Wet Granulation
–
Why and How Continuous?

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CONTINU-PHOBIA - a Pharmaceutical Phenomenon?

- The food industry is since decades in continuous processing e.g. SCHUGI granulator for soups, spray-drying for dairy products
- Already in the seventies: BROGLI presented it’s continuous ointment machine - it never was fully accepted by pharmacists
- Questions, which hampered our industry:
  - How to define a batch in a conti-process?
  - How to convince authorities - especially the FDA?
  - How to overcome the “time to market” dilemma?
  - How to achieve a close co-development supplier- + pharma-company?
  - How to overcome mental barriers in our tradition-bound industry?
- But: Many of our processes are continuous (tabletting, sizing,...)
CONTINU-PHOBIA - a Pharmaceutical Phenomenon?

An Example from our Industry: Continuous Lyophilisation

- In 1990 the company BURROUGS WELLCOME had a Lyo-product which required more than 24 hours of Lyo-time. In order to reduce time and cost they approached PA-CONSULTANTS in Cambridge to jointly develop a continuous Lyo-technique.
- PA-C did a good job and offered an interesting result (Novel filling technique, Micro-wave heating, etc.). But in the meantime GLAXO had taken over B/W and the project was stopped.
- The technology required few additional development (1:1 scale pilot). Thus PA-C approached all “Big-Pharma” companies involved in Lyo-production to collect money for continuation.
- No one could have been found: Everyone agreed to be a “follower” - no one wanted to be a “fore-runner” (German: Hahnemann, geh Du voran!)
- Thus Industry works in a very inefficient way until today - Moreover: for a product-range which has an increased importance due to innovative Bio-Products.
The History - Justifications and Solutions

Granulation-History in a Nutshell:

- In the Sixties granulation was mainly wet mixing plus shelf drying
- In the Seventies the big hype was - Fluid Bed Granulation - until it was found that the granulate was weak and too light
- Then the “High-Shear-Mixer-Granulators“ were combined with Fluid Bed Driers offering best compaction properties
- In parallel dry compaction by “Bricketting” (with tablet presses) and Roller-Compactors were introduced - Continuous Processes!
- In the late Eighties the “Single-Pot” - machines with or without Microwave-Drying were seen as the future solution

Today: More than 90% is done with “High-Shear plus Fluid Bed”
The History - Justifications and Solutions

In 1983 Sandoz AG in Nürnberg/Germany developed and introduced a Continuous Wet Granulation technology - WHY?

- The main product had to be granulated with organic solvents
- The Production facility was in the town centre. Thus stringent emission-control measures were required by local authorities
- Batch-wise fluid-bed driers have a high emission peak which was difficult to capture by technical means (Absorption, Adsorption, etc.)
- In contrast: Continuous driers offer continuous solvent-content in far less drying-air per time (1600 vs. 5000 m³/h)
- In Sandoz the “SRS-Technology” for organic film coating was developed which now could have been applied for granulation

Remember: The Single-Pot Technology was not yet on the market!
The History - Justifications and Solutions

The Sandoz-Approach / Granulation:

- We had to find a continuous granulation technique
- We found SCHUGI - good in food-industry too large for pharma
- We tried BAKER-PERKINS extruder - too much force was applied
- We tried NICA - Not feasible for our products
- Finally we decided to develop a new granulator together with GERICKE/Switzerland
- It was an inclined Tube with mixing-screw plus chopper, simulating a high-shear Mixer
- Capacity: 30 - 100 kg / hour
The History - Justifications and Solutions

The Sandoz-Approach / Drying:

- All existing Conti-Dryers like Vibra, Niro, Anhydro were too large and not feasible for pharma-application (e.g.: segregation of fines by cyclone)
- HEINEN in Varel/Germany made Vibration-Fluid-bed-Dryers for the Tobacco and Food industry
- Together with them we developed a vibrating fluid-bed chute in which the vibration-vector’s angle was directed backwards, thus withholding the wet granules, whereas the Conidur-Bottom was driving the well dried granules to the outlet
- Integrated Gore-tex filters kept the fines within the process
- A “Solvent-Recycling-System” allowed for emission-free operation
What the SANDOZ Granulation Suite in Nürnberg looked like:
Why did the SANDOZ-Approach finally not succeed?

- Organic granulation was replaced by aqueous processes (toxicity, safety)
- In case of organic: “Single-Pots” were a better choice
- The Sandoz process was “batch-continuous” and thus a “hybrid” solution
Why Continuous? Today’s dominating OSD Technology

- Today’s Technology is a permanent mix of batch and continuous process.
- Every Container-Transport means intermediate storage.
- This extends lead-time and decreases yield.
- Fixed batch size - costly up-/down-scaling measures.
- Expensive in case of product-dedicated production suites.
- Extensive space- and room-height requirements.
Why Continuous? The Future: An ideal continuous approach

“Serial-Dedicated” means:
• One API in one suite over a defined time span (e.g. one week)
• Next API after Cleaning
• 24h / light-off shift approach possible
Why Continuous? A Multi-Suite / Multi Product Facility

Different Suites for ....
• ... a multitude of different (API-) products
• ... different process-steps (e.g. with or without coating)
• ... small or large throughput per hour
• ... fixed-dedicated or serial-dedicated
Why Continuous and why a Continuous Hype NOW?

- Cost of Goods have not been a major issue in our Industry - **so far**
- Due to Pipe-line / Generics / Globalisation cost **is** an issue now!
  - Investment cost: GMP-Space is costly
  - Running cost: Air Handling drives energy cost high
  - Automation / light-off shifts save personnel cost
  - Less lead time saves inventory
- Easy up- and down scaling required (uncertain market performance)
- The big hampering argument “FDA will not allow for” is not valid anymore:

..... see what FDA says now:

Office of Pharmaceutical Science (OPS)
Process Analytical Technology (PAT) Initiative
Why Continuous and why a Continuous Hype NOW?

A desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency. Gains in quality, safety and/or efficiency will vary depending on the product and are likely to come from:

- Reducing production cycle times by using on-, in-, and/or at-line measurements and controls.
- Preventing rejects, scrap, and re-processing.
- Considering the possibility of real time release.
- Increasing automation to improve operator safety and reduce human error.
- **Facilitating continuous processing to improve efficiency and manage variability**
  - Using small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities.
  - Improving energy and material use and increasing capacity.
Why Continuous and why a Continuous Hype NOW?

Facilitated Up- and Down-scaling

- Novel batch-definition: Output/time x Running-time
- Example 1: Output = 30kg/h, Run-time = 3 hours
  Batch size = 90kg eq. to 0.45 - 0.9 mio Tablets
- Example 2: Output = 30kg/h, Run-time = 3x20 hours
  Batch size = 1800kg eq. to 9 - 18 mio Tablets
- Small batches for clinical trials up to large batches for medium to large products can be processed on the same core equipment
- The essential message for novel, continuous processes is: small is beautiful
- The old paradigm was: “Continuous suits only for Aspirin”
Why Continuous and why a Continuous Hype NOW?

NCE’s are getting more potent / toxic

- As shown before: Small dedicated suites are suitable to serve as “containments” for highly potent drugs (OEB 4 and 5)
- The number of products requiring dedication according to FDA is increasing (hormones, ....)
- Investment cost for Multi-Product facilities for highly potent OSD products are exaggerating due to segregation measures (locks)
- Same “suite-approach” for highly potent and less potent compounds
- Even for potent drugs: “Serial dedication” is acceptable after validated cleaning

(OEB: Occupational Exposure Band)
Why Continuous and why a Continuous Hype NOW?

Financial Justifications - follow me to a future scenario:

- Supposed that a future OSD Facility consists of a multitude of fully automatic “Serial Dedicated Suites”
- Those suites can be operated in a 24 hours light-off shift approach
- Saving in investment:
  - Significantly lower equipment cost due to smaller units
  - Significantly lower space requirement
  - Significantly lower HVAC investment
- Saving in running cost:
  - Significantly less energy consumption for equipment (process air)
  - Significantly less energy for HVAC

The numbers, however, to quantify “significantly” must be elaborated!
The Beginning - Multi-Component Dosing and Mixing

- Remember: The SANDOZ-approach required a precise Premix before the continuous wet-granulation step

  ![Diagram of Type A process]

- Some of the processes, explained in the next chapter, offer a combined mixing and granulation capability which are able to disperse the active ingredient(s) into a premix of the excipients

  ![Diagram of Type B process]

- Space for Handling of Actives is limited - providing thus containment-properties for highly active components!
The Beginning - Multi-Component Dosing and Mixing

In case of „Type B“ - Approach (Conti-Mixer and Granulator)

- All excipients can be dosed and mixed in a common „material preparation department“
- There all received goods (Actives and Excipients) can be
  - transferred from external vessels/bags/etc. to internal containers
  - if required sifted/deglomeronated
  - however: highly active components should be handled in containment
- Excipients can be
  - dosed precisely batch-wise or campaign-wise
  - homogenised in a mixer
  - and transferred by containers to the “Conti-Suites”
The Beginning - Multi-Component Dosing and Mixing

- The “Excipient Preparation department” serves all OSD products and can thus be highly automated
- For no actives are handled, “Cross-Contamination”- risks are eliminated
- Example: AZO Dosing/Weighing plus Blending
Integrated Solutions - Granulation and Drying

Despite extensive research the author has found only the herewith described solutions. This, however, does not mean that there are no other techniques offered in the marketplace.

More solutions are available for the food industry. But those are providing by far too high throughput amounts and no Pharma-cleaning properties.

- **“Type A” approach:**
  - The LOEDIGE solution
  - The BOHLE solution

- **“Type B” approach:**
  - The BOHLE solution (eventually)
  - The GEA Pharma Systems solution
“Type A” approach: The LOEDIGE solution
“Type A” approach: The LOEDIGE solution

Continuous Mixer KM

or

Batch Mixer FKM

Granulator CM
- rotation speed: 1000-3000 rpm
- very short residence time (10–20 s)
- throughput: 50 to 100 kg/h
- hygienic design

Dryer WFP
continuous fluid-bed type
(DMR-Prozesstechnologie)
“Type A” approach: The LOEDIGE solution

Comments:
- The diagram shows a continuous pre-mixer
- A Batch-wise mixer can be alternatively used
- The smallest conti-granulator is designed for a throughput of 50 - 100 kg/h
- In larger units up to 50 tons/h can be granulated
- A Continuous Fluid-bed type dryer from DMR-Prozesstechnologie Switzerland is directly connected
“Type A” approach: The BOHLE “BCG” solution
“Type A” approach: The BOHLE “BCG” solution

Comments:
- Granulation and drying under vacuum
- The granulator is a twin-screw extruder
- The throughput of 8 kg/h to 30 kg/h is controlled by a dosing unit
- The residence time varies acc. to the throughput (over-flow principle)
- Drying by IR and vacuum provides for little energy consumption
- The system could be used for organic binder solutions due to vacuum
“Type B” approach: The GEA “Consigma” solution

Why „Consigma“?

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<th>yield</th>
<th>cost of quality</th>
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<td>12-18%</td>
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<td>233</td>
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<td>6σ</td>
<td>3.4</td>
<td>99.99966%</td>
<td>1-3%</td>
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</table>

Our Industry is far away from “Six-Sigma” as the Semiconductor Industry. According to GEA, Conti-Techniques can contribute to improve the status.
“Type B” approach: The GEA “Consigma” solution

Granulation Unit – Production Mode Parameters
“Type B” approach: The GEA “Consigma” solution

Drying Unit

...is it continuous?
“Type B” approach: The GEA “Consigma” solution

The “Evaluation-Unit”

Vacuum - Transport - Receiver
Section for “PAT” sensor
Sieving/Sizing
Hopper

A Lubricant-Blending Device can be Added acc. To GEA
“Type B” approach: The GEA “Consigma” solution

The “Through-The-Wall” GMP-Concept
“Type B” approach: The GEA “Consigma” solution

Comments:

- The granulation unit is a Co-Rotating-Twin-Screw Extruder which humidifies and granulates. If two units of 30cm each are used, an active ingredient can be mixed in - therefore “Type B”
- The capacity of the smaller version is up to 30 kg/h; a larger unit for up to 100 kg/h is available
- The dryer is a conventional batch-wise FBD - working in “segments”
- It requires only appr. 300 m$^3$/h of process-air (30kg/h-Version)
- According to GEA an in-line lubricants-blender can be added if required
Stand-alone Solutions - Granulation or Drying

The LEISTRITZ Approach for Agglomeration/Pelletisation/Hot-Melt-Extrusion
Stand-alone Solutions - Granulation or Drying

The LEISTRITZ Approach: The Screws - the essential elements of extruders
Stand-alone Solutions - Granulation or Drying

The LEISTRITZ Approach

Comments:
- Well introduced in Hot-Melt-Extrusion and Pelletisation
- Humidification / Agglomeration not yet established
- Drying can not be offered
Application of Lubricants - When and Where?

What has to be lubricated:
1. The surface of upper and lower punch-tip
2. The surface of the die-wall
   ➢ In order to avoid sticking of the tablets

What should not be lubricated:
• The granules inside the tablet, because e.g. Magnesium Stearate hampers the interlocking characteristics of granules
• Thus deteriorating the tableting properties of granulates

That’s why “Die Chamber Lubrication” was developed already in 198X!

Only, if the process of batch-wise blending can be avoided, continuous granulation and (continuous) tableting can be directly linked
Application of Lubricants - When and Where?

Two different Approaches for Die Chamber Lubrication (also “External Lubrication”)

Dry Powder blowing

Suspension in Ethanol
Prerequisites for a *TOTAL-OSD-LINE* approach

What do I mean with “Total-OSD-Line”?

- Here: One of my old, visionary slides (from 1997):
Prerequisites for a *TOTAL-OSD-LINE* approach

- Application of “Die Chamber Lubrication”
- Fully integrated in-line Analytics (PAT) for
  - Identity-Check in Dispensing
  - Water Content and Homogeneity-Check in Granulate
  - Homogeneity, Hardness, etc. in Tabletting
- Novel approaches for continuous / semi-continuous coating:
  - GEA “SuperCell” system
  - DRIAM “Driaconti” (shown at the ACHEMA-fair)
  - Bohle “COCO” Continuous Coating
  - Electrostatic Powder Coating
  - Laser-Print Coating

*And: A radical change in the mind-set of OSD Product Developers*
Conclusion

- Since approximately two years more interest in Continuous Granulation Processes from the industry is evident
- One reason might be the higher toxicity of new chemical entities
- The handling of the risky portion of manufacturing should be clearly separated from excipient handling
- More effort should be invested in calculating the financial benefits of further integrated production lines
- The paradigm of "large is beautiful" with respect to equipment and batch-size should be overcome
- Novel equipment for Conti-Coating is badly needed
- More openness for Change is required -

  *Innovation-hampering authorities are no argument anymore!*
Thank You for your kind attention

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