based pellets (from 47% to 65%). The findings are supported by investigating other formulations (data not shown). MCC II behaves in a different manner than MCC I in spheronisation: A deeper insight into the spheronisation of MCC II-based pellets was obtained providing a basis to control and influence the spheronisation process of MCC II-based pellets.

Figure 1. Spheronisation behaviour of MCC II- (left) and MCC I-lactose formulation (right).
Physical properties of pharmaceutical pellets

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Pellets are spherical particles with size between 100 and 1000 μm. They are common pharmaceutical product, packed into capsules and used orally. They are produced by extrusion spheronisation process or by direct pelletization using with rotor fluid bed. Pellets are usually coated with one or more layers of drug and/or polymer film that provide protection of the drug or control the release of the drug [1].

In this study we have analysed various properties of different pellets that are available as a medicine and microcrystalline pellets as a common core that is used for layering. This data will provide better understanding of pellets and processes involving pellets as well as provide information for models that are used in discrete element method (DEM) simulations. DEM simulations or DEM simulations coupled with computational fluid dynamics (CFD) of processes involving pellets are nowadays becoming increasingly more useful due to increase of computational power in the last ten years.

Coefficient of restitution was measured for various impact velocities using high speed camera and coefficient of friction was estimated using a tilt test. Force displacement measurements were performed in order to obtain Young’s modulus and to obtain hardness of the pellets. Size and shape was done with image analysis and surface roughness and imaging was performed with atomic force microscopy (AFM). Apparent density was measured with helium pycnometry and bulk density was measured as well. With these two densities maximum packing was calculated. Flowability was tested using standard pharmaceutical test flow through a funnel and assessment of static angle of repose as well as dynamic angle of repose using a rotating drum was performed.

Many products in chemical and process engineering are produced as particulate substances, for example powders. These are preferred over others forms, because they are in general more easily transported, stored, and used by customers. The product quality can often be described by distinct particle properties, for example size, moisture content, or temperature. In order to guarantee these product qualities, some sort of process control has to be applied. Current applications are restricted to the control of some integral values, e.g. mean diameter, of the underlying particle property distribution. Although good results can be achieved -- with respect to the integral values, the actual property distribution can deviate significantly from the desired one. Therefore the direct shaping of property distributions by control methods is needed to guarantee high quality products.

In this contribution we will address two aspects of control of particle property distributions, with a special focus on size distributions in fluidised bed granulation: At first we will present solutions to the important problem of dynamically measuring or reconstructing particle property distributions from noisy and limited measurement information. Here we will show results for three different types of so called model-based measurement systems: Infinite-dimensional Luenberger observer, unscented Kalman filter, and moving horizon observer. Afterwards we will show how these systems can be incorporated into process control systems -- highlighting the need of model-order reduction methods -- and present control approaches that will allow the direct shaping of property distributions in fluidised bed granulation processes, e.g. passivity-based methods.
10 - Fluidised bed agglomeration of skim milk powder: follow-up of agglomerates growth

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Agglomeration of solids particles is often used in food industry for the production of instant powders. Fluidized bed spray granulation is one of the techniques employed. Initial particles fluidised in rising hot air are sprayed at their surface with a liquid or a binder solution to render them locally sticky. When moving particles collide, bridges are created between them, first viscous, then solid due to drying. This leads to the formation of dry agglomerates with structure where initial particles can be identified and presenting good instant properties. Efficiency and kinetics of the agglomeration as well as agglomerates properties depend on several parameters related to the equipment, the operating conditions and the product. Obtaining powders with tailored properties requires knowing how agglomerates are built and the influence of these parameters.

In this work, the mechanisms of agglomeration are investigated through skim milk powder agglomeration spraying water in a batch fluidized bed at pilot scale. In skim milk dry matter is made of lactose (about 53% w/w), proteins (about 37% w/w), minerals (about 9% w/w) and lipids (less than 1% w/w). When wetted by sprayed water droplets, lactose and proteins at the particle surface may become sticky while, when the particle temperature increases in hot air, lipids may melt. All these three constituents may therefore contribute to bridges formation.

At pilot scale, favourable operating conditions (fluidizing air temperature 55°C, sprayed water flow rate of 5 g.min⁻¹) allowed increasing the particle size from about 100 µm to about 700 µm and improving the powder handling properties (flowability, wettability). Decreasing the air temperature (45°C) or increasing the water flow rate (7 g.min⁻¹) led to caking of the particle bed.

Evolution of powder water content and particle size distribution along a full agglomeration process (33 min) was followed by taking samples (~10 g) at different times (every ~5 min). Then shorter agglomeration experiments, with the same operating conditions, were stopped at the same times and the whole powder was analyzed for water content and particle size distribution to compare with the samples picked-up at the same times in the full process. These samples were found to be representative for the particle size distribution of the whole powder but not for the water content, due to non homogeneous humidity in the fluid bed. From the evolution of the particle size distribution, agglomerates formation and growth were found to occur in stages with the appearance of intermediate populations/structures till reaching a maximum size depending on conditions.

These results allowed a better understanding of how agglomerates structure is built along the process and of the influence of the operating conditions on the mechanisms at play for a better control of powders properties.
Discontinuous fluid bed granulation processes and equipment are widely used for manufacturing pharmaceutical products. In comparison to discontinuous processes, the continuous fluid bed granulation is characterized by low investment and maintenance costs and high energy efficiency. The application of this process in the pharmaceutical industry is still limited due to the strict control of the quality of the coating layer, i.e. amount of active substance.

In the present study a new process solution for the production of dosage forms with several functional coatings, which have defined layer thickness, is designed and tested experimentally. The new process combines the advantages of the Wurster fluidized bed-coating process and the continuous mode of operation.

In the framework of the experimental investigations a ProCell-granulator was modified with an external separating tube for controlled discharge of product with predefined layer thickness.

For the coating experiments a model suspension of 30% sodium benzoate was sprayed onto large Cellets® 200 beads. With this material system continuous granulation experiments were conducted and the dependence of the separating effect of the discharging tube from the output particles mass flow rate was examined. Different process conditions such as gas temperature, gas and liquid mass flux were varied and the influence of this parameter on the quality of the coating layer was analysed. In this way, the feasibility of the new single-stage continuous fluidized bed process with the Wurster type fluidized bed was verified. Based on the results obtained, a multi-stage prototype can be designed and tested.

In order to describe the continuous coating process, a mathematical model based on one dimensional population balances (PBE) was developed. A balance area around the granulator and around the separating tube is described, including all input and output mass flows. The PBE makes it possible to calculate the particle size distribution of granulation changing over time. By means of the model, the system performance is estimate in respect of the process parameters and the continuous fluid bed granulation process can be optimized.
The effect of varying viscosity and surface tension of liquid binder on granulation conditions (residence time and torque) and granule properties (size, shape, structure, strength and flowability) was studied in a co-rotating twin screw granulator. The increase in the viscosity increased the residence time, torque and penetration time. The granule size distribution reached unimodality and their strength, flowability increased at high viscosity. The reverse was observed with decreasing viscosity. The surface tension had only a minor influence on granule properties.
Solid lipid extrusion is a reliable and robust process for a number of active pharmaceutical ingredients (API). The smaller the diameter of the dies, the more challenging is the extrusion. However, successful extrusion with enrofloxacin through 0.3 mm dies was reported earlier [1]. Several active pharmaceutical ingredients (API) resulted in unstable solid lipid extrusion giving rise to blocking of dies and finally a termination of the extrusion process. After excluding other possible reasons for this problem the shape of the API particles was analysed and the impact of particle shape on the solid lipid extrusion process was studied.

Three different needle shaped APIs (caffeine, mesalazine, praziquantel) were extruded in a 50/50 (m/m) mixture using glycerol behenate as lipid for solid lipid extrusion. The extrusion was performed with a 27 mm twin-screw extruder using dies of 0.3 mm diameter. The feeding rate was 30 g/min and the screw speed 60 rpm. The barrel temperature was adjusted to 68° C, which is below the melting range of glycerol dibehenate. Further experiments were performed after milling of the APIs. Size and shape distributions of the original and milled API particles were determined by image analysis.

All three needle shaped APIs blocked the dies after short extrusion and the pressure exceeded acceptable values. The relatively best results were obtained for mesalazine, which had the largest particles. The needles of mesalazine were broken down to shorter particles during extrusion. Particles of the two other APIs were broken to a much lesser extent. The length of the needles for praziquantel was more than 10 times smaller than the die diameter. Milling of the APIs resulted in more isometric particles. The solid lipid extrusion of milled APIs was stable and even in all cases. It can be concluded that the particle shape has a considerable influence on the performance of solid lipid extrusion.

[1] A. Michalk et al, Controlled release of active as a consequence of the die diameter in solid lipid extrusion, J Control Rel 132, 35-41, 2008.
In this contribution the impact behaviour of spherical granules has been studied. The normal impact has been modelled using the Discrete Element Method (DEM). DEM was applied originally by Cundall and Strack to solve problems in rock mechanics [1]. A granule, which consists of 1,000 primary particles bonded by parallel-bonds, has been modelled. Different micro and macro properties are necessary for generation of the granule, for example diameter, solid density, Young's modulus and breakage force. Properties of zeolite 4A granules have been used to adjust the simulation. For calibration of the mechanical properties the force-displacement behaviour of the granule has been fitted to the force-displacement behaviour of zeolite 4A granules. Therefore, a compression test of the modelled granule between two rigid walls has been carried out. Zeolite 4A granules have been investigated experimentally by preliminary compression tests until breakage. The granules exhibit an elastic-plastic material behaviour. After calibration the force displacement curves show good agreement.

The normal impact has been modelled against a rigid wall at different impact velocities, which has been increased until breakage of the granule. The rebound velocities have been determined and the coefficient of restitution has been calculated. The coefficient of restitution has been compared with experimental results of zeolite 4A granules. A good qualitative agreement between simulation and experimental results has been achieved.

Heap leaching is a method used to recover metal from low-grade ores at low capital cost and operational cost [1]. Low-grade ores often go through milling and concentration process which lead to fine mineral particles. Agglomeration of fine mineral particles as a precursor to heap leaching is an important means of enhancing leaching rates and metal recoveries. Among the quality parameters of the agglomerates, its mechanical strength is the most important parameter as agglomerates must be strong enough so that no dead zones of fine particles are formed in the heap due to the disintegration of agglomerates. The characteristics of the nuclei formed from the initial stage of granulation process are very important as their properties directly determine the final agglomerate quality.

In this work, the characteristics of the nuclei formed from nickel laterite ores with diluted sulphuric solutions as a binder are investigated. The nuclei are produced by dropping the binder solution onto a stationary powder bed. The mechanical integrity of the nuclei formed, the relationship between the nuclei diameter and binder drop diameter are studied. The time required for a binder drop to penetrate the powder completely has been recorded. The effect of feed powder size, concentrations of sulphuric acid on the nuclei quality is also studied so that theoretical insight into the relationship between granule strength and powder and binder properties is gained. A mechanistic nucleation model which includes nuclei breakage was developed and validated with ex-granulator drop-penetration experiments and drum granulation experiments. The essence of the nucleation model is that only in systems where primary nuclei can withstand the impact forces in the granulator will form the initial conditions for the growth and coalescence stage. The methodology developed will also be useful in screening potential binders for producing robust agglomerates for heap leaching as the final agglomerate strength is directly related to the initial nuclei strength.

Unilever and other detergent manufacturers make and market Detergent powders manufactured by high shear granulation processes. Although powders are prepared and sold using this process the understanding of the major parameters that contribute to the final product properties are poorly understood. Batches with apparently the same formulation and process can possess different properties when prepared on different days. Granulation is often described as a black art rather than a science!

A great deal of research has been performed to examine high shear granulation by Universities and other companies but these tend to use melt or evaportative binders and as such are not directly relevant to detergent granulation. The major difference with the detergent granulation process to other granulation processes is that we use a reactive binder that changes from a liquid to a sticky solid as the granulation process progresses.

For the past 3 years Unilever have had hosted MEng students from University of Strathclyde who each spent 12 weeks looking at aspects of variability in the granulation process attempting to establish which variables have the greatest impact on product properties. The variables studied included binder temperature, humidity at which raw materials were stored prior to granulation (to simulate different climates) and raw material particle size.

It was found that humidity had minor effects on product properties whereas raw material particle size and binder temperature appeared to have more significant effects. So far only binder temperature has been studied in further detail.

It was found that increases in binder temperature do in fact appear to result in more dense, less porous powder granules, but with very little change on the overall size distribution of the product. The evidence for this was clear changes in bulk density, attrition and porosity, X-ray tomography also supports this conclusion. The more dense particles produced at higher binder temperatures may be caused by changes in the agglomeration mechanism.
Quantification of mass transfer during spheronisation

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Pellet manufacturing by extrusion/spheronisation is a common technique in the pharmaceutical field because the obtained product is characterized by a high sphericity and a narrow particle size distribution. After extrusion of the bulk material, the cylindrically shaped extrudates are transferred to the spheronizer where they are plastically deformed into spherical pellets. The currently established mechanisms only consider deformation as the driving force of the spheronisation process and do not account for the occurrence of fine particles. However, preliminary work suggests that a non-negligible amount of mass is transferred between particles (Figure 1).

In this work, experiments were performed to quantify the amount of mass transferred between single particles during spheronisation. Extrusion/spheronisation experiments were performed using microcrystalline cellulose (MCC) as a pelletisation aid and acetaminophen as a model drug in combination with lactose as a filler. Two different formulations, one containing 25% acetaminophen and one being a placebo, were extruded separately at different water content levels. Afterwards, 250 g of each formulation were spheronised together for 5 min.

The data indicate that mass is transferred during spheronisation and that the amount of mass transferred is not negligible (Figure 2). The amount of mass transferred correlated with the water content. In addition to MCC and acetaminophen, kappa-carrageenan and Ibuprofen were used in this study.

In conclusion, the mass transfer between particles must be taken into account in order to explain pellet formation during spheronisation.

Figure 1 (above). (I) cylinder, (II) rounded edges and fractures fines, (III) dump-bell with agglomerated fines, (IV) ellipse, (V) sphere.

Figure 2 (left). Amount of mass transferred per pellet in relation to the water content for n = 50 pellets containing MCC/lactose and...
Granulation is an important particle-size enlargement process, used in many applications. Granulation within the Pharmaceutical industry has, for many years, been a batch process and the reasons for this are many. However, the technique of using a twin screw granulator has been found to be very effective at granulating. The quality and manufacturing attributes of the granules produced vary depending upon a number of different machine and powder parameters. One of the key factors that influenced the successful outcome of this work, was the effective feeding of materials, including Active Pharmaceutical Ingredients (API) onto the twin screw granulator.
19 - Unified compaction curve: A potential link between the wet granulation and tabletting processes

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Tablets are common vehicles for drug administration, making up approximately one third of drug dosage forms. Although the process is common in the pharmaceutical industry, the manufacture of tablets can currently be seen to be an “artwork” on a blank canvas. The aim of this study is to provide a “scientific canvas” for the tabletting artwork and this is to be achieved by investigating how the wet granulation process affects the tablet tensile strength.

A potential model for representing this relationship can be found with the “Unified Compaction Curve”, a model developed for the looking at the roller compaction conditions on the tablet properties [1]. By measuring the tablet tensile strength for a range of roller compaction forces, a master compaction curves was able to be established representing the effect of the roller compaction forces and compaction pressure on the tensile strength. The unified compaction curve can then be used to help predict which roller compaction conditions and formulations help achieve the tablet strength criterion required by industry.

The unified compaction curve concept was adopted to investigate the effect of the granulating a basic formulation of microcrystalline cellulose, lactose and polyvinylpyrrolidone on the tablet strength. The effect of the powder formulation, granulation liquid level and wet massing time on the final tablet tensile strength was explored. A variety of compaction pressures were employed to generate a master compaction curve relating the tablet tensile strength, compaction pressure and the granulation condition. The origin points for each of the varying granulation conditions were extracted from the master curve to form a simplified prediction line to find the optimum compaction pressure and granulation conditions to achieve a specified tablet strength during the formulation/process design process.

The unified compaction curve is expected to help in formulation and manufacture design in optimising the tabletting manufacturing process and tablet properties.

21 - Relationships between milk powders morphology and its rehydration properties

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The influence of the physical properties or the chemical composition of a dairy powder on powder functionality has been quite extensively investigated [1]. The surface of the powder is expected to play also an essential role. For example, the surface was systematically found different from the bulk composition [2-3]. In the present study, we investigated the influence of milk powder morphology on functional properties. Very little work has been carried out in this field for food powders whereas the literature was extremely furnished for minerals powders. Indeed, the morphology of the powder is expected to play also an essential role and should certainly not be neglected.

Recent and novel advances in image analysis methodology have been useful for quantitative evaluation of morphology and structure of food materials. In this study, a laser diffraction system coupled with an image analysis processor (Qicpic, Sympatec) was used or measuring the shape of a representative number of particles (more than 90000 per experiment). The following morphological parameters (Figure 1) were investigated: mean diameter, convexity, elongation, sphericity, aspect ratio, straightness, ect. Concurrently, some functional properties related to powder hydration were determined following the IDF standards (wetting, dispersibility, solubility). Five different milk powders (whole milk, skim milk, low-fat milk, native micellar casein and native whey isolate powders) more or less agglomerated (310, 285, 220, 185, 150, 105 and 75µm) were studied.

As expected, the instant properties of the powders were found dependent on powder composition but also on powder morphology. Then, from multivariable data analysis (Unscrambler v7.6) tentative models were developed; the objective being to predict from morphology and size parameters the rehydration properties of the powders. In conclusion, the Qicpic equipment could be considered as an attractive instrument to evaluate the quality of the powders.

Figure 1. Representation by the Qicpic apparatus of the Diameter of a Circle of Equal Projection Area (A) and the shape factors: sphericity (B) and convexity (C).

\[ S = \frac{P_{QICPC}}{P_{\text{real}}} = \frac{2\sqrt{\pi \cdot A}}{P_{\text{real}}} \]

\[ \psi_c = \frac{A}{A + B} = 1 - \frac{B}{A + B} \]
22 - Parameter study of an Eulerian-Eulerian CFD model in high-shear granulation

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High shear granulation is a commonly used process in pharmaceutical industry. Attempts have been made to describe the granular flow field in high shear granulation equipment with an Eulerian view on the granular phase[1] [2]. In these cases closures from the Kinetic Theory of Granular Flow (KTGF) with an added frictional contribution to the solid phase viscosity and pressure was used. The KTGF model is not valid in a dense particulate system such as the dens regions of a high shear granulator and the addition of a frictional term is unproven [3]. The models have, even so, been shown to be able to describe main features of the flow inside complex granulation equipment. Since granulation is a dynamic process in many parameters there is a need to investigate the numerical stability and parameter sensitivity of the models.

A disk impeller high shear granulator was modeled in the commercial CFD program ANSYS FLUENT 12.1. The system is the same as in Reynolds et.al.[4] and Gantt and Gatzke[5]. The models used were the same as in Darelius et.al.[1]. The parameters studied were the angle of internal friction, restitution coefficient, frictional packing limit, particle diameter and solid phase velocity wall boundary condition. All these parameters can be expected to change during a granulation. The model was calibrated against the experimental data of bed surface tangential velocity and bed surface granular temperature from [4]. All parameters, except slip condition and restitution coefficient, were set according to values found in the literature.

The results show that the model is numerically stable within the tested range of the parameters. The general flow field of this system is rather insensitive to parameter changes even though the viscosity changes with orders of magnitude. The results were qualitatively evaluated in the context of a real granulation to see if the viscosity models capture the main influence of parameter changes.

[3]. C.S. Campbell, Granular material flows - An overview, Powder Technology, 162, 2006
24 - Effect of disintegrants on the properties of multiparticulate tablets comprising starch pellets and excipient granules


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The Design of Experiments (DOE) approach was used to investigate the effect of formulation and process variables on the properties of fast disintegrating tablets comprising starch-based pellets (model drug: 2% Riboflavin) and excipient granules. The effects of varying: 1) percentage of starch pellets (30 - 50 %) 2) type of disintegrant (Ac-di-sol, Explotab or crospovidone) 3) percentage of external disintegrant (4 - 8 %) and 4) compression force (5 - 15 kN) on the tablet properties such as hardness, friability and disintegration time were evaluated using full-factorial design (24 runs + 9 center points = 33 experiments).

Starch pellets were prepared by extrusion-spheronisation. Excipient granules containing microcrystalline cellulose and lactose as filler, internal disintegrant (either one of 3 disintegrants: 8%) and polyvinylpyrrolidone K-30 (4 % w/w) were prepared by wet granulation method. The resulted granules were evaluated for density, porosity and friability. Pellets and granules (size: 700-1000 µm) and the external disintegrant were mixed and compressed on a single punch tablet press using oblong punches (17.1 mm long, 8.2 mm wide).

The results for DOE were analyzed by MODDE® software. The percentage of starch pellets and compression force affected the tensile strength and disintegration time of the tablets. Lower concentration of starch pellets and higher compression force were required to have tablets with high hardness, low friability (< 1%) and acceptable disintegration time (< 3 min). On examining the results for granule properties the crospovidone granules had lower porosity and friability comparing to ac-di-sol and explotab granules. These results were reflected in the DOE study where the crospovidone tablets were harder, less friable and had lesser disintegration time compared to ac-di-sol and explotab tablets. This can be attributed to increased binding efficiency of crospovidone in wet granulation and as external disintegrant. Further more, the content uniformity and drug dissolution test were performed for tablets having 30% starch pellets, 4 % crospovidone and compressed at 10 kN. The content uniformity was in acceptable range according to European pharmacopoeia. The 99% Riboflavin was released within 15 min. By using DOE, it was possible to select the variables that have a significant effect on the properties of the multiparticulate tablets.
Polymer bonded explosives (PBXs) are typically highly loaded composite systems consisting of in excess of 90% (by weight) of crystalline explosive filler dispersed in a polymeric binder matrix. Such materials are manufactured via a solvent paste granulation method to coat the filler with a thin layer of binder. To achieve this, the binder component is dissolved in an organic solvent and subsequently mixed with the filler. Granulation of the dispersion is achieved by removal of the solvent under vacuum which may be considered in three stages: (1) formation of a slurry, (2) formation of dough and (3) formation of granules. Control of solvent removal at each stage is important as variations in rate of removal will have an affect on the physical form of the final product. For explosives this is important since the granular nature of the composite needs to be optimised so that it can be pressed to as high a density as possible.

This paper describes formulation of a fluoropolymer binder with an inert filler using a vertical double acting planetary mixer. The relationship between variations in the mixing process and final powder properties such as density and powder flow are presented.
The granulation process is considered as one of the most significant advances in the fertilizers industry, providing products with higher resistance and lower tendency to caking and lump formation. Among nitrogen-based fertilizers, granular urea is the most often used with a market in continuous expansion (a net growth of 46.8Mt between 2008 and 2013, to reach 210.3Mt in 2013) [1].

Generally, in fertilizer granulation plants only a relatively small fraction of the material leaving the granulation unit is in the specified product size range; thus, high recycle ratios are common. Besides, the industrial urea fluidized bed granulators are usually operated by trial and error, and it is difficult to run the plants at steady state undergoing frequently undesired shut-downs. Therefore, there is need to understand more deeply the dynamic behavior of these units in order to develop tools to maximize plant productions while maintaining marketable products.

In this work, a dynamic model of a complete urea granulation circuit, (developed in previous contributions [2]) is used to perform dynamic optimizations. The circuit flowsheet includes a fluidized bed granulator, a cooling unit, double-deck vibrating screens, and double-roll crusher models, the last two validated against industrial data. All models were implemented under the gPROMS Model Builder Environment, which allows to simulate and optimize processes in steady and dynamic states. Several optimizations cases were developed in order to maximize plant production over time. For each case, different combinations of possible manipulative variables were tested (i.e., urea melt flowrate, upper and lower crusher GAPs, granulator fluidization air flowrate and temperature, granulator discharge area). For all the performed optimizations, time-constraints regarding product quality, granulator beds heights, and growth chambers temperatures were set. The obtained results provided new promising operating points that satisfied the imposed constraints through theoretical time-trajectories of the selected manipulated variables. Therefore, it is possible to improve the plant performance under the correct selection of the manipulative variables and their feasible control intervals.

27 - Process analysis: A fluidizing granulation industrial case study

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Process Analysis and Process Understanding is one of the key issues expected by registration authorities for a new pharmaceutical product. Widely referred FDA draft Guideline “Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance” describes a set of Process Analysis tools, from which off-line laser diffraction Particle Size Distribution measurement and Loss on Drying were used to follow the fluidizing granulation process. A placebo composition of starch, lactose of two different particle size range and pre-gelatinized starch powder blend was granulated by a binder (polyvinyl-pyrrolidone solution and starch paste). One part of the binder was applied on the powder as pre-granulation, followed by an organic solvent addition and the second part of the binder as end-granulation. Particle size measurement shows precisely the granule building-up during granulation phases and breakage during drying phases, meanwhile more detailed analysis of Particle Size Distribution Data help to understand the structure of the produced granules. These understandings of the product properties and the effect of the process (e.g. entrainment effect) helped to improve and optimize the process. repeated trials and slight modification of process parameters give information about the variance of the Moisture content time function ("wetting curve") and Particle Size Distribution Data.

![Fluidizing Granulation Diagram](image-url)
A CFD-DEM study of the complex granular flow in a fluid-bed rotor processor

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In addition to the actual main function pharmaceutical, chemical and food products (e.g. pain relief by active agent) are designed on their appearance. Thus many drugs require exact spherical substance carriers with well-defined resistance and strength profiles. For the classical fluidized bed or spouted bed technology these product specifications are hardly met, because the specific fluid dynamics and mechanical conditions in the process chamber do not allow a desired extent of the final grain geometry and strength.

Rotary fluid-bed processors can carry out a single step production of spherical and dense grains. The additional horizontal rotating disk affords a homogeneous and defined spiral particle motion in the process camper and allows a uniform mechanical stress of the product. The particles are dried by the fluidized air stream, which passes through the gap between the rotor and stationary camber wall. Several processing operations (e.g. powder layering, film coating or spherization) can be performed with fluid-bed rotor processors.

A three dimensional coupled CFD-DEM simulation has been performed to study the fluid dynamics and particle motion in a rotary fluid-bed processor. Under consideration of the model substance (micro crystalline cellulose), material parameters and collision behaviour have been investigated and considered into the simulation model. The influence of several parameters, like rotor speed and air gap distance has been studied. Furthermore the influence of the atomization air on the particle motion and mixing behaviour has been investigated as well.

These results are compared with experimental observations by using a transparent rotor-apparatus in laboratory scale.

Figure 1. Simplified DEM-geometry of the Rotor granulator Glatt® Rotor 300 (a). DEM-simulation of particle motion and velocity: (b) processing camber (c) central vertical plane of the rotor processor.

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Experimental and numerical study on the effect of an elevated spout on spout fluidized bed dynamics

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Spout fluidized beds are frequently used for the production of granules or particles through granulation, which are widely applied for example in the production of detergents, pharmaceuticals, food and fertilizers. Spout fluidized beds have a number of advantageous properties, such as high mobility of the particles preventing undesired agglomeration and enabling excellent heat transfer control. In industry, the spout is slightly elevated from the bottom of the bed to enable spraying of liquid. However, research has so far mainly been focused on non-elevated spout fluidized beds and hence, little is known about the effect of spout elevation on the bed dynamics. Therefore, the objective of this work is to both experimentally and numerically study the effect of an elevated spout on the bed dynamics. The experiments are conducted on a pseudo-2D and a cylindrical 3D bed, where the Positron Emission Particle Tracking (PEPT) and combined Particle Image Velocimetry - Digital Image Analysis (PIV/DIA) are applied on the pseudo-2D bed, and PEPT and Electrical Capacitance Tomography (ECT) on the cylindrical 3D bed. A discrete element model is used as numerical technique, which describes the dynamics of the continuous gas-phase and the discrete particles. For each element momentum balances are solved, and the momentum transfer among the two phases is described in detail at the level of individual elements. Several cases are studied, i.e. non-elevated spout, 2 cm elevated spout and 4 cm elevated spout fluidization. In Figure 1, the time-averaged horizontal volume flux obtained from PIV/DIA measurements for the three cases is presented. One would expect that increasing the spout height would lead to dead zones in the annulus and that the horizontal flux would reduce accordingly. The opposite effect is observed however, i.e. the horizontal flux is increased leading to higher particle circulation rates in the bed. In this paper, we study the effect of spout elevation, both in pseudo-2D and cylindrical 3D beds. The experimental results are compared mutually and with simulations.

Figure 1. Time-averaged horizontal volume flux for non-elevated spout (h = 0 cm), elevated spout with h = 2 cm and with h = 4 cm, obtained from PIV/DIA experiments on a pseudo-2D bed.
Granulation is a common process in various industries such as pharmaceutical, agricultural, mineral processing, detergents and food industry. In particular high shear wet granulation has the advantage that mixing, wetting and massing can be performed jointly in few minutes in the same equipment. The process needs to be controlled with care since the granulation progresses so rapidly that a good granule can turn into an unusable product very quickly. Process and formulation variables related to the binder are perceived of major importance in controlling the basic mechanisms of agglomeration and the physical properties of the final granules [1]. The nature of the binder and the way of adding it affect the granule growth kinetics and the properties of the final product [1,2]. In the previous International Symposium on Agglomeration (2009) several contributions were focused on the role of the binder [3, 4, 5]. In particular the use of alternative binding techniques is challenging. The aim of the present research is therefore to evaluate the effect of four ingredients used in food industry and food supply industry on the granule growth behaviour and on the final properties of granules produced by wet granulation in a high shear mixer. The binder selected for the experiments were povidone, maltodextrin, carrageenan and xanthan gum. These binders have been mixed with cellulose microcrystalline and the mixture has been granulated in a lab-scale high shear granulator using water as granulating liquid. The dispersion obtained by contacting the binders in the mixture and the added water present clearly different viscosities. Influences of the amount of binders and water on the technological properties of final granulates were evaluated. In particular flowability, particle size distribution, mean diameter and particle shape have been evaluated. Preliminary trials have shown the feasibility of the process with the selected binders and that the amount of water required to granulate can decrease up to a 20% with increasing the viscosity of the binder solution.

A widely used oral controlled drug delivery mechanism is to embed the active drug into a slowly eroding hydrophilic matrix that hydrates in the intestine. As the hydrophilic matrix erodes and/or swells the drug is slowly released. The ability to produce consistent high quality matrix tablet dosage forms is critically dependent upon understanding the influence of not just process parameters but also of the nature of excipients, intermediate product and how formulation processing or storage might affect them. [1]

Process understanding is an integral part of Quality by Design (QbD). QbD is a systematic concept to product development as opposed to the traditional, more empirical method. This approach to product development requires a systematic evaluation and understanding of the formulation and manufacturing process. [2] In this investigation a range of different studies were carried out to assess the influence of critical processes parameters (CPP) and materials critical quality attributes (CQA) on target product performance (TPP) of controlled release tablets, the drug dissolution.

The impact of granulation end point was assessed at three torque levels. The influence of granule particle size was studied by segregating granule batches produced into 2 distinct size ranges, and producing tablets from each size range. Studies were also carried out on excipient variability where this involves changing supplier. A one factor at a time (OFAT) study of two different manufacturers of HPMC, Dow Chemicals and Shin-Etsu Chemicals were compared. Batch to batch excipient variability of the matrix agent hydroxylpropyl methylcellulose (HPMC) was investigated using a full factorial $3^3$ DOE. Using a fractional factorial $3^{(3-1)}$ design of experiments (DOE) the influence of temperature, time and relative humidity during the storage of granules prior to blending and tableting was evaluated.

The study found that the dissolution of matrix tablets containing a model BCS class II drug was not influenced by granule intermediate storage conditions. Drug dissolution did increase with decreasing granulation end torque; however the overall effect was minimal. HPMC batch variability was influential on dissolution when both the supplier of hypromellose was changed and when the lower viscosity batch was varied. Dissolution was influenced by the granule particle size distributions studied.


32 – Twin screw wet granulation: Influence of formulation parameters

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Similar to most pharmaceutical unit operations, wet granulation has traditionally been a batch process, where raw materials are granulated under a specified set of conditions, followed by downstream processing in subsequent unit operations. Recently, there has been interest in the use of twin screw extruders for continuous wet granulation in the pharmaceutical industry owing to the design flexibility of the equipment that may allow better control of granulation subprocesses. As a continuous process, it will minimize scale-up hurdles and improve process reproducibility. However, the maximum benefit of a continuous wet granulation process can only be attained through mechanistic understanding of the influence of formulation and process variables on the end product attributes. Yet, there is limited work in the literature on the influence of formulation variables with regard to raw material attributes on granule properties such as granule size distribution, shape, density, flow and strength.

In this work, granulation experiments are conducted on a co-rotating twin screw granulator (Euro lab 16 TSG, Thermo Fisher Scientific). Raw material characterization is performed to identify critical material attributes pertaining to a twin screw granulation process. This is achieved through comparative trials involving the use of common pharmaceutical excipients to understand the influence of physical and mechanical properties of starting material on the granulation process and the properties of the resulting granules. The default design of a twin screw granulator involves a multitude of process variables that can interact in different ways with each other as well as with formulation variables, resulting in often ambiguous effects on the properties of produced granules. Therefore, a simple stepwise approach is adopted to allow a more fundamental understanding of the influence of process variables such as screw element design, liquid/solid and powder feed rate on the physical and mechanical properties of the granules, with the aim of developing regime maps that would be useful for twin screw granulating equipment.
33 - Tests for multiple compression of solids

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In the compacting of fine-grained powders with subsequent comminution, fractionation often takes place downstream, since only part of the particle size range obtained has the desired particle size. The fine material which arises is usually continuously mixed with fresh feed material and compacted again. Thus, this product is compressed multiple times. The compression properties of the aggregate may change owing to the reintroduced fine material. Often, this is associated with an improvement in the pourability or an increase in the bulk material density of the useful fraction and is desired. From various tests [1], negative effects on the properties are also known.

During the course of this work, a change in the compression properties was simulated by means of multiple compression on a single stroke press. The advantage of this approach is a reduced use of material and time [2]. The materials were tableted, the tablets were comminuted, and the fine material portion was removed. This fine material portion was mixed with fresh material and tableted again. As a measure of the quality of the compaction, the strength of the tablets and of the fine material portion after the comminution were used. Commonly used products in pharmacy and catalyst production, such as dicalcium phosphate, aluminum hydroxyoxide, which were tested showed no effect. In contrast, microcrystalline cellulose exhibited, at low pressure, a continuously increasing portion of fine material which is associated with a distinct reduction in the strength of the tablets. Higher compression pressures showed this effect only after the first compression. SEM micrographs of the fracture surfaces of tablets show that the structure hardly changes in unaffected materials, whereas significant changes are visible in microcrystalline cellulose. The goal of simulating compression procedures on a compacting system operated in a circulation with a tablet press was achieved.


Aggregation of particles is fundamental for improving the performance of many solid/liquid processes. Aggregation can be induced by different means one of the most common being based on the addition of polymeric additives, namely polyelectrolytes. Flocculation by polyelectrolytes is of importance to many industrial areas, namely in food manufacturing, pharmaceuticals and also in papermaking.

Various processes occur simultaneously during flocculation: adsorption of polymer molecules at the particles surface; re-arrangement (or re-conformation) of adsorbed polymeric chains; collisions between destabilized particles to form aggregates (flocs); and break-up of flocs. The importance of each process depends on the flocculant characteristics, like structure, molar mass, charge density and concentration; on the characteristics of the suspended particles, like size and charge; on the characteristics of the suspending medium, like pH, conductivity and ionic charge; and, finally, on the contact time and turbulence intensity, among others.

In this work we have studied the flocculation of precipitated calcium carbonate (PCC), used as filler in papermaking, induced by a range of cationic polyacrylamides with different structures, varying in molar mass, charge density and degree of branching. The flocculation process was monitored continuously using the LDS technique (laser diffraction scattering), which supplies information about the size distribution and structure (fractal dimension) of the aggregates [1], for each sampling instant and, thus, about the kinetic curve for the flocculation process.

All this information has then been used to produce a model, based on an experimental design strategy, which allows us to relate flocculation efficiency with the PEL characteristics and concentration.

The results obtained so far led us to conclude that the polymer intrinsic viscosity (related with the PEL molar mass and charge density) and the degree of branching are the parameters with a stronger influence on flocculation efficiency. Apparently, when flocculating PCC particles, the PEL concentration does not influence significantly the flocculation efficiency, for the range of concentrations studied.
All tests were conducted in distilled water. Flocculation efficiency, having in mind the application under analysis, papermaking, has been defined to take into consideration not only the size of the flocs but also the kinetics of the flocculation process (flocculation rate).

35 - Modifications of fluid-bed coater and study of their influence on the coating uniformity, yield and degree of agglomeration


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Particle coating is a commonly used process in pharmaceutical industry. An ultimate objective of the fluid-bed coating is to prepare individual particles, each with a well-controlled, even coating. More uniform coating results in lower quantities of coating material needed to assure a desired result, shorter process time and lower power consumption during coating process. The agglomeration of particles represents the unwanted process in coating operation.

In the present study the influence of different construction modifications of conventional Wurster process chamber on the coating uniformity, yield and degree of agglomeration were evaluated. The influence of different process parameters such as intake airflow rate and height of the draft tube were studied as well.

Use of novel design of distribution plate with attached swirl generator represent the first case of modification of existing conventional Wurster process chamber studied in our experimental work [1]. Swirling airflow inside the draft tube contributed to much more uniform deposition of the coating material when compared to conventional Wurster process. Spectrophotometric evaluation of coating uniformity was based on the dye concentration measurements, which was evenly distributed in a coating layer. In comparison to conventional Wurster coater also lower degree of agglomeration and higher yields were determined.

In the second case the funnel shaped distribution plate was tested. Funnel shape distribution plate was found to improve coating uniformity of tablets in comparison to conventional one [2], but in case of pellet coating the results were just the contrary. Agglomeration rate was found to be reduced and yield improved in experiments conducted in a modified coater.

In case of the third set of experiments series of tangentially oriented slots inclined at 16 and 32 degree angle in a lower part of the process chamber enabled introduction of air directly above the distribution plate and therefore influence the flow of particles in that region. When applying additional air, the coating layer was more uniformly deposited on the pellet cores and formation of agglomerates was found to be lower compared to the results obtained in a conventional Wurster coating chamber. Some improvement was also noticed in a process yield.

Additional modification of air introducing system was performed, with an emphasis on simultaneous air intake on two different distances from the distribution plate. Results show an additional improvement in coating uniformity.

A multi-scale modelling approach to batch/continuous multi-component wet granulation processes

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The overarching goal of this work is to quantitatively understand the interactions between material properties, process parameters, equipment design and environmental conditions to predict product performance of multi-component granules. This is especially vital in the pharmaceutical industry where product performance (e.g. composition and dissolution) is critical to the value of granulated products. In granulation, which is a particle design process, fine powdery solids are formed into larger granules with the aim of achieving targeted product attribute(s). Due to a lack of a systems-based understanding, target attributes are often not met in a timely and cost efficient manner, with many of the industrial granulation operations suffering from high recycle and batch rejection rates. It has been recognized that studying the granulation process involves a multi-scale operation where final product quality is influenced by the interplay of particle interactions and collision-scale behavior, granule rate processes and granular flow regimes. However, there is still significant disconnect in terms of incorporating fundamental physics and chemistry in model forms at the different scales, and addressing and integrating the multi-scale nature of the granulation process, largely due to fundamental questions that remain unsolved for single-component granulation.

Therefore, the proposed objectives at the different scales to be studied are 1) Micro- (single granule) scale: Study liquid distribution, liquid surface coverage of particles, particles-particle collisions and their frequencies. 2) Meso- (population of granules) scale: Study granule rate processes based on liquid/powder properties and process parameters. 3) Macro- (vessel) scale: Study particle flows, stresses and velocities to account for non-idealities in granulators. 4) Multi-scale: Integrate partial models at each scale and to facilitate information exchange between each scale for the purpose of simulating and validating evolutions/distributions of key granule properties. Results obtained from the proposed work enables a more quantitative and predictive understanding of multi-component granulation. Results also contribute to three specific advances in the field of particle technology, namely 1) Theoretical understanding of the formation and interactions of multiple solid components with liquid droplets, 2) A multi-scale model coupling fundamental physics/chemistry with systems level process parameters and equipment level flows, stresses and velocities and 3) Novel numerical techniques for the efficient solution and application of the multi-scale model to granulation process design. The multi-scale simulation will also be combined with model-based experiments to demonstrate global validity of the model. Proposed computational and experimental approach will impact our fundamental understanding of the granulation process, thus advancing the current state of knowledge both in granulation and in the general class of particulate/solids process.
Due to the fact, that in an early phase of the clinical development of a new medication only a small amount of drug substance is available, batch processes and a subsequent scale-up of the batch process play an important role. One of the most critical unit operations for manufacturing solid dosage forms such as tablets is the wet agglomeration process and its scale-up. The necessary amount of granulating liquid is usually determined on the basis of trial and error experiments. Such an approach does not comply with the actually pursued concept of manufacturing "Right First Time".

The problems of the scale-up of the wet agglomeration process originate from the violation of Buckingham's theorem [1]. The equipment involved, i.e. the mixer/granulators involved being different in size do not show a self-similarity concerning geometrical design, kinematic and dynamical behaviour. In this context, the correct amount of the granulating liquid plays a major role.

The correct amount of the granulating liquid, usually demineralized water, depends on the composition of the powder mix, which may consist of swelling excipients, of a drug being capable of forming hydrates and depends on the particle size distribution of the powder mix. It is important that the excipient added as a binder is readily soluble and forms a newtonian liquid. The rest of the power mix should show only a reduced solubility and a moderate swellability in the granulating liquid. Thus, it is possible to obtain during the continuous addition of granulating liquid a power consumption or torque profile, which can be used for the determination of the correct amount of granulating liquid needed in the scale-up exercise. In fact, it is often possible to define a minimum amount and a maximum amount of granulating liquid needed to obtain pharmaceutical granules, which show a native self-similar granule size distribution within a certain range of a mean granule size. Interestingly, this window of acceptable amount of granulating liquid can be explained on the basis of percolation theory, i.e. the minimum amount corresponds to the lower and the maximum amount to the upper percolation threshold [2].

Wet granulation is a complex, multi-phase, multi-component unit operation often used in the pharmaceutical industry. Various attributes such as particle morphology, size, porosity, wettability, and binder viscosity play key roles in determining the overall size and composition of the granules that are produced. Recently [1, 2], we adapted constant-number Monte Carlo (CNMC) so that semi-batch conditions and previously reported experimental data [3] could be analyzed. Specifically, in [1] we examined 2-component systems where a single powder (component 1) is granulated while liquid binder (component 2) is continuously added to the system; the simulations (employing only a single adjustable parameter) matched well with experimental data for powders with surface morphologies that ranged from relatively smooth to pretty rough (see the figure below). In [2] we studied a more complex 3-component system that accounts for the evaporation of water from the binder solution that is present on the granules. In this study, we expand this research to examine the impact of binder drying for (practically very common) systems with 2 solids (excipient + API) during fluidized bed granulation with continuous addition of binder. Such an analysis requires the simultaneous tracking of four components: 2 powders, the liquid portion of the binder, and the solid portion of the binder. We accomplish this task through the use of multi-component population balance equations that are numerically solved via CNMC. Simulation results can then be directly compared with experimental particle size distributions (PSDs) and granule moisture (LOD = loss on drying) data.

40 - Analysis of aerodynamic dispersion of cohesive clusters

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The dispersion of bulk powders is important for a number of applications including particle characterisation, and the delivery of therapeutic drugs via the lung using dry powder inhalers (DPIs). In recent years the distinct element method (DEM) coupled with continuum models for a fluid phase to simulate fluid-solids interactions has received much attention.

In this paper these computational techniques are used to investigate the aerodynamic dispersion in a uniform fluid flow. As intuitively expected, it is seen that with increasing surface energy it is progressively more difficult to disperse a loose aggregate. However, once the relative particle-fluid velocity goes beyond a certain threshold, dispersion occurs quickly and approaches a completely dispersed state asymptotically. A relationship between the fluid drag forces acting upon a spherical aggregate and the adhesive force, given by the JKR model, leads to a dimensionless group termed the dispersion index, which includes the Weber number. It is shown that the effect of surface energy on dispersion behaviour can be described by this dimensionless group [1]. In particular, this paper focuses upon the effect of relative aggregate size (ratio of aggregate diameter to primary particle diameter), whereby, two different dispersion processes are possible. If the aggregate size is small, the aggregate disintegrates. However, for larger aggregates, the dispersion process switches to a gradual peeling of the surface particles (Figure 1).


Figure 1. For sufficiently large aggregates, particles peel away from the surface.
41 – Discrete element modelling of seeded granulation in high shear granulators

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Based on a recently-concluded study of high shear granulation using Cyclomix granulators of Hosokawa Micron (B.V.), the Netherlands, we have come up with a novel method which consistently produces granules with a large particle from the tail end of the particle size distribution at their cores, referred to as seeded granulation. Figure 1a shows an X-ray micro-tomograph of the central cross section of a granule. Figure 1b shows the internal structure of about 100 granules by SEM.

A regime map is proposed for the production of consistent seeded granule structure based on an evaluation of the process in the granulator sizes: 1 L, 5 L, 50 L, and 250 L using calcium carbonate particles and aqueous polyethylene glycol (PEG) as binder.

The formation and breakage of seeded and non-seeded granules have been simulated by the use of the Distinct Element Method to elucidate the mechanism of seeded granulation. The modelling results are compared qualitatively with experimental data in terms of the conditions for formation of seeded granules. It is concluded that the seeded granulation effectiveness is a function of the feed particle size distribution and the Stokes Number describing the condition for frequent breakage and coalescence of the granules as they grow, promoting the survival of granules containing seeds.

Figure 1. (a) X-ray micro-tomographic image of the central cross section of a granule (b) SEM image of internal structure of about 100 granules.
In pharmaceutical manufacturing, especially with formulations that are sensitive to heat and moisture, dry granulation is the preferred agglomeration process, which generally involves roll compaction and subsequent milling of the compacted ribbons. For most cohesive feed powders, a lubricant is generally required to improve the flowability and to prevent adherence to the roll surfaces. However, it is still unclear how such lubrication will affect the properties of the granules and the final products, i.e. the tablets. This was addressed in the current work by a systematic experimental study.

Two commonly used pharmaceutical excipients, microcrystalline cellulose (MCC) and di-calcium phosphate dihydrate (DCPD) were selected as the model feed powders with magnesium stearate (MgSt) as the lubricant. Roll compaction was carried out with instrumented equipment, which was developed at the University of Birmingham, and the ribbons were milled using an oscillating mill (AR 401, Coeply). The granules were compressed into tablets with a die having a 13 mm internal diameter using a universal test machine (Zwick, Germany) in the pressure range 50 – 200 MPa. The compressibility of the granules was described using the Johanson’s relationship. The tensile strength of the tablet was measured by diametric compression. The compactibility of the granules was calculated by normalising the tensile strength of the tablet with the specific work of granule compression to form the tablet.

Lubrication mainly reduced the wall friction coefficient for DCPD but not the internal friction whereas the opposite changes were observed for MCC. In addition, lubrication lead to a reduction in the size of the roll compaction zone and the maximum pressure. A first order kinetic model was employed to describe the mass of the granules formed as a function of the number of cycles of the reciprocating blades on the mill. The characteristic number of cycles decreased with increasing cycle frequency of the blades, which is consistent with an increase in the efficiency of the process. Lubrication of the feed powders resulted in a reduction characteristic number of cycles of the blades of the mill.

The fundamental concepts behind FDA Quality by Design initiative have driven the Pharmaceutical Industry to put greater emphasis onto the scientific understanding of their data and processes, thus focusing their efforts not only on getting a suitable drug product but on understanding the impact of the manufacturing conditions on it as well. Multivariate analysis techniques are very useful and effective to rapidly review numerous inputs, thus improving the understanding of the process. We have used multivariate tools to analyze granule (obtained by high-shear wet granulation) and tablet properties manufactured at commercial scale in comparison with lab scale trails. Differences among batches have been identified. API properties and manufacturing process parameters have then been examined to see whether they could help explaining these differences. Evidence of correlation between API, granulation conditions and final drug product characteristics could be shown. Particularly, we were able to characterize the API from a granulation process that is difficult to control because it follows an induction growth mechanism. This work contributed to a clearer definition of API requirements, corresponding optimization of granulation conditions and process control through the statistical process control chart below.
44 - Influence of initial mixing on granule properties

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Wet high shear granulation is a common step in the manufacture of many pharmaceutical tablets. The granulator bowl is charged with selected components of the formulation. Following an initial mixing period, the liquid binder is sprayed onto the formulation to form granule nuclei which then grow and develop until the process is stopped. The conditions and the length of time of the initial mixing period are often selected empirically.

In this work, placebo formulations are granulated with a high shear granulator while varying the conditions and length of time of the initial mixing period. The granules from the trials are extensively examined using average particle size and size distribution, shape and composition from scanning electron microscopy and many flowability measurements such as density ratios, angle of repose measurements and avalanching behaviour.

Changes in the initial mixing period led to differences in granule properties indicating that this period is important and should be carefully considered to achieve granules with specific properties.
This study investigates the physicochemical property and functionality of a novel co-processed excipient composed of crystalline mannitol and α-chitin. The prepared multifunctional excipient offers a unique base for oro-dissolving formulations. The driving force behind the fast dissolving behavior of the co-processed mannitol and chitin mixture is obtained from the fare aqueous solubility of mannitol and the super-disintegration capabilities of the chitin. Optimal physicochemical properties of the excipient, from a manufacturing perspective, were obtained for the co-processed chitin-mannitol (8:2 w/w) mixture produced by dry granulation (Cop-CM). Disintegration time, wetting time, water absorption, crushing force and friability of tablets, produced from Cop-CM using sodium stearyl fumarate as a lubricant, were not significantly altered by the change in the particle size of the prepared granules. The good compaction and compression properties shown by Cop-CM were found to be dependent upon the added chitin quantity in addition to the processing technique used in the preparation of the co-processed excipient. FTIR, DSC, XRD studies proved the absence of any chemical interaction between the mannitol and chitin in the Cop-CM mixture. The compressibility (α-Value) of Cop-CM was analyzed using the compression parameters derived from Kawakita plot and found similar to that of chitin. These excellent binding and fast disintegration properties of Cop-CM can be successfully used in the formulation of fast disintegrating/ dissolving tablets in addition to the conventional immediate release formulation as a multi-functional excipient.

Disintegration time and crushing strength of various commercial excipients compared to chitin processed with mannitol
The wet granulation process plays an important role in the pharmaceutical industry. With the introduction of Twin Screw Extrusion Technology (TSE), wet granulation can be run continuously, in contrast to conventional batch processes such as High Shear Mixer (HSM). However, the mechanism of TSE wet granulation is not understood and the aim of this study is to investigate this process and compare it with conventional mechanisms that include wetting and nucleation, coalescence and consolidation and breakage and attrition [1].

Various properties of granules obtained from a co-rotating TSE and a HSM at different formulation and process conditions were measured and compared. Furthermore, properties of tablets formed from the granules were also compared. In order to gain an insight into the flow and mixing processes within the compounder, Positron Emision Particle Tracking (PEPT) technique was used to track the trajectory of single particles through the mixing and conveying zones.

It was found that the granules produced by the TSE and HSM have different properties. Granules produced by the HSM are round and dense whilst TSE granules have an irregular shape and are porous with tiny pores spread uniformly throughout the granules. Moreover, TSE granules have a lower fracture strength and this strength is independent of granules size as well as the various process parameters. Tablets produced from the TSE exhibit high tensile strength. The fracture surface of this tablets shows an amorphous structure that fragments on fracture. On the other hand, tablets produced by HSM granules retain distinct particle boundaries, that seem to initiate and propagate cracks easily, resulting in a lower fracture force being required.

It has been suggested [2] that the mechanisms of granulation in the TSE are different, in particular that the consolidation step is absent. This might be explained, at least in part, by the PEPT study: fill levels obtained from local residence time distribution shows that the extruder is partially filled throughout, even within 90° kneading blocks. This suggests little opportunity for high squeezing pressures to be achieved. Work continues to study the flow and residence time in the nip region between the kneading discs. PEPT is also being used to help understand how feed variance reduction can be optimised in continuous granulation.

47 - Granulation of lactic acid bacteria using fluidized bed technology


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The application of lactic acid bacteria has an economic significance as probiotic additives for the food industry. Therefore a crucial point in the commercialization of lactic acid bacteria is the development of a storable culture which retains the viability of the primary culture. Freeze and spray drying are established methods for preserving bioactive materials. Freeze drying is a gentle but long term and expensive method, which is therefore uneconomical. The benefit of spray drying is the formation of free flowing particles in a short time but it is disadvantageous that the required high temperatures reduce the viability of mesophilic microorganisms.

The fluidized bed drying technology is an alternative, gentle and cost saving method for the preservation of microorganisms. The present study analyses the influence of the fluidized bed drying technology on cell viability and storage stability of the lactic acid bacteria strain Lactobacillus plantarum. Different carrier materials were tested such as sugar pellets, lactose and maltodextrin. The recent studies have shown that the usage of maltodextrin results in the highest viability of bacteria by using the protectant trehalose additionally. For shelf life determination, the granulated microorganisms are stored at -20 °C, 4 °C and 20 °C. Three months of storage at room temperature resulted in none viable Lactobacillus plantarum cells whereas high recovery of viable cells was achieved at 4 °C and -20 °C.

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Behavior of wetted insoluble granular materials: effect of particle shape

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In recent work [1, 2] we studied the behavior of the mixing of insoluble granular media in the liquid phase. It was showed that the evolution of the mixing energy consumption depends on the rate of liquid and on the material properties (nature of the solid and particle size). However, the mechanisms behind the observed behavior are not yet understood.

In this paper, we investigate the role of the frictional and cohesive forces into the mixtures and the impact of the particle shapes (spherical and irregular) on the macroscopic behavior resulting from the interaction between particles in presence of small liquid quantity. The used materials here were composed from spherical glass (shape indice = 0.97) and irregular (shape indice = 0.74) calcites (CaCO3). The evolution of the frictional and cohesive forces into these two wetted mixtures was characterized using a ring shear tester in quasi-static conditions.

It was observed that, for all the materials, the water added modify the cohesion and the friction (espacially for fines particles). The cohesion show a linearly increases with the pre-consolidation load and with the inverse of the particle size. It was also observed the increase of the friction with the inverse of the particle size. Elsewhere, for a given particle size, pre-consolidation load and liquid amount, equivalent cohesions were obtained for the two materials whereas the friction was higher for the calcites. This last result suggests that the higher calcite mixing energy [1, 2] is principally caused by higher friction forces between particles. It was also favored by the irregular shapes of particles.


49 - Simulation and experimental investigation of product moisture distribution in a continuous fluidized bed dryer

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Continuously operating fluidized bed dryers are common in the chemical and food industries. Also in the pharmaceutical industries there is a growing interest in the continuous operation of dryers. Especially in the pharmaceutical industries it is of major importance to have a homogeneously dried product. Since with regards to the solids the fluidized bed is near to an ideally mixed reactor, it is characterized by a wide particle residence time distribution. The moisture of the individual particles will strongly depend on their individual residence time inside the dryer. Therefore a wide distribution of the particle moisture might be expected at the outlet of the dryer. Measurements by Kettner et al. [1] have proven the existence of such moisture distributions.

Based on a model suggested by Burgschweiger [2] a stationary model of continuously operated fluidized bed dryers has been implemented into the flowsheet simulation package SolidSim [3]. The model takes into account the residence time distribution, a moisture distribution at the entrance and also the particle size distribution. Furthermore a simple model has been included to describe the influence of the convective flow through an elongated fluidized bed. As a result the model gives the moisture distribution of the outflowing solids, thus allowing to predict the homogeneity of the product.

The inclusion of the model as a unit into the flow sheet simulation program SolidSim allows to simulate drying processes with any kind of liquids and gases and to simulate the interdependency of the operation of a dryer with preceding or subsequent solids processing units. Therefore the whole process can be optimized instead of only the dryer.

The model has been validated by measurements in a continuous fluidized bed dryer. These measurements confirm that the moisture distribution of the individual particle at dryer’s outlet depends not only on the particle residence time but also on the particle size.

Fluidized bed spray granulation is commonly used in the chemical, pharmaceutical and food industry for the production of dust-free and free-flowing powders with well defined particle size distributions and particle shapes. For the modelling of the particle growth within the granulator population balance models can be used. These models describe the growth of the particles by help of agglomeration kernels. The agglomeration kernel itself consists of a time-dependent ($\beta_0$) and a size-dependent ($\beta(u,v)$) part. By use of the flux number approach the value of $\beta_0$ can be calculated based on the binder mass flow, the superficial gas velocity within the granulator and the solids density.

Nowadays, software tools for the flowsheet simulation of industrial processes are commonly used for design, simulation, balancing, troubleshooting and optimization purposes. However, the applications normally are restricted to fluid processes, since the established simulation systems are not able to describe bulk solids in an adequate way. In order to fill this gap, the flowsheet simulation system SolidSim has been developed with a special focus on the description of bulk solids.

In this contribution the flowsheet simulation tool SolidSim is used for the modelling of fluidized bed granulation processes. The build in model for fluidized bed granulation was extended such that the value of the time-dependent part of the agglomeration kernel ($\beta_0$) can be determined by use of the flux number approach. This allows to investigate how the particle size distributions, mass flows, temperatures etc. in the overall process change, if for example the binder flow rate or the fluidization gas flow is changed.
Figure 1. SolidSim flowsheet of an urea granulation production process.
Multi-holed die extrusion for assessing paste formulations for granulation by extrusion-spheronisation


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In extrusion-spheronisation (E-S) a wet powder mass is first extruded through a screen or die plate featuring many holes to generate strands of paste. These are then broken up on a rotating friction plate (spheroniser) to yield granules. E-S can yield highly spherical, dense granules which are ideal for downstream processing. Scaling down the extrusion step in order to develop formulations with small amounts of material has led several workers to use capillary (ram) extrusion with single-holed dies for forming strands for spheronisation. Scaling up from such tests to screen devices has proved problematic in certain cases, particularly where the ram extrusion tests are subject to problems such as liquid phase migration (LPM) promoted by the use of low extrusion speeds.

The use of multi-holed rather than single holed dies was investigated in a systematic study wherein the number of 1 mm diameter holes in a ram extruder die plate was varied from 1 to 137, where the latter afforded a hole area fraction approaching that of commercial extrusion screens. Multi-holed dies also allow pastes to be extruded at velocities approaching those used in screen systems with a reduced risk of encountering LPM. The extrusion and spheronisation behaviour was studied using a standard micro-crystalline cellulose (MCC)/water paste. Extrusion pressures, flow behaviour, liquid phase distribution, pellet size and shape were monitored and compared with results obtained with single-holed dies.

Extrusion pressures were compared with the model for die paste extrusion described by Benbow and Bridgwater [1]. The rheological parameters for the paste were obtained from a systematic study, involving different die diameters, that confirmed the importance of wall slip and plastic yielding behaviour. The model underpredicted the observed extrusion pressures. A similar underprediction was also reported by Rahman et al. [2] in their study of extrusion of starch-based food pastes through multi-holed dies. The contribution from redundant work in the die entry was quantified, which can be used in modelling the performance of screen extrusion devices.

The multi-holed dies yielded pellets with product qualities comparable to those obtained using single-holed dies. Narrow (log-normal) pellet size distributions, with size aspect ratio values > 0.8, were obtained for pastes which had not experienced LPM, whereas pellets of poor quality were obtained from those that had. The velocity at which LPM was observed varied with the number of die holes, decreasing as the number increased. Reasons for this behaviour are discussed. The results show that multi holed dies can be used in systematic studies for assessing formulations for E-S. This is illustrated by a short study using calcium carbonate as a model active ingredient with MCC/water as the excipient platform.

Agglomeration and granulation is often perceived as a maturated technology where hardly any significant innovation seems to be possible. Considering agglomeration as a technology to only improve flowability and possibly dissolution this might be partially true. There are various technologies which have been developed to aggregate fine food particles to larger granules. Despite the variety of available processes and a large number of studies performed with model substances our understanding of the role of material parameters for adhesion and granule growth is limited. This missing knowledge hinders a true modelling of real manufacturing processes. Accordingly there is further scientific work to be performed in order to model food agglomeration.

There is also a need for development of innovative processes for agglomeration of modern food products. On one hand formulations are getting more natural and thus adhesion to equipment surfaces is increasingly getting a serious issue. On the other hand agglomeration technologies including reduced thermal stress are needed to reduce thermal degradation of micronutrients. New low-cost technologies have to be developed to address low income consumers in developing countries. Furthermore we have to reduce the environmental impact of food agglomeration by moving increasingly to low binder quantities and avoiding drying through solidifying binder solutions. Granulation processes delivering larger, highly porous and still mechanical stable agglomerates which are fast dissolving are required for development of innovative single dose powder products. Last but not least agglomerates with a time controlled release of active substances are desired for delivering new product features such as controlled flavour release. Such processes include co-spraying or controlled recirculation of fines during spray or fluid bed drying.
Wet agglomeration aims in associating powder particles under the concomitant effect of mixing and wetting. Mixing promotes contacts between particles while the binder ensures their sticking. Agglomerates finally obtained results from the probabilities sum of collision and sticking. Results of the studies related to colloidal aggregation are rich in analogies to whom works on wet agglomeration. In this type "of assembly", nanometric particles aggregates thanks to (i) collisions resulting from a motion dependent on Brownian agitation and (ii) sticking resulting from electrostatic and Van der Waals forces. According to the prevalence of sticking and collision, Kolb et al. [1] showed that two great typologies of aggregation mechanisms could be identified: the mechanism of aggregation limited by diffusion (DLA) and that of aggregation limited by reaction (RLA). In the first case the motion of the particles is weak but any contact between them will generate an association, in the second case sticking is weak and association will only be possible if particles collide strongly. Depending on the aggregation mechanism, aggregated structures will be more or less porous but their density will always be related to one of their characteristic length by a law power that characterize a fractal growth process. Considering wet agglomeration, analogy with colloidal aggregation is direct if one considers that the motions promoting collision are ballistic (and either Brownian) and if the interparticle forces, which cannot be Van der Waals or electrostatic considering particles size, are represented by capillary interaction. This analogy led us to regard agglomeration as a fractal growth process [2] during which agglomerates will continuously expand during growth. Based on this fractal approach, a model was developed in order to connect the agglomerates diameter evolution to their water saturation degree. It describes a power law relation between these two parameters and was experimentally confirmed on various powders. Above all, the observed path is in conformity with the bibliographical data as presented by Ritala et al. [3] The fractal approach of the agglomeration enables us to propose a new description of the agglomeration mechanisms compared to the classically described phases (wetting/nucleation, consolidation/coalescence, attrition/breakage). The first stage of wetting and nucleation is indisputable insofar as it is during the contact between drops and particles that will be generated the nuclei. The second stage is more questionable insofar as a consolidation cannot occur on nuclei whose solid volume fraction was experimentally measured close to the random close packing value.

Fluidised bed granulation is commonly used in many process industries, particularly when porous granules are required. Powder is typically fluidised by air, and atomising sprays are used to deliver binder liquid to the fluidised bed. The drop size distribution produced by these sprays is generally very small, often much smaller than the size of the fluidised particles. This results in distribution nucleation, where relatively large particles are coated by many small drops, and small granule nuclei are formed through particle-particle collision. Most granulation nucleation research however has focussed on immersion nucleation, which is characterised by large drops penetrating into a powder bed of relatively smaller particles. There is currently very little research into distribution nucleation. The aim of this work is to help address this gap in granulation knowledge.

A new parameter, the single particle spray flux ($\Phi_p$) has been developed to describe and predict the fraction liquid coverage of particles. This parameter has been used in conjunction with several discrete element method (DEM) simulations coupled with CFD and a novel method for incorporating the liquid spray. The objective of these simulations is to investigate mixing and liquid distribution in a fluidised bed granulator.

The effect of superficial air velocity, liquid spray rate, spray zone size and spray zone geometry are investigated in this work. Increasing superficial air velocity resulted in a narrowing of the particle surface coverage distribution. Both the average and distribution breadth of particle surface coverage increased with increasing droplet addition rate. Decreasing spray zone size resulted in similar values of average particle coverage fraction, but greatly increased the number of poorly wet and very wet particles. The addition of these innovations to fluidised bed granulation modelling represent a significant improvement over existing models for fluidised bed granulation, which assume uniform liquid coverage or use an increase in surface energy to simulate the effect of particle wetting.
55 - Adhesion mechanisms between water soluble particles

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In order to obtain powdered food products of good handling and dissolution properties, single food particles are agglomerated and transformed into a particle network. Food powders are mostly water soluble. According to their molecular and supra-molecular structure three water soluble material groups can be distinguished from each other: amorphous, crystalline and semi-crystalline materials. The materials can be distinguished by different material properties such as hygroscopicity, hygro-sensitivity and mechanical/rheological properties. Different adhesion principles can be applied to adhere/fuse water soluble particles together:

• Van der Waals forces (decreasing distance and increasing contact area).
• Liquid bridges generated by condensation or addition of low-viscous binder solutions.
• Viscoelastic bridges generated by sintering of amorphous materials.
• Viscoelastic bridges by addition/in-process generation of high-viscous binder solutions.
• Solid bridges generated by solidification of liquid or viscoelastic bridges.

To generate such adhesion forces between particles suitable parameter combinations and the required process type have to be selected based on the material properties of the powder to be preprocessed. However since in any agglomeration process the mentioned process parameters are distributed, modelling techniques are required to fully master agglomeration processes.

For compression DEM can be used to simulate the three-dimensional stress distribution in a powder bulk as a function of compression time. In the frame of fluid bed agglomeration, DEM techniques combined with CFD are very useful to determine the time and location dependent distribution of temperature and moisture content. Knowing the distribution of these process parameters in the equipment allows modelling the distribution of material properties and the probability of adhesion. This finally enables to estimate agglomeration kinetic through population balances.
56 - Pharmaceutical application of the segregation tester


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Segregation of blended powders or granules is a critical failure mode associated with solid dosage form manufacture within the pharmaceutical industry, the risk of which increases on scale-up. Factors such as excipient choice and blending technique may have an impact on the tendency to segregate. Currently, very limited capability for the measurement or prediction of segregation potential is available. Without this capability, there is a danger that segregation issues will only be discovered in the later stages of development, necessitating remedial development work and resulting in product failure.

In this work, the factors influencing segregation of pharmaceutical blends and granules, were assessed using a Jenike Fluidisation Segregation Tester, which simulates air flow experienced as the powder is transferred to a hopper. Samples of powder were fluidised within the chamber for a set period of time. The sample was then split into three sections and each sub-sample analysed using Near-Infrared (NIR) spectroscopy. NIR analysis was performed using a PerkinElmer Spectrum One NTS. The degree of segregation observed in the tester was quantified using the content uniformity data generated using NIR. To rank the material segregation potential, a novel S-Factor parameter was developed using the content uniformity of the segregated and the initial blends. The effect of blending technique and excipient choice on the tendency of pharmaceutical powders to segregate was analysed and correlated to the S-Factor classification.
Microbial precipitation of carbonate can be achieved using the hydrolysis of urea due to ureolytic bacteria. For example, the reaction for the precipitation of carbonate (calcite) is as follows:

\[
\text{CO(NH}_2\text{)}_2 + 2\text{H}_2\text{O} \rightarrow 2\text{NH}_4^+ + \text{CO}_3^{2-} \quad (1)
\]

\[
\text{Ca}^{2+} + \text{CO}_3^{2-} \rightarrow \text{CaCO}_3 \downarrow \quad (2)
\]

The reaction (1) is promoted by catalysis due to the urease enzyme produced by the bacteria.

Carbonates produced are possibly calcite, dolomite, magnesite etc., in the existence of Ca and/or Mg ions. Since the carbonate precipitation will occur in liquid phase and on the surface of suspended particles, the agglomeration of suspended solids can be improved. The precipitation of carbonates on the surfaces of suspended particles makes their size greater. Accordingly, the sedimentation rate of particles will be increased.

In this study, the sedimentation and agglomeration of suspended particles were examined by comparing with and without the microbial precipitation of carbonates. The microbes used are an ureolytic strain NO-A10 which isolated from soil. The bacteria show a strong urease activity and can live in a very high concentration of electrolytes. A carbonate concentration of 1.0 M can precipitates within 10 hours.

The size of carbonates precipitated on a glass plate was approximately 0.1 mm. The sediment with carbonate precipitations was observed using SEM. The photo presented shows sedimentation tests using red soils obtained from Okinawa. In the photo, from the left, cylinders show the sediments in the chemical solution with the microbes, in the chemical solution without microbes and in the distilled water, respectively. As the color of the carbonate precipitated is white and the soil particles used are orange, it is easy to distinguish both of them.

An application of this study is to remove contaminated fine particles from liquid phase. For example, the washing technique for soil remediation may require the treatment of washed water with fine particles which is usually heavily contaminated.
(a) initial dispersion  (b) after one day  (c) after 4 days
Silica is constantly gaining importance as a reinforcing filler for rubber compounds. It offers several advantages compared to carbon black. In tyre treads, silica can yield a lower rolling resistance at equal wear resistance and wet grip than carbon black.

We aim at identifying the synthesis conditions (temperature, chemical composition) that lead to silica granules with high dispersion capacity in the elastomer but without impairing the breakage resistance during the conveying steps.

In this work, we first characterize the physico-chemical properties and the morphology of the granules (BET, laser granulometry, SEM, X-Ray tomography). Then, we investigate the behavior of silica granules under mechanical stress in air (fluidized bed and impact on wall) and water (ultrasounds). Different fragmentation mechanisms are observed (erosion, attrition, breakage, splitting) and a quantification of the fragmentation kinetics is performed. Also, we compare our fragmentation mechanisms and stress thresholds in water and air with published data in more viscous media (elastomers and oils).

All these experiments give us information about the influence of the synthesis process on the granule structure and mechanical properties.
62 - Prevention of segregation of pore former by granulating with MOX powder in low density pellet fabrication for fast breeder reactors

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Japan Atomic Energy Agency (JAEA) has been working to advance fabrication technology of mixed plutonium-uranium oxide (MOX) fuel pellets for fast breeder reactors (FBRs). In brief, the usual fabrication method of MOX pellets for FBRs consists of granulating raw MOX powder by a tabletting method, followed by pressing into compacts. Then, the compacts are sintered at 1700°C to get the MOX pellets.

For the FBR “MONJU”, MOX pellets having low density are required as the fuel pellets. The low density pellets are fabricated by adding an organic additive called a “pore former” to the MOX powder. The pore former is a granulated powder of crystal cellulose and its particle size is about υ90μm. The pore former is thermally decomposed and pores are incorporated into MOX pellets by sintering the compacts containing the pore former.

In the past, the pore former was blended with the granulated MOX powder after the granulation process (Figure 1). But the pore former became segregated from the granulated MOX powder during feeding to the press machine, because the specific gravity of pore former is significantly lower than that of granulated MOX powder. So, the standard deviation of density of obtained MOX pellets was large. In order to solve the problem, blending the raw MOX powder with the pore former was carried out before the granulation process to keep the pore former in the granulated MOX powder (Figure 2). As the result, segregation of pore former was prevented and the standard deviation of density of obtained MOX pellets was decreased.
Crystalline ammonium sulphate was granulated with dissolved ammonium sulphate and acidified palygorskite at concentrations up to 4.2 % palygorskite. The recovery of water soluble nitrogen and sulphur was investigated along with granule hardness, chemical composition by XRD and surface and internal granule morphology using SEM and EPMA. The acidified palygorskite binder is gel-like and cements adjacent crystals together thus increasing green granule strength by 2 kg and long term granule strength by 1 kg. Granule strength was increased by a combination of the precipitation of the water insoluble amorphous silicate cement, adhesion of residual palygorskite at interfaces and the dense packing of microcrystals of ammonium sulphate crystals. The concentrations and solubility of ammonium and sulphate were not significantly reduced by the incorporation of palygorskite in the fertiliser.
In this work, granule compression is studied both by experiments and by numerical discrete element method (DEM) simulations with the overall objective of investigating the ability of DEM to accurate simulate powder compression in-die. In the experiments, granules of microcrystalline cellulose (MCC) in the size range 100–500 μm were used as model material.

Compression of granular materials typically involves a series of consecutive stages [1]. Particle rearrangement dominates initially, with predominantly elastic particle deformation. At increased compression pressure, plastic deformation of the particles and finally elastic deformation of the compact occur. At unloading, the compact first recovers elastically which often is followed by an inelastic deformation at the end.

Uniaxial compression of individual granules was performed to determine granule properties such as the yield pressure and elastic modulus in order to facilitate the selection of appropriate parameters in the simulation model. Compression profiles of the MCC granules were obtained from bulk compression experiments.

Bulk compression of granular materials is a complex process that is challenging to simulate. In this work, simulations of non-cohesive granules of varying size were performed. By utilizing the truncated Hertzian contact model developed by Thornton and Ning [2] for elastic-perfectly plastic materials, the rearrangement and plastic deformation stages of the force displacement curve were found to be in reasonable agreement with experiments. In an attempt to account for the final stage, elastic deformation of the compact, a simple modification of the contact model was proposed. The modification was introduced as a maximal plastic overlap, beyond which elastic deformation was the only deformation mode possible. Our results suggest that the improved model more accurately describes the compression process at high relative densities. Although the correspondence between experiments and simulations is not completely satisfying, the model is considered promising and may be used as a basis for future improvements.

This paper presents a coupling of Discrete Element Method (DEM) and Constrained Interpolation Profile (CIP) mainly designed for simulations of the nucleation process in wet granulation. The governing equations for fluid (liquid and gas) phases are the volume averaged form of the Navier-Stokes equation, continuity and colour function equations. These equations are solved by use of a meso scale fixed Cartesian grid whose cell is larger than individual particles. The surface tension effect on the fluid motion was modelled in three different ways depending on the relative position of the liquid-gas interfaces to powder beds: the models outside, inside, and on the surface of powder beds correspond to a free surface, capillary action and bed surface wetting. A new model to account for the surface tension acting on the particle phase (capillary force), which is suitable with meso scale grid, is proposed in this paper.

Simulations of single droplets impinging on static powder beds are shown to look into the effect of the liquid properties on both droplet spreading and penetration. Then simulations of single droplets impinging on dynamic powder beds in a high shear mixer are presented. The results show that the droplet penetration rate into the bed differs depending on the landing position of the droplet.
Compaction processes is a common practice related to many practical and basic scientific problems. Many attentions have been paid to the mechanical properties of the compacted products, such as failure or its strength. Shear banding, the localization of deformation into thin zones of intense shearing, is a phenomenon commonly found in brittle materials. Thus far, the most effective approach for modeling shear band phenomenon in granular materials has been the discrete element method (DEM).

This paper presents a DEM based study on the strength of compacted wet particles. Uniaxial powder compaction is simulated in the square die with periodical boundaries to obtain a compact with certain density. After a relaxation time during which two boundaries are moved off, the sample experienced a breakage process by exerting a pressure on its top. The crushing pressure is used as a measurement of the strength of the compact. A shear band is observed in the crushing process (Figure 1) in accordance with the experimental observations. The relationship between the compact strength and parameters related to particle and liquid properties are studied. It is found that the strength increases with particle sliding friction, liquid content and consolidation pressure. The spatial inhomogeneities of density and stress are also observed.

Figure 1. Formation of a shear band in crushing.
New method for measuring tensile, shear and torsional strength of solid bridges between particles

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The mechanical strength of solid bonds between particles in bulk solids is a wide research field and of high interest for most of the industries, especially the chemical industry since 60% of their products are sold as solids. Solid bonding can be either a desired mechanism, e.g. in industrial agglomeration processes but also an undesired occurrence during the production, storage or transport of a product, often called caking.

Is the aim of research different for both areas, high qualitative well designed products by selective utilization of solid bond formation in agglomeration processes and the total prevention of inter-particle bonds to achieve a free flowing product in the case of caking, the underlying mechanisms at the particle contacts are the same.

A new experimental set-up is presented that enables to measure the strength of solid bonds between double-particle systems in the millimetre range. Beside the tensile strength, the shear and torsional strength can be measured as well. Fixed in special holders, the solid bond formation takes place in a climatic chamber at defined values for temperature and relative humidity. The experimental equipment and the measurement procedure are described and results are presented in detail.

Urea prills were chosen as a test material. Urea is well known for solid bridge formation at climatic conditions near the critical relative humidity. The results show that the strength of the solid bridges is increasing with time, whereas the shear strength is slightly higher than the tensile strength in average. Further, the gathered results are discussed regarding their valuable use in DEM modelling describing the strength and failure of bulk solids.
69 - Coating of fertilizer granules with biodegradable materials as a preparation method of controlled release fertilizer

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The efficiency of nutrients assimilation by plants is rather low and this is a serious problem in view of environmental protection. Little assimilability of mineral components also has unfavourable effects in the economic aspects of the issue: materials losses, spent energy and human work effort negatively affect the total economic balance of the whole agrochemical production process. It seems that the task of great importance is to increase the effectiveness of nutrients' absorption by plants and to decrease material losses, while at the same time to limit the amount of waste material produced by the fertilizer industry. This may be carried out through developing, producing and applying fertilizers with controlled release of mineral components, i.e. the so-called controlled release fertilizers (CRFs).

A granule of controlled release fertilizer is encapsulated or coated with an inert layer, mainly made of different kinds of polymers (for instance: polyolefins, polyacrylic acid, polyvinyl alkohol, polyesters). One of the CRFs' drawback is that after nutrients' consumption there is still a considerable amount of useless polymer left in the soil. A good and possible solution, although not as yet used in technological scale, is to produce CRFs using biodegradable materials, manufactured from raw materials renewable in the process of biosynthesis.

In this work, different biodegradable materials like chitosan, chitin, soybean protein, starch, linseed oil were used to cover fertilizer granules with an inert, unpermeable layer in order to get a material with controlled release properties. The process was performed in a laboratory drum granulator: granules of fertilizer were sprayed with dispersions of biodegradable materials at elevated temperatures. Prepared materials were characterized with available analytical methods (XRD, SEM, optical microscopy). Degree and time of nutrients' release were determined with standardized method and compared with commercial fertilizers. Exponential, sigmoidal and power equations were used to describe the kinetics of nutrients' release.
An experimental evaluation of an effective medium based compaction equation

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Tablet production involves compression of free flowing powder in an enclosed cavity of defined geometry. The complexity of the powder bed system necessitates that a way be found to better understand what occurs during compression. One such approach is by means of compaction equations, the parameters of which can be interpreted in terms of physical processes. The empirical equations of Heckel [1] and Kawakita [2] are the best known of these. Both are based on the inverse relationship between powder bed porosity/volume and pressure. Frenning et al have recently published work which introduces a mathematically derived compaction equation where plastic deformation of the particles is considered as the dominating compression mechanism [3].

They applied the effective-medium-based compaction equation to experimental data from mm sized spherical agglomerates, and found that the analysis was able to adequately describe the behaviour of the more plastically deforming particles, whereas the more brittle particles were not so well described. The current work extends the scope of the above mentioned equation to a much smaller size scale. Two powder types (sodium chloride and lactose), each consisting of three size fractions were characterised and compressed to a pressure of 500 MPa. These two powders were chosen because of their differing mechanical properties (plastic and brittle). The size fractions were <40 μm, 125–212 μm and 212–300 μm. The smallest size fraction was obtained by milling the powders in a pin disk mill, and the particle size was determined via a transient air permeability apparatus. The two other size fractions were obtained via dry sieving. The effective-medium-based compaction equation was found to provide a good description of the compression profile for the more plastically deforming sodium chloride powders, regardless of particle size. However, the equation failed to adequately describe the compression behaviour of the brittle lactose powder. In conclusion, the equation appears to be accurate when the material conforms to the mechanistic assumptions made in its derivation.

Characterisation of granulated and sintered chromium oxide

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Spray drying is mainly use for manufacturing ceramic powders for many applications. In this study granulated and sintered chromium oxide powders were characterised. Powders were manufactured via spray-drying and sintering method, giving special attention to the slurry preparation. After granulation the powders were sintered in Ar-6H₂ atmosphere at three different temperatures. The morphology and cross section of the powders were analysed with scanning electron microscopy (SEM) to study grain growth and density. The particle sizes were measured with laser diffractometer and the mechanical strength with an axial pressure test. The effect of slurry preparation, granulation and sintering conditions to density, particle size, mechanical strength and grain growth are presented.
Influence of binder liquid viscosity and superficial tension on granule properties in high shear granulation process

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In the wet granulation process, binder liquid distribution and binder liquid properties are known to be key parameters to control granulation rates and the final granules properties. However in literature, very few studies tackled this problem and the dynamic of the liquid distribution is still not very well understood, especially in high shear mixers. The few published studies are more concerned with liquid re-distribution after the complete addition of the binding agent.

In this study, we are especially interested in characterizing the time evolution of granules properties during binder liquid addition. Three properties have been followed: the size distribution, the porosity and the binder liquid content of the granules. The effects of two physico-chemical parameters have been studied: the viscosity and the superficial tension. The challenge was the de-correlation of the two parameters more explicitly the modification of surface tension without viscosity variation and the viscosity modification without surface tension evolution.

Granulation experiments are carried out in a 0.5 L high shear mixer Mi-Pro (Pro-C-epT, Zelzate, Belgium) using lactose and polyvinylpyrrolidone powders as pharmaceutical excipients. In order to follow the binder distribution kinetics during granulation process, an original tracing method has been developed. Nigrosine dye was used as tracer of the binding liquid. After drying at ambient temperature, granules are sieved into 12 classes and dye content is analysed in each granule diameter class by spectrophotometry after complete dissolution. Granule size distribution was measured using a Malvern Mastersizer 2000 dry particle size analyzer.

The effects of variation of these physico-chemical parameters were measured on the torque curves during the granulation, on the evolution of the particle size distributions and on the D50 and D4,3 diameters. The distribution of the binder liquid in each particle size range was also realized.

We notice that the binding liquid is highly heterogeneously distributed in the particles population until a homogeneous state is obtained, characterized by an equal binding liquid amount in each diameter class. The time required to obtain this homogenous state is variable depending on the operating conditions. We also show that both viscosity and surface tension change the evolution of median diameter D50.

Finally, it is deduced that binder liquid distribution is quite linked to the granule size properties, especially granule size distribution is narrowed after a homogeneous binder liquid distribution.
74 - Measurement of cross sectional area of powder profile and its effect on drop behaviour

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Knowledge of vertical cross sectional shape and flow behaviour of powder bed is necessary in order to develop quantitative process models that enable better process controlling, predictive scale-up and process optimisation. So far number of research workers has focussed on different non-invasive experimental techniques to measure and observe the particle velocity distribution and flow pattern in high shear mixer. However there are very few studies which measure or observe changes in the vertical cross section of the powder bed during passing of the impeller blade. This paper does so using an in-house technique to capture illuminated powder profile curve. This curve was smoothed; phase averaged and fitted with three parameter sigmoid curve. Area under the curve gave vertical cross sectional area at time ‘t’. Any changes in vertical cross sectional area during single pass of impeller blade were used to explain earlier published results about drop de-acceleration in powder bed. Separately, a moving powder bed was simulated using DEM. Simulated curves showed good similarity with experimental results.

Schematic arrangement of powder profile experiments. Camera is perpendicular to plane of the figure and at 30 degrees to the horizontal.
Gelatin capsules are solid dosage forms in which one or more medicinal and inert ingredients are enclosed in a small shell or container usually made of gelatin. There are two basic types of gelatin capsules namely, hard gelatin capsules and soft gelatin capsules. In general, the gelatin capsules are used to enclose powders or water-insoluble liquids dissolved in a non-polar solvent for several reasons, such as masking flavors or unpleasant smells, reducing contamination of the product, and protecting the active drug against oxidation.

Enteric coating of hard gelatine capsules can be useful in situations in which the drug may be degraded by the gastric juice and/or can cause irritation to stomach. However, due to physical characteristics of the hard gelatine capsules, such as shape, size, shell fragility and smooth surface, the coating application is challenging. On the other hand, the spouted bed has been widely used to apply coatings to agrochemical, chemical and pharmaceutical products such as seeds, pesticides, fertilizers and tablets. In this work, the enteric coating of acetaminophen loaded hard gelatin capsules (HGC) by spouted bed was investigated.

Oval shape HGC (number 0), filled with acetaminophen and, a composition based on Eudragit L-30-D-55, an enteric polymer, were used in the coating experiments. The coating experiments were carried in a spouted bed with a column diameter of 200 mm and included conical base angle of 40° and 60°, connected to a cylindrical column of 455 mm. An atomizer was placed in the inlet of the bed and the coating suspension was fed concurrently with the spouting air. The coated product was characterized through determination of the dissolution test, shape factor, coating mass distribution and coating morphology (scanning electronic microscopy). The gastric resistant effect was obtained with a coating layer mass between 4 and 22. Mg.cm⁻². M.E.V. results show a better quality of the coated surface obtained for longer coating times.
Influence of the installed in-line spatial filter velocimetry (SFV) probe on fluidized bed stability

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Fluid bed granulation is a primary process used in pharmaceutical industry to improve flowability, compressibility and homogeneity of powders for tablet compression. Granulates of high quality can be obtained by in process measurement and control of the critical process parameters. In this study, an in-line probe for particle size measurement was installed directly into the centre of the fluid bed below the spraying nozzle in a batch laboratory fluid bed granulator, and stability and homogeneity of the fluid bed process, yield losses due to material precipitation and reproducibility of the product parameters were investigated. The optimum fluid bed process parameters were evaluated in earlier investigations.

The model formulation consists of lactose monohydrate (Tablettose 70, Meggle-Pharma, D-Wasserburg) and microcrystalline cellulose (MCC 101 L, Sanaq AG, CH-Basel) in relation 1:1, aqueous hydroxypropylmethyl cellulose solution 7.5% w/w (Pharmacoat 606, Shin Etsu, D-Mülheim) was used for agglomeration. The process was performed in a fluid bed granulator (GPCG 1.1, Glatt, D-Binzen) without and with installed in-line spatial filter velocimetry probe (IPP 70-S, Parsum, D-Chemnitz). Spraying rate was varied from 8-16 g/min, the other process parameters were kept constant (process air temperature 60°C, atomization air pressure 2 bar, nozzle diameter 1 mm, batch size 150 g). Increasing agglomerate weight was compensated by adjusting process air volume (45-70 m³/h). With installed probe particle size was measured continuously during the whole agglomeration process. Product quality was evaluated by particle size (sieve analysis, Retsch, D-Haan), bulk and tap density (tap volumeter, Erweka, D-Heusenstamm) and angle of slope (flow tester PTG S3, Pharma Test, D-Hainburg).

Independent of spraying rate the fluid bed was stable over the whole process. The batches with installed as well as without probe yielded more than 90% at different spraying rates. Product precipitation was negligible. Also the injected air of the probe responsible for dilution and homogenisation of the specimen did not disturb the stability of the fluid bed. Product particle size, bulk and tap density and angle of slope gave similar values independent of probe presence or not, only at a spraying rate of 12 g/min the d50 values deviate about 45 µm (Fig.1). The in-line spatial filter velocimetry probe can be used as a process analytical technology (PAT) tool.
Figure 1. Mean particle size d50 of granulate prepared without and with SFV-probe.
Layered powder compacts such as multi-layer pharmaceutical tablets and detergents are becoming increasingly attractive for functional or marketing reasons. However, the manufacturing process presents technical challenges which can be traced back to die fill and die compaction operations. For example, die fill influences weight and content uniformity and cross-contamination between the layers. Compaction affects the microstructure which determines the delivery of the active ingredient or the creation of cracks and fractures at the interface which can lead to delamination.

In this paper we examine the creation of interlayer cracks in flat and curved faced bilayer tablets produced using a range of compression pressures for the different layers. The cracks at the interface are visualised using X-ray Computed Tomography. The mechanical interaction in normal and tangential directions between the layers are characterised using a custom build testing rig. The data are used as input parameters for detailed stress analysis at the interface. A criterion for failure at the interface is developed and validated for a range of curved faced bilayer compacts. The conditions leading to failure at the interface are discussed for stress states experienced during die compaction, unloading, ejection and further external loading of the layered compacts.
The improvement of the bioavailability of poorly soluble drugs has been the focus of a significant amount of pharmaceutical research for decades. One major aspect of this field is the increase of the oral bioavailability of drugs with a low solubility and a high permeability (BCS Class II), which has been addressed by several technologies. One quite traditional approach is the micronization of drug particles in order to enlarge the specific surface area, which leads to a higher dissolution rate and a higher bioavailability for dissolution limited drugs. Recently, a new concept called Solid Crystal Suspensions was proposed in which the drug is ground and dispersed in a crystalline carrier using hot melt extrusion technology.

In this study, the Solid Crystal Suspension technology was investigated at a larger scale than described previously. This was done in order to demonstrate the relevance of this technology for manufacturing processes at an industrial scale. The obtained granulates were formed into tablets which were used to perform the first bioavailability study using a Solid Crystal Suspension.

Griseofulvin (Hawkins, USA) and Mannitol (Roquette, France) were co-processed in a twin-screw extruder (Mikro 27GL-28D, Leistritz, Germany). The hot extrudates were placed on a conveying belt (Brabender, Germany), cooled and transported continuously to a centrifugation mill (ZM 200, Retsch, Germany). The mill was equipped with a screen containing 1mm diameter holes. A sieve fraction (100-200µm) of obtained granulates were blended with Prosolv HD90 (JRS, Germany) in a bin blender (Turbula, Switzerland), and biplane tablets of 12mm diameter and 600mg (125mg Griseofulvin, 375mg Mannitol and 100mg Prosolv) weight were compressed (Flexitab, Röltgen, Germany).

In order to avoid crystallization of molten Mannitol within the extrusion barrel and the die, additional heating devices had to be applied, and the temperature regulation units had to be adjusted to the formulations. The temperature profile of the barrel, the screw configuration and the screw speed were varied systematically, and a significant effect of each these process parameters to the drug release was found. Using a drug load of 25% Griseofulvin, granulates with a rapid drug release were obtained, which were compressed into tablets. These tablets showed a 10-fold faster drug release than the physical mixture. The results from the in vitro investigations were confirmed with in vivo data from dogs.

This study confirms that Solid Crystal Suspensions can be manufactured using a lab scale extruder with a throughput of 2.4 kg/h in a continuous manufacturing processes. The bioavailability of the formulation was increased by this technology and was similar to a commercial product.
82 - Simulation of fluidized bed spray agglomeration focusing on the pre-drying of droplets

M. Dernedde, M. Peglow and E. Tsotsas


Fluidized bed processes are widely applied in all kinds of particle processing industries. The process principle combines a compact construction of apparatuses, high exchange rates of heat and mass and a variety of micro processes in a single vessel. While in the past scientific work mainly featured the experimental investigation, nowadays complex theoretical approaches arise to describe the process mathematically. In the focus of these works the continuous population balance is used to follow the density distribution with respect to certain properties of the dispersed phase over time.

The presented study describes the simulation of a fluidised bed granulation process by means of probabilistic modelling; namely the Monte Carlo method. Due to its discrete manner, it naturally adapts to the granulation process which can be described as a network of simultaneous and sequential micro processes. The physical interactions between single particles and droplets are fed into a model which is then solved with an event-driven, constant-number Monte Carlo method. The stochastic solution allows to overcome some significant drawbacks of the integro-differential population balance: discretization is not required and the number of internal coordinates can be extended easily. Although an explicit formulation of macroscopic kinetic expressions is unnecessary, the Monte Carlo approach still allows the monitoring of distributed properties such as composition or particle size. Process and material parameters can be coupled directly with resulting product attributes.

This contribution presents a more general model to calculate the particle size distribution under consideration of

- the continuous addition of size-distributed droplets,
- the pre-drying of droplets before deposition under consideration of a radial concentration profile within the droplet leading to solidification and its complex movement in the nozzle spray cone,
- the deposition, drying and penetration of droplets on the carrier, as well as
- the binary collision of particles, their selective aggregation and breakage behaviour resulting in a 3-dimensional particle structure.

As an example for an experimental validation of a single micro process the drying of premature binder droplets after leaving the nozzle tip is shown. To evaluate droplet size, droplet solidification, droplet velocity and spatial distribution in the nozzle spray cone, experimental results with an acoustic levitator and a PDA device have been obtained and are compared to the simulation.
Investigation of growth kinetics in fluidised bed spray granulation

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The fluidised bed granulation is an important process for the formulation of various solid products. The desired product quality can be reached in one production step. As industries need products with defined properties, like a special range for the particle size, it is indispensable to have a detailed knowledge over the dynamic of such a granulation process. The development of the particle size during this process is one of the main product qualities and depends on parameters like temperature, gas flow rate, spraying rate and hold up.

Previous models for the process dynamics extinguish size-independent particle growth, the formation of compact shells and a uniform distribution in the fluidised bed of the injected liquid [1]. These approaches are oversimplified and were replaced by an extended model which includes size depending particle growth, formation of a porous shell and subdivision of the fluidized bed in spraying and drying zone. The new model includes the earlier approaches as limiting cases.

To prove the taken assumption several experiments in a fluidised bed granulator were conducted to investigate the development of the particle size distribution. To detect the growth kinetic which describes the experimental results well different kinetic were used for the simulation. The change of the particle size during the experiments was recorded by taking samples out of the fluidised bed and measuring them in a digital image analyser (Camsizer). Additional to that measuring method some online measuring with a Parsum-probe was conducted. In opposition to the Camsizer the Parsum probe provides a current and continuous value for the particle size distribution during the granulation. This can then be used in order to achieve a regulation of the process in a favoured direction.

The present work focuses on the study of the effect of process variables (powder feed rate and liquid to solid ratio) and formulation variables (viscosity of binder) on dry and wet formulation velocity in a co-rotating twin screw granulator. The formulation used in this study consisted of α-lactose monohydrate, microcrystalline cellulose and crosscarmellose sodium. The surface velocity of the dry and wet formulation powder were obtained in the conveying zone of the co-rotating twin screw granulator using Particle Image Velocimetry (PIV) and Discrete Element Modelling (DEM) simulation. The dry formulation powder possessed a higher velocity compared to its wet granules. The increase in viscosity of binder increased the velocity of wet powder mass. The results helped to qualitatively understand the twin screw granulation process.
85 - Influence of punch deformation on models describing compressibility of powders during tableting

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The ability of a powder bed to deform under pressure during e.g. tableting is known as compressibility. Different mathematical models are available for evaluation of powder compressibility. The most commonly used are the Heckel [1], Walker [2], Kawakita [3] and Adams [4] models. One of the bigger problems associated with their usage is large variability of produced results. For instance, the yield pressure ($P_y$) obtained by Heckel model of Avicel® PH 101 is reported in the range of 48 MPa-104 MPa. Paracetamol yield pressure is reported in the range of 79 MPa-124 MPa [5].

In this work the deformation of the Euro B tooling was measured using instrumented hydraulic tester Instron 1255 and a 25 mm Instron extensometer. The measured Young modulus of the punch was 146,8 GPa. Commonly used pharmaceutical fillers such as CaHPO$_4$ x 2H$_2$O (Bekapress), isomalt, spray-dried lactose (DCL-11), milled lactose (NF 312), NaCl, microcrystalline cellulose (Avicel PH 101 and PH 200) and corn starch were compressed at different pressures using fully instrumented single-punch tableting press Killian SP300. Compressibility was evaluated using Heckel, Walker, Kawakita and Adams models and the influence of punch deformation on the results was investigated. Figure below shows the Heckel and Walker plots for CaHPO$_4$ x 2H$_2$O (Bekapress). Punch deformation profoundly influences both results: Heckel yield pressure ($P_y$) with punch deformation included is 441 MPa and without 320 MPa; Walker's coefficient $w'$ increases from 21,8 % to 26,9 % due to exclusion of punch deformation.

\[ y = 0.003129x + 0.648 \]
\[ R^2 = 0.999 \]

\[ y = 0.002266x + 0.6873 \]
\[ R^2 = 0.991 \]

\[ y = -0.2183x + 1.04 \]
\[ R^2 = 0.9992 \]

\[ y = -0.2686x + 1.12 \]
\[ R^2 = 0.9997 \]
The characterisation of granulation wet masses using powder rheometry

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The wet granulation of powders is a widely used unit operation in many process industries to primarily increase the particle size, which has the benefits of reducing segregation and improving flowability and compaction properties of a formulation. Simply measuring variables such as particle size distribution does not provide sufficient information to predict downstream processing behaviour, which may be influenced by properties such as permeability, compressibility and flowability [1].

The results of a series of laboratory based experiments are presented where simple granulation formulations were created and the physical characteristics (permeability, flowability, compressibility and shear properties) of the wet masses were evaluated, using a powder rheometer immediately following the granulation experiment, with respect to the proportion of water added.

The data shows that there was a significant and distinct change in the flowability energy at the point of granule formation in all cases. Permeability was also found to increase linearly up to the granulation formation point, after which a deviation from a straight line was observed. These trends in permeability and flow energy are known to be influenced by large and stiff particles, thus the results correspond to the traditional concept of granule formation. Using these physical characteristics of granulated wet masses, it is possible to derive relationships between the process parameters and the tablet performance to achieve a model for determining scaling parameters from the laboratory bench to full scale granulators.

The drying of suspensions containing micro or nano scaled particles in order to produce small solid particles or coatings is a technological process that is utilized in many industries, e.g. medical, pharmaceutical, material or chemical industry. A very interesting process for particle formation is spray drying. For designing such processes, the modelling of transport phenomena inside a single droplet is required. Such modelling should be based on population balances to describe the volume distribution of solid particles inside the droplet. In fact, some approaches for crystallisation and growth processes can be found in literature. However, the very important case of drying droplet containing suspended nano scaled particles, which can aggregate depending on the degree of stabilisation of the suspension, has not yet been treated.

In the present study a mathematical model based on population balances is proposed, describing the drying of a single droplet containing micro or nano particles in order to predict the final structure of the dried particles. The model includes aggregation as well as diffusion of the micro or nano particles inside the droplet under conditions of droplet shrinkage due to drying. Aggregation and diffusion are linked together since the mobility of the nano particles depends on their size. Furthermore, the aggregation is influenced by concentration profiles of the particles inside the droplet resulting from both limited mobility and droplet shrinkage. Thus, the external (spatial) coordinate has to be considered besides the inner coordinate (volume of particles).

For the numerical solution of the population balance two methods are applied. On the one hand a method known as Direct Quadrature Method of Moments (DQMOM) is used [1]. In the DQMOM-approach the distribution function appearing in the population balance equation is thought of as a summation of Dirac delta functions and its moments are forced to be correctly predicted by the method. The results of this approach are compared with a direct solution of the discretized population balance.

Until now, all results are applied to the first drying period, meaning the time before an immobile crust at the droplet surface is formed. To validate the model, experiments are conducted by means of an acoustic levitator.

**Pellet layering: Scale-up considerations using different kinds of processing equipment**

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In pellet layering processes, drug particles should be affixed onto the surface of provided starter cores. In case of solution / suspension layering, the drug is dissolved / dispersed in an aqueous or an organic binder liquid, which is sprayed onto the cores by air atomization. Solid drug layers are obtained after solvent evaporation.

Suitable processing equipment for layering purpose requires a spraying device and an inlet for heated process air to vaporize the liquid. Furthermore, flow pattern of the product plays an important role to obtain single pellets with a uniform layer. The available processors are drum coaters, fluid bed equipment and rotary disc machines. [1]

This study investigated the process efficiency and the facility to scale up, using an aqueous suspension layering model. Wurster fluid bed equipment, regarded as the state of the art, was compared to a conventional drum coater and to a modified rotary processor. All the three techniques differ regarding nozzle position, direction of air flow, product movement and mechanical forces.

Scale-up of the equipment dimension directly influences the batch size capacity. However, the area of process air inlet and the nozzle may have a different multiplicative factor and have to be taken into account for the up-scaling of drug load speed and solvent evaporation rate. Consequently results for process performance can vary at a different scale.

The laboratory Wurster process resulted in high yield and drug layering was very efficient. However, it was a challenge to find suitable parameters in a pilot scale equipment on the basis of laboratory scale settings. The rotary process was robust at small scale and even more at the pilot scale. Scale up was successful and led to a fast process. Product quality and process efficiency, using a pilot scale drum coater, was comparable to other techniques, but it took more time to achieve the same mass gain.

90 - Twin screw granulation: influence of process and formulation variables on granule quality

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Experiments were done using the Consigma™ system (a continuous oral solid dosage tablet manufacturing system) to improve process understanding and knowledge about the formulation and process variables which determine granule quality. The Consigma™ consists of 3 modules: a wet high shear granulation module, a segmented dryer module and an evaluation module. This work focuses on the wet granulation module that uses twin screw granulation as a particle size enlargement technique. A premix of theophylline anhydrate, α-lactose monohydrate and PVP (ratio: 30/67.5/2.5, w/w) was granulated with an aqueous 0.5 % sodium laurylsulphate solution. Using an experimental design the influence of process (powder feed rate, screw speed, barrel temperature) and formulation parameters (water content) on granule quality was investigated. A 19-run full factorial design was used with 4 variables on 2 levels: powder feed rate (10 and 25 kg/h), screw speed (700 and 950 rpm), barrel temperature (25 and 40°C) and water content (8.38 and 9.94 %) and 3 replicates of the design centerpoint.

The particle size of the granules was significantly influenced by powder feed rate and barrel temperature. A higher powder feed rate and barrel temperature resulted in a high amount of oversized agglomerates (> 1400 µm). Granule friability was low (< 16.7 %) and independent of process and formulation conditions. However, increasing the barrel temperature and water content yielded less friable granules. The random variability of particle size and friability was higher than the variability due to the variation of screw speed. No significant effects were found for compressibility and Hausner ratio. These results show that for this formulation the process and formulation variables have an impact on the particle size and friability, while the process is robust regarding the compressibility and Hausner ratio of the granules produced by twin screw granulation.
91 - Real-time particle size measurement for granulation optimization

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Real-time particle size measurement is extremely valuable for the optimization and consistent operation of granulation processes. For the pharmaceutical industry it is also critical for the implementation of the FDA's Process Analytical Technology (PAT) initiative.

On- and in-line analyzers allow the real-time monitoring of a granulation process, towards an appropriate endpoint, supporting the efficient, well-controlled manufacture of materials with precisely defined characteristics. Such systems simultaneously address HSE concerns surrounding product containment/manual sampling and provide a secure basis for automated process control.

This presentation considers two analytical techniques that are successfully used for real-time particle size measurement: spatial filter velocimetry and laser diffraction. It examines the principles of operation of both techniques but focuses on demonstrating the practical benefits these methods deliver in granulation monitoring and control. Commercial application to batch fluidized bed granulation, pellet coating, high shear, continuous granulation, and/or roller compaction is illustrated through industrial case studies. These examples fully demonstrate the multiple benefits that real-time measurement brings, which include: continuous, monitoring of the process; instant upset detection; more consistent product quality; automated control; and reduced manpower requirements.

In simple terms, with spatial filter velocimetry, particle size is determined by measuring the time for which a particle interrupts a laser beam of light. Optical probes employing this technique, as exemplified by the Parsum IPP70 (Parsum, Germany) are compact, highly robust and suitable for the measurement of particles from 50 up to 6000 microns in diameter. Such probes are easily inserted in granulators and perform reliably even when measuring damp, cohesive particles.

Laser diffraction analyzers determine particle size from the scattering pattern produced as light passes through a particulate sample. Well-established as both an off- and on-line technique laser diffraction, like spatial filter velocimetry, is rapid and non-destructive, and requires no external calibration. Widely used on-line systems such as the Insitec (Malvern Instruments, UK), measure up to four complete particle size distributions per second and are specified for ease of integration within automated control systems.
92 - Energetical approach of wet agglomeration process: methodology and measurements


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Considering wet agglomeration, the function of the mixer is double and ambivalent: on one hand it has to structure the medium by forming agglomerates, on the other hand it has to homogenize the medium by distributing the liquid binder. These two aspects induce an energy expenditure. The energy expenditure of mixing process was rather evaluated during dry mixing (Demeyre, 2007). When wet agglomeration process is considered, energetic expenditure was only considered as a tool to characterize the evolution of product properties during the operation (Rondet, 2008; Collet, 2010). These studies showed that the energy consumption is related to the blade rotation speed and to the cohesion of the powder/binder mixture. Wet agglomeration process was little considered under the scope of its energetic optimisation within the framework of its reduction to minimize the environmental impact.

The aim of the present work is to set up a methodology making it possible to measure the energy really used for the wet agglomeration of durum wheat semolina and to compare it to the global energy consumption of the mixer. In that way, expended energy (active power) will be measured according to various process parameters using a planetary mixer (rotating blade speed, mass load and water content of the mixed product). The work consists then in identifying, on a graph Active Power=f(time), the different components of the total power (input power, mechanical, magnetic, and Joule losses). This methodology makes it possible to quantify the proportion of energy that is really used to distribute the water within the medium and to structure it in the form of agglomerates. It is also possible to quantify the energy necessary for the motion of the product. This last is directly related to the cohesion of the medium. It turns out that the decomposition of the energy signal allows the identification of the energy expenditure only ascribable to the agglomeration phenomenon. The present results demonstrate that this energy only represent a third of the total energy consumption of the process. The remainder energy is consumed by the motion of the rotor and the medium and thermal dissipation lost. This study will give opportunities to conduct energetical investigation concerning the wet agglomeration process.

Explosive compositions are often composed of a highly crystalline filler material and a polymeric binder. Addition of the binder may improve both the mechanical and safety properties but can result in loss of performance as it dilutes the energy of the composition. The quantity of binder must therefore be kept to a minimum; formulations are typically in excess of 90 % filler, and some explosives can be pressed neat with no added binder. This makes processing (compaction and handling) difficult and can result in poor mechanical stability of the composite.

In this study a series of trials were undertaken to investigate the effect of binder type, binder concentration and processing conditions on the compaction properties and mechanical properties of the composite. Compaction was investigated via measurement of the pressed density achieved using different pressing loads and friability testing (tumble testing) was used to determine the mechanical stability.

The effect of different binder types on the compaction and mechanical properties of the formulation was investigated using fixed binder content (1 volume %) and processing conditions. Binder types included thermoplastics, curable elastomers, plasticized elastomers, thermoplastic-elastomers, natural gums and viscous liquids. Further composites were prepared using one of the thermoplastic binders at a concentration varied between 0.5 and 2.0 volume % and compacted under different processing conditions; compacted pellets were produced at a range of different densities via pressing at ambient and elevated temperature (above the softening point of the binder). The weight loss on friability testing was then determined.

Pellet robustness was found to be significantly improved by addition of very small quantities of binder (0.5 volume %) and by compacting at elevated temperature. Pressing to a higher density also resulted in more mechanically robust compacts.
94 - Investigation into particle size effects on the processability of highly filled composites

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Structure Properties

Explosive formulations typically consist of a crystalline filler and polymeric binder material. To ensure suitable performance, explosive formulations are typically highly loaded (upwards of 90% by weight) and so the filler particle size distribution will have a strong influence on the manufacturing conditions (during both formulation and compaction) as well as affecting the safety, performance and mechanical properties of the composite.

This work discusses a series of non-explosive compositions manufactured using different particle size distributions of spherical glass beads. The powder flow properties of the unbound fillers are presented and the effect of filler size and distribution on the compaction and mechanical properties of the pressed composites reported.
95 - Prediction of liquid coverage in fluid bed granulation

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Nucleation is a very important step in wet granulation, as it affects the appearance and function of the final granules. Over the last decade the dimensionless spray flux was developed (Litster et al., 2001) for immersion nucleation – where the drop is much larger than the particles. However, no dimensionless groups have been developed for distribution nucleation - where the drops are much smaller than the particles, as tends to be the case in fluidised beds.

In this paper, a newly derived dimensionless parameter, particle spray flux (p) has been derived, with the objective of understanding liquid distribution of small drops over a relatively large particle. To validate the particle spray flux parameter, experiments were conducted by allowing drops to land randomly over the particle and the surface coverage of the particle was measured using image analysis. The results demonstrated the capability of the dimensionless particle spray flux to predict surface coverage and allows the surface coverage of a particle to be predicted a priori using simple, known parameters (without any fitting coefficients). In addition, the new parameter can be shown to be closely related to the empirical fitting parameter κ used in Stepanek and Rajniak's [1] model. The results are expected to be valuable in a variety of particle wetting and coating applications where small drops are distributed over larger particles.

The new particle spray flux parameter avoids the need for sophisticated modelling and fitted coefficients and will be able to be used in DEM modelling of fluid bed granulation, particularly for predicting the probability of particle collision at a wetted section. It is also expected to form part of a new set of design rules for fluid bed granulation.

Granular products with optimal dosage, flow and transport behaviour are of particular interest in modern industries. Those products can be produced in fluidised beds. A well-known configuration for the granulation is the fluidised bed bottom-spray. This configuration is conventionally extended with an internal riser or so-called Wurster tube due to its advantages in offering system stability and enhanced controlling in particle growth. To mathematically describe the particle growth in that kind of system population balance models (PBM) are applied. These models can be extended by compartment models which separates the granulation process into a spray compartment and a drying compartment. Decisive parameters in the compartment models are the compartment size and the particle residence time. In this work the parameters are obtained by a gas-particle flow model predicting the particle flow inside the spray compartment. The model validity is proven by PIV measurements and image analysis at a particular test facility. By using an extended PBM the influence of spray zone shaping, substantially influenced by the dimensions of the riser, as well as a particle size dependent residence time in the spray compartment is computationally determined and presented in this work.
Product makeup, defined as the adhesion of material to the internal surface of process equipment, is a negative transformation which can occur during agglomeration processes in many industries, such as detergent, pharmaceuticals, food and chemicals. It leads to altering the process performance which can often affect product quality. Equipment clean out results in unnecessary process down time and thus affects process reliability. However, little has been done in the field so far to understand the makeup mechanisms. This work focuses on identifying the key drivers for the transformation via establishing a simply stress balance at the interface between the moving powder bed and equipment wall surface. A hypothesis was proposed that product makeup is the result of the balance of two key stresses at the powder-equipment contacting surface. One is the shear stress from equipment moving parts, such as paddle or blade which drives the movement of the powder bed moving hence preventing the product makeup. Another is the resistance stress which is responsible for product makeup and is the sum of adhesive and friction stress between the powder bed and equipment wall surface. The current work establishes the correlation of these two stresses to the mixer power draw and process parameters such as mixer geometries (bowl and moving parts), material properties (cohesiveness and coefficient of wall and internal friction) and operating conditions (such as mixer speed). It was found that both shear and resistance stresses increase with mixer speed. The resistance stress becomes dominant over the shear stress as mixer speed increases above a critical point, hence posing the risk of product makeup inside the equipment wall.
Granular material processing often requires mixing steps in order to blend cohesive powders, distribute viscous liquids into powder beds or create agglomerates from wet powder mass. These are very common operations in several types of industry, such as chemical, detergents, food, metallurgical or pharmaceutical industries. Among all the various equipments, high shear mixers are widely used both for blending and agglomeration [1].

Despite the great importance of these mixers in powder processing, the granular flow behaviour inside the vessel is generally not totally clear. Many techniques have been used in order to carry out a good description of the powder flow within the mixer. For example, motor power consumption and impeller torque have often been monitored in order to identify how the flow patterns in a mixer depend on the geometric configuration and the impeller speed [2].

The aim of the present work is to propose a new and more detailed method for describing the complex powder rheology inside a high shear mixer based on impeller torque and power consumption analysis. Particularly, a new dimensionless torque number is proposed. This model clearly isolates the contribution of mass fill and impeller height, identifying the transition from the “bumping” regime to the “roping” regime [1]. Results are compared with those obtained by Knight et al. [3].

Extensive experimentation was performed using a lab-scale mixer (2 l vessel volume) and a pilot-scale mixer (65 l vessel volume) in order to validate the model. Some common pharmaceutical excipients (e.g. lactose, cellulose) were processed. A high speed CCD camera was furthermore used in combination with particle image velocimetry (PIV) to obtain more information about the surface velocity variation and flow pattern changes. Mass fill resulted to be one of the most critical variables as predicted by the model, strongly affecting both torque profiles and powder flow patterns.

Pharmaceutical industries frequently turn to high shear wet granulation (HSGW) in order to convert fine cohesive powders into dense and round granules. [1]. Among formulation components, the active substance is usually the most critical ingredient. For example, differences in physical properties between drug and excipients or non-optimal process conditions often lead to selective agglomeration of certain components, causing content uniformity problems. Despite the essential importance of the active relatively few works presented a detailed analysis on the role of drug characteristics in the granule growth kinetics [2,3]. The aim of the present research was to determine the main effects of drug physical properties and some important process parameters on the granule growth behaviour and final drug distribution. A mixture composed of drug, some excipients and a dry binder was processed using a lab-scale high-shear mixer. Three common active pharmaceutical ingredients (paracetamol, caffeine and acetil salicylic acid) were used within the initial formulation. Drug composition was 50% (on weight basis). Influences of drug physical properties (e.g. primary particle size, hygroscopicity and crystalline degree) on the granule growth behaviour were analysed. PSD and granule morphology were monitored during the entire process through sieve analysis and scanning electron microscope image analysis. Resistance of the wet mass to mixing was furthermore measured using the impeller torque monitoring technique [4]. Results showed that the finest primary PSD leaded to slower and more gradual granule growth. On the other hand, as primary PSD increased, growth was more likely to occur via a crushing and layering mechanism. Moreover, drug distribution in final product strongly depended on the process conditions: worse liquid distribution conditions determined poorer content uniformity, especially in the case of fine primary PSD.

100 - Investigation of the influence of different organics combination on processing properties of spray dried ceramic granules

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Sub μm primary particles show a poor flowability that can be improved by an agglomeration step. Spray drying is one of the most common agglomeration processes to enhance handling and processing properties of fine raw ceramic materials. An optimized flowability of spray dried ceramic granules is achieved by narrow size distributions, round granule shapes and defined granule strengths that are necessary to withstand further handling processes. For die pressing applications the granules have to show an ideal deformation behavior, what means a complete disintegration during the die pressing step to form homogeneous green compacts without defects. To produce optimized ceramic granules for this task a compromise concerning these contrary specifications has to be found.

The deformation and breaking properties of spray dried ceramic granules can be modified by the selection of defined kinds, amounts and / or combination of organic additives. The definition of useful single additives and additive combinations for improved mechanical properties is done empirically in most cases. Systematic and complete investigations concerning the influence of defined single additives throughout the whole process chain (suspension, granules, compact) are missing or are only reported in sections.

Aim of the investigation is the systematic documentation and discussion of the influence of single additives on suspension properties; resulting mechanical and basic granule properties as well as on resulting properties of the die pressed compact to optimize product design. By using defined chemical additives with specifically changed characteristics, the influence of e.g. varied chain length on processing properties is reported. Further experiments with additive combinations give information about the interaction of the organics. A combination of dispersant and polyvinyl alcohol PVA in comparison to pure PVA shows e.g. a wider single granule strength distribution but no measurable effect of compressibility during die pressing.

Measured fracture loads: blue (framed): pure PVA; red (massive): PVA and Dispersant
Granulation is the process of adding liquid to a powder bed in order to produce larger agglomerates of primary particles. The three phenomena that occur during granulation are nucleation and binder distribution, consolidation and growth, and attrition and breakage [1]. Key parameters that influence these rate processes include feed powder properties, liquid/binder properties, and process parameters. These three groups of parameters interact in a complex way, so that predicting the outcome of a granulation a priori is difficult. In order to help predict how these parameters influence the rate processes, nucleation and growth regime maps have been constructed in previous studies [2, 3].

This study aims to predict changes in granulation mechanisms due to changing excipient properties using nucleation and growth regime maps. It is hypothesized that powder property changes can lead to crossing of regime boundaries in either or both regime maps. This deviation would lead to different granulation mechanisms and a different final product. Therefore, if a formulation was close to a regime boundary, lot-to-lot variability of excipients could cause large property differences in the final granules.

To study the effects of excipient variability, 13 different grades of lactose from 5 different manufacturers were characterized by size distribution and a drop penetration time [4]. After scaling to account for drop size, it is clear that this degree of variation in lactose could lead to crossing of nucleation regime boundaries. From this data, 5 of the 13 grades of lactose were selected to make blends of 95% lactose, 3% crospovidone, and 2% acetaminophen by weight. These formulations were characterized in order to place each formulation on the regime maps. Granulation experiments were performed on various formulations in a Diosna 10L granulator in order to relate predictions to actual granulation results.

Agglomeration is a way to improve particle properties and agglomeration processes are widespread in many industries: pharmaceuticals, detergents, cosmetics, fertilizers, food... Specific properties like particle size, granule porosity or tablets mechanical strength can be obtained by controlling wet granulation process or compaction process. However, only a very small part of excipients could be easily granulated or are directly compressible. Therefore, a large number of formulations have to include a binder in order to increase adhesion forces and finally to contribute to the mechanical strength of the agglomerate but its role is not well understood. So in this work, we aim at studying thoroughly interactions between binder and particles.

Very simple formulation has been chosen, and this paper focuses on characterizing binding between glass beads and sugar used as binder. One fraction of glass beads was used (diameter between 70 µm and 110 µm), mixed with one of the two sugar solutions (D-glucose or saccharose), at different concentrations and at different amounts, in order to vary saturation ratio of these binders in manufactured agglomerates.

Glass beads and sugar solutions were homogenized by a Turbula® powder blender during 20 minutes. Then, cylindrical compacts (20 mm diameter) were manufactured by an Instron universal testing machine 5569, using a compaction pressure of 110 MPa.

These tablets were stored at controlled conditions for drying: they were put in a desiccator with Silica gel as desiccant, at a temperature of 25°C for 3 days. A Brazilian test of tablets was then carried out to determine their tensile strength. Moreover, Dynamic Vapor Sorption (DVS) technique allowed us to determine gravimetrically water sorption and desorption isotherms of both sugars.

Thanks to results obtained from the measurements of tensile strength, we have shown the impact of the sugar solutions concentration and the saturation ratio of tablets on the bonding strength between particles and sugars. According to these experimental results we can observe the existence of optimal values and conclude that the total amount of binder and the saturation ratio are coupling parameters. Moreover, tensile strength decreased with increasing atmospheric relative humidity which implies to control not only the tablets drying conditions but also the crushing test conditions. To complete the originality of this study, DVS technique allowed us to acquire fundamental knowledge for the bonding between glass particles and sugars, and then suggested that atmospheric relative humidity is a critical parameter for crushing test implementation but also for the storage of the tablets.
Characterization of the particle dynamics in a prismatic spouted bed apparatus

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Spouted beds are well known for their good mixing of the solid phase and their intensive heat and mass transfer characteristics between the fluid and solid phases. Consequently, the spouted bed technology has become an established tool for mixing of particulate systems, for heat and mass transfer processes, e.g. drying, calcinations, combustion and gasification as well as for complex multiphase processes such as spray granulation, agglomeration and particle coating. Furthermore, in spouted beds additional classes of particles can be fluidized which cannot be treated in conventional fluidized beds (particles having a wide size distribution, being small and light or very large, non-spherical or cohesive). The fluidization behaviour in a spouted bed has a profound influence on the particle morphology and thus on the product quality.

The general goal of the investigations presented here is the further development and optimization of a prismatic spouted bed apparatus having two symmetrical gas inlets in form of slits. We will present results of discrete particle modelling (DPM) coupled with the computational fluid dynamics (CFD) of the gas phase to characterize fluid dynamics and the particle-particle and particle-fluid interactions in the apparatus. Furthermore an experimental arrangement for the optimization of the apparatus shape regarding the fluidization behaviour will be described.

Figure 3. D-DPM/CFD simulations of the vertical particle velocity distribution in a novel spouted bed.

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The deposition of a thin layer of a composite material on the surface of solid particles used in the food industry aims to ensure the protection of the powder against environmental parameters. Nevertheless, the permeability and solubility of this film, having a thickness of a few fractions of millimetre should not impair the release in the body of the active ingredient. The layer should have certain physico-chemical properties: it must be compatible with the product, it must be impermeable to water and oxygen, it must have good mechanical strength and a good adhesion on the surface of the coated powder. Furthermore, the layer must fulfill the regulatory requirements for food ingredients. The properties of the film like continuity, permeability, mechanical resistance depend on the choice of the excipients included in the formulation and the operating conditions which can modify the constraints generated at the interface film-powder. As a consequence, the scientific issue consists in combining the local phenomena happening at a microscopic level on the surface of the particle with the processing technology and the process parameters. The chosen scientific way consists in uncoupling the various phenomena. In a first step, the attention is focused on the film and its formulation. For this step, films are prepared separately and they are dried under very smooth conditions. The characterization of the films by different technical tools enables to optimize the parameters of the formulation (composition and process conditions to produce the composite coating). Test sample are film of three components composite made with hydroxypropyl methylcellulose as matrix (67% of dried material), micronised stearic acid as hydrophobic filler (20% of dried material) and a plasticizer (13% of dried material). The procedure of the film formation and the test method will be described in details. The effect of the type of plasticizer (different grades of PEG) will be studied on mechanical, thermal and permeability properties of the coating film. The results show that PEG with higher molecular rate provides a better plasticizing effect for the film but increases the water vapour permeability of the film.
Granulation is a complex process whereby fine particles agglomerate to form larger granules, due to adhesive forces brought about by the liquid binder. Many of the existing granulation operations are in continuous mode and given the pharmaceutical industries' recent initiative to shift from batch to continuous, granulation in continuous operation assumes more importance [1]. In a continuous pharmaceutical granulation process, feed material (active + excipient) is continuously introduced into the granulator alongside the interplay of the various granule mechanisms such as nucleation, aggregation, consolidation and breakage. The granulator is fitted with several spray nozzles through which the liquid binder is introduced into the granule bed. The granules formed are then dried and classified based on product specification(s). Granules that do not conform to these specification(s) are recycled and reprocessed, or even discarded. Prior to the actual design and implementation of the controller for the granulation process, it is important to ascertain how well the process can be controlled and what factors may hinder the control-loop performance. It is also imperative that appropriate process inputs and outputs are selected for model-based feedback control and that they are paired correctly as incorrect pairings may limit and hinder control-loop performance.

In this work, controllability and control studies will be performed on a simulation of a multi-component continuous high-shear wet granulation process that is commonly employed (or would be employed) in the pharmaceutical industry. Via novel first-principles based mechanistic models that are described using a population balance model framework, controllability studies are performed by performing open-loop step tests. In this manner, the controllability of the process can be ascertained by quantifying the effects of admissible inputs (e.g. powder feed rate, binder spray rate, angular velocity) on important controlled variables such as (size distribution, bulk density, granule composition and dissolution rate), the latter two being a novel addition to the model, thus resulting in them being considered as controlled variables. Thereafter a multiple-input multiple-output control problem is posed. Control loop performance is quantified by different control strategies such as regulatory feedback control, model predictive control (MPC) and hierarchical control. Results show that hierarchical control achieves the best control loop performance for such a complex and interacting system where lumped and distributed properties need to be regulated. Hierarchical control is implemented by controlling the individual granule mechanisms that determine the overall distributions (rather than attempting to control the final distributions as in the case of feedback control and MPC). This results in a the formulation of a multi-objective optimization problem due to conflicting control objectives. We solve the optimization problem via a genetic algorithm that is able to produce pareto-optimal solutions that result in the best possible control loop performance given the conflicting constraints.

Schaefer and Mathiesen[1] proposed two nucleation mechanisms for melt granulation: immersion and distribution, which were shown to be mainly dependent on binder particle size and viscosity. Many works have been published regarding experiments on melt granulation (both in high shear and fluidized bed situations); from the modeling point of view, PBE models have been proposed for fluidised bed melt granulation [2], and insights on the kinetics of the immersion mechanism have been theoretically studied [3]. In this work a criterion to determine the driving mechanism between immersion and distribution is discussed, based on the comparison between characteristic times describing the interaction between the binder and the powder: the melting time of the solid particles, the penetration time of the liquid into the bed, the local mixing time. Experiments for various type of binders in different conditions (binder particle size, melt viscosity) are carried out in order to quantify the characteristic times; results are compared with theoretical calculations, from which a dimensionless analysis is performed: new dimensionless numbers are formed, which are simply ratios of characteristic times. The analysis is then used to interpretate melt granulation data obtained in both high and low shear systems.

In a wet agglomeration process inside a low shear mixer, the blade function is to induce collisions of grains, disposing in bed in the mixing bowl, and the wetting liquid, sprayed on the powder surface. The design of the bowl and the mixing blade along with the values of the processing parameters directly related to this design (load, rotation speed, etc.) contribute to agglomeration mechanisms. The nucleation stage comes prior to a growth kinetic and during these stages the movement of the blade disturbs the stress profile at the static state of the powder bed. The optimization of the capacity of a mixing device to agglomerate necessitates an excellent knowledge in marrying the mechanical input with the properties of the granular medium. Characteristics of powder flow, that follows the mechanical disturbance induces by the blade, are direct consequences of the latter mutual interaction. These flows are tridimensional and specific to their localization regarding the blade. Their direct monitoring requires the application of image acquiring methods, such as the PEPT (Positron Emission Particle Tracking), X-rays, PIV (Particle Image Velocimetry). The application of these methods often remains specific to a certain kind of mixing device. In order to guarantee the transposition of the acquired results, it is necessary to define non-dimensional criteria, including characteristic lengths and times of the phenomena. These phenomena are difficult to identify on a real scale of the mixing device.

Consequently, this work suggests a deep analysis of a particular zone of the powder bed disturbed by the blade. This work is based on the establishment of the distribution of vertical stresses in a static state, and on the characterization of the typologies of movement of the bed bulk, disturbed by the blade that moves in one sole direction. This experimental simplification relies on measuring the force exerted on a blade by the powder bed, laterally confined and with an open surface. Particles' dynamics are monitored using the PIV method. The dimensions of the reactor and the blade, and the motion speed of the blade are the main processing parameters.

In the case of semolina wet agglomeration (with water), the so-called: couscous, we indicate respectively the influences of particles' size and water content on the static and dynamic states of powder bed.

In a static state, stresses distribution of the bed is conformed to a Janssen's distribution, well-known in the static of silo. We prove the significant role of Janssen's length, starting from which the vertical stress does not vary linearly (like a hydrostatic case), due to a redirection of vertical stresses towards the walls of the cell. The measurement of the forces felt by the blade in the dynamic state enforces the role of Janssen's length. This length represents the transition between a frictional resistance and an essentially gravity resistance. This rheological test allows to identify different types of particles transportation, individual or collective, depending on the relative position of the blade, Janssen's length and surface: compaction, shear associated to dilatancy, avalanches…We will describe more precisely the phenomena taking place under the blade by proving the role of the angle of repose.
110 - Granulation of hierarchically structured ceramic/polymer composites in a spouted bed apparatus

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The applicability of ceramic materials for structural applications is often not limited by their elastic moduli or strengths, but by their high brittleness and scatter of mechanical properties resulting in the lack of predictability of the material failure as compared to metals. In this work, we use a spouted fluidized bed apparatus to generate granules that are made of polymer-coated ceramic particles. Our goal is to create a novel tough hierarchically structured composite material with different polymers as layer material on different length scales. The polymer acts as a solid bridge binding the ceramic particles together. By varying the type and amount of the soft phase we expect to obtain customized properties. We present different approaches to produce the hierarchical structure in the spouted bed apparatus using microstructured primary particles as solid seed materials and particles dispersed in a polymer/water solution as liquid phase.

We also present results from Discrete-Element-Method (DEM) simulations of the mechanical properties of the (compressed) seed material, in which the influence of polymeric properties and ratio of ceramic / polymer contents on the mechanical properties of the obtained structures is outlined.

Figure 2: Concept of the hierarchical structure of the ceramic/polymer composites

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Wet agglomeration is a process combining the motion of solid particles and their sticking by the addition of a liquid binder. This process is widely used in industry in order to give shape, size, texture and other specific characteristics that depend on the functionality of the final product. The control of size distribution around the mean value is an important challenge to ensure a good quality of the granule population. The initial medium, which is discontinuous, heterogeneous and composed of polydisperse particles, must be changed in agglomerates having characteristics tightened around median values. Granule formation and growth is commonly described as the succession of: wetting and nucleation, coalescence and growth, and erosion and breakage. Nevertheless, the mechanisms involved in these steps are described and quantified thanks to mean values that do not express the real heterogeneity of the medium. In the case of wet agglomeration in low shear mixer, Rondet et al. (2010) described agglomeration as a fractal morphogenesis process linking the median size of the agglomerates to their texture via a fractal dimension. It appears now fundamental to integrate the polydispersity of the generated structures in the analysis of this process in order to approach the industrial problems. Size for example, should be described by a distribution function and not by a mean value. For example, in the case of couscous elaboration from the wetting/mixing of durum wheat semolina, the agglomeration stage controls directly the efficiency of the production line because it can generate large amounts of recycling (up to 2.5 times the initial semolina flow) due to the important polydispersity in agglomerates characteristics. The objective of this study is twofold. Firstly, it aims to correlate the influence of physicochemical characteristics of the liquid binder on the mechanisms of fractal agglomeration. The value taken by the parameters of the fractal morphogenesis model and the granulometric dispersion of the agglomerates population are the chosen criteria. This first stage will enable us to test the relevance of the fractal model on agglomeration lead with reactive powder and binders with several physicochemical characteristics. The second objective is to study the evolution of agglomerates properties by considering the characteristics (mainly the solid volume fraction and the water content) of each size fraction. The results confirm the fractal morphogenesis for agglomeration lead with various binders with different physicochemical properties. They also show a marked influence of these physicochemical properties on the value of the fractal model parameters. By taking into consideration the discrepancy of the agglomerates properties, this study makes it also possible to identify specific growth mechanisms for each size fraction. It’s showed that during wet agglomeration in low shear mixer, the mechanisms implied in the agglomeration (wetting, nucleation, coalescence, growth) do not follow each other but coexist throughout wetting.

Characterization of the impact of magnesium stearate lubrication on the tableting properties of chitin-Mg silicate as a superdisintegrating binder when compared to Avicel® 200

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The influence of the lubricant magnesium stearate (MgSt) on the powder and tablet properties of chitin-Mg silicate coprecipitate was examined and compared with lubricated Avicel® 200 and Avicel-Mg silicate coprecipitate. Crushing strength and disintegration time studies were conducted in order to evaluate tablet properties at different compression pressures. Lubrication of chitin-Mg silicate powder with MgSt was evaluated using a high speed rotary tablet press. The compactability and disintegration time of chitin-Mg silicate are unaffected by the possible deleterious action of up to 2% (w/w) MgSt. The deleterious effect of MgSt on Avicel® 200 compaction was found to be minimized when magnesium silicate was coprecipitated onto Avicel® 200. Lubrication of chitin-Mg silicate with MgSt does not enhance particle agglomeration, whereas the opposite is the case for Avicel® 200; the foregoing was ascertained by measurements of the fixed measured bulk density, constant powder porosity using Kawakita analysis and by the absence of variation in particle size distribution in the presence of up to 5% (w/w) MgSt.

Effect of MgSt concentration on tablet crushing strength of chitin-Mg silicate, Avicel® 200, calcium hydrogen orthophosphate, and Avicel-Mg silicate coprecipitates at different compression pressures
A novel multifunctional pharmaceutical excipient: modification of the permeability of starch by processing with magnesium silicate

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A directly compressible excipient has been developed by co-processing starch with magnesium silicate. The foregoing was achieved either by co-precipitation of magnesium silicate onto different types of starch or by dry granulation of maize starch with magnesium silicate. A variety of techniques were used to characterize these systems. The permeability of the formulations produced using the two methods was evaluated experimentally using Darcy’s permeability law. Magnesium silicate, as an anti-adhering agent, increases the permeability of both maize and partially pregelatinized starch, resulting in compacts of high mechanical strength, short disintegration time and low lubricant sensitivity. Formulation with this novel excipient system, using paracetamol as a model drug, indicated its suitability as a single multifunctional excipient.

Permeability of native and commercially modified starch samples (10 g) unprocessed or processed with 30% (w/w) Mg silicate by physical mixing, with a particle size of 10-20 µm.
115 - Twin screw wet granulation: Development of a modified release formulation

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Granulation is an important densification and particle-size enlargement process, used in many applications. Granulation is often used to incorporate polymers into a formulation to control the rate of drug release. Batch granulation has most commonly been used as the process to achieve this. The technique of using a twin screw granulator has been found to be very effective at incorporating rate controlling polymers into the granule. The quality and manufacturing attributes of the granules produced vary depending on a number of different process and formulation parameters. These formulation and process parameters are investigated here with a poorly flowing API in order to achieve control over the critical (quality) attributes.
The objective of this study is to understand and optimise the dry particle coating process. To do so, the dry particle experiment and simulation of the particles movement by discrete element method (DEM) have been done.

In this process, powders relatively large (called "host particles") are covered with fine particles (known as "guest particles") by the application of mechanical forces without using any solvents or hydraulic binder. The materials chosen as host particles are SUGLETS® (spherical granules mainly consisting of sugar) and magnesium stearate (MGST) as guest particles. These two materials are introduced in a high shear mixer called Cyclomix. The treatment is performed at different rotational speeds and at various durations of operation. The properties of the final products such as flowability, wettability and particle sizes were characterized. Figure 1 shows the flow rate index (flowability) as a function of operating time of Cyclomix at each rotational speed. At 500 and 1000rpm, the flow rate index decreases with an increase in the operating time so the flowability of the mixture is better. However, at 1500rpm, it increases rapidly after only 1 min of operation. One possible cause of this tendency is the fragmentation of host particles (this hypothesis is also confirmed by the evolution of PSD versus operating time).

In our simulation, the distribution of forces, speeds and number of collision of the particle movement in a Cyclomix have been investigated (Figure 2). From this simulation, we can observe that particles at the bottom are forced to flow toward the top along the conical shaped vessel by the rotating impellers and then, after reaching the top, the particles flow downwards into the centre of the vessel. The first step of the model of particle flow has been done and the validation of this model would be discussed in near future.
Granule attrition by coupled particle impact and shearing

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A novel continuous shearing and repeated impact device has been developed to simulate granule attrition and dust formation under realistic plant conditions of mechanical stresses, shear strains and strain rates. The device subjects granules to multiple impacts at a range of velocities prevailing in typical process plants, and to shear deformations using two rollers with an adjustable gap to simulate the level of stresses and shear strains experienced during bulk motion such as discharge from silos.

In this paper, results of granule breakage experiments performed on a number of enzyme granules are reported and compared with data obtained by more established methods such as using an annular shear cell or single particle impact testing.
118 - Agglomeration of amorphous food powders in a fluidised bed: Comparison of different granulator configurations

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Fluidized bed spray granulation and agglomeration both play an important role in the manufacturing of powder granules in the food, fine chemicals and pharmaceutical industries as dust-free and free-flowing particles can be produced in a process with favourable heat and mass transfer conditions and good solids mixing. Liquid binder is sprayed into a bed of solids to achieve granule growth by adhesion of surface-wet particles.

A homogeneous distribution of the spray liquid is a prerequisite for uniform growth, whereas local overwetting leads to the formation of particle clusters. On the other hand, too homogeneous liquid distribution or high air humidity can also cause a collapse of the fluidised bed. The moisture distribution in the apparatus is a key parameter affecting both particle size and structure of the product.

The performance of two fluidised bed granulator configurations with internal circulation of the material was compared experimentally and numerically. The Wurster-coater (Fig. 1 a) is a common device in the pharmaceutical industry used to coat tablets. A cylindrical draft tube is inserted vertically into the granulator, where liquid suspension is injected from a bottom spray nozzle. In a spouted bed (Fig. 1 b) the powder is entrained by a spout at the centre of the bed. This setup allows handling of both cohesive material and particles with a wide particle size distribution. The obtained agglomerate size distribution, structure and strength show a significant effect of the granulator geometry and the wetting conditions.

Coupled DEM-CFD simulations of the particle and fluid dynamics in both granulator configurations reveal that the liquid distribution among the particles is a key influence factor for the agglomeration process.

Figure 1. Schematic representation of the investigated fluidised bed granulator configurations: a) Wurster-coater, b) spouted bed.
119 - Wet granulation of hydrophobic powders: drop penetration, drug distribution and liquid marbles

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Granulation research has historically concentrated on the granulation of hydrophillic or easily-wetted powders, where the liquid penetrates and wets the powder to form granules. There has been some pharmaceutical research work looking at the effect of adding a hydrophobic drug to the formulation, and how this affects the product properties eg granule size or drug distribution but there has been little focus on how the addition of hydrophobic powders affects the granulation mechanism, particularly nucleation.

Using a model formulation of hydrophillic lactose powder and hydrophobic salicylic acid, we investigated the mechanisms affecting nucleation formation & drug distribution. Small scale tests were used to determine the drop penetration time and nucleation ratio as a function of powder composition and binder type (water or 5% PVP solution). These formulations were also granulated in a 5L mixer and the granule size and granule composition were measured. Changes in the drop penetration mechanism (see Figure) were used to define a critical percolation threshold, which predicts whether the granule drug distribution will be uniform.

Formulations which are highly hydrophobic or non wetting will not form traditional nuclei but will instead form liquid marbles (see Figure). Although forming a single liquid marble is straightforward, manufacturing liquid marbles in large quantities is more complex. A framework for liquid marble formation in the drop controlled or mechanical dispersion regime has been proposed, linking independant work at several institutions. However the mixing energy applied in the granulator must be within an upper and lower bound for ensure liquid marble formation and survival. The next step to enable wide-spread use of liquid marbles in wet granulation is to be able to quantitatively predict these mixing energy limits.
Fluidized bed spray granulation and agglomeration both play an important role in the manufacturing of powder granules in the food, fine chemicals and pharmaceutical industries as dust-free and free-flowing particles can be produced in a process with favourable heat and mass transfer conditions and good solids mixing. Liquid binder is sprayed into a bed of solids to achieve granule growth by adhesion of surface-wet particles. The kinetics of the agglomeration process are governed on the microscale. While the global process time is in the order of hours, the underlying micro-mechanisms have much smaller time constants in the order of seconds. This is a challenging situation in the field of process modelling, as a detailed simulation cannot cover the entire process time, while on the other hand a macroscopic model cannot take into account material microproperties.

For this reason a multiscale simulation system was developed. On the microscale, the fluid and particle dynamics as well as wetting and drying of the individual particles is modelled. From this simulation, rate constants such as the collision frequency and relative collision velocity are extracted. Agglomeration and breakage criteria are defined based on the kinetic energy of an impact and the moisture content of the colliding particles. Using this data, a simulation at full process scale is performed using the flowsheet simulation system SolidSim. An one-dimensional population balance model is employed to calculate particle size distribution on the macroscale. Applying an interscale iterative simulation scheme, the convergence of the global system is reached.
Assessment of the surface energy to characterize the surface modification of talc particles by dry coating with hydrophobic silica nano particles

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The physico-chemistry of powders in particular its surface energy, is the subject of several studies. That takes into account the various models with the different components used to characterize the solids surface energy as well as the various ways for obtaining them. The purpose of this study is to compare some methods to determine the surface energy of powders and to apply them on the evaluation of the surface modification of talc particles with hydrophobic silica nano particles. For the surface modification of particles, dry coating seems to be an efficient way to create new generation materials by combining different powders exhibiting different physical and / or chemical properties. In this study the experiments are performed with a planatery ball mill (Frisch) using Talc ($d_{50} 5 \, \mu m$) as host particles, coated with hydrophobic fumed silica Aerosil® R972 ($d_{50} 16 \, nm$) as guests particles.

Inverse gas chromatography (IGC) is one of the techniques carried out to follow the effect of hydrophobic silica coating on the surface properties of talc. In IGC at infinite dilution (IGC-ID), very small amounts of probe molecules are injected, only the highest energy sites contribute significantly to the adsorption of the probe, that is to say for talc, sites on edge surfaces (Figure 1). With this technique, the decrease of the dispersive component of the surface energy $\gamma_s^d$ (from 165 to 150 mJ/m$^2$) with the increase of the silica ratio (from 0 to 10 % w/w), indicates the shielding by silica of the highest energy sites on the edge surfaces of talc particles shown by SEM picture (Figure 2). The contact angle measurements, using the Owens-Wendt model with two liquid probes (water and diiodomethane), show the hydrophobization of talc. The polar component of the surface energy $\gamma_s^p$ decreases from 20 to 15 mJ/m$^2$. However, the average surface energy increases due to the increase of the dispersive components from 33 to 53 mJ/ m$^2$. In complement, the sorption isotherms have also been determined with different techniques, DVS, IGC at finite concentration (CGI-FC), Nitrogen adsorption-desorption, and with different probes, octane, isopropanol, nitrogen and the results confirm the coating effect.

This study highlights the complementarity of the different techniques used to characterize the surface energy of powders. All of them support the efficiency of the dry coating process.

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Figure 1. Alcane probe adsorption on high energy edge surface of a talc particle

Figure 2. SEM picture of hydrophobic silica nanoparticles inserted into the inter-lamellar space of a talc particle
122 - Experimental validation of a 2-D population balance model for spray coating processes

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Population balance (PB) models have been widely used to improve the coating process in pharmaceutical and other manufacture industries. This study reports spray coating experiments within a paddle mixer designed to validate a multidimensional population balance model developed previously. A fully 2-D distribution for the coated particles, with particle mass and coating mass as the internal variables, was obtained and compared with model simulation results. The advantage of the new model lies in its integration with other particle level modeling tools to account for the particle flow heterogeneity and growth characteristics during the coating process. Intrinsic mechanisms of the preferential growth rate as a function of particle size were also investigated, both experimentally and using a Discrete Element Method (DEM) simulation of the paddle mixer.
An engineering design model for a granulation process will predict the distribution of product properties as a function of well characterized formulation properties and known process variables. Such models minimize the need for laboratory and pilot scale experimentation during the roll out of a new product or process. Macroscopic models for granulation processes, eg. those based on population balances, have been under investigation for many years now. However, these design models have not had the same impact in industrial practice as similar modeling efforts for other particulate processes such as milling and crystallization. There are many reasons for this including (1) the inability of the models to fully capture the important physics of the process; (2) the lack of fundamental understanding of cohesive powder flow and stress transmission in the processes; (3) difficulty in validating the models with high quality experimental data on granule property distributions.

Multiscale and compartment models offer at least a partial solution to the issues described above. They allow a practical approach for incorporating particle level information into macroscopic models, better incorporation flow data into the models and recognize the inherent heterogeneity of many granulators. This presentation will review current status and highlight areas where ongoing research is required. Two cases studies from our own research will be presented: (1) Compartment based modelling of a layered granulation/coating process in which data from DEM simulations is used to developed a compartment model for particle mixing that is incorporated into a macroscopic population balance; and (2) FEM modeling for a roll compactor to predict ribbon density distributions in which multiscale approaches are used to predict the powder constitutive property parameters for input to the FEM model (see figure).
This study investigates how the spatial density distribution of roll-compacted powder ('ribbon') varies with roll pressure (45-65 bar), roll speed (7 rpm, 11 rpm), and formulation (different mixtures of microcrystalline cellulose, acetaminophen and magnesium stearate). Results show that the density in the center region of the ribbon is higher than that at the sides. Due to cantilever effects, the ribbon density distribution is not symmetric against the ribbon centerline; the densest portion of the ribbon is instead offset towards the side closest to the roller shaft support bearings. Such effects occur to a greater extent when the process is operated with parameters that increase the average ribbon density: an increase in roll pressure, a decrease in roll speed, and an increase in powder compressibility. To provide further understanding, the process is also simulated via Finite Element Method (FEM). In general, the FEM models are capable of semi-quantitatively replicating the experimental results. More quantitative predictions, however, will require more accurate modelling of the feed-screw action.
This work aims to investigate and quantitatively measure “liquid marble” phenomena using hydrophobic powder poly-methyl methacralate (PMMA) with the aim of encasulating a concentrated solution of gentamicin sulphate antibiotic. This antibiotic is extensively used to prevent microbial infection in orthopeadic acrylic bone cement. PMMA particle size 42µm and contact angle of 120° was used to determine the potential for liquid marble formation. The experimental investigations indicated that for successful formation of liquid marbles a number of variables in addition to hydrophobicity need to be considered, namely: powder density; powder particle size; powder shape; liquid marble formation technique. Using PMMA with particle size 42µm and contact angle of 120°, complete coverage of droplets of concentrated gentamicin solution was found. Moreover, a procedure developed, from previous work [1], to increase the mechanical strength of the liquid marble, by polymerising MMA on the surface of a PMMA powder - liquid marble, with the aim of maintaining gentamicin within a more robust PMMA - liquid marble shell. This technique is a novel method of encapsulating drug compounds in for use in orthopeadic bone cements.

126 - Scaffolds made of nanostructured phosphates, collagen and chitosan for cell culture

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In the present study a new strategy of syntheses is developed for silicon substituted hydroxyapatite of controlled properties by precipitation reactions. The resulted powder is characterized by physicochemical methods and used to prepare scaffolds for cell cultures. Further, nanostructured calcium phosphates (CP) with or without various Mg, Zn, and SiO$_2$ contents of controlled porosity and crystalinity as well as composite biomaterials formed of calcium phosphates nano particles of controlled properties (shape, size and density) mixed with collagen type I (COL), and chitosan (CHI) at different CP/COL/CHI weight ratios were designed, prepared and in vitro structurally characterized. The calcium phosphates nano powders, collagen, chitosan and the resulted composite biomaterials were characterized using FTIR, X-ray diffractions, SEM, TEM and AFM. The BET and porosity were also used to analyze their micro-structure and TEM and AFM to analyze their nanostructures. The inorganic nano powder incorporation within collagen and chitosan matrix leads to biocomposites with good mechanical properties, which can be controlled by the CP/COL/CHI weight ratios. Further, the optical microscopy, scanning electron microscopy and AFM were used to evaluate the behavior of osteoblasts, like MG-63 cells, cultured on scaffolds made of the different mixed inorganic powder/collagen/chitosan self-assemblies for several days. Results showed a good adhesion, growth and proliferation of osteoblasts on the surface of investigated scaffolds, especially when they were made of complex hydroxyapatite and from CP/COL/CHI biomaterials of at least 20 % COL weight content. These data demonstrated that the bioactivity of hydroxyapatite can be improved by introducing within its structure substituents like Mg, Zn, and SiO$_2$. The data have revealed the high importance of granulation of inorganic powders in the preparation of scaffolds biomaterials of controlled properties with applications in particle technology, pharmacy and nano medicine.
Roller compaction is a dry agglomeration process which means it has added advantages such as being cheaper and more efficient than conventional wet agglomeration processes. As there is no liquid binder present it is the high compaction pressures in dry processes which force the particles together to form an agglomerate which is held together by different adhesion forces (Van der Waals, sinter bridges and interlocking). The understanding of the development of the bonding mechanism in an agglomerate is critical when trying to produce agglomerates with desirable characteristics.

In this work an agglomerate (ribbon) was produced from an amorphous food polymer, dextrose syrup IT21, out of a roller compactor using different compaction pressures. The powder had been equilibrated at different relative humidities prior to compaction. The strength of the agglomerate (ribbon) produced was evaluated by ball milling and using a breakage function. The temperature of the ribbons was followed during production using a thermal camera.

It was found that increasing the compaction pressure increased the fragment size after milling therefore showing an increase in strength of the ribbon. It is suggested that this is due to a change in the dominant bonding mechanism, as increasing the water content of the initial powder also increases the strength of the ribbons. It was shown that increasing the compaction pressure increases the temperature of the ribbon and this causes the material to surpass its glass transition temperature. At this point, sintering of the material occurs causing the dominant bonding mechanism to be solid bonding.
129 – A novel method to quantify tablet disintegration


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One of the aims in the food industry is to produce fast dissolving products. The dissolution of tablets is often accompanied by disintegration which is the process of breaking up the tablet into smaller pieces. Disintegration increases the dissolution rate by increasing the surface area available for dissolution to occur. Such a process is supported by the use of disintegrants which are widely used in the pharmaceutical industry. This paper deals with the introduction of food grade disintegrants in a model food tablet.

A novel method based on image analysis allows the size of the tablet to be followed as a function of the dissolution time. In addition, the size and number of particles released due to disintegration are captured. The results show that incorporation of disintegrant decreases the disintegration time and thus dissolution for the formulation and conditions used in this paper. Moreover, it was shown that different sized particles were released in the presence and or the absence of disintegrants. The number and size of these particles also varies during the dissolution time.
A lot of raw materials, ingredients and food products are produced in a powder form. As a consequence, there is a relatively new branch of science and engineering known as particle technology [1]. Food powders represent a large variety of powder materials that differ in their chemical composition and physical characteristics. Surface characteristics in food are a clearly influence of powder functionality (wettability, flowability, dispersability, oxidation...), as a consequence surface powders determine the attributes for handling, processing and final application. It has been assumed that the chemical composition of the particle contribute to obtain information of surface properties [2] as well as microscopic techniques.

In this work four industrial milk powders (Lactalis): Whole Milk Powder Standard (WS), Whole Milk Powder Granulated (WG), Skim Milk Powder Standard (SS) and Skim Milk Powder Granulated (SG), were studied searching a relation between the surface composition of the particles and handle characteristics, taking in count size, shape and real density of the particles. Surface composition was measured by XPS [3] and EDS to obtain information about the extreme surface (XPS), and the next 1 micron layer, also surface structure was observed by SEM (figure 1). Powders were characterized in size and shape by Qicpic, and the real density was determinate by a gaseous picnometer. Results were compared with handle properties measured by freeman FT4 powder rheometer.

As expected results shown an influence of size and shape in the handle properties, but also the surface composition and structure may have an effect in these properties. As conclusions this preliminary essays may permit to find some models for predict handle properties by knowing powder size and shape and particles surface structure and composition, also freeman FT4 and Qicpic are new tools that can be useful for evaluate powder properties.

Figure 1. SEM pictures of an industrial milk powder to 300X and 2500X.
131 - Blade-granular bed stress in cylindrical high shear granulator: Online measurement

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In granulation processes, careful selection and control of the process parameters for each selected formulation is often crucial to achieve the required granular product attributes, be it the size, morphologies or mechanical properties. These attributes depend largely on the complex interactions of binding and separating forces experienced by the granular bed in the granulator. For high shear granulators, the rotating impeller blades exert forces on the granules, which are subsequently transmitted throughout the granular bed through inter-granule collisions. The effect of these collisional stresses on the granule growth behaviour is varied; as the granules could deform, consolidate and/or break under stress.

In wet high shear granulation, binder is typically added in liquid or form into the powder bed, consequently creating an assembly of wet mass subjected to agitation by an impeller. Wet granular bed flows have been studied [1-2] especially in evaluating the changes in the frictional and transport properties for different amounts of liquid added and throughout difference phases of the granulation process.

In this work, the blade-granule stress for both dry and wet granular beds are characterised for a vertical axis, cylindrical high shear granulator. For dry beds, perfectly spherical polymer balls and prepared, dried granules with pre-determined physical properties are used. Stress is measured using two methods: a build-in pressure sensor in the impeller blade and pressure films (FujiFilm) affixed onto the blade. High speed imaging of the granular bed is also carried out to evaluate the characteristic bed speed. For the wet beds, liquid binder is added and binder properties, namely the binder amount and viscosity are varied to elucidate the effect of the transport properties of wet granular beds on the stress.

The blade-granules stress, particularly at the blade tip region, is evaluated at different operating conditions and granular bed attributes (bed height, particle size and density). The experimental values for each materials in the dry beds are then fitted to a blade-granule bed stress model for cohesionless materials derived based on the inertial force transferred from blade to the bed and the effective area of impact [3]. The validity of the model for wet granular beds is also investigated.

132 – Origin of particle aggregation mechanisms in a pilot-scale counter-current spray drying tower.

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Obtaining a better insight into the inter-particle interactions associated with spray drying has driven a considerable research effort during the last decade. Within food related industries, co-current units have been studied in major projects using stochastic modelling tools to describe the multi-phase flow system, yet computational constraints have so far limited its application in different contexts [1] [2]. Understanding of counter-current spray dried products (such detergent formulas), is lacking fundamental knowledge of the mechanisms leading to particle growth, yet they determine a critical range of product properties and quality. In practice, discrete phase level of interaction and generation of undesired agglomeration defines operation boundaries for large units. Due to a lack of any discrete phase interaction model, current optimization tools fail to provide a robust description of product properties whenever inter-particle contact becomes significant. A detailed review allows definition of all the potential inter-particle and wall-particle interactions as a function of the drying state of droplets/particles in the unit.

In this work, an intensive experimental plan is laid out to clarify the role each factor plays in the actual experimental patterns. Several sets of results have been gathered on an industrial spray drying tower at P&G Newcastle Technical Centre. The same initial population of droplets has been processed under several different sets of operating conditions to enhance different relative values of inter-particle collision frequency and efficiency, from best case scenario to over agglomeration. Initial analysis confirmed the presence of particle growth and breakage processes and highlights the critical impact of collision frequency and efficiency on the measured growth patterns, wall build up deposition rates and product distributed properties from composition to morphology. Further work reveals the impact of several growth and breakage mechanisms not only due to “in flight” inter-particle collisions but also to the relevant role that wall build-up phenomena plays on the process.

Example of counter-current spray dried detergent granules.
134 - Determination of the tensile strength of elongated tablets

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The objective of this work was to derive an equation to calculate the tensile strength of elongated tablets by means of the standard test method of diametral loading. The tensile strength of a tablet is an important attribute as the tablet needs to be mechanically strong enough to withstand further handling such as film-coating, packaging, transport and end-use by the patient, but to be weak enough to break apart in the human body and so release its contents. Mathematical solutions are known for round convex-faced tablets [1]. The analysis described here aims to extend this knowledge to capsule-shaped and oval-shaped tablets.

In this work 2D and 3D Finite Element Analysis (FEA) software COMSOL was used to determine the stress distribution when tablets are loaded diametrically. The program was first validated by comparing with the accepted stress solutions for flat-faced and convex-faced circular tablets, prior to it being applied to elongated tablets. Analysis was undertaken along the X, Y and Z co-ordinates where X is the width of the tablet, Y is the length and Z is the tablet thickness. The solution was then checked by applying it to commercial tablets of differing shapes to demonstrate its utility.

The stress analysis showed that as the Y axis of the tablet was elongated from a standard circular tablet to become that of an extended tablet shape, the peak principal tensile stress reached a limiting value. This limiting value was reached as the ratio of the X to Y dimensions exceeded 1:1.7, which encompasses most modern pharmaceutical tablets. In addition the stress analysis shows that the limiting value reached approximated to 2/3 that calculated for circular tablets. Consequently for a convex-faced elongated tablet the calculation for tensile strength would become:

$$\sigma = \frac{2}{3} \left( \frac{10P}{\pi D^2} \right) \left( 2.84t/D - 0.126t/W + 3.15W/D + 0.01 \right) - 1$$

where $\sigma =$ tensile strength, $P =$ fracture load, $D =$ length of short axis, $t =$ overall thickness, $W =$ tablet wall height

Hence the tensile strength of capsule shaped and oval shaped tablets can now be readily estimated, so facilitating the development and scale-up of formulations and processes between different shaped tablets.

Upflow anaerobic reactors have been the anaerobic reactor not only the most efficient but also the most widely-used worldwide. Granule disruption is one of major cause of sludge washout, one of the top practical problems of upflow reactors. Two 40-day-experiments, referred as DI and SI, were conducted to investigate the effects of shear force on disruption. DI was under daily shear increase mode with increase rate of average shear rate of reactor (IR) of 0.2 $s^{-1 \cdot d^{-1}}$ with the maximum shear rate reached at 24 $s^{-1}$ in about the 34th day. SI was under stepped shear increase mode (once increased each 10 days) with IR of 0.3 $s^{-1 \cdot d^{-1}}$ and the maximum shear rate reached at 26.5 $s^{-1}$ after the 30th day. During DI, about 45% sludge lost. The sludge loss rate increased from 0.04 to 0.41 gSSL$^{-1 \cdot d^{-1}}$ and the disruption increased significantly after the average shear rate reached about 24.0 $s^{-1}$. During SI, sludge concentration decreased after the 20th day with the sludge loss rate of 0.15 gSSL$^{-1 \cdot d^{-1}}$ and the disruption existed during the whole experiment. Thus the daily increase mode with IR of 0.2 $s^{-1 \cdot d^{-1}}$ did greater harm to the reactor performance as compared to the stepped mode with IR of 0.3 $s^{-1 \cdot d^{-1}}$. Shear stress is a type of ambient stress on granules, acting as an external destructive force. On the other hand, it would affect the key factors of granule strength such as extracellular protein content and bioactivity while granules have microbial self-restoration to resist the changes of shear conditions. The daily increase mode does not provide granules sufficient time to adapt the ambient changes and leads to the accumulation of the negative effects on granules and then triggers large scale granule disruption appeared. As a consequence sludge washout is accelerated. The direct washout accompanying with large scale granule disruption is very dangerous on reactor performance. Clearly, it is necessary to avoid the daily shear increase mode in practice.
138 - Particle-particle agglomeration and use of the hard-sphere model

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The hard-sphere model is one of the two main approaches for modelling particle-wall and particle-particle collisions in multiphase and granular flows. The objective of this type of impulse-based model is to find the post-collisional translational and angular velocities of the particles as a function of the pre-collisional velocities, eliminating the need to model the collisional interaction in detail in a numerical scheme. The model is relatively simple and robust. Nevertheless, in its standard form, this technique cannot model cohesive interaction between the colliding particles: this constitutes a serious drawback for many applications.

In our previous papers [1-2] we took the first steps to incorporate adhesive and cohesive forces into the hard-sphere model so that phenomena such as deposition on walls or particle agglomeration could be modelled. We considered an additional attractive interaction (an attractive impulse) and repeated the derivation of the hard-sphere model taking this interaction into account. As there exist various formulations of the hard-sphere model we based our work on the perhaps most complex and developed formulation, described in [3] and also more recently in detail in [4].

The objective of our recent papers [1-2] was not, however, to quantify the attractive impulse precisely but rather focus on the extension of the standard hard-sphere model. Therefore the aim of this current research is to investigate the issue of quantification more thoroughly using a Discrete Element Method that allows to study collision dynamics correctly in a numerical scheme to directly compute the attractive impulse. To describe cohesion/adhesion in this scheme we use the Johnson-Kendall-Roberts theory [5]; the dissipative force due to particle deformation is modelled according to [6].

The calculated attractive impulse is a function of various parameters, such as the initial relative velocity of the particles before collision, as well as particle radii and their material properties, and to obtain a useful expression for implementation in the hard-sphere model we make use of the the Buckingham Π theorem to relate the impulse to the input data based on the results of the numerical analysis. The resulting expression for the attractive impulse can be then directly implemented into the extended hard-sphere model.

Producing monosized granules of defined shape via a robust process is crucial to many industries. Nucleation only granulation, where one drop forms one granule, is used to produce granules of well controlled and well defined attributes. Different nucleus formation mechanisms were identified for loose and packed powder beds. “Tunneling” mechanism and “Spreading /Crater” mechanism were associated with loose and packed powder beds, respectively. “Tunneling” mechanism is robust and produces round granules irrespective of process conditions; whereas, in “spreading/crater” mechanism, the granule size and shape is very sensitive to process conditions and formulation properties. The aim of this study is to predict the size and shape of the granules produced in “crater” regime, where the liquid drop forms a crater on the powder bed. The nucleus formation process in “crater” regime is complex. Therefore, the process is divided into several steps to better identify the effects of process conditions and formulation properties. Different steps can be listed as first impact and drop deformation on the powder bed, particle entrainment and recoiling, forming equilibrium position, spreading and penetration to form final size and shape. The governing forces in each step are identified. Based on the governing forces, dimensionless groups to scale crater size and granule size (diameter and height) are introduced. The maximum diameter that the drop reaches during first impact and the equilibrium size of the drop after recoiling play important role in determining the final morphology of the granule. Quantitative relations were developed to predict maximum drop diameter during impact and equilibrium drop diameter. Also, the link between maximum drop diameter during impact, equilibrium drop diameter before penetration and the final granule morphology is established. The quantitative relations are tested experimentally with different liquid and powder combinations.
In many powder handling processes in industry, e.g. wet granulation and coating, liquid is often mixed with the powder in order to increase the cohesiveness and stickiness of the particles. This can change the dynamics of the powder flow significantly, and therefore, can influence the quality of the final products.

In this work, the behaviour of dry and wet particles in a high shear mixer was simulated using Discrete Element Method (DEM). For the simulation of wet particles, the pendular liquid bridge force was taken into consideration between a pair of particles. The velocity of the particles obtained by the simulation was compared with experimental results using Particle Image Velocimetry (PIV) in order to check the accuracy and limitation of the simulation model. It was found that the existence of the liquid significantly affected the particle behaviour, and the surface velocities in the simulation and experiment showed a similar fluctuation pattern. The effect of the moisture content and the liquid properties were also examined in the simulation.
142 – DEM investigation of the transverse mixing of wet particles in a rotating drum

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Mixing of particles in a rotating drum is an important process but still elusive due to the complexity of the granular flows. Previous studies indicate that the mixing in the axial direction is slow and primarily driven by self-diffusion while the mixing in the transverse plane is a consequence of convection-diffusion coupled kinematics. When cohesion is presented, for example due to liquid bridge, mixing is more complicated. It is generally believed that cohesion restricts particle motion and therefore results in poor mixing. However, it was observed that particles of weak cohesion have better mixing behaviour than non-cohesive particles. It was attributed to the stick-slip behaviour occurring in the shear layer between solid rotation and surface flow layer. While these studies suggested that the effect of cohesion on mixing is much more complicated than expected, investigations of wet drum mixing from the fundamental kinematical perspectives are still limited compared with the rich studies for non-cohesive particles.

In this work, a discrete element method (DEM) model considering explicitly liquid bridge cohesion is applied to study the transitions of mixing kinematics of pendular wet granular system in a rotating drum. Axial mixing is characterised by self-diffusion coefficient and mean square displacement with a description on the local diffusion intensity on the flow surface. The transverse mixing is elaborated through individual particle motion trajectories, with the intention of reflecting the contribution of convection and diffusion respectively, which might provide some clue on the nonmonotonous trend of variation of mixing rate with cohesion magnitude.
Existing dry powder inhalers (DPIs) have low efficiency and high variability of dosing, and generally less than 30 % of the dose loaded to the device will deposit in lungs [1]. So far the principal mechanisms leading to powder de-agglomeration in inhalers remain unclear.

This paper presents an investigation of powder dispersion in a commercial inhaler based on a combined computational fluid dynamics (CFD) and discrete element method (DEM) approach. The mannitol agglomerates are dispersed in the inhaler at different flow velocities. Micro-dynamic information (i.e. forces, velocity, fragment number and so on) obtained from simulations are combined together to fundamentally understand the dispersion process. It is observed that agglomerates experienced two different de-agglomeration processes respectively in the chamber and the barrel before discharging from the outlet. Two periods which can be identified from the figures both are significant to the final dispersion results. De-agglomeration behaviour is expressed as a percentage of total mass of fine particles below 5 micro in the aerosol (FPF_Loaded). While increasing impact velocity increases dispersion efficiency, increasing the number of agglomerates decreases both deposition and FPF_Emitted. Therefore FPF_Loaded only slightly changes as a result of the combined effects of FPF_Emitted and deposition. An index based on the ratio of impact energy and agglomerate strength is proposed to provide a quantitative characterization of dispersion efficiency.

Food fortification is usually achieved by formulating products with bioactives or nutrients, such as vitamins, trace elements, carotenoids or probiotic bacteria. However these bioactive ingredients are often oxygen- or photo-sensitive, or react with other food matrix components. This usually leads to degradation of the bioactives during manufacturing and shelf-life. It can also induce an alteration of the organoleptic properties of the food products which can result in significant colour deviation or off-note formation. One approach to prevent these reactions in solid foods consists of entrapping the active ingredients in amorphous particles. These amorphous matrices can be produced by spray-drying, spray-cooling, agglomeration, granulation, vacuum drying, melt extrusion or fluid bed coating for example. The type of encapsulation process and the processing parameters have a direct influence on the microparticle structure. The relationship between the microencapsulate structure and their properties will be discussed during the lecture. Glassy-matrix encapsulates for example can be very effective for stabilizing oxygen-sensitive bioactives. The physical properties of such amorphous polymer particles will be reviewed in relation to their hosting food matrices. It will be shown also that the density of such amorphous particles can be optimized to achieve improved microencapsulation performance. Some concrete examples of food applications will also be discussed.
Scale-up of high-shear wet granulators is currently difficult to perform and there are no universally applicable scale-up rules. It is not completely clear how changes in granulator geometry and processing conditions can affect the granule growth [1]. An investigation on the scale-up effects in high-shear wet granulation is here described. Particularly, the present research focuses on the effects of impeller rotational speed and mass fill at different scales for geometrically non-similar granulators. Granule growth behaviours as well as final granule properties (e.g. final particle size distribution, bulk and tap density) are compared.

Firstly, a mixture of some common-used pharmaceutical powders was processed using a small-scale granulator (2 l vessel volume). Impeller speed was changed in order to arrange different liquid dispersion conditions [2]. Impeller torque was furthermore measured in order to monitor the process.

Secondly, the same powder mixture was processed using a pilot-scale granulator (65 l vessel volume). A Focused Beam Reflectance Measurement (FBRM) probe was used in combination with other particle size distribution measurement techniques (e.g. sieve analysis, laser diffraction methods) in order to carry out a detailed analysis of the granule growth behaviour. As already demonstrated by Cavinato et al. [3], FBRM technique presents a good degree of accuracy and reproducibility. A high speed CCD camera was furthermore used in combination with particle image velocimetry (PIV) software in order to measure the surface velocity variation at different mass fills and rotational speeds. Whereas impeller speed strongly affected both granule growth behaviour and final granule properties at small scale, mass fill resulted to be the most important processing parameter at pilot scale. Optimization of the ratio of rotational speed on mass fill was therefore required at pilot scale in order to achieve good liquid dispersion conditions and avoid the formation of poorly mixed areas.

147 - Recent advances in fluid bed agglomeration of beverage powders

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Fluid bed agglomeration is an evolving technology that allows producing powdered food products with specific end-use properties. Consumer's demand for more nutritious, convenient, appealing and tasty products have motivated the food industry to move from “conventional” to “advanced” processing of powders in order to achieve specific physical properties in terms of particle size, flowability, structure, dissolution and overall quality.

This work attempts to review the potential of different fluid bed configurations and process parameters to significantly improve the quality of beverage powders.

Beverage powder mixes were agglomerated in different conditions varying the fluid bed type (conventional, spouted, Wurster) and process conditions (spray rate, airflow, temperature, nozzle position). New in-line probes were applied to measure the temporal evolution of particle size and moisture content of the particles during the agglomeration process. In addition, particle size, bulk density, flowability, structure and dissolution were analysed on the agglomerates.

In-line and off-line results were in good agreement, they allowed to identify the different agglomeration regimes and to better understand particle build-up mechanisms. Altogether, it allowed to better control the functional properties of food agglomerates, and even to save energy in some cases.
149 - Kinetics of dry neutralization of dodecyl-
benzenesulfonic acid with respect to detergent granulation

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Sodium dodecyl-benzensulfonate is a common anionic surfactant that is widely used in detergent powders. In the so-called non-tower processes (i.e., not based on spray drying), it is produced by the so-called dry neutralization reaction between sodium carbonate particles and dodecyl-benzenesulfonic acid in a mechanically agitated or a fluid-bed reactor/granulator [1]. The overall conversion (the residual acid) as well as the size distribution and internal structure (e.g. porosity) of the resulting detergent granules depend on the local wetting [2], phase behaviour [3] and reaction-diffusion phenomena at the droplet-particle interface. The quantitative description of these elementary processes is therefore key to the understanding of reactive granulation as a whole and optimization of the resulting granular product properties.

In this work the reaction kinetics and wetting phenomena occurring during dry neutralization are being investigated by observing the behavior of a micro-scale droplet of dodecyl-benzenesulfonic acid on a well-defined sodium carbonate substrated. The reaction rate is evaluated from the increasing volume of the drop due to the formation of carbon dioxide bubbles. Wetting kinetics are represented as a relation between the three-phase contact line velocity and the dynamic contact angle. The dependence of both reaction and wetting kinetics on temperature has been obtained and the rate-limiting step was found to change from the surface reaction to diffusion-limited with increasing temperature. The wetting and reaction kinetic data have subsequently been used for the modeling of granule microstructure evolution, and a comparison between simulated and experimentally obtained granule structures has been carried out.

150 - Effect of powder bed inclination on binder drop behaviour

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Drop impact on powder bed and subsequent behaviour has profound effect on nucleation and binder dispersion regime in granulation. Inclinations of the powder bed as well as agitation are major variables affecting the drop behaviour in powder bed. This paper studies effect of powder bed inclination on drop behaviour by capturing and analysing drop behaviour in inclined powder beds.

Phenomenon associated with change in shape was explained with analogous examples form liquid-solid systems. Drop showed three different behaviours for 15, 30 and 45 degrees inclination of the powder bed. At 15 degrees drop spread but regained its shape, when inclination was changed to 30 drop regained its shape but started rolling down the surface. Due to viscous drag flow and capillary forces which were opposing the rotation of the drop, rolling velocity of drop was found to be exponential with respect to time. At 45° inclination drop spread but failed to regain its shape and broke into two unequal parts and started rolling down the surface.
Simulation of in-line particle sizing techniques during agglomeration processes

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For an increasing number of particulate processes in-line particle sizing emerges as rewarding technology in terms of quality monitoring and process control. Yet, the majority of in-line particle sizing techniques at hand only provides random length quantities, so called chord length distributions (CLD), but not the actual particle size. Whilst a transformation algorithm exists for several basic geometries of particle shapes resembling crystals and granules, agglomerates still remain a challenge to perform an equivalent transformation of recorded chord length into characteristic sizes. In order to capture the manifold shapes agglomerates with varying numbers of primary particles have been generated. Each agglomerate was rotated in all angle alignments and the respective contour projection was detected. By casting parallel, equidistant chords onto every contour projection, single particle CLDs have been created. The superposition of large numbers of CLD-simulation results yielded a preliminary relation between CLD and number of primary particles as a characteristic size quantity.
Aerogels are nanoporous materials which have extremely low density, high surface area and excellent insulation properties. However, the limitation of aerogels in a number of applications is their open-pore structure, allowing the penetration of liquids therein. This drawback could be overcome by coating of aerogels with polymeric materials in the fluidized bed.

In this work a novel process for coating of spherical aerogel particles in a spouted bed apparatus is suggested, which avoids the fluidization and coating of this light and cohesive particles. The spherical hydrophilic silica aerogel particles with a surface area of 1100 m²/g and size ranging from 30 µm to few millimeters were produced using supercritical extraction of a gel-oil emulsion [1]. The coating with ph sensitive polymers (Fig. 1 left) was performed successfully in a spouted bed apparatus. The experimentally obtained mechanical properties of aerogel particles (i.e. stiffness, modulus of elasticity, friction and restitution coefficients) were used in the performed simulations of a spouted bed apparatus using a Discrete Particle Model (DPM) [2] (Fig. 1 right) which is coupled with the gas phase (CFD) in order to study the influence of the polymeric liquid layer of the particles on the fluidized bed dynamics. To predict and to reduce the breakage of aerogels during coating the particle dynamics were investigated.

Figure 1. (left) Aerogel particle coated in spouted bed apparatus with Eudragit® and the cross section area of the layer; (right) Instantaneous particle positions and velocity distributions inside the spout bed apparatus calculated using DPM.

Calcium carbonate scale deposition and aggregation in production facilities is a challenging problem in the petroleum industry. Therefore, scale mitigation and prevention programmes are critical for sustained oil and gas production. Scaling can cause deposits in surface equipment, well-bore flow restriction and block near well-bore formation. Thus, it is essential to know if and where this scale will form, as such scale deposits have a detrimental effect on the oil exploration industry.

In the past, various techniques have been tested for their potential to reduce the formation of calcium carbonate scale. One such technique popularly used is ultrasound. These studies have either been based on precipitation or deposition of the precipitants and the measurements tend to be offline. Our present work involves the use of inline in-situ measurements, based on focused reflectance beam measurement (FBRM). The effect of ultrasound on the precipitation, aggregation and deposition of calcium carbonate using this technique is reported here.

Using this approach, it is observed that the effect of ultrasound causes calcium carbonate to precipitate in solution rather than on the solid surface. Our findings show that not only does ultrasound affect the rate of scale deposition, it also has an affect on crystal number and size. This inline technique can be used to provide an insight into the relationship between precipitation and deposition. Furthermore, the scaling mechanism on the surface is proposed. It is suggested that at relatively high supersaturation, the scaling mechanism is controlled by surface adhesion rather than secondary heterogeneous nucleation.
The deposition of calcium carbonate on solid surfaces under certain conditions poses a serious problem to many industries. This scaling may lead to a lowering of heat transfer efficiency, increased energy consumption and unscheduled equipment shutdown. In order to prevent potential scaling problems it is, therefore, important to understand the mechanism of calcium carbonate deposition.

This paper is an extension of previous work on the understanding of calcium carbonate crystal formation, aggregation and deposition. It describes the application of an inline technique based on Focused Beam Reflectance Measurement (FBRM) to determine the rate of calcium carbonate formation. FBRM provides a real time measurement of the dimension and number of crystals and this technique has proven to be a sensitive method with which to monitor the initial stages of the scale formation process. The effect of initial calcium ion concentration and temperature on the scaling rate has been determined, and these inline results validated from complementary offline scale measurement techniques.
Granulation research in industry is more focused on the business decision making rather than fundamental understanding. The type of decisions normally includes: What is the target formulation to yield the right product performance? What is the right process centerline? What are the product qualities under different process and formulation changes? What is the consumer acceptance of the product quality? Given the multitude of process and material factors affecting granulation process, it is often difficult to find the right causal effects between factors and results via typical single variable test, not mentioning the optimization. Empirical modeling (via Design of Experiments) is highly recommended as the most efficient way to address these issues. It will provide not just the causal effects between factors and results, but also reliable prediction and confidence level for company to make decisions. This talk will illustrate how this is done via a series of real case studies examples.
Agglomerates are being developed to be used for moisture transport in HVAC applications. When tiny silica gel particulate is agglomerated and used in a desiccant coating it increases the surface area of the desiccant while simultaneously reducing the amount of contact surface area needed to bond the silica gel to surfaces that can be used for desiccant drying (e.g. desiccant coated regenerative wheels used in HVAC systems.) In theory this should increase the rate at which moisture is absorbed and also it should increase the moisture capacity of the desiccant. In regenerative HVAC wheels there are two types of energy that can be recovered sensible heat and latent heat. Latent heat applies directly to the moisture transport and by improving the transport it will improve the overall performance of the system. The agglomerates being tested will be comprised of 1 to 10 µm sized particles being agglomerated and sorted in the range of 60 to 90 µm. These are then coated onto aluminum foil surfaces, tested, and directly compared to an aluminum foil sheet coated with only the bonding material (i.e. no desiccant particles), and a current desiccant coating that was applied to an energy wheel. Test results show that the agglomerate particles will be able to increase performance in desiccant coated surfaces for HVAC systems.
Fluidised bed is widely employed in various industries, including the food and the pharmaceutical industries. Among the different configurations of the fluidised bed, the bottom spray processing ‘Wurster’ is commonly used for coating and granulates liquids. This studies shows that a best efficiency of the process can be performed with the study of circulation of particles and of temperatures in the reactor. This work permits the conception of a new configuration.

To determine the best circulation of particles, the fluctuation of pressure drop is measured in function of the airflow rate. This method shows that it is existed a range of airflow rate where fluctuations of pressure drop are minimal corresponding to the best circulation of particles. To assure homogeneous temperature in the reactor, temperatures are measured on different parts. This experiment shows that in the central zone, evaporation compensates the heating by the fluidisation air. In the annular zone, no compensation exists and particle temperature may rise up to 15°C in regard to central zone. A modification namely spouted bed has been introduced in the reactor (Figure 1). In this condition, no air circulates in the annular zone and permits to obtain a similar temperature in the central and annular zones. Moreover with the new configuration, the fluctuation of pressure drop is more stable and particle circulation is more homogeneous.

To test the impact of the new configuration, particles have been coating with a suspension of probiotics either in the traditional Wurster and modified equipment. Table 1 shows that depending the type of celullules; the surviving may be increased by up to 100 % while using the spouted bed.

<table>
<thead>
<tr>
<th>Probiotic strain</th>
<th>Wurster</th>
<th>Spouted</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Casei Lc 1</td>
<td>40±7 %</td>
<td>54±7 %</td>
<td>35 %</td>
</tr>
<tr>
<td>L. Acidophilus R0052</td>
<td>8±1 %</td>
<td>15±1 %</td>
<td>90 %</td>
</tr>
</tbody>
</table>

Figure 3. Wurster bottom + insert = spouted bed
159 - Design of Lansoprazole delayed release fast melt tablets using fluidised bed processor

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In pharmaceutical the novel drug delivery system increasingly being become popular. The delayed release fast melt tablets are more patient friendly and rapid disintegrated on contact with saliva in the oral cavity and dispersion of coated microparticles in the mouth and no solubilization of enteric coating material in the salivary millieu so that both taste masking as well as gastroresistant properties of the coated particles remain intact.

In present study Lansoprazole delayed release fast melt tablets are prepared. The steps involved in formulation of acid labile and bitter Lansoprazole are preparation of core drug pellets by suspension layering technique in a fluid bed processor. Application of seal coating on core drug pellets in fluid bed processor to prevent direct contact of drug surface with the outermost enteric coating that has inherent acidic nature. Application of delayed release polymeric coating in fluid bed processor on seal coated drug pellets to impart gastroresistance to the product.

The prepared orally disintegrating Lansoprazole tablets are evaluated as per pharmacopoeial guidelines. Taste masked, gastroresistant, rapid-disintegrating tablet formulation of Lansoprazole with desired physicochemical and sensory attributes are successfully developed.

160 - Hot-melt extruded complexes of basic polyelectrolyte and poorly water-soluble drugs

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Polyelectrolyte complexes are defined as oppositely charged polyelectrolytes “bound together by electrostatic interactions” [1]. In pharmaceutical sciences embedding of drugs in polymer-polymer matrices as well as polymer-drug associations are of major interest. This study deals with the formulation of hot-melt extruded polyelectrolyte complexes in equimolar ratio. These should be composed of poorly water-soluble acid drugs naproxen and furosemide and basic polymethacrylate.

No crystalline signals occurring in XRPD measurements and one glass transition temperature in DSC measurements proved the formation of a single phase amorphous system. Milled extrudates were stable under storage using long-term and intermediate conditions. An acid-base reaction performing hot-melt extrusion could be revealed by FT-IR and Raman spectroscopy. In both cases significant vibrations of amino and carboxylic groups respectively disappeared comparing the extrudate and the physical mixtures of drug and polymer. The complexes proved to be stable in demineralized water (< 10% drug release after 60 minutes). Drug release could be drastically increased by addition of neutral electrolytes in the rank order chloride > bromide > iodide.

The sticking propensity of a dicalcium phosphate based roller compaction platform: an observational study

E.L. McConnell and M.J. Pollitt

Punch sticking, and hence tablet picking, can be problematic in producing elegant, economical tablets. Sticking can occur during tablet compression when a portion of a blend or granulation adheres to tablet tooling surface. Often sticking propensity is not picked up during development due to short runs and low compression speeds. A small scale sticking test was developed by Holstine and colleagues [1]. This qualitative test involves the use of embossed punches and optical imaging. The method is simple, straightforward and has been validated against large-scale manufacturing. An investigational compound demonstrated sticking and hazing at 20 % drug loading using a roller compacted (RC) granule. This was despite the reputation of dicalcium phosphate to reduce sticking. In this study we examined the potential of the placebo RC-granule itself to be implicated in the sticking process.

A blend was prepared using 60% Microcrystalline cellulose (Avicel PH102), 36% dicalcium phosphate anhydrous (A-Tab), 3% sodium croscarmellose (Ac-Di-Sol) and lubricated using 0.5% Mg Stearate. It was roller compacted (RC) then split. Half was passed though 2.0 and 1.0 mm Conidur screens (for coarse granules) and half through 1.0 and 0.5 mm screens (fine granules). Each RC lot was then lubricated (0.25% Mg stearate). For comparison a direct compression (DC) blend was prepared (same formulation) with 0.75% magnesium stearate. 250 x 200 mg tablets were compressed using a Korsch XP-1 tablet press at 360 or 200 MPa. Photographs of the punches were taken under consistent lighting. The photographs of punches are shown in the Figure and tensile strength in the Table. Sticking can be seen clearly in the lettering. Punch scratching (seen as a hazed surface) was also worse with the coarse granules. No sticking or scratching was observed with a DC blend.

The observation of sticking with the placebo formulation was a surprising result as sticking was anticipated to be mainly a function of the active material. It was expected to see more sticking with the fine granules due to lower lubricant per surface area of granule and the increased surface area interacting with the punch. However, the Figure shows more sticking with the coarse RC granules. Given finer granules produced stronger tablets, this study is consistent with the adhesion-cohesion balance hypothesis [1]. The extra cohesion from fine granules (as measured by tensile strength) is more significant than the extra adhesion to tablet punches from lower relative lubrication. The direct compression formulation has low sticking propensity because of higher cohesion and possibly higher relative lubrication as all of the magnesium stearate is available rather than being compressed into granules. Furthermore this study demonstrates the abrasiveness of a dicalcium phosphate RC formulation, as observed by hazing / scratching of the tooling. As expected, smaller particles are less abrasive than large ones. Sticking represents a complex balance between ad- and cohesion, abrasion and particle size. These results demonstrate the use of an imaging technique to assess sticking propensity, and also highlight that the issue is not as simple as a "sticky" active material; the placebo formulation, when roller compacted, may also demonstrate sticking to the punches and could contribute to the problem.

<table>
<thead>
<tr>
<th>DC blend</th>
<th>8.3 MPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC coarse</td>
<td>3.9 MPa</td>
</tr>
<tr>
<td>RC fine</td>
<td>7.5 MPa</td>
</tr>
</tbody>
</table>

Tablet tensile strength at 360MPa compaction pressure

Images of the tablet punches
Fluidized bed coating is a commonly applied technology to microencapsulate pharmaceutical or food powders. But the most operational problem encountered during fluid bed coating is the agglomeration. It could be due to lack of drying or temperature over the glass transition. In both case, particles are sticking leading to agglomeration. To avoid the agglomeration, an automatic control system is developed with the determination of the control parameter and acting parameter.

The acting parameter should be atomisation or drying parameters. On this study, atomisation pressure, coating solution flow and airflow are identified to be an acting parameter. To choice the most appropriate parameter, an experimental design is carried out with two response factors: the percentage of agglomerates and the coating level. Analyse of the experimental design shows that the coating solution flow is the most influencing parameter on the two response factors. The action of the coating solution flow is made with the switch on/off of the atomization pump.

The control parameter is a measurement online during experiment. Actually, three measurements are often taken: outlet temperature, outlet relative humidity and pressure drop on the fluidized bed. To determine the most sensible measurement, each parameter is following and a perturbation is realized on the fluidized bed to simulate an agglomeration. It appears that the pressure drop is the most sensible response. In fact, the pressure drop is an indicator of the homogeneity of fluidisation and when a agglomeration occurs, the fluidisation would change.

The last step of this work is to develop the control system. For that, a bang-bang control is used. The illustration presents this control system. Several conditions were testes (air temperature, atomization pressure, particle load...) without observing any agglomeration and a process time mainly 2 times shorter than with “manual" control. With the control system, it also seems that the coating is more homogenous.
If granular potash fertilizer in a packed bed has a moisture content greater than 0.25% (w/w) and is then dried, caking of the bed will occur. Crystals will grow near the contact points or in the area between any two particles in contact. Cake strength is proportional to the amount of crystal deposited per unit volume.

In this research the geometry of a 2 D planar saline film between two potash particles is determined by the Young-Laplace equation. A 2-D theoretical model is developed for the ion diffusion process and crystal growth during a bed drying process. The finite volume method is used together with the alternating direction implicit (ADI) technique [1] to solve the two dimensional mass transportation process.

The numerical predictions illustrate the transient distribution new crystals along the solid surfaces and these results imply that the average salt deposition starts from the location where the liquid film is thinnest and moves toward the particle contact point with increasing average crystal mass deposition, causing the formation of crystal bridges near the contact point. The average crystal height increases with decreasing the initial angle of the contact region, but the deposition is nearly dependent of the evaporation rate. [1] M.N. Ozisik, Finite Difference Methods in Heat Transfer, CRC Press, Inc., 307-357, 2000
Experimental study on the hygroscopic relationship to fracture strength of potash particulate test specimens

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Potash particulate products can take in water vapor from the neighboring environment and form brine bridges between particles when the relative humidity is beyond 50%. Once the surrounding air becomes drier the water will be evaporated out of the potash bed and brine bridges will turn into solid crystal bonds. When a significant amount of crystal bonds have been generated, the potash particulate media will develop into a solid mass. This is the so-called potash caking phenomenon. Since potash is transported globally potash caking will unavoidably occur during long haul transport and during storage. This study is focuses on the influence of two factors on caking, the external compressive load and the environmental humidity, on the moisture absorption and desorption process in potash particulate beds and their fracture strength. The experimental exploration of this work provides significant evidence that high external pressures can cause rapid moisture absorption and the strong potash cakes when the relative humidity is maintained below 75%. It is also found that at relative humidities above 75% but below 84%, the fracture strength will decrease with an increase of the external pressure.
Partial dissolution and recrystallization at controlled relative humidity to predict caking

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Both, producers and end users of powders in food, pharmaceutical or cosmetic industry regularly face the problem of caking after periods of storage and/or of transport. The agglomeration of particles depends on water content and temperature, but also on the relative humidity at which the product is stored. In this study, we focus on kinetics of partial dissolution and evapo-recrystallization for deliquescent soluble substances. The aim is to predict the dissolution and evapo-recrystallization rates as a function of time in order to anticipate caking in industrial conditions. Measurements of the water uptake at controlled relative humidity and temperature are performed using the Dynamic Vapor Sorption machine (DVS).

We show that dissolution and evapo-recrystallization rates are proportional to the difference between the imposed relative humidity and the deliquescence relative humidity (DRH) and follow a simple diffusion model, based on the Knudsen law [1]. More precisely, the measurements of evaporation rate reveal a growth of partially dissolved crystals and nucleation of solid phase from the supersaturated solution. This study will also provide experimental data of vapor pressure of supersaturated solutions and allow the comparison with well-known models such as the Pitzer model [2].

We will discuss the validity of the quoted models with reference to the measurement data for Sodium Chloride (DRH=75%).

Focused beam reflectance measurement (FBRM, Mettler-Toledo, Switzerland) is an increasingly popular particle growth analysis technique. FBRM tool was installed with two different locations inside a fluidized bed granulator (GPCG2, Glatt) in order to monitor the granulation growth kinetics. An experimental design was created to study the effect of process variables using FBRM probe and comparing the results with those measured by sieve analysis. The probe location is of major importance to get smooth and robust curves. The excess feeding of binder solution might lead to agglomeration and thus to process collapse, however this phenomenon was clearly detected with FBRM method. On the other hand, the process variables at certain levels might affect the FBRM efficiency by blocking the probe window with sticky particles. A good correlation was obtained (R^2=0.95) between FBRM and sieve analysis mean particle size. The proposed in-line monitoring tool enables the operator to select appropriate process parameters and control the wet granulation process more efficiently. This implementation will provide a final product with high quality at real time release and at the same time reducing rejects and the reprocessing of batches in the manufacturing of granulates.
168 - High shear granulation with Starch 1500® - Evaluation of process parameters by design of experiments

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Purpose:
To evaluate the impact of process variables on the granulation and tablet properties of a formulation utilizing Starch 1500 as a binder and disintegrant through Design of Experiments.

Method:
A placebo formulation containing lactose monohydrate, microcrystalline cellulose, and Starch 1500 was used along with dye and dextrose in place of drug. A Niro TK Fielder PMA 10 was used to granulate the batches. Drying was performed in a Glatt GPCG-3 fluid bed. Blends were compressed on a Piccola, rotary tablet press. Tablet properties were analyzed on an Erweka Multicheck. DOE Fusion Pro from S-Matrix Corp. was used to generate and analyze the DOE. A model robust screening design was used. The design evaluated water quantity (5 -15%), starch level (5 - 20%), impeller speed (150 – 500 RPM), spray rate (50 – 200g/min), and wet massing time (1 – 5min). Responses analyzed were granulation particle size, geometric standard deviation, bulk & tapped density, tablet hardness, friability, and disintegration time.

Results and Discussion:
The study showed that water quantity had the largest impact on the granule and tablet properties overall. Particle size (76 – 254 microns) was influenced by water quantity, starch quantity, and impeller speed. Increasing these created larger particles. Particle size geometric standard deviation (1.67 – 2.29) and disintegration time (0.5 – 8.4min) were affected by water quantity only. Higher levels of water decreased the standard deviation and increased disintegration time. The bulk density (0.54 – 0.68g/cc) was affected by water quantity, impeller speed, spray rate, and wet massing time. Tapped density was similar to bulk density. Tablet hardness (4.5 – 8.3kp) was affected by impeller speed and wet massing time. Tablet friability (0 – 0.33%) was affected by impeller speed only. The effects on tablet hardness and friability can be linked to bulk density. As water quantity, impeller speed and the length of time in the granulator increased, the density of the granules increased. This resulted in lower tablet hardness and higher friability.

Conclusions:
The granulation parameters impacted the resultant granule and tablet properties. Optimal granule and tablet properties were obtained when a moderate amount water was utilized with low impeller speeds, fast spray rates, and short wet massing times.
Mechanical material properties and their influence on particle deformation and the formation of particle-particle contact points in agglomeration processes


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In agglomeration processes of powders (e.g. pressure agglomeration, fluid bed agglomeration or sinter/caking processes) the primary particle contacts are exposed to different pressure and time profiles. As a consequence of viscoelastic properties, especially of food materials, the process parameters contact time and applied pressure have a big impact on the creation of particle-particle contact areas. These areas influence the occurrence and extent of all potential binding mechanisms like Van der Waals forces, sinter bridges, high viscous liquid bridges or solid bridges by re-drying of liquid bridges. Theoretical calculations of the deformation behaviour and resulting adhesion between particles have been performed, taking viscoelastic effects and Van der Waals forces into consideration.

The viscoelastic particle deformation of amorphous material is thereby mainly governed by the difference between the material temperature T and the glass transition temperature Tg. The glass transition temperature is dependent on the water content and the material used. To obtain the viscoelastic parameters necessary for the prediction of particle deformation and adhesion, steady-state three point bending tests on material samples with differing T - Tg were performed.

Different deformation profiles in the particle contact areas were shown to occur for a change in the investigated process parameters pressure and contact times as well as viscoelastic material properties. In dependency of the time-scale of the process, changes in the resulting pull-off forces to separate particles could be observed.
170 - In-line monitoring of a continuous pharmaceutical granulation and drying process

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Introduction: The main general motives for switching from batch- to continuous production are avoiding scale-up issues, reducing cycle times, reducing production costs, ensuring faster product release, reducing variability, increasing flexibility and efficiency, and improving product quality. It is obvious that the current conventional quality control systems of production processes, based on off-line analyses in analytical laboratories, would annul the advantages of continuous processing, and that real-time quality evaluation is indispensable for continuous production.

Aim: The aim of this study was to investigate the possibilities for monitoring critical product quality attributes during a continuous granulation and drying process using several process analyzers.

Materials: A particle size analyzer and a Raman- and NIR spectrometer were introduced in a continuous high shear granulation and drying system (Consigma™, Collette, Belgium). Theophylline – Lactose – PVP (30-67.5-2.5%) was used as a model formulation. The granulation liquid was distilled water with 0.5% SodiumLaurylSulfate. A Design of Experiments was performed to study the influence of 4 factors (screw speed, powder feed rate, liquid concentration and barrel temperature) upon the in-line monitored critical product aspects (PSD and API solid state).

Results: Process induced transformation can occur during granulation and drying. Solid state changes were monitored, as well as moisture content and particle size distribution of the granules. A low liquid concentration, a high barrel temperature and high barrel filling were the parameters resulting in an incomplete conversion of anhydrous theophylline to theophylline monohydrate. High barrel filling and high temperature led to larger granules.

Conclusion: This study shows the possibility of monitoring some critical product aspects using Raman- and NIR spectroscopy and a particle size analyzer during continuous twin-screw granulation and continuous drying.
171 - Evolution of the structures and properties of microcrystalline cellulose granules during high shear wet granulation – implications for bulk powder compaction and flow performance

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High shear wet granulation (HSWG) is a common operation to improve powder processing and handling properties through size enlargement. Herein, we investigated the changes in the structures and properties of microcrystalline cellulose (MCC) as a function of water level during HSWG.

With increasing amount of granulating water, granule size slightly decreased between 0% and 35% water and then increased continuously until a paste was formed. The initial size reduction was caused by the elimination of the fine surface protrusions (0% - 25% water) followed by particle rounding (25% - 35%) and consolidation. The subsequent granule size enlargement (≥ 45% water) corresponded to the classical nucleation and growth of granules and could be explained by the reduction in the yield strength of granules due to the plasticizing effect of water. The elimination of the finest surface protrusions (5% water level) significantly improved powder flow but had no effect on powder tabletting performance. As MCC particles were further smoothened, powder tabletting performance deteriorated rapidly while flow performance increased. With further increase in water level, granules grew in size while being further consolidated, eventually leading to extremely poor tabletting performance (over-granulation). Surface smoothing, shape rounding, consolidation, and size enlargement played dominating roles in turn when the granulation process proceeded with increasing water level.

By simultaneously monitoring surface roughness, morphology, granule porosity, specific surface area, and size, mechanisms to the profound changes in bulk powder flow and tabletting performance were clearly understood. On the basis of a mechanistic understanding, we showed that granule size reduction was effective in overcoming the over-granulation problem of MCC.
Fluidized bed spray agglomeration is an important process to form specific powder granules in the food, fine chemicals and pharmaceutical industries. Dust-free and free-flowing particles can be produced as well as agglomerates with desired particle size distribution and dissolution behaviour. The fluidized, well mixed, particles are wetted with a binder liquid by a spray nozzle leading to the formation of agglomerates due to adhesion forces between the wetted surfaces.

Many food powders have an amorphous supra-molecular structure. Thus their mechanical behaviour strongly depends on the temperature and the moisture content. The wetting of amorphous particles leads to a change in their surface properties. Glass transition appears and due to a decrease in viscosity the particle surfaces are activated for agglomeration. Colliding particles will interact according to the viscous-plastic behaviour of their surfaces and either stick together or rebound.

The agglomeration process can be split into two parts each one described by a combination of several micro mechanisms. The first one is the activation of particles surfaces by the wetting in the spray zone consisting of droplet spreading, penetration of binder liquid into pores, dissolution of solids material into the liquid, diffusion of binder liquid into the amorphous matrix and drying of the droplet. The second one are the collision scenarios between either wetted or dry particles describing the agglomerate growth and consolidation.

This work focuses on the droplet deposition on the particles in the spray zone as it is a key parameter for the agglomeration process. Experimental and numerical studies were carried out to validate the model of the spray zone. Coupled DEM-CFD simulations of the spray zone reveal important information about the wetting degree of the single particles.
173 - Laundry detergent build-up in auger fillers

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Build-up is the accumulation of a solid mass of material on a surface, no longer identifiable as a powder. The Build-up of powders is a particularly challenging subject as it is often fundamentally the smearing of powder on a surface, which has attracted very little attention in literature. This reflects in the lack of an established powder characterisation technique capable of reproducing powder smearing under laboratory conditions. As a result of this there is a need to utilise data taken for manufacturing scale equipment such as an auger fillers, which have been shown to have significant issues with powder build-up within the auger/straight funnel clearance, particularly when packing small pack sizes. To facilitate the collection of data from an auger filler a semi empirical technique has been developed which measures the rate of build-up via manual torque measurements. This technique test is performed by filling powders, while making manual torque measurements. An example of some data generated via this test can be seen in the below figure.
174 - Influence of raw material particles size to properties of granulated fertilizers

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The crushing strength of granules and size distribution are two the main physical-chemical properties of granulated fertilizers.

Wet granulation of fertilizers in drum granulators is the process when fine particles of raw materials are agglomerated to form large particles as granules.

Agglomeration processes which occurs in drum granulator depend from the mixture composition, moisture content, temperature, recycle content and particles size of raw materials and play an important role to the physical-chemical properties of fertilizers granules.

Influence of size distribution of raw materials particles as potassium chloride, ammonium sulphate, monoammonium and diammonium phosphates in granulation of compound NPK fertilizers of grade 8-20-30 was studied.

A raw material particles size, moisture, fine recycle content and ratio was changed in the industrial range. A constant temperature of raw material, a constant rotation speed and angle of inclination of granulation was maintained. For moisturising of granulation mixture a 0,1% solution of phosphoric acid was used.

The main physical-chemical properties of granular 8-20-30 compound fertilizers – granular composition, mass change after drying, pH of 10, solution and static crushing strength of 3–5 mm granules–were identified.

Returning recycle to the granulated mix the marketable parameters of a product changes positively when fine particles of raw material were used. The optimum parameters of granulation were determined and for the industrial process were proposed.
Wet granulation process is used in the production of pharmaceutical tablets. If the active pharmaceutical ingredient (API) is soluble to the granulation binder liquid, the subsequent drying process may cause API, or other soluble constituents, to migrate to the outer layers of the granule with the evaporating solvent [1-4]. Accumulation of the solute produces a stronger outer crust, while the inner core will be softer [5-6]. This affects strength and compaction behaviour of the granules. In addition, attrition during the drying and elution of the dust can lead to the loss of API.

The objective of this work is to compare fluidized bed drying and oven tray drying at different drying temperatures on granule structure. Intrgranular structure and migration of the water soluble constituent are investigated by computerized X-ray microtomography (MicroCT) in both qualitative and quantitative manner. Statistical analysis is done on the morphometric parameters obtained from MicroCT analysis to further assess the effect of drying method on granule structure and mechanical properties. In addition, intragranular distribution of the solute is visualized by light microscopy and maximum intensity projection analysis of the MicroCT data.

Results showed differences in intragranular porosity and structure complexity between the two drying methods. Oven tray drying caused lower intragranular porosity and complexity in granule structure than fluidized bed drying. In addition, the migration of the solute was stronger in oven tray dried granules, while fluidized bed drying resulted in a more homogenous distribution of the water soluble constituent.

Wet high shear granulation is a common step in the manufacture of many pharmaceutical tablets. The granulator bowl is charged with selected components of the formulation. Following an initial mixing period, the liquid binder is sprayed onto the formulation to form granule nuclei which then grow and develop, until the process is stopped. The conditions and the length of the initial mixing period are often selected empirically.

In this work, a placebo formulation was granulated with a high shear granulator while varying the conditions and length of time of the initial mixing period. The granules from the trials were extensively examined using average particle size and size distribution, shape and composition from scanning electron microscopy and flowability measurements.

Minimal changes in granule formulation were observed with flowability and particle size measurements. However, changes in the initial mixing period observed from SEM images led to differences in granule properties indicating that this period is important and should be carefully considered to achieve granules with specific properties.
Wet granulation involves the addition of a liquid binder to the feed powder. The binder is usually in the form of a solution or a polymer melt and the granules are stabilised by drying or cooling. It is well established that the capillary and viscous forces are responsible for the cohesion of the granules in the wet state. The current work involves an experimental study of the interparticle adhesive properties of polymeric liquids that show Newtonian behaviour at small strain rates and shear thinning at strain rates greater than a critical value. The interparticle forces were measured using colloid probe atomic force microscopy for different separation velocities. This involved the spin coating of silicone fluids, with molecular weights 7-250 kg/mol and film thicknesses of 200-2,000 nm, onto silicon substrates and colloid probes with radii 6-12 μm. The data were consistent with theoretical models of capillary and Newtonian viscous bridges provided that the maximum strain rate is less than the critical value associated with shear thinning. In particular, there is a transition from a regime dominated by capillary forces to one that is controlled by the viscous forces as the Capillary number increases. At large Capillary numbers, the forces are smaller than those calculated from the theory due shear thinning.
In pressure agglomeration of amorphous food powders, Van der Waals forces are commonly regarded as the dominant interactions to hold particles in contact together. In contrast to this, the observed high strength of amorphous compacts suggests that other mechanisms like sintering creating stronger material bridges are governing the adhesion between primary particles.

Sintering is a concept that is traditionally applied in the ceramic manufacturing industry and describes material diffusion driven by the tendency of reducing the total interfacial energy. This mechanism is especially interesting for the food industry, since sintered compacts can have both high porosity promoting fast dissolution and satisfying stability for product handling purposes.

It is the aim to adjust process conditions like contact time, applied pressure, temperature and humidity in a way that promotes sintering as well as to find out, which effects lead to sintering. Both rise in temperature due to interparticle friction or capillary condensation between rough particle surfaces can plastify water-soluble amorphous substances and accelerate material diffusion into an evolving bridge.

This study comprises predictive calculations, DEM-modelling and experimental sintering studies with and without applied external pressure by means of a micromanipulation particle tester in a controlled environment to learn more about material flow kinetics in dependency of the mentioned process conditions. It is the aim to reveal the probability of sintering in industrial applications and to gain information about the evolving bridge strength and structure.

Based on that, a focused selection of agglomeration process parameters to generate a beneficial internal compact structure will be facilitated. Better knowledge about sintering between amorphous food particles will also help to explain and prevent unwanted sintering like caking and post-hardening processes.
Wet granulation is the formation of powder particle assemblies bound by a liquid binder. Granules are produced in order to prevent mixture segregation, improve flow characteristics and ease of powder handling. In a high shear mixer, the liquid binder droplets penetrate into, and bind together, powder particles being agitated by the impeller blades. Real granulation formulations are complex, with each component carefully selected to deliver the functionality of the end product. The powder feed for a granulation process may include an active ingredient, diluents, surfactants, wetting agents, lubricants and fillers. The kinetics of the liquid droplet-powder interaction is strongly linked to the properties of the granules produced, with shorter penetration times often leading to a more desirable narrower distribution of properties. Despite this, a reliable penetration theory that can be applied to both single- and multi-component powder mixtures remains elusive.

The penetration behaviour of single liquid drops into static single- and multi-component powder beds, including for hydrophobic powders, is captured using high speed imaging. Image analysis results indicate that the relationship between the penetration time ($T_p$) and the original drop volume ($V_0$) is more complicated than the $T_p \propto V_0^{2/3}$ predicted by current theory [1-3]; as liquid viscosity and/or powder particle size increases, the degree of deviation increases. The existing drop penetration time theory was modified to incorporate an ‘effective drawing area’, thus allowing for the influence of liquid and powder bed properties on spreading extent. A maximum spreading diameter is related to this ‘effective drawing area’ by a factor $\alpha$ by incorporating a pore scale Capillary number and an initial inertial velocity. The new $T_{dmax}$ model was tested by applying it to multi-component powder bed penetration time data and shown to perform significantly better than the existing $T_{CDA}$, including for increasing hydrophobic content.
180 – Granulation behaviour of increasingly hydrophobic mixtures


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Wet granulation is the formation of powder particle assemblies bound by a liquid binder. Granules are produced in order to prevent mixture segregation, improve flow characteristics and ease of powder handling. The liquid binder droplets penetrate into, and bind together, powder particles being agitated in a high shear mixer. Real granulation formulations are complex and challenging. The difficulty of achieving controlled water based wet granulation of a formulation containing a hydrophobic component is one such challenge that is receiving increasing attention in academic and industrial research.

This present work has focussed on the granulation of multicomponent batches, specifically mixtures of hydrophilic Granulac230 (lactose) and hydrophobic limestone, using different spray droplet sizes and impeller speeds. The granulation behaviour of the batches is assessed in terms of granule size and compositional distributions on increasing the hydrophobic content of the batch. Transitions in granulation behaviour are reported as the hydrophobic content of the batch is increased. The granulation behaviour is linked to static powder bed penetration times by assigning ‘compositional zones’, which could be used as a predictive tool in formulation and process development. In addition, a new preferential nucleation and layering mechanism is proposed to describe the experimental data and better understand how the ‘compositional zones’ of granulation behaviour have arisen.
Numerous food products consist of hydrophilic solid particles dispersed in a continuous fat phase. Examples of fat-continuous products are margarine, spreads and confectionery products such as chocolate and fillings. Particles in food systems are usually densely packed so that numerous particle-particle interactions may occur during manufacture and storage. Moreover, in food products hydrophilic liquids like water are usually present, either naturally or upon incorporation during processing. The effect of these humectants is undesirable in several food products and, therefore, the understanding of the nature of these interactions is essential.

In this project, food model systems were established as highly saturated suspensions of crystalline sucrose or glass particles in vegetable oil, and water was chosen as the hydrophilic liquid. The particle size distribution of the systems was assessed using a light scattering technique and preliminary results showed that there was an increase in particle size upon humectant addition. This could be supported by the fact that fine solid particles agglomerate because they are preferentially wetted by the hydrophilic humectant (water). This was investigated by means of contact angle and wettability measurements of the model systems. The sessile drop method was used, and the results showed the time dependency of the contact angles and also the good wettability of the hydrophilic surfaces in hydrophobic media.
Pharmaceutical tablets are usually manufactured by compressing granular material in between two punches. Lubricants are used to reduce the ejection force and improve the die filling during the compression. This paper characterises the early stage of the compression by capturing the granular velocity using Particle Image Velocimetry (PIV). These results are compared external lubricant and internal lubricant formulations.

The measurement of the velocity of granules gives information about its behaviour during the compression. The granules show dominant horizontal movement at the start of the compression. Due to punch movement and non availability of the space the granules start to move vertically downward. The external lubricated case shows high peak in vertical as well as horizontal velocity.
Lubrication is an important aspect of tablet production. Not only does it reduce friction between the die wall and punch, it also improves granule flow properties, which ultimately influences final tablet properties. This paper highlights the behaviour of granular velocity as well as changing pore volume during compression whilst using three different lubrication addition methods.

Particle image velocimetry (PIV) and Synchotron X-ray Tomography are used to calculate granule velocity and the localised pore volume of compact. The results are compared between non-lubricated formulations, external lubricant formulations (where the lubricant is added to the granules following granulation) and internal lubricant formulations (where the lubricant is added to the powder before granulation).

The changes in the pore volume and granular velocity with respective compression pressure are discussed in this paper. As the compaction pressure increases, the span of the velocity distribution increases, showing a reduction in the pore volume inside the tablet. The highest span value is shown by the internally lubricated granules. The pore volume and velocity distribution both show uniformity at higher compression pressures.

The internally lubricated granules have a lower strength and show more uniform pore volume and velocity distributions. The externally lubricated granules tend to have a longer relaxation time during decompression even when higher compression forces are used. This is not as prominent in the internal and non-lubricated addition methods.