



21st EAFP Annual Conference

May 2015



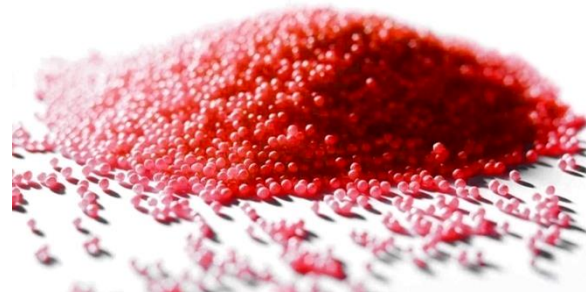
Updated approaches in the manufacturing and coating methodologies

Dr. Anne Ettner, Glatt Pharmaceutical Services

1. Introduction

2. Pellet manufacturing methods

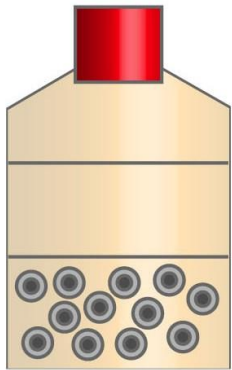
- Direct pelletization methods
 1. Batch Processes including case studies (Rotor, CPS)
 2. Continuous Processes including case studies (MicroPx, Procell)
- Pellet layering and coating methods
 1. Wurster bottom spray system
 2. Tangential spraying system



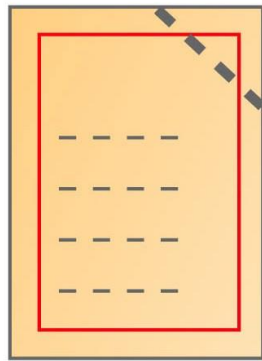


Introduction

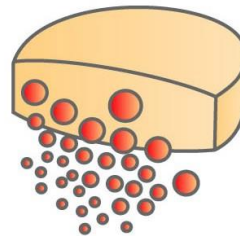
Pharmaceutical Pellets



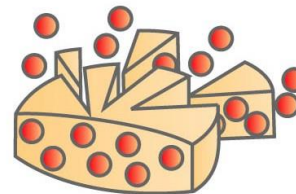
oral suspension



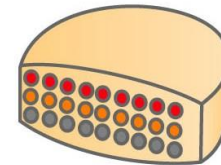
sachets / stick pack



ODT's



MUPS



fixed dose combinations



capsule

< 500 μ m

< 800 μ m



Introduction

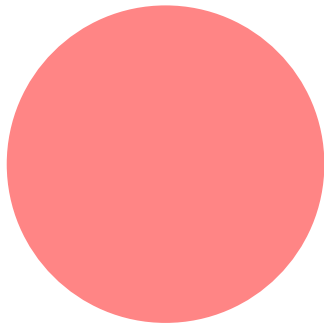
Pharmaceutical Pellets

- Spherical particles with smooth and uniform surface
- Particle size range: 50 - 2000 μm
- Narrow particle size distribution
- Layering of active pharmaceutical ingredients and coating (functional) excipients

Pharmaceutical Pellets

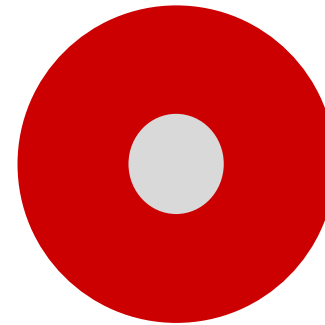
- **Formulation concepts**

Matrix Structure



- uniform and homogenous matrix
- manufactured by direct pelletization

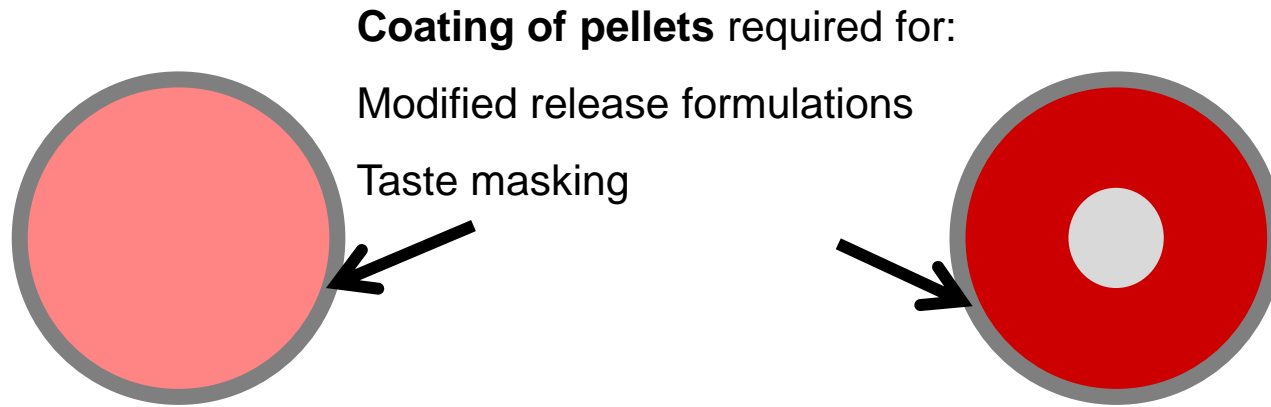
Membran Structure



- multi-layer composition
- manufactured by layering / coating processes

Pharmaceutical Pellets

- **Formulation concepts**



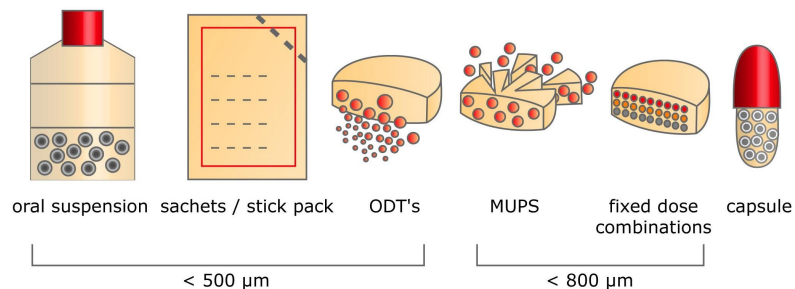
Combination of matrix and membrane approach

Pharmaceutical Pellets

- **Benefits**

- reduced variability in dosage
(low intra- and inter- individual variability)
- controlled onset time of drug release
- delivery of API to distal sites within GI tract

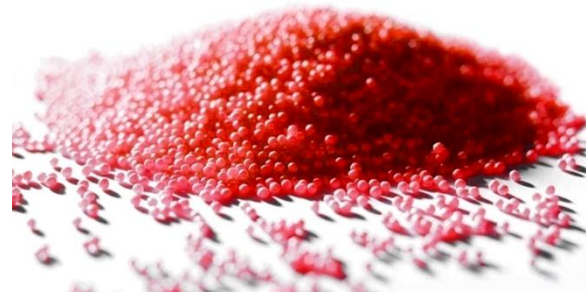
- **Pellets can be administered as capsules, tablets, sachets and oral suspensions**



1. Introduction

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- Direct pelletization methods
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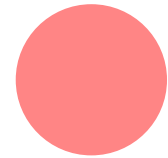




Pellet Manufacturing Methods

Direct pelletization: Batch process

State-of-the-art Pelletization Technologies



- **Extrusion / Spheronization**

- Multitude of manufacturing steps → Multitude of manufacturing equipment (mixing, wet granulation, extrusion, spheronization, drying, sieving, coating)
- Particle size > 500 μm
- Broad particle size distribution
- Mostly particles not totally spherical

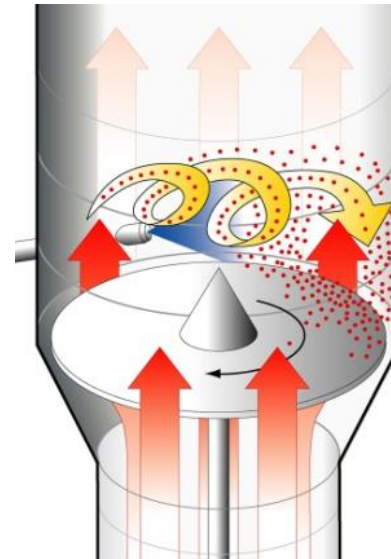


Pellet Manufacturing Methods

Direct pelletization: Batch process

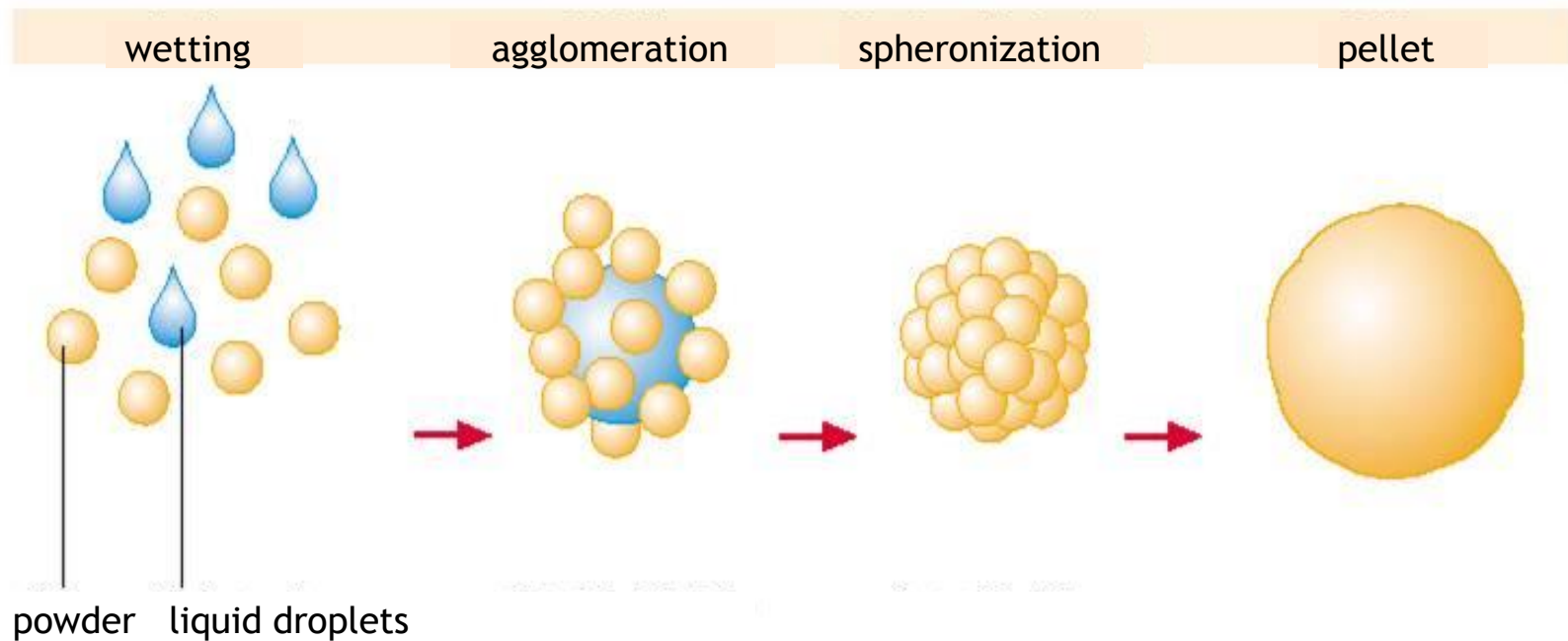
State-of-the-art Pelletization Technologies

- **Rotor fluid bed granulator**
 - Broad particle size distribution



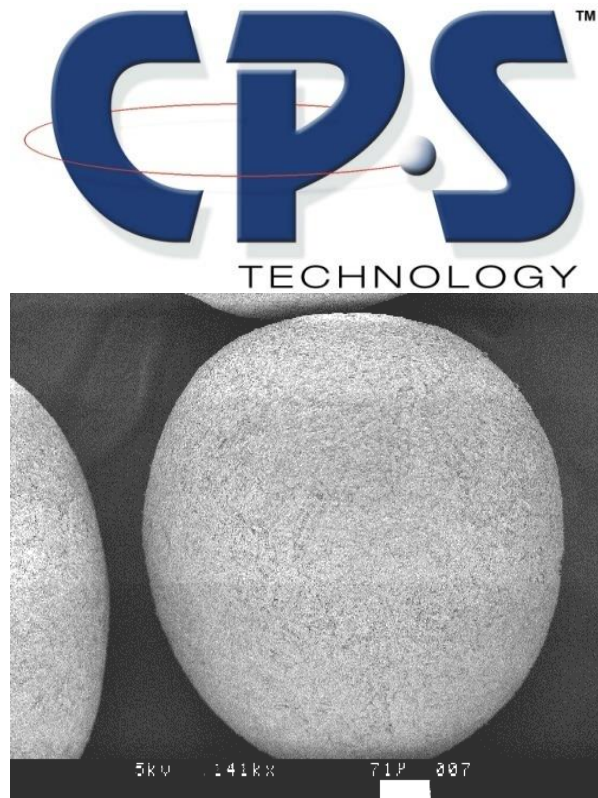
Direct pelletization: Batch process

- Principle of Rotor direct pelletization
- No starting beads!



Direct pelletization: CPS Batch process

- **Modified Rotor fluid bed pelletization**
 - Perfectly round shaped pellets
 - Smooth surface(perfect surface quality for further layering and coating applications)
 - Matrix pellets with high drug load available (depending on API quality)

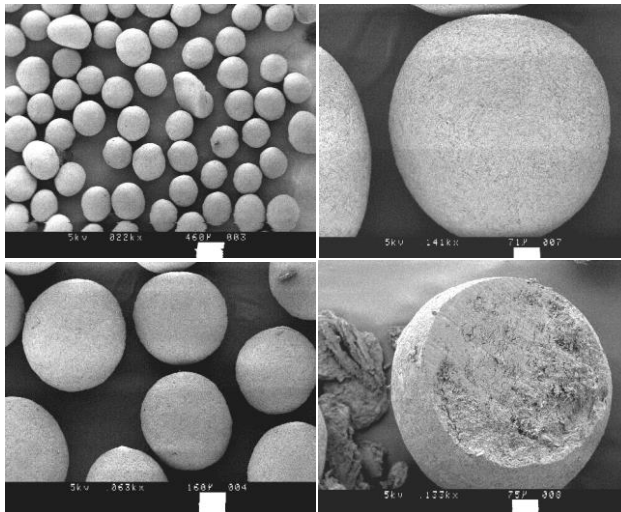
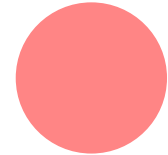




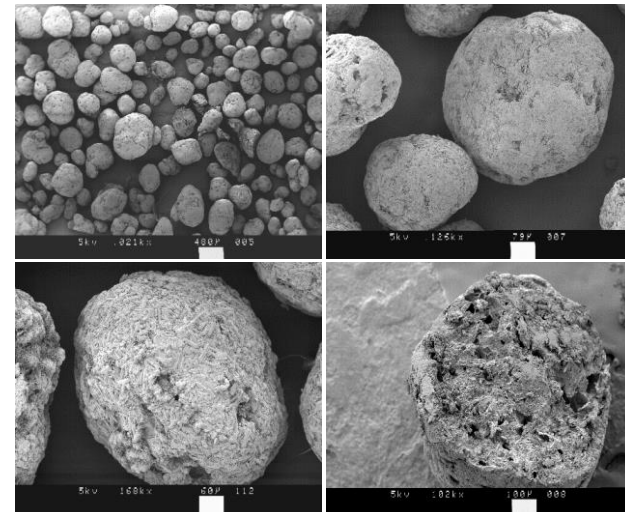
Pellet Manufacturing Methods

Direct pelletization: CPS Batch process

- Modified Rotor fluid bed pelletization CPS



Pellets with 60% potency processed by CPS



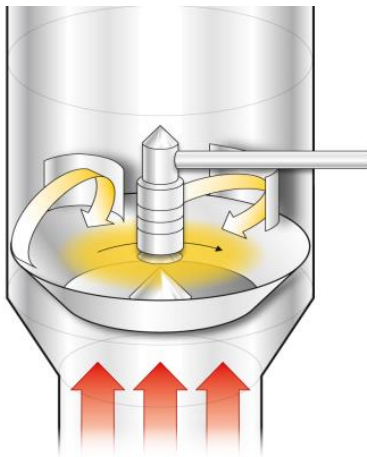
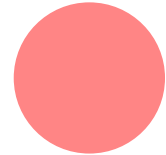
Pellets with 60% potency processed by Extrusion Spheronization



Pellet Manufacturing Methods

Direct pelletization: CPS Batch process

- Modified Rotor fluid bed pelletization CPS

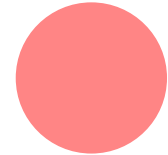




Pellet Manufacturing Methods

Direct pelletization: CPS Batch process

- **Modified Rotor fluid bed pelletization**

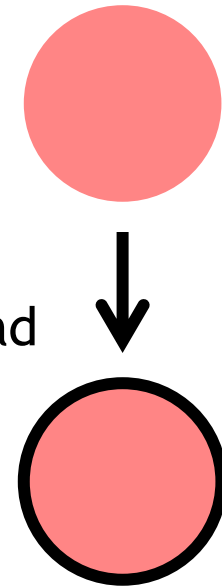


[CPS_Process.wmv](#)

Direct pelletization: CPS Batch process

Case Study I: Matrix pellets with modified release coating

- **Drug Substance:** water soluble
- **Requirements:** matrix pellets with 60% drug load (patent)
controlled release coating
- **Goal:** reproducible thin coating (2 - 3 %)



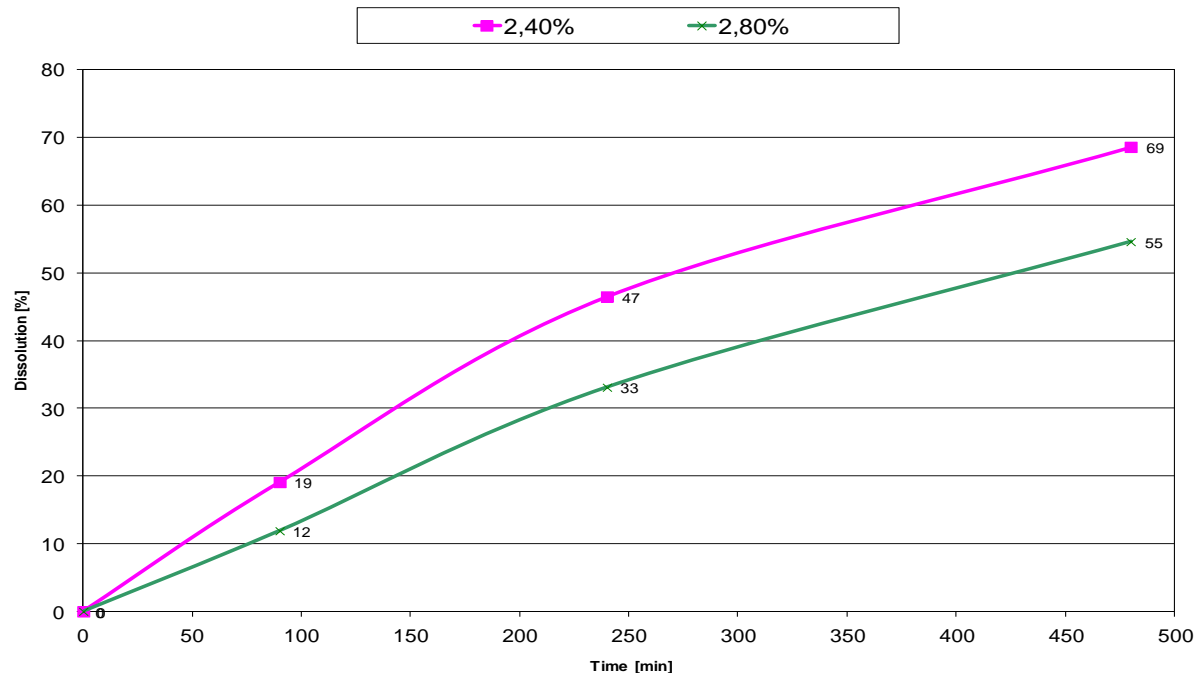


Pellet Manufacturing Methods

Direct pelletization: CPS Batch process

Case Study I: Matrix pellets with modified release coating

in vitro dissolution profiles of the controlled release pellets:
different coating levels applied on CPS core pellets

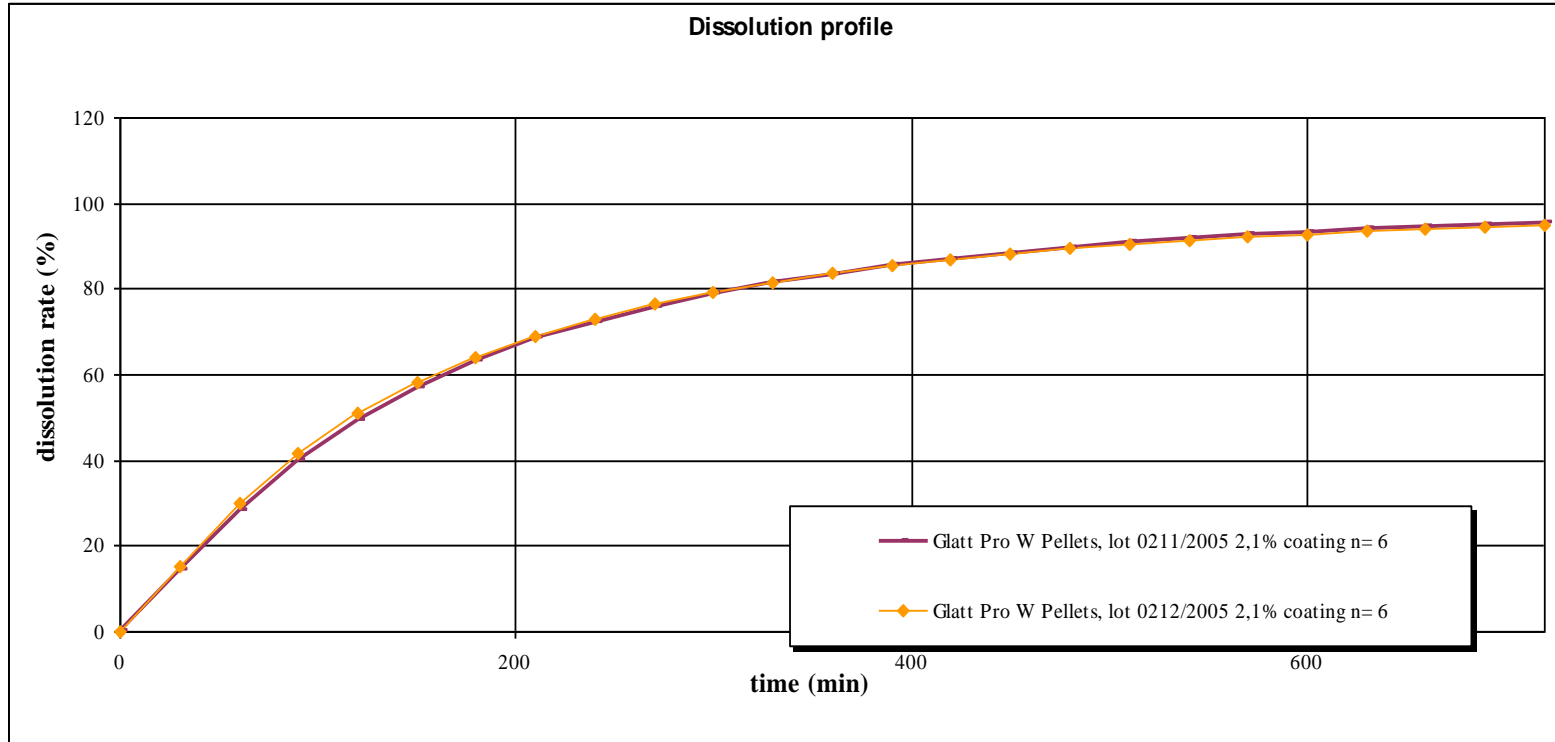




Pellet Manufacturing Methods

Direct pelletization: CPS Batch process

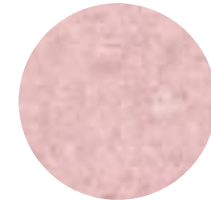
Case Study I: Matrix pellets with modified release coating



Direct pelletization: CPS Batch process

Case Study II: Matrix pellets with modified release profile

- **Drug Substance:** water soluble
low dosed API
- **Requirements:** matrix pellets with drug load < 1%
pH dependent functional polymer in pellet matrix (Eudragit L based)
- **Goal:** correlation of dissolution profile and pellets particle size
 $d_{50} = 650 \pm 150 \mu\text{m}$

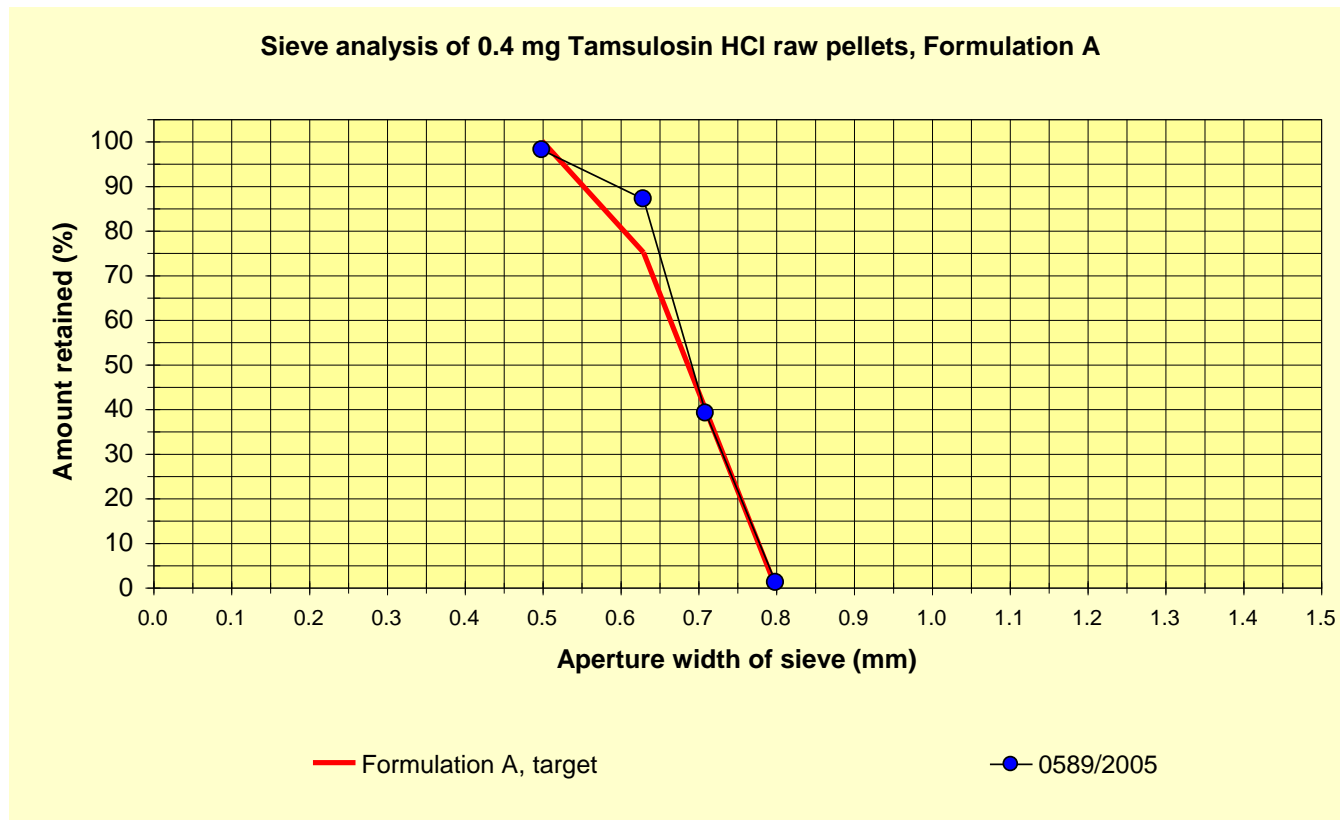




Pellet Manufacturing Methods

Direct pelletization: CPS Batch process

Case Study II: Matrix pellets with modified release profile

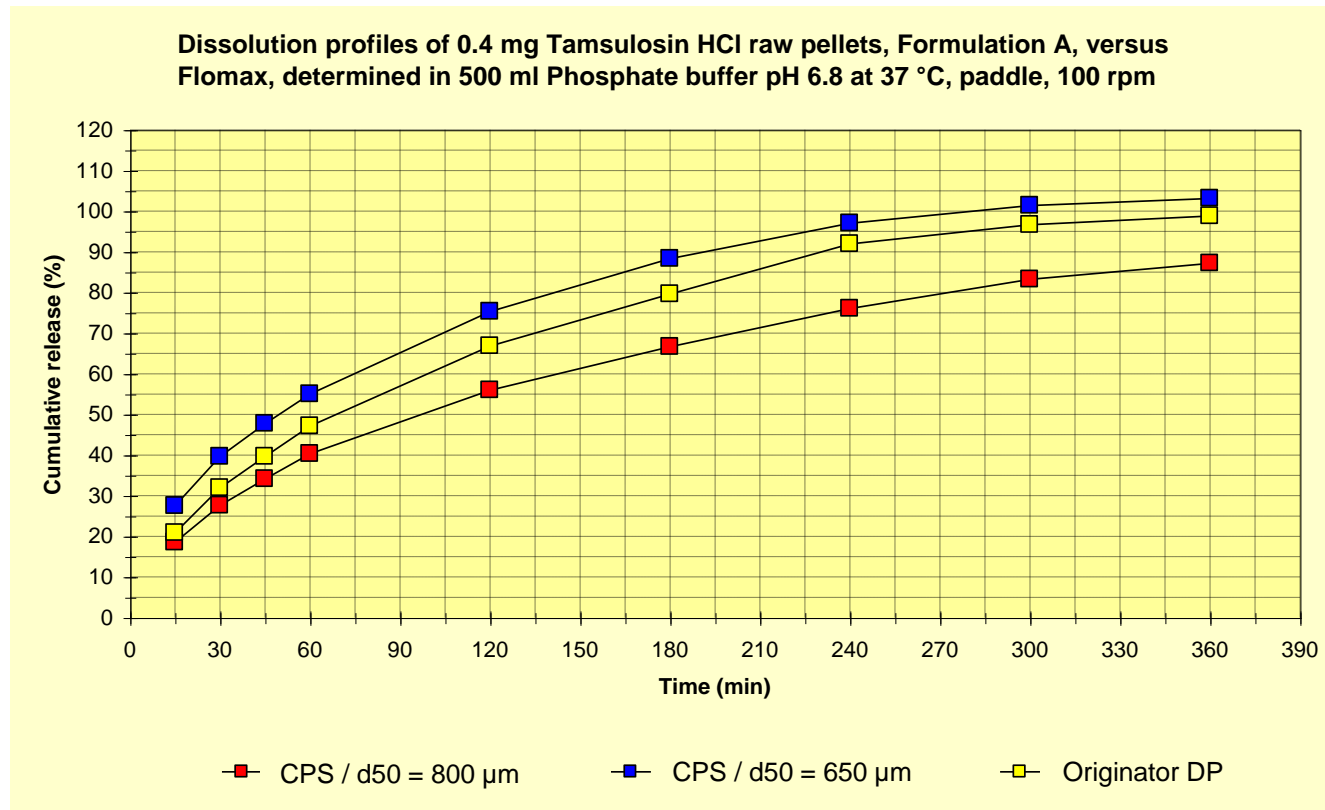




Pellet Manufacturing Methods

Direct pelletization: CPS Batch process

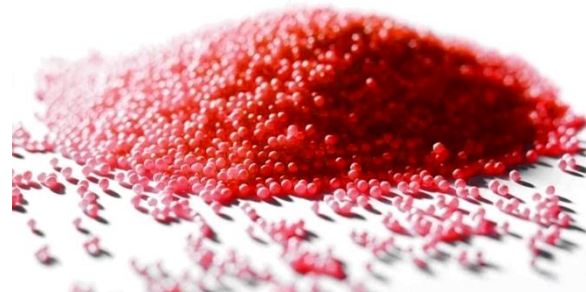
Case Study II: Matrix pellets with modified release profile



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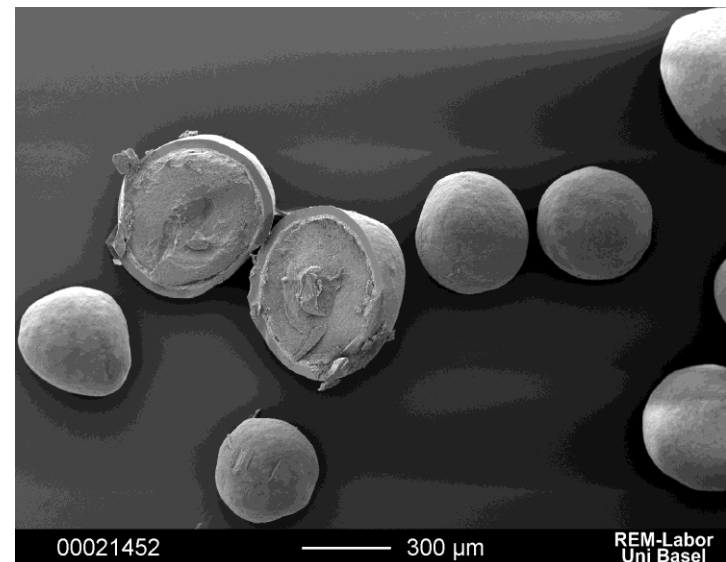
2. Pellet manufacturing methods

- **Direct pelletization methods**
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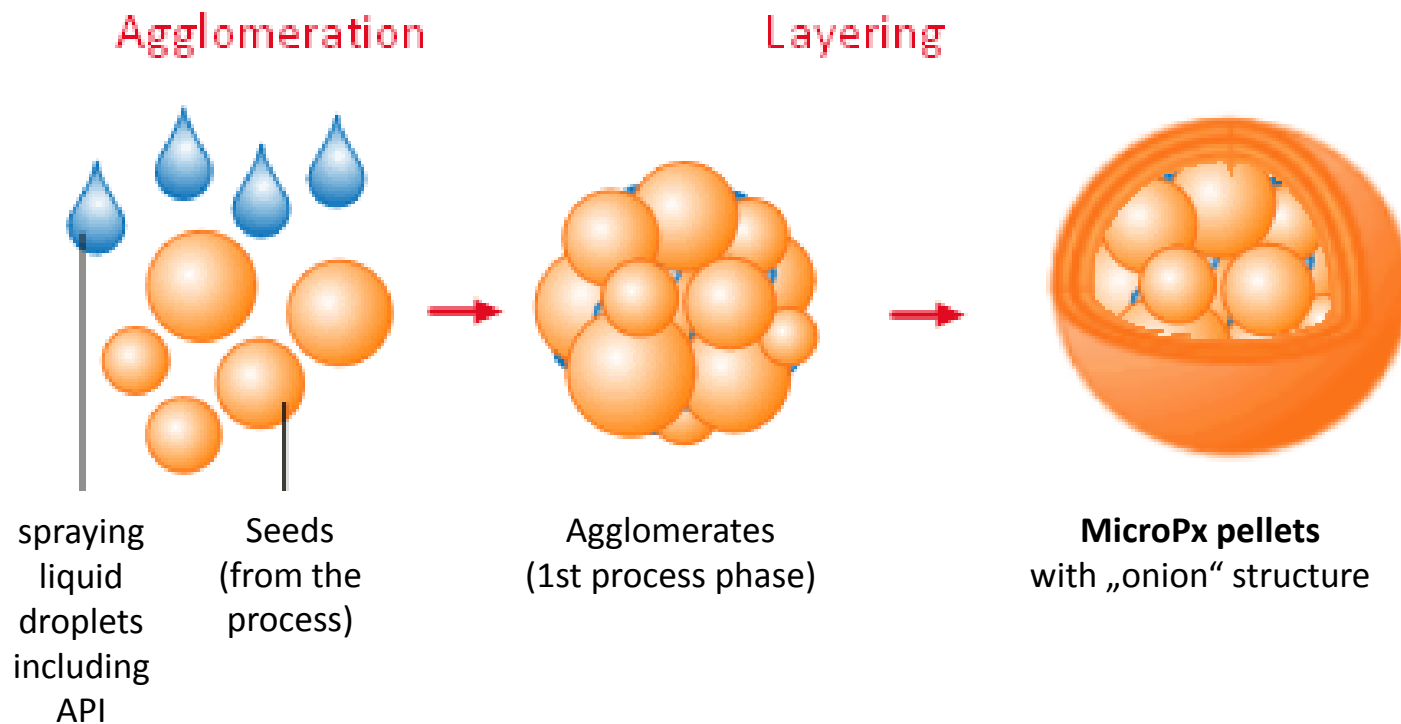


Direct pelletization: Continuous MicroPx process

- **Continuous agglomeration technology**
 - **MicroPx = MicroPellets**
 - $d(0.5) = \sim 100 - 500 \mu\text{m}$
 - high drug loaded pellets
 - perfectly round shaped pellets
 - smooth surface(perfect surface quality for further layering and coating applications)



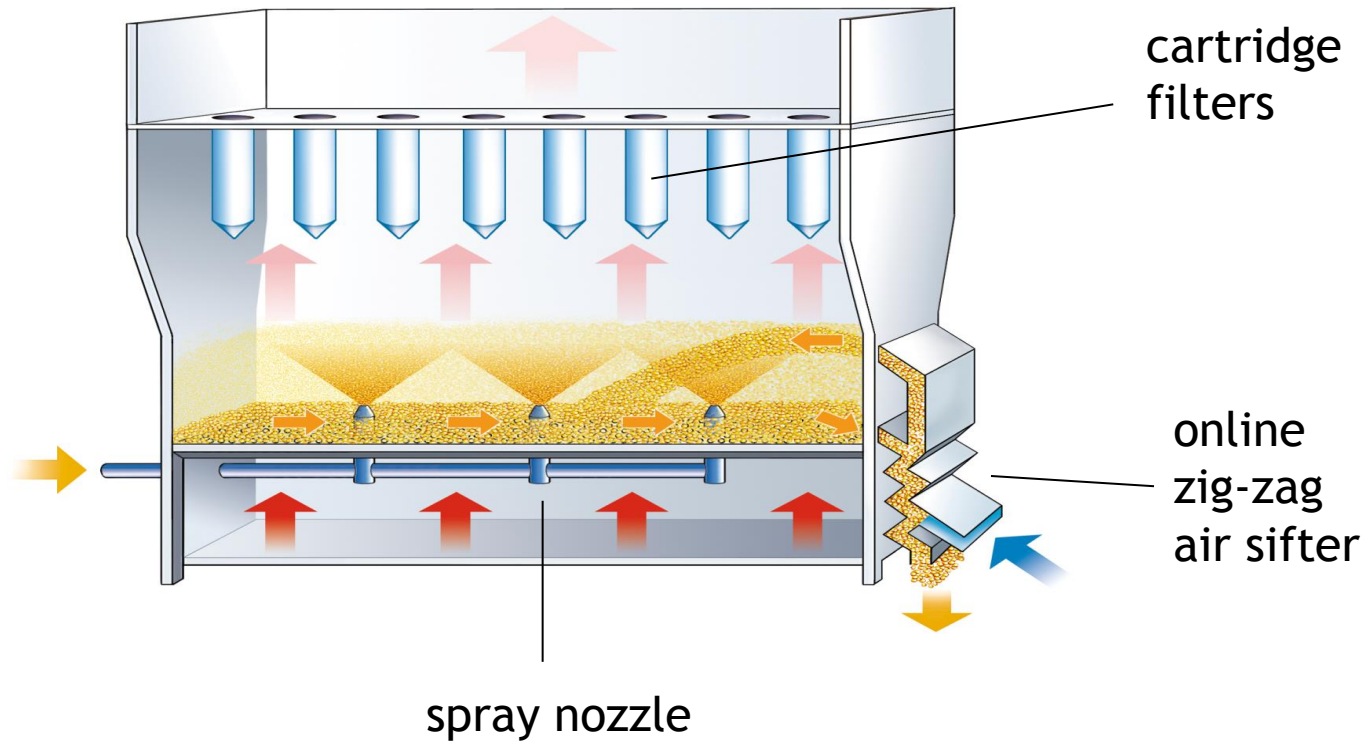
Direct pelletization: Continuous MicroPx process





Pellet Manufacturing Methods

Direct pelletization: Continuous MicroPx process





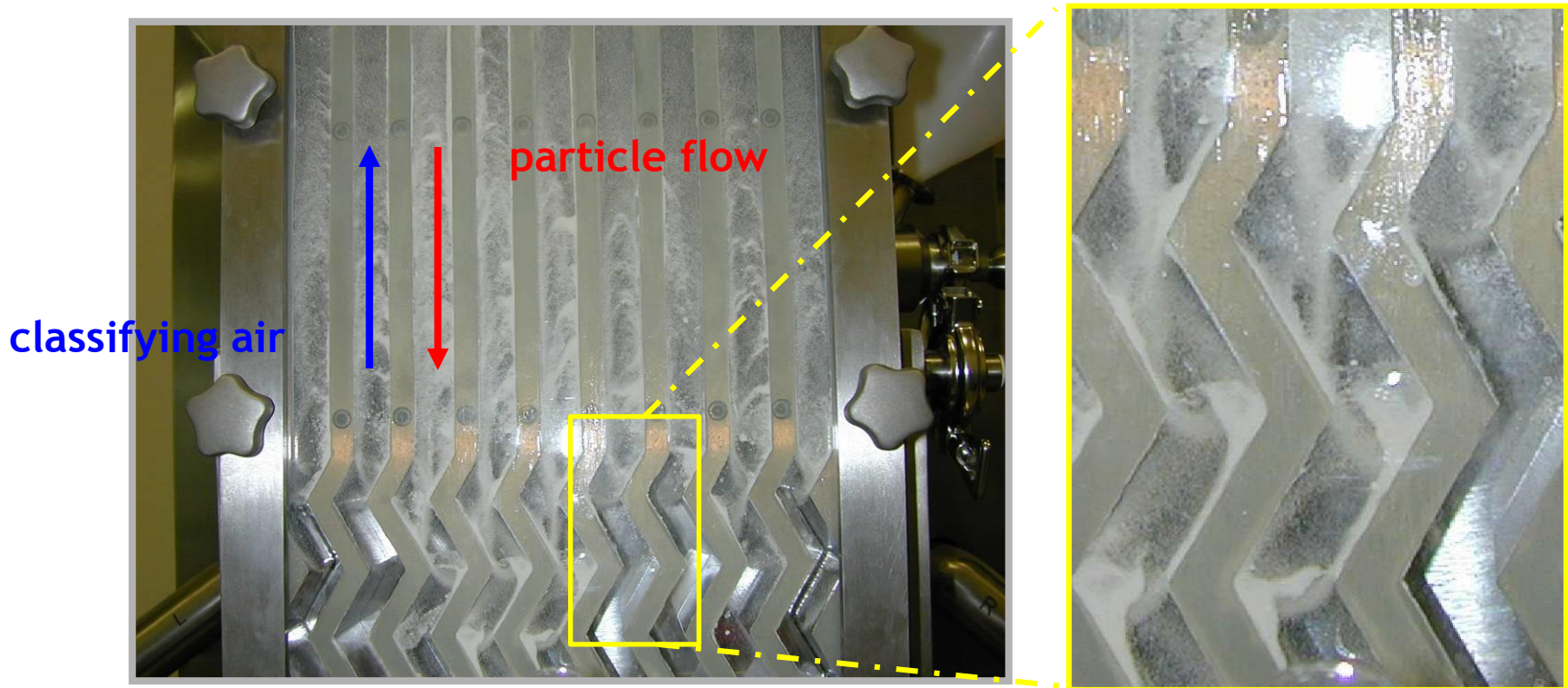
Pellet Manufacturing Methods

Direct pelletization: Continuous MicroPx process



Zig-Zag air sifter

Direct pelletization: Continuous MicroPx process

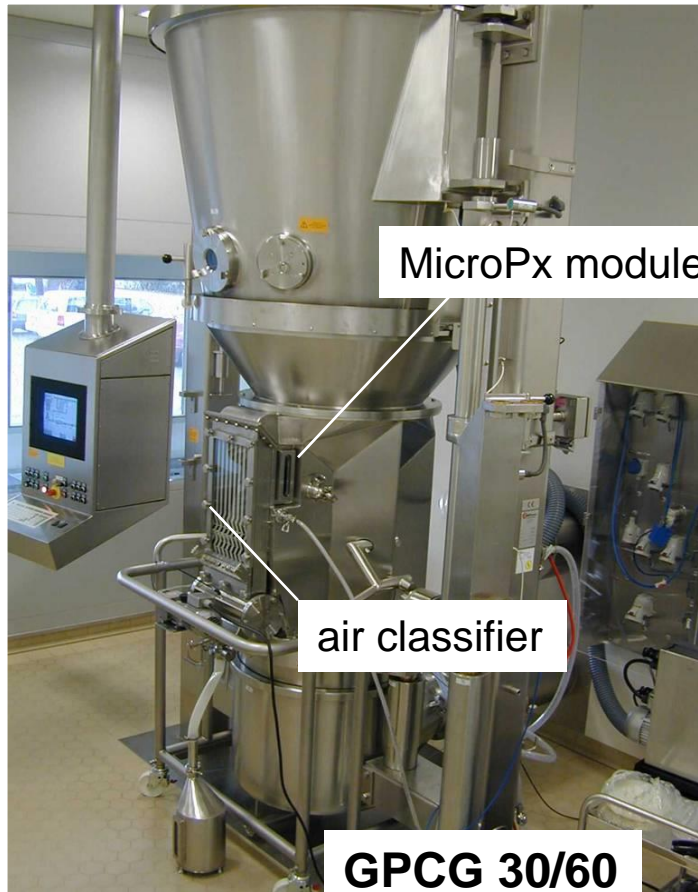


particle flow and online classifying procedure



Pellet Manufacturing Methods

Direct pelletization: Continuous MicroPx process





Pellet Manufacturing Methods

Direct pelletization: Continuous MicroPx process

Case Study III: Micropellets for MUPS tablets

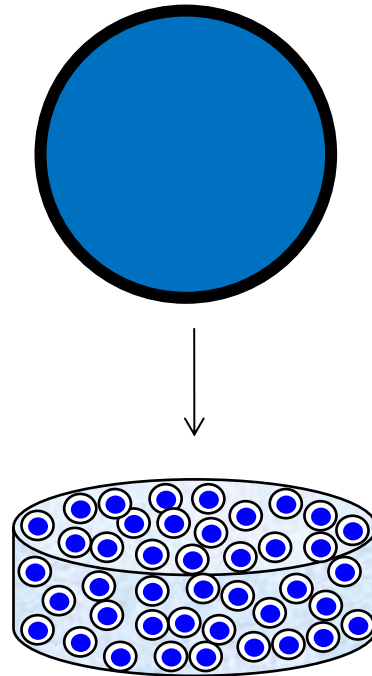
- **Drug Substance:** water soluble API
~ 20 - 250 mg dose in tablets
- **Requirements:** controlled release coated (micro)pellets
compressible to tablets
- **Goal:** in vitro dissolution profile ~ unchanged
after compression
effect of pellet size on dissolution
profiles after compression ?



Pellet Manufacturing Methods

Direct pelletization: Continuous MicroPx process

Case Study III: Micropellets for MUPS tablets

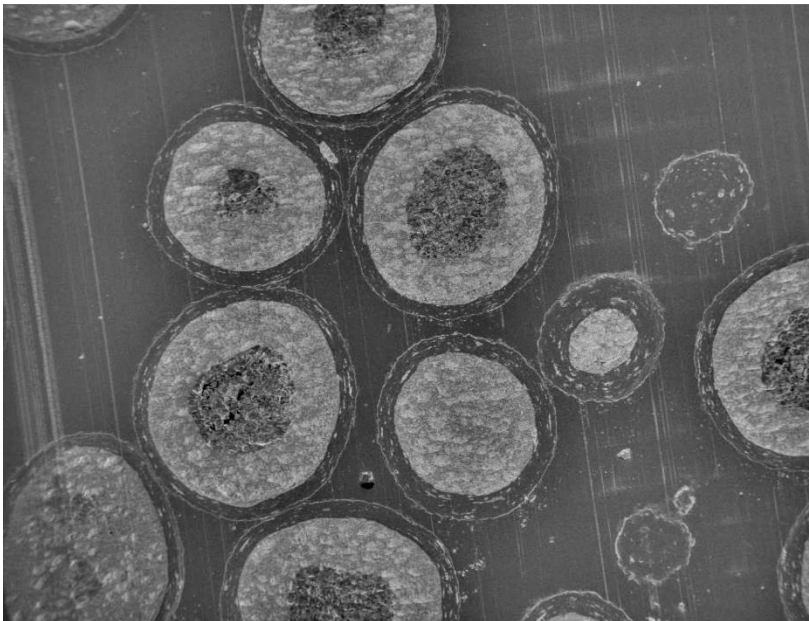




Pellet Manufacturing Methods

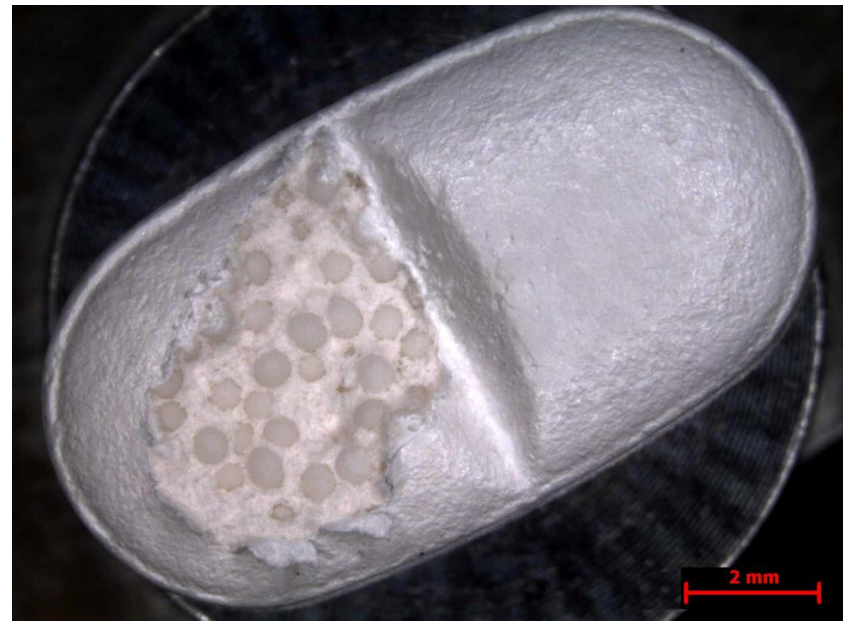
Direct pelletization: Continuous MicroPx process

Case Study III: Micropellets for MUPS tablets



50 : 1

500µm

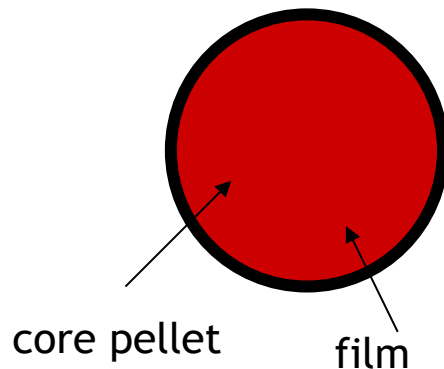


Direct pelletization: Continuous MicroPx process

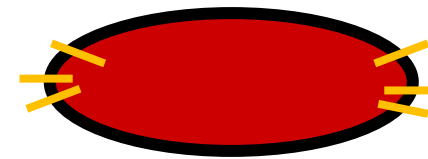
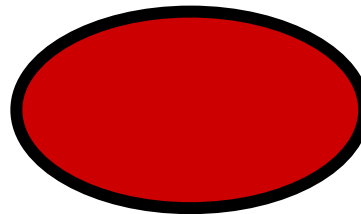
Case Study III: Micropellets for MUPS tablets

Potential damaging of pellets / film coatings during compaction

before compaction



deformation during compaction



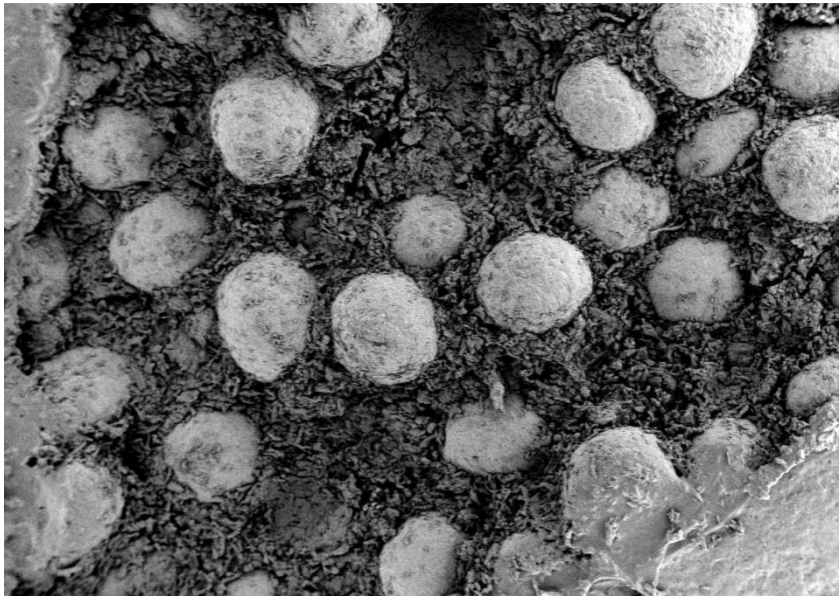
breakage of film



Pellet Manufacturing Methods

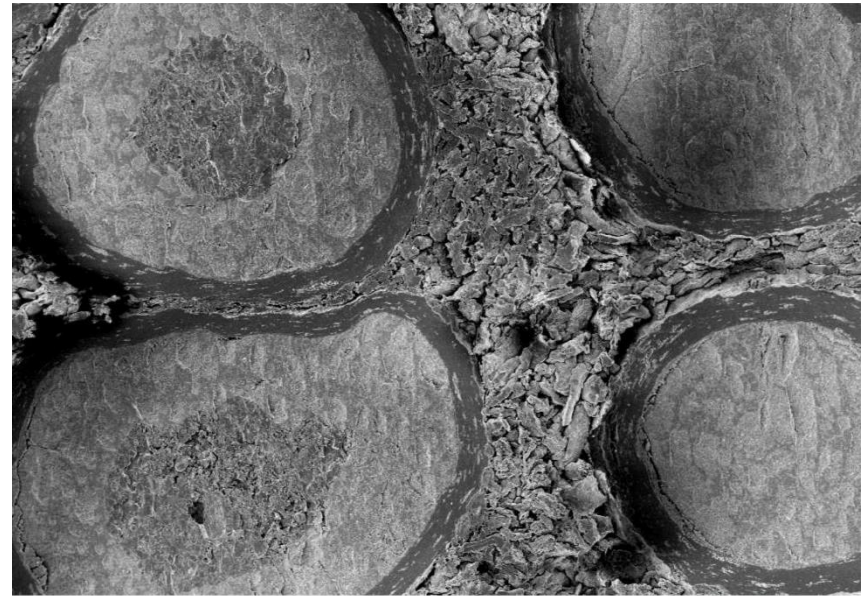
Direct pelletization: Continuous MicroPx process

Case Study III: Micropellets for MUPS tablets



25 : 1

1mm

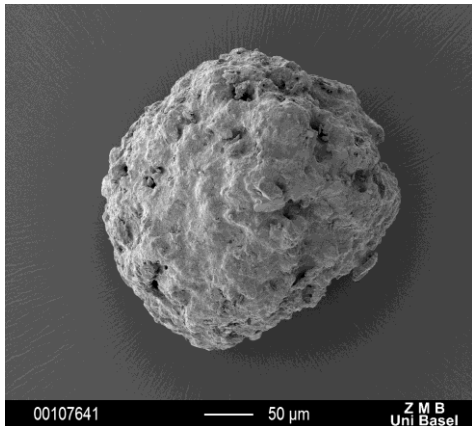
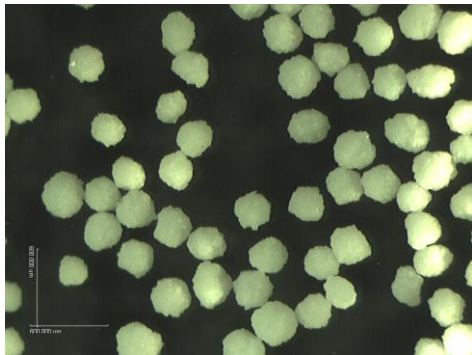


100 : 1

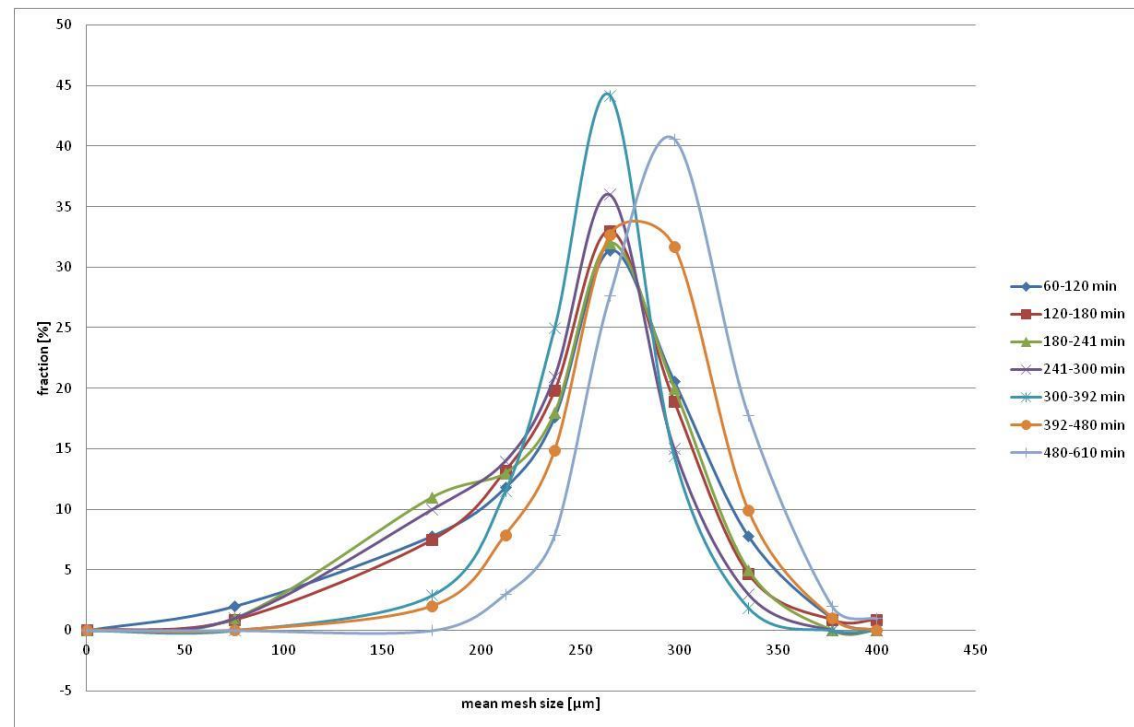
200µm

Direct pelletization: Continuous MicroPx process

Case Study III: Micropellets for MUPS tablets

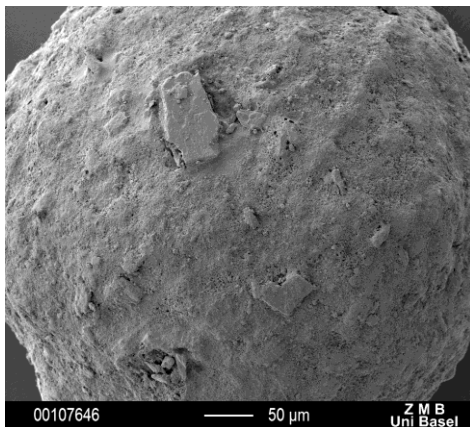
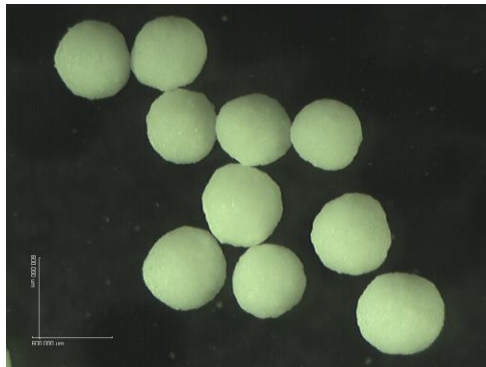


MicroPx pellets ~ 200 - 355 μm

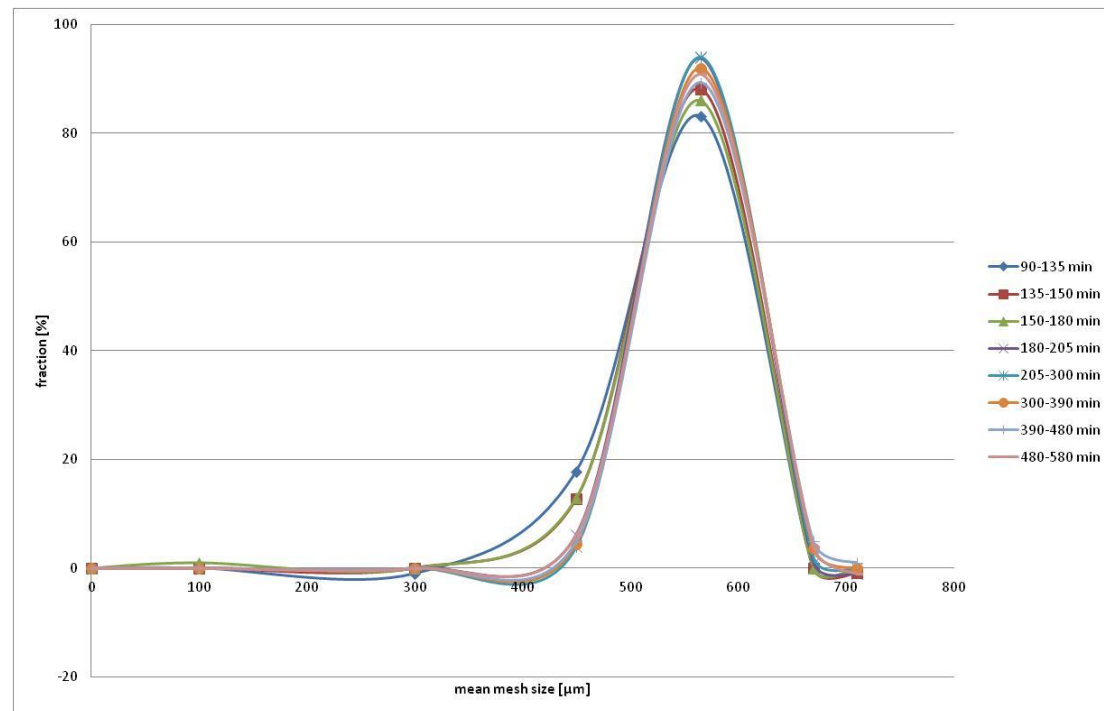


Direct pelletization: Continuous MicroPx process

Case Study III: Micropellets for MUPS tablets

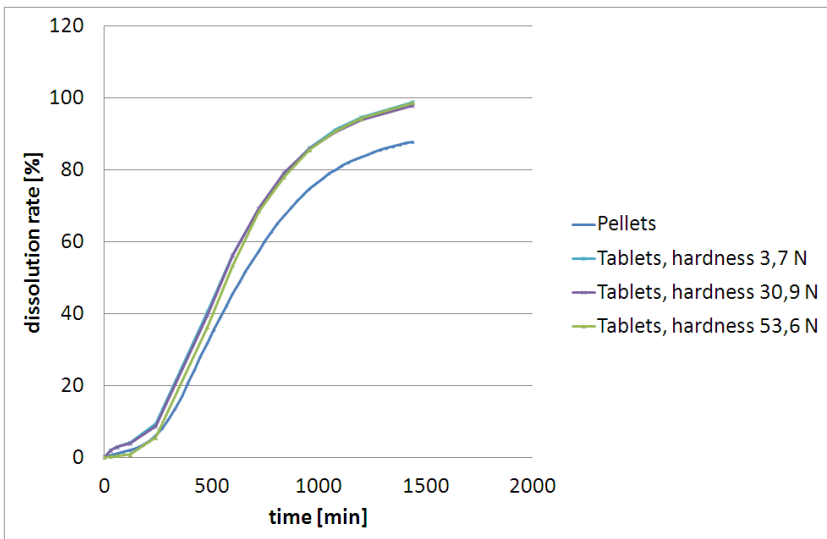
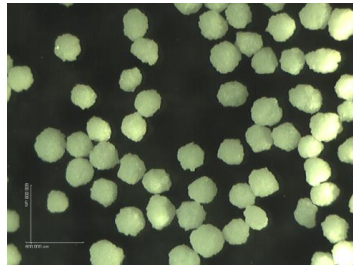


MicroPx pellets ~ 400 - 630 µm

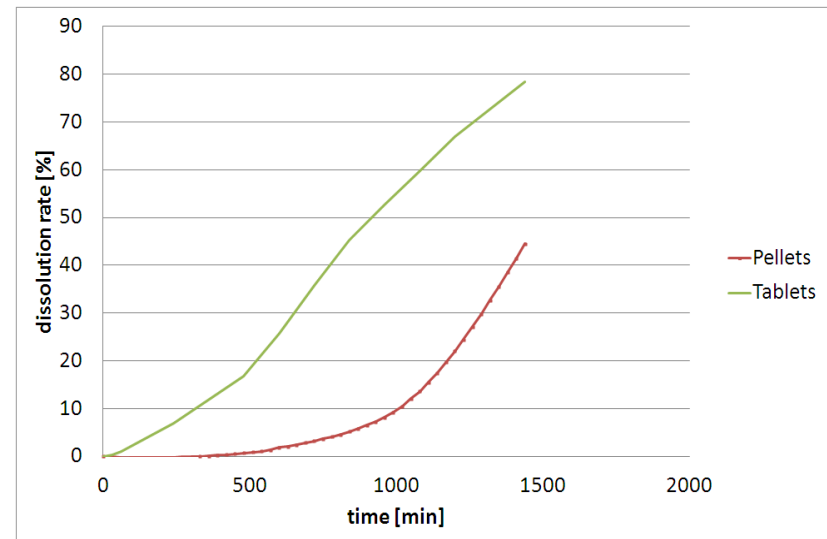
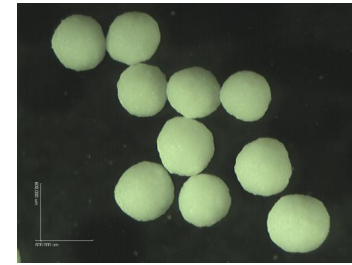


Direct pelletization: Continuous MicroPx process

MicroPx pellets coated ~ 200 - 355 μm

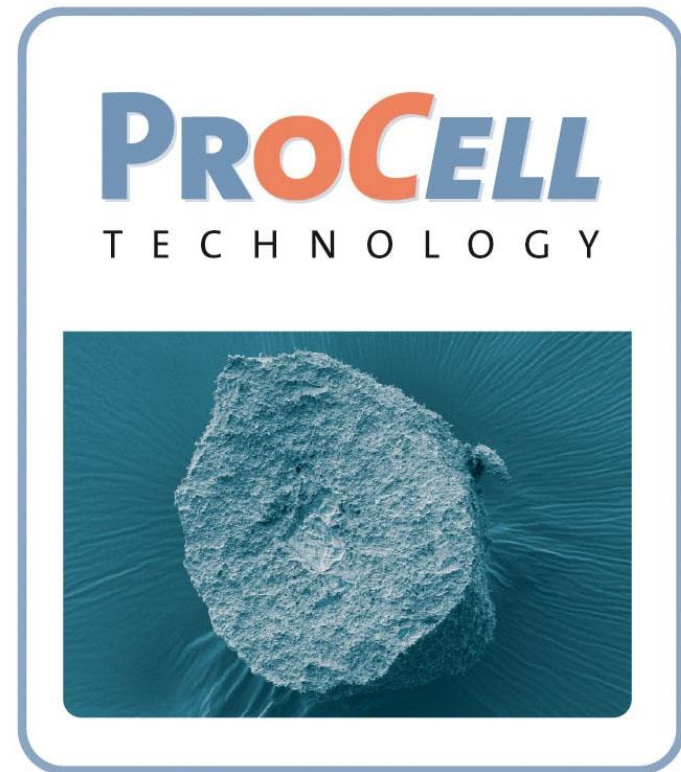


MicroPx pellets coated ~ 400 - 630 μm



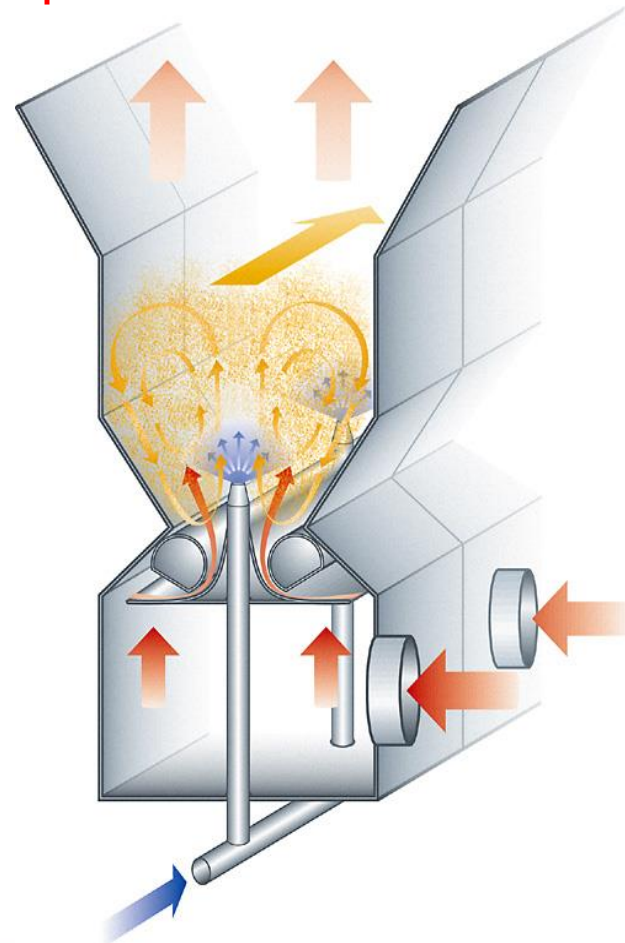
Direct pelletization: Continuous ProCell process

- Direct pelletization technology
- Spouted bed technology, which combines drying + granulation (close to MicroPx™)
- No inlet air distribution plate
- ProCell processes can be performed from solutions, melts, suspensions and emulsions

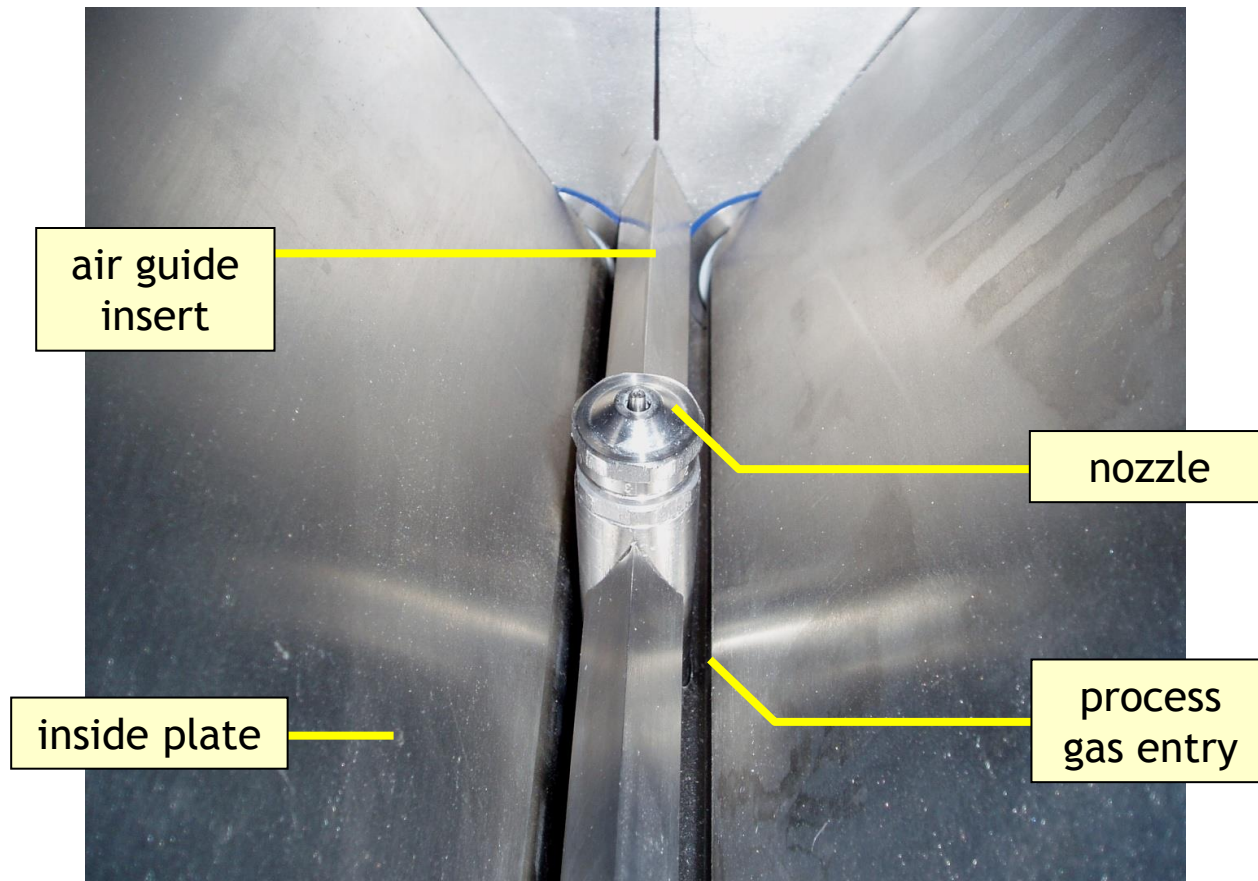


Direct pelletization: Continuous ProCell process

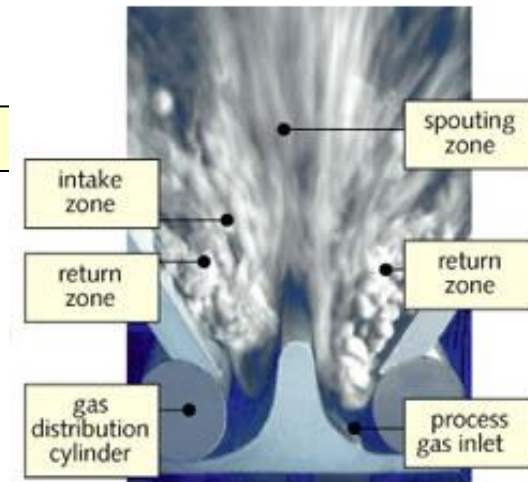
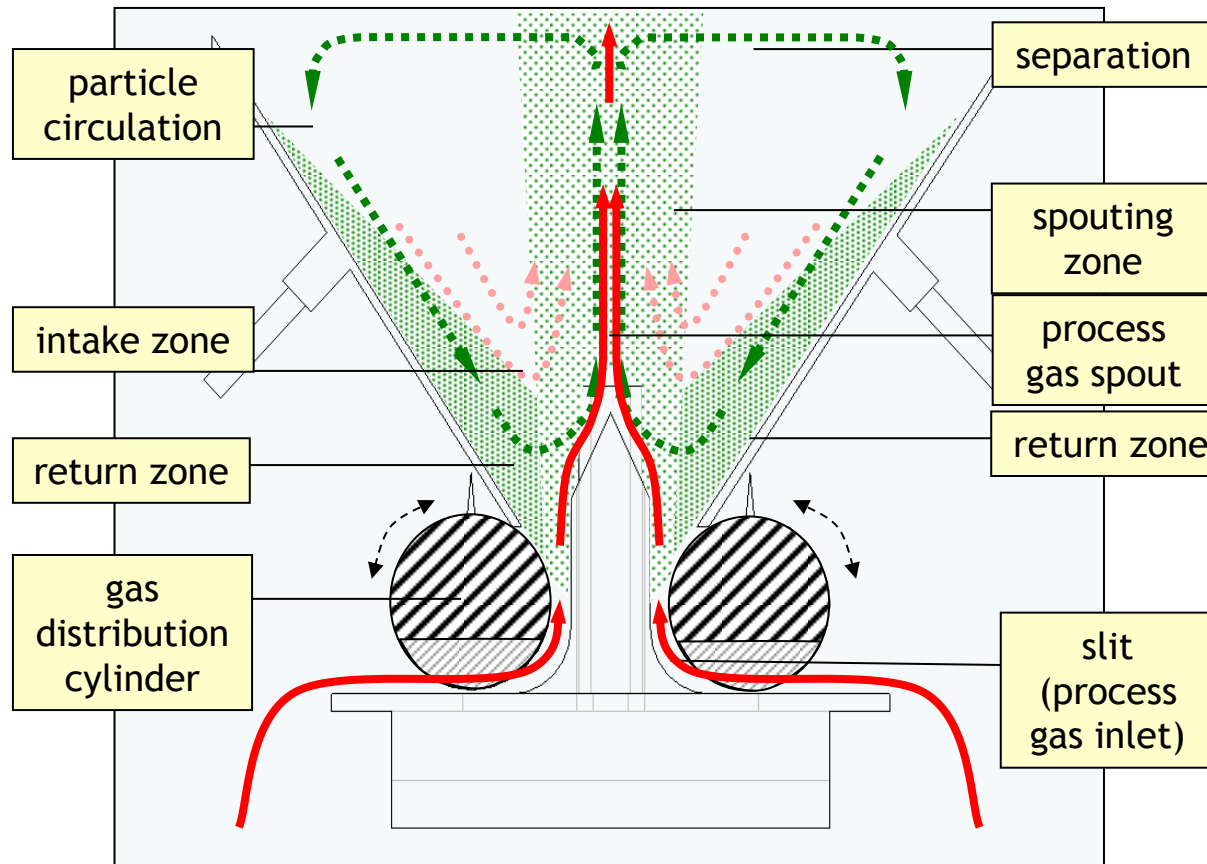
- No inert starter materials required
- Controlled particle movement
- Continuous process
- Highly efficient, large throughput, low cost



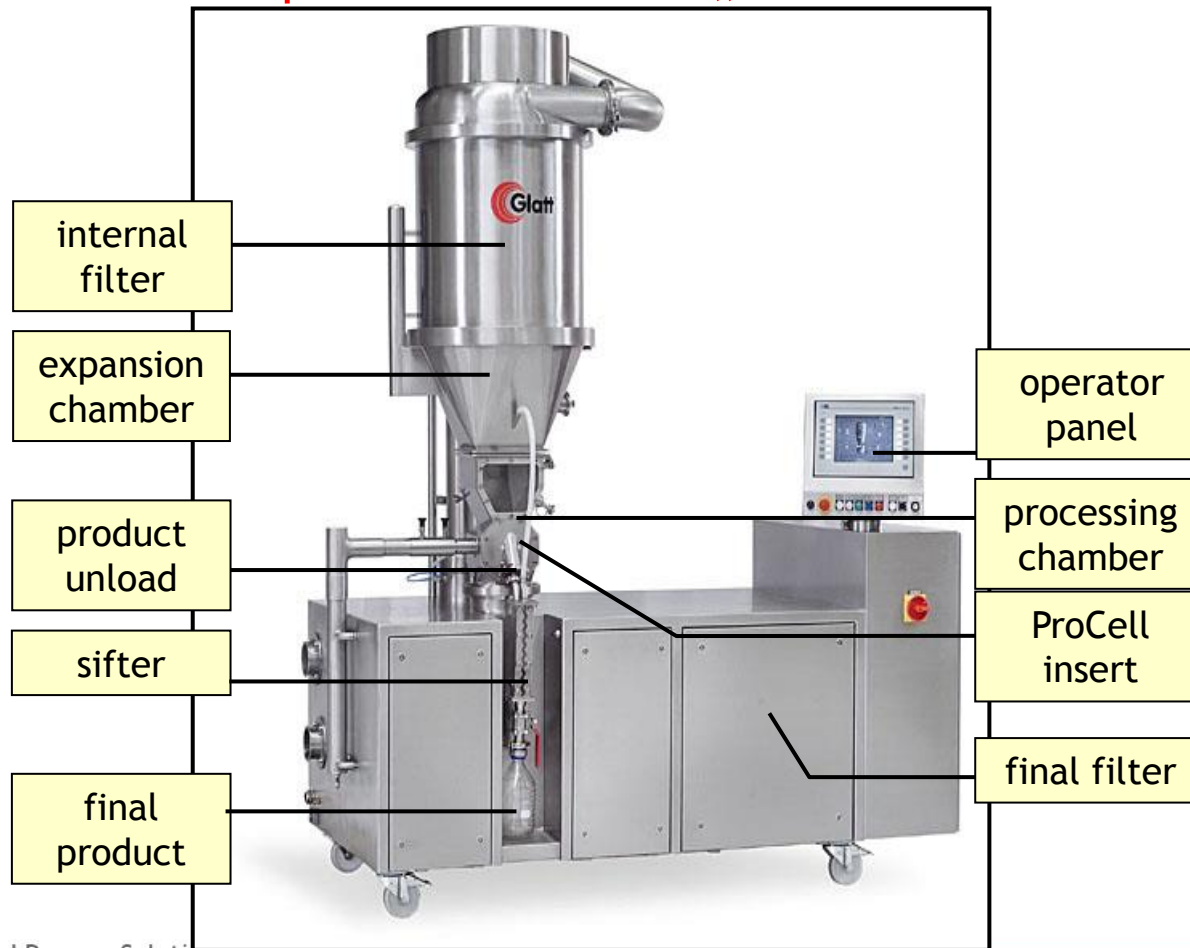
Continuous ProCell process: Principle of operation



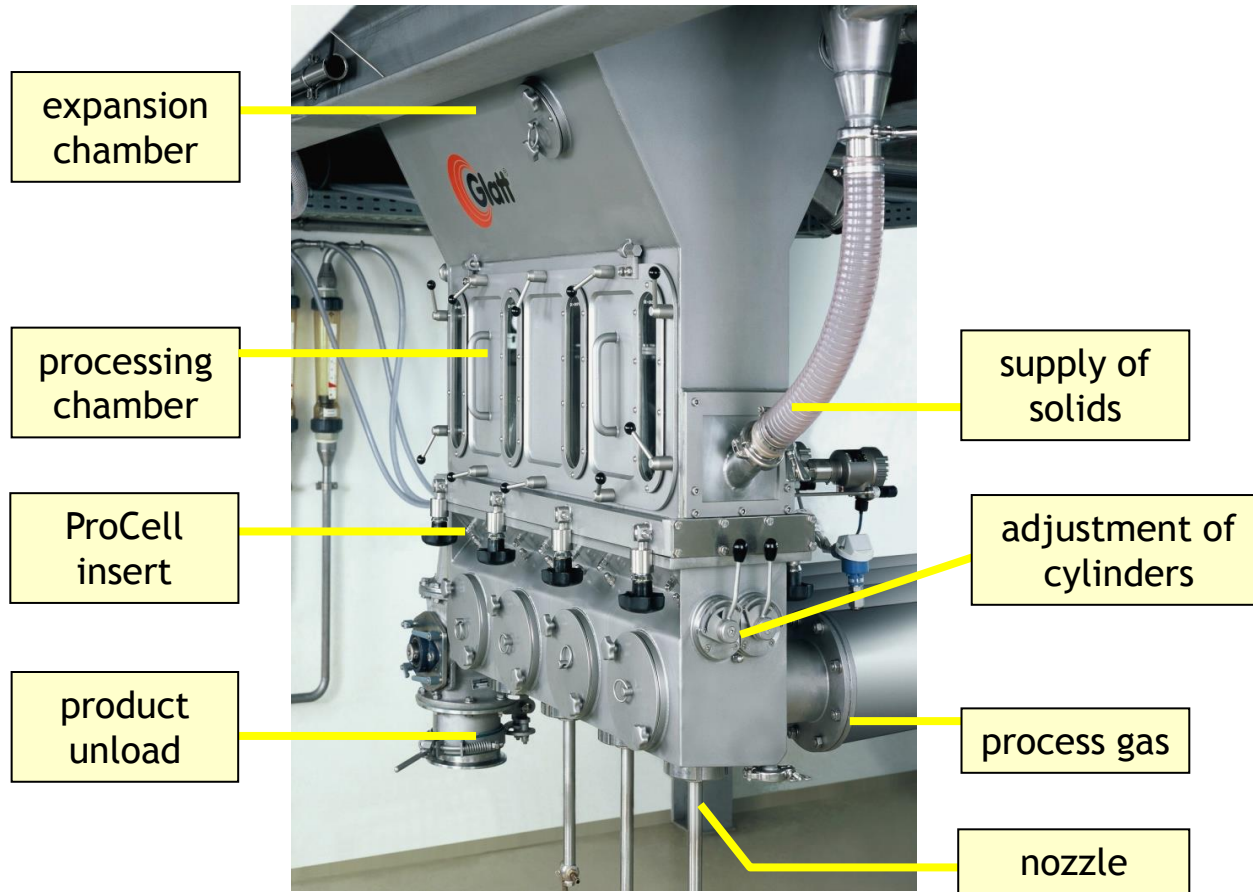
Continuous ProCell process: Zones



Continuous ProCell process: Lab Unit „Procell 5“



Continuous ProCell process: Pilot Unit „Procell 20“





Pellet Manufacturing Methods

Continuous ProCell process

Product Characteristics:

- Products processed by melt granulation, suspensions, solutions
- Highest drug loading possible (up to 100 %)
- Particle size range from 50 - 1500 μm possible
- High density, low attrition, low friability
- No loss of material by means of recirculating product
 - high yield
 - recirculation procedure has to be individually evaluated with regards to product quality (stability, degradation)



Pellet Manufacturing Methods

Continuous ProCell process

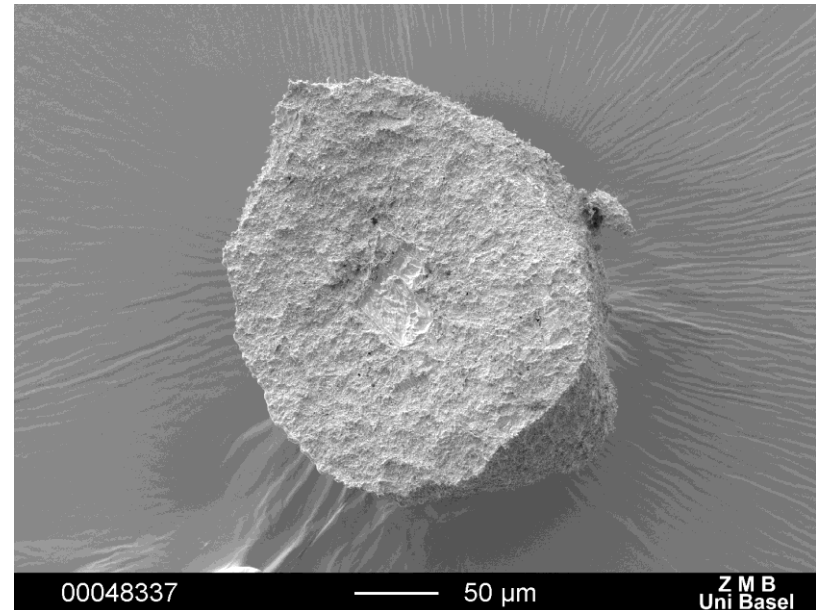
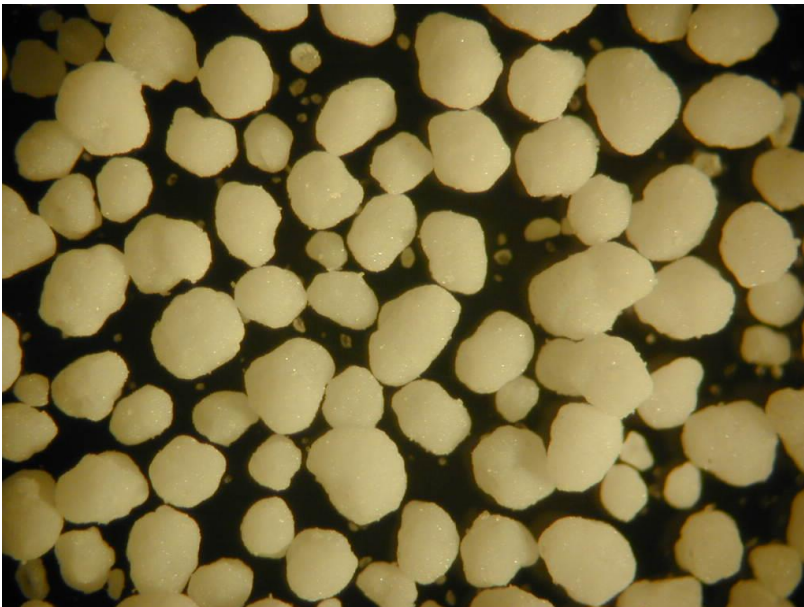
Case Study IV: 100 % Ibuprofen pellets for direct compression

- Ibuprofen is known for its critical compression behaviour on high performance tableting machines
- Ibuprofen ProCell pellets (Ibuprofen DC 100), comprising 100 % drug substance
- Processed by melt granulation/pelletization, subsequent compression into immediate release tablets
- Ibuprofen ProCell pellets exhibit excellent compression characteristics, robust process feasible

Continuous ProCell process

Case Study IV: 100 % Ibuprofen pellets for direct compression

100 % Ibuprofen pellets processed from ProCell™
melt granulation/pelletization, aspect



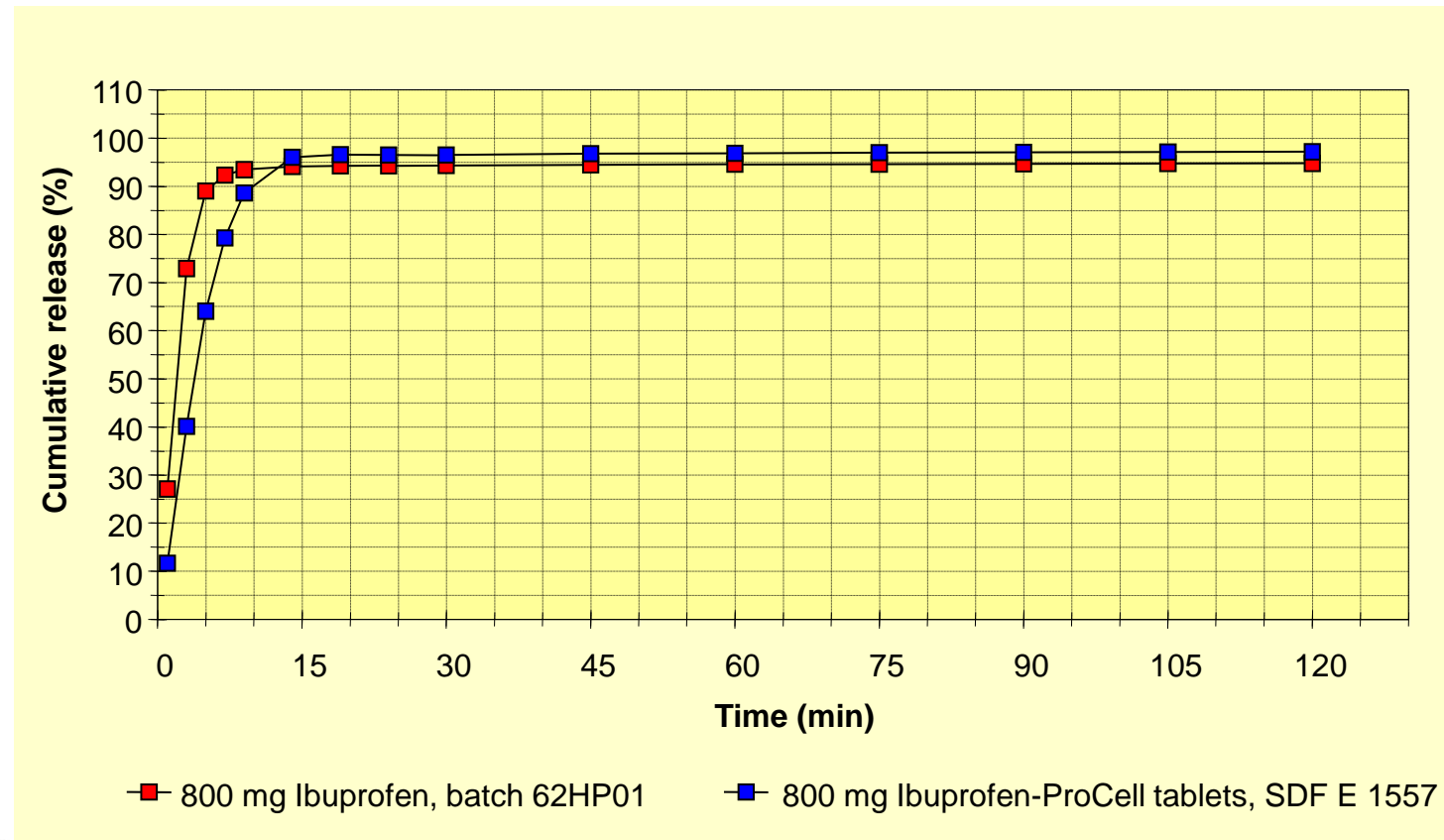
Particle size range: 200 - 400 µm



Pellet Manufacturing Methods

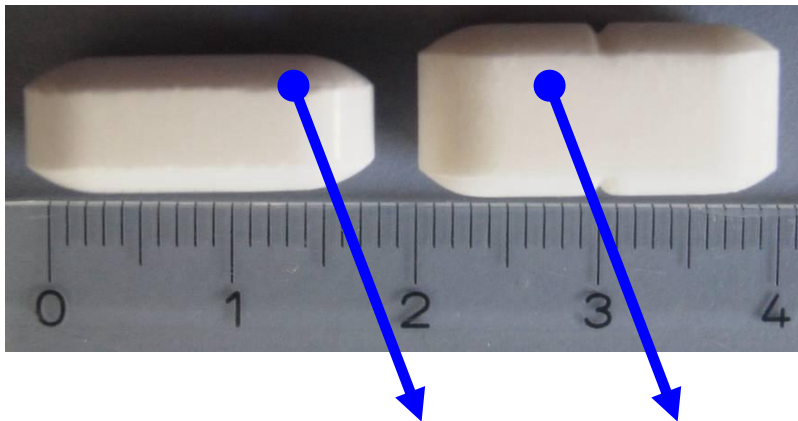
Continuous ProCell process

Case Study IV: 100 % Ibuprofen pellets for direct compression



Continuous ProCell process

Case Study IV: 100 % Ibuprofen pellets for direct compression



Evaluation of high drug loaded ER matrix tablets manufactured by direct compression with Ibuprofen-ProCell pellets

High API loading possible

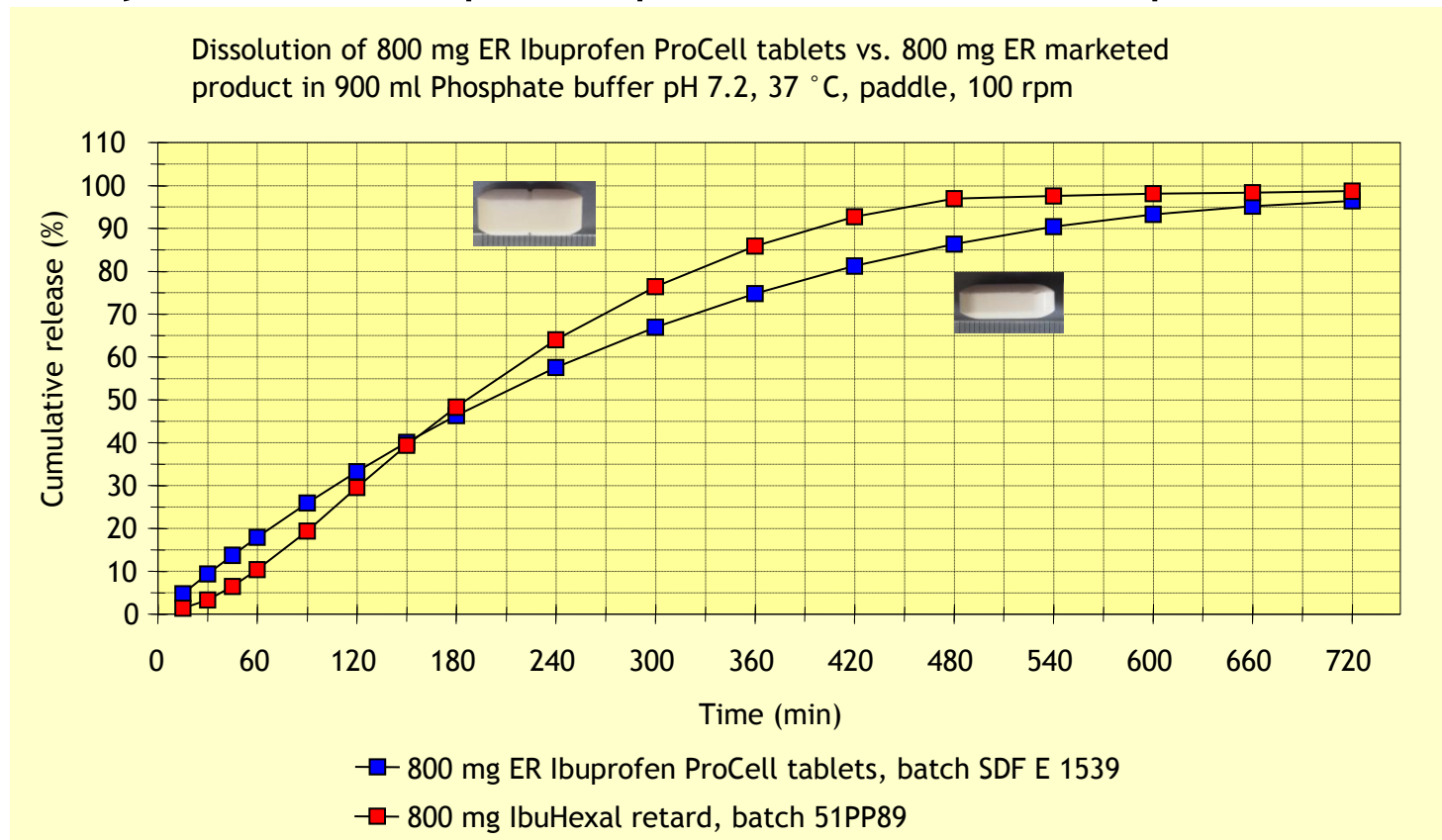
ER dissolution characteristics feasible

Significant reduction in tablet size

| | ProCell product | Market product |
|-----------------------|-----------------|----------------|
| Mass (mg) | 833 | 1220 |
| Dosage strength (mg) | 800 | 800 |
| Tablet dimension (mm) | 18 x 8 | 18.7 x 8.1 |
| Height (mm) | 7,15 | 8,85 |

Continuous ProCell process

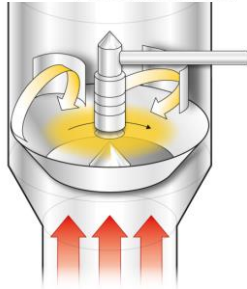
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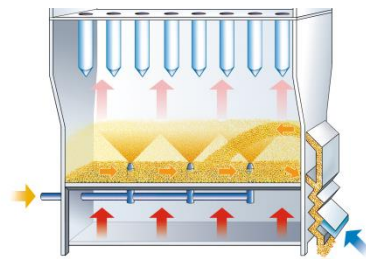
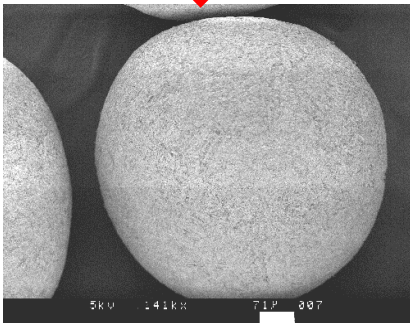


Pellet Manufacturing Methods

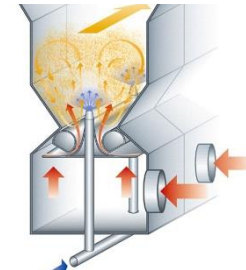
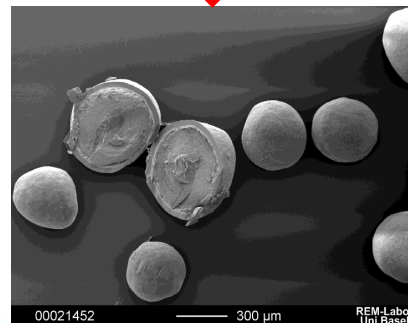
Summary Innovative Direct Pelletization Technologies



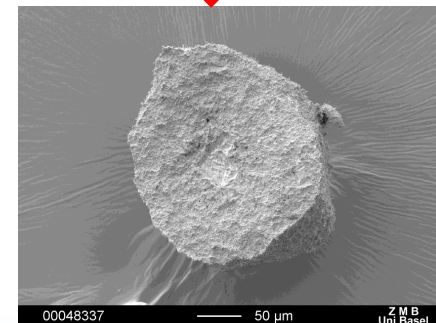
modified fluid bed rotor batch process for



continuous direct fluid bed pelletization process



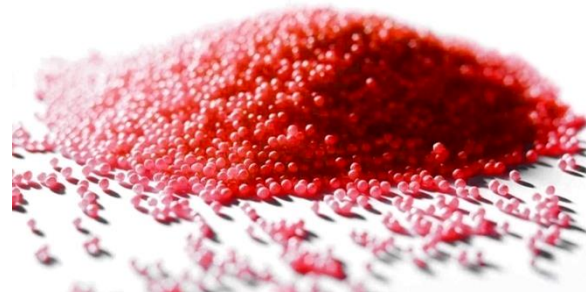
continuous spouted bed spray granulation process



1. Introduction

2. Pellet manufacturing methods

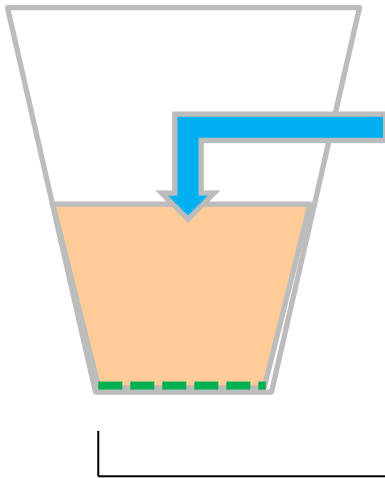
- Direct pelletization methods
 1. Batch Processes including case studies (Rotor, CPS)
 2. Continuous Processes including case studies (MicroPx, Procell)
- Pellet layering and coating methods
 1. Wurster bottom spray system
 2. Tangential spraying system



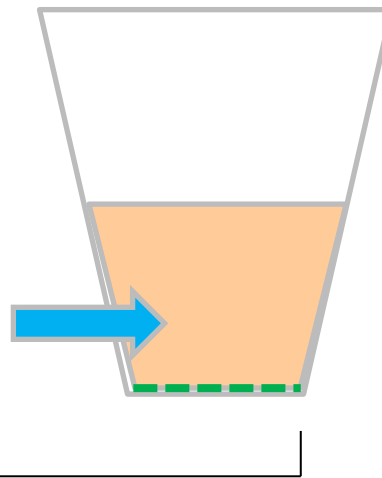
Pellet Layering and Coating Methods: Introduction

Spray nozzle positions

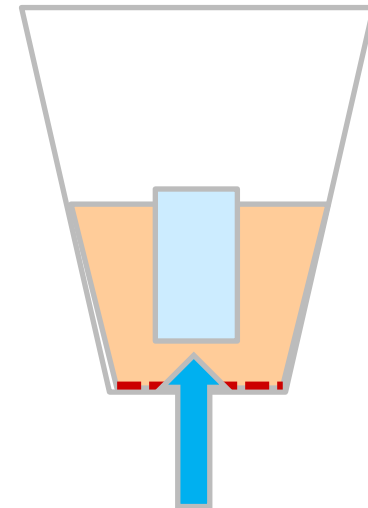
top spray



tangential spray



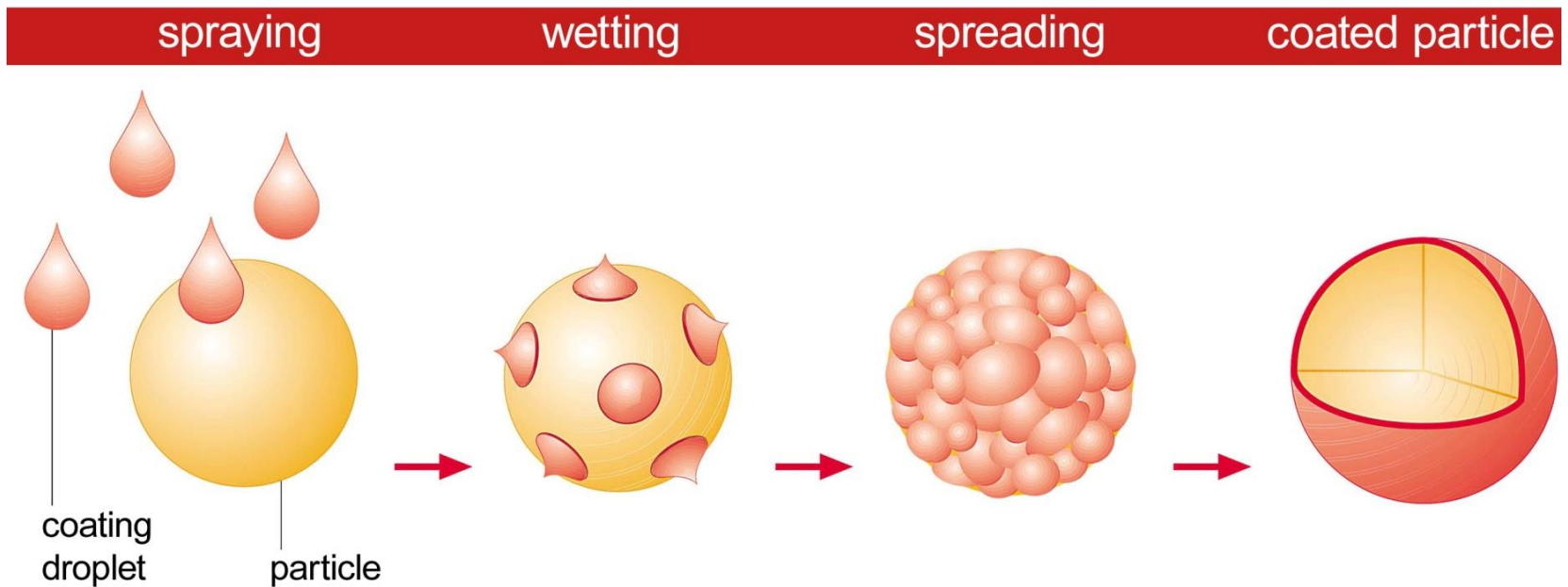
bottom spray
(Wurster)



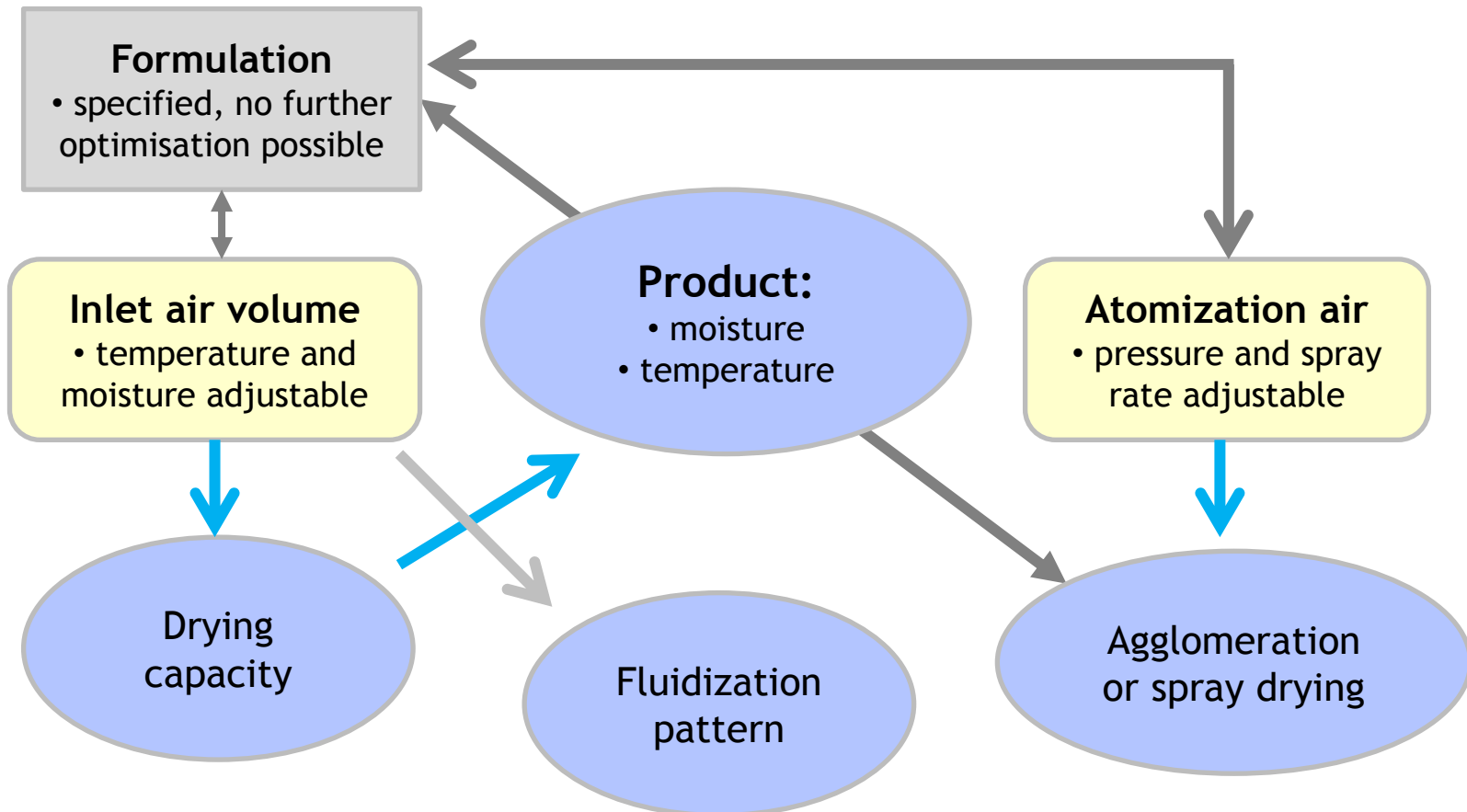
granulation

Pellet Layering and Coating Methods: Principle

Starting beads + liquid to be processed



Pellet Layering and Coating Methods : Formulation and process parameters





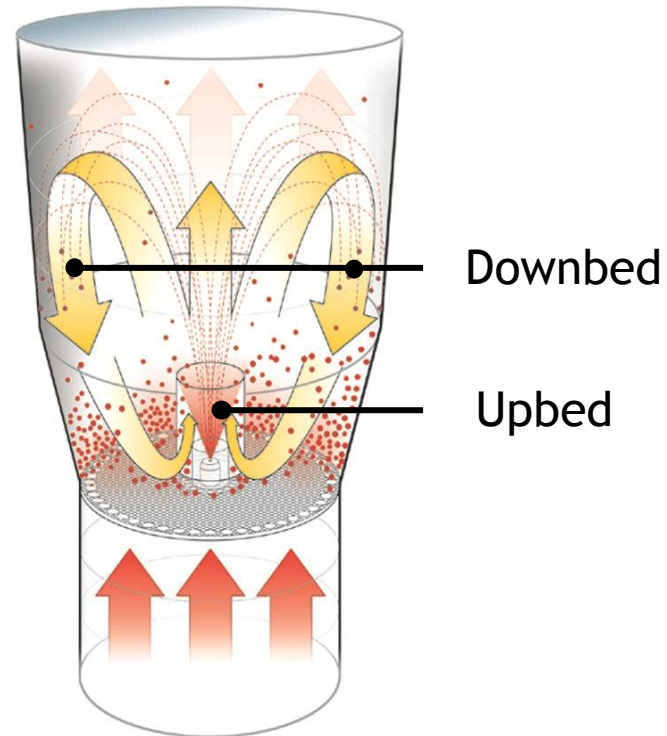
Pellet Manufacturing Methods

Pellet Layering and Coating Methods: Wurster technology

- Starting beads
 - Application of drug → Layering
 - Application of functional Coat → Coating
-
- application of liquid(s) on pellets
 - no losses
 - no agglomerates
 - specified dissolution profile to be achieved

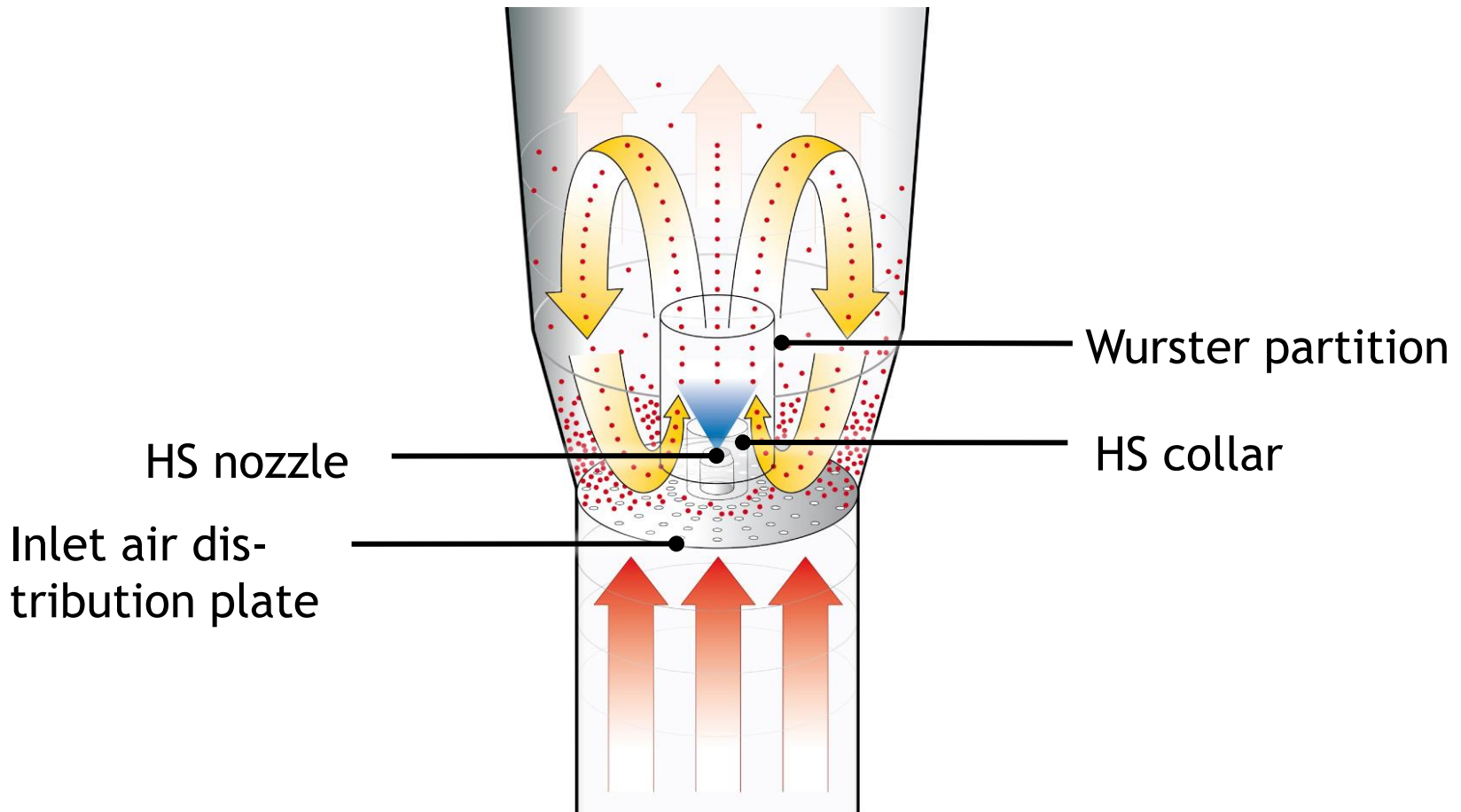


Wurster technology: Fluid bed unit in bottom spray configuration



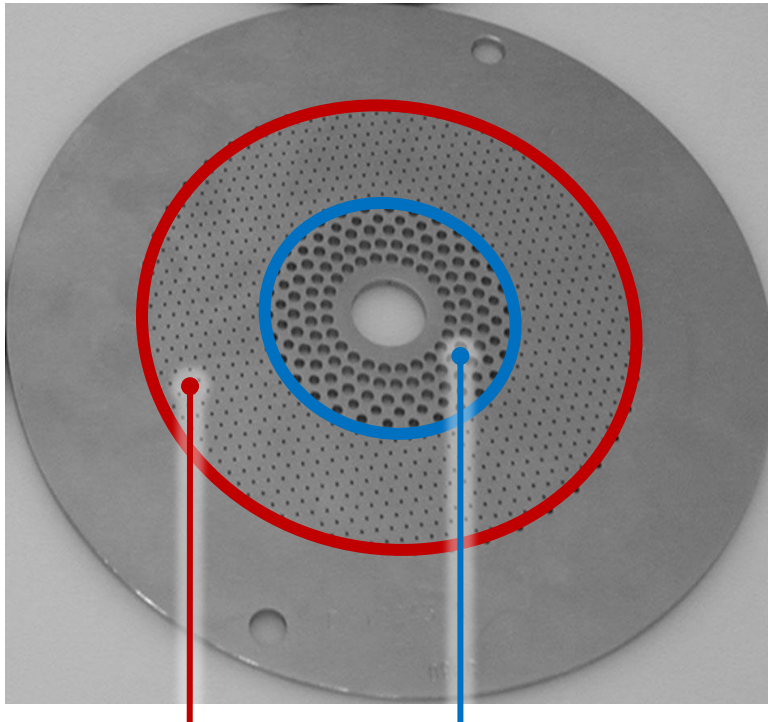
Spray nozzle position:
Bottom-spray ("Wurster")

Wurster technology: Characteristics of bottom spray processes



Wurster technology: Characteristics of bottom spray processes

Inlet air distribution plate



Downbed
zone

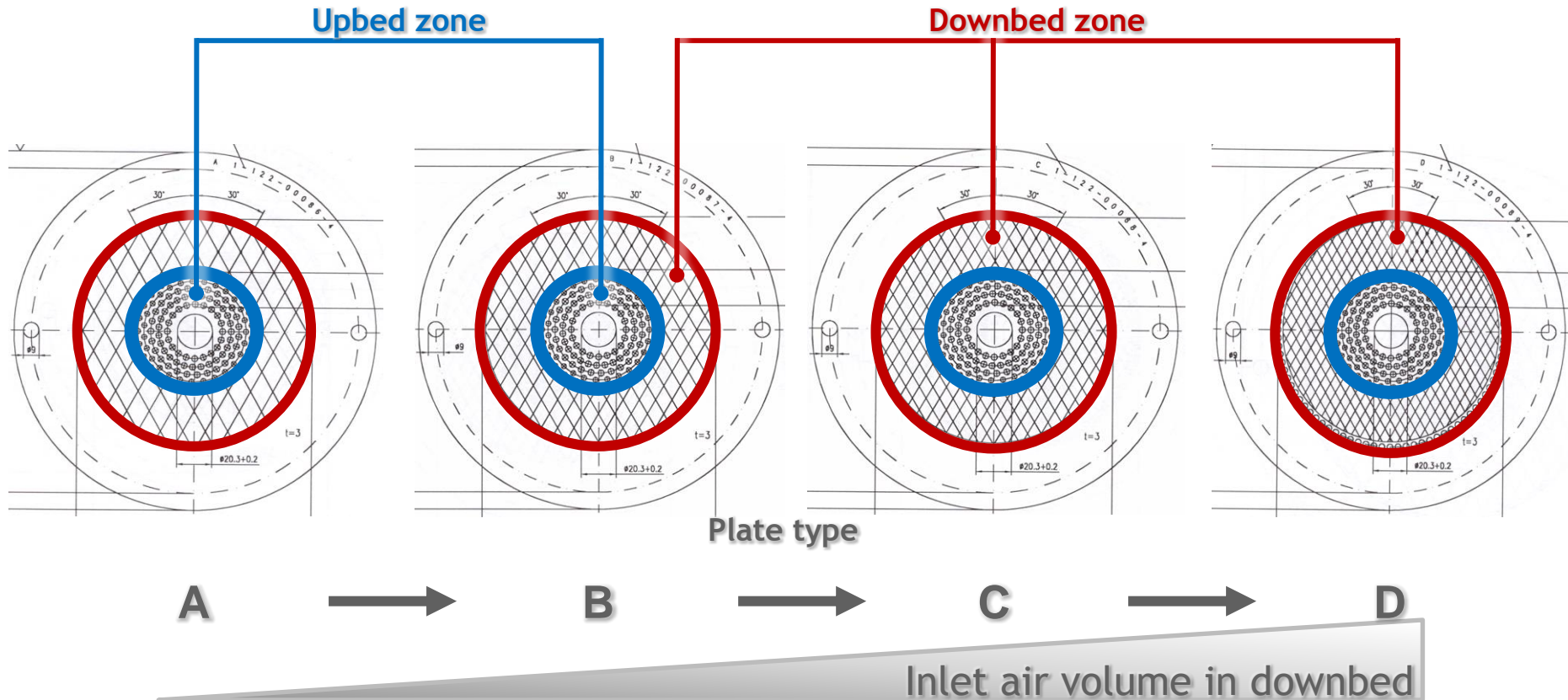
Upbed
zone

The air flow in the upbed zone is most important for the homogenous application of the film.

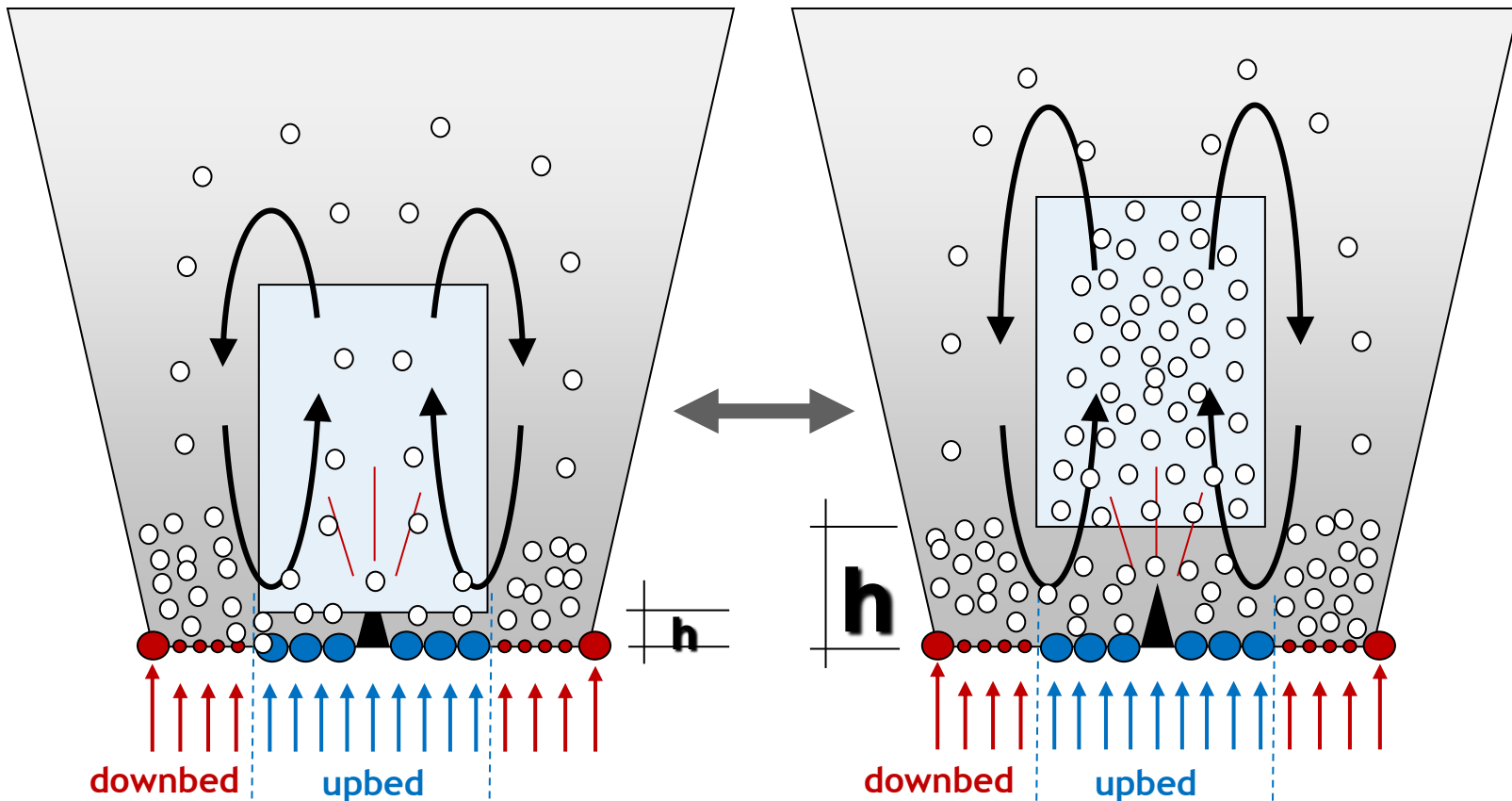
The most feasible configuration is selected for each product quality (particle size of substrate).

Wurster technology: Characteristics of bottom spray processes

Inlet air distribution plate



Wurster technology: Characteristics Wurster Partition



Wurster technology: Characteristics of bottom spray processes

High Speed (“HS”) nozzle system



HS nozzle

+ Collar



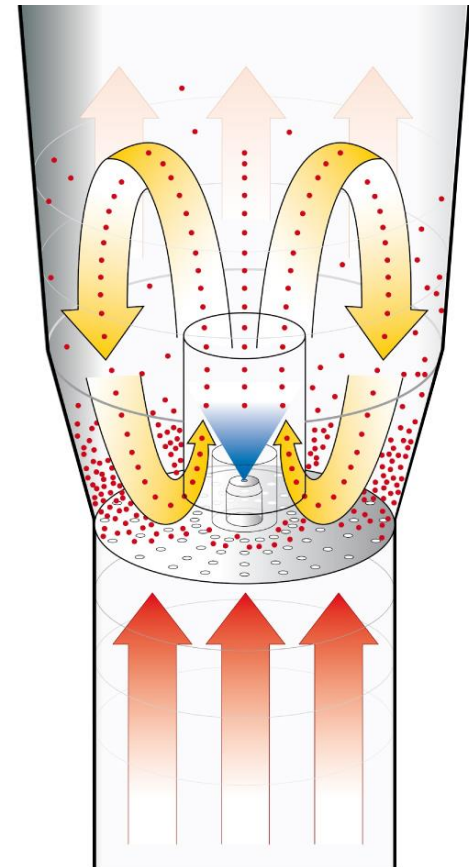
HS nozzle + collar



Pellet Manufacturing Methods

Wurster technology

[Wurster_HS_Process.wmv](#)





Pellet Manufacturing Methods

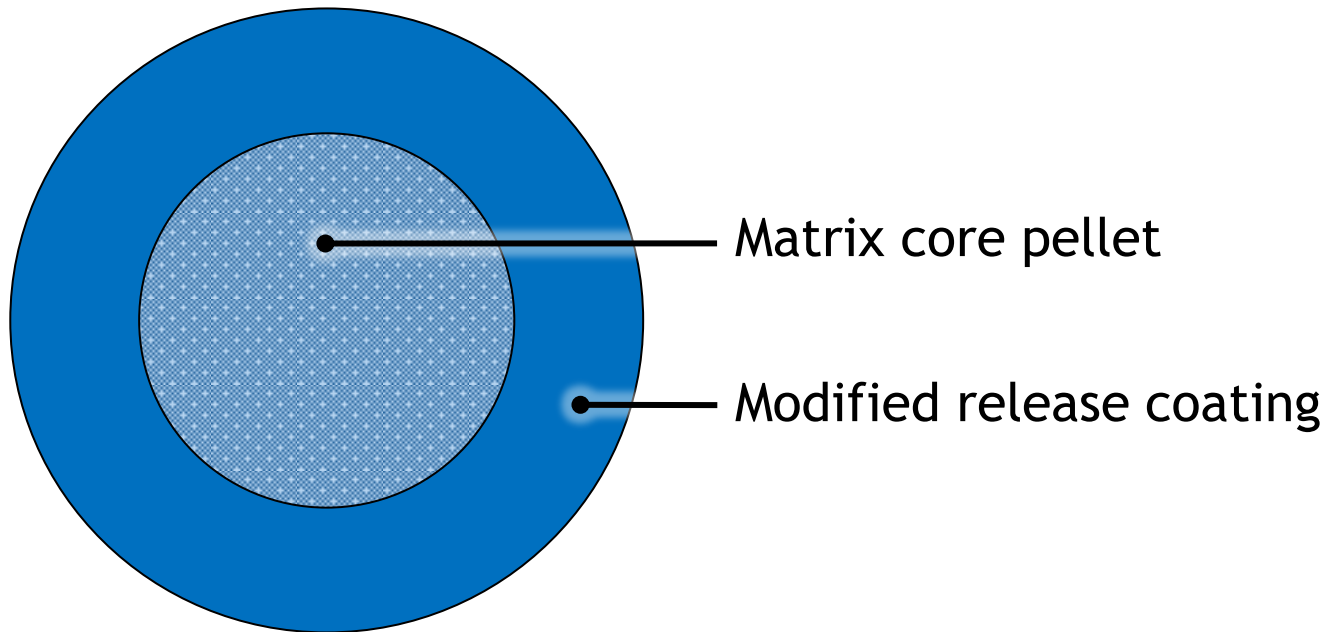
Wurster bottom spray process

Case Study V: Wurster or Top spray technology for pellet coating?

Wurster bottom spray process

Case Study V: Wurster or Top spray technology for pellet coating?

Formulation:





Pellet Manufacturing Methods

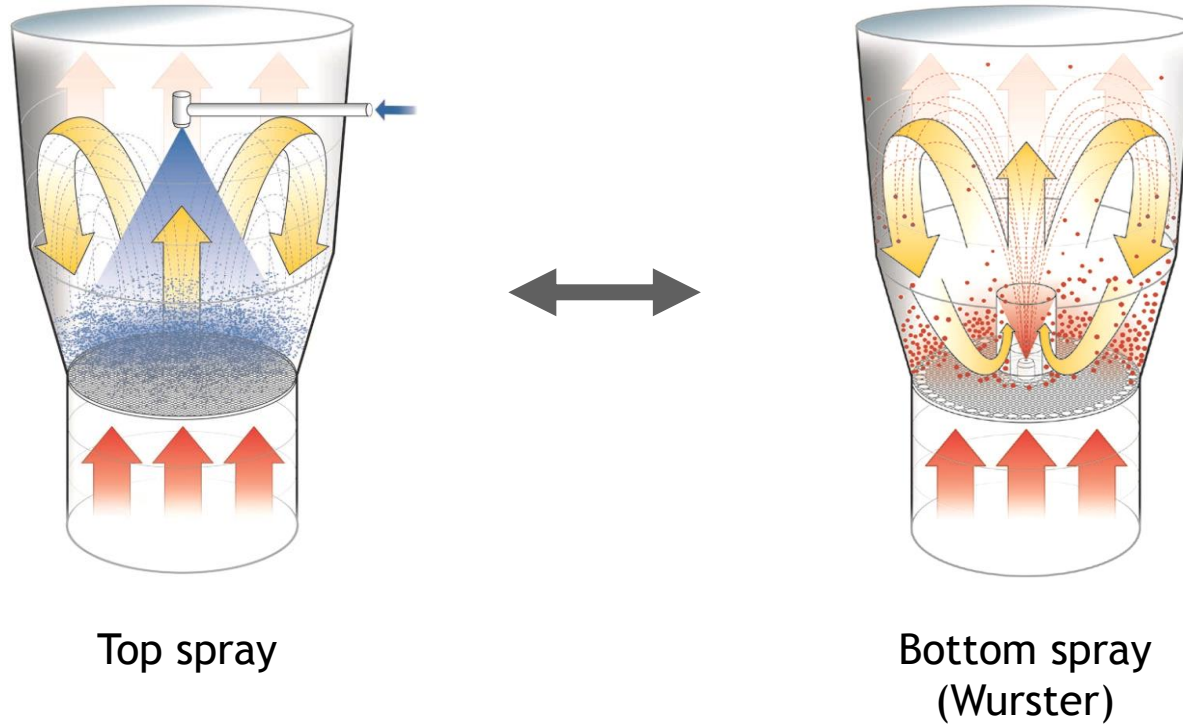
Wurster bottom spray process

Case Study V: Wurster or Top spray technology for pellet coating?

- **Scenario:** Impact of fluid bed configuration on coating performance
- Coating of drug pellets with an organic solvent based polymer solution
- Target in-vitro dissolution profile must be achieved
 - comparison of film quality and yields (overall weight gains)
 - comparison of in vitro-dissolution profiles
- **Target:** Selection of feasible coating technology for scale up and industrial process (**Top spray** / **Wurster**)

Wurster bottom spray process

Case Study V: Wurster or Top spray technology for pellet coating?

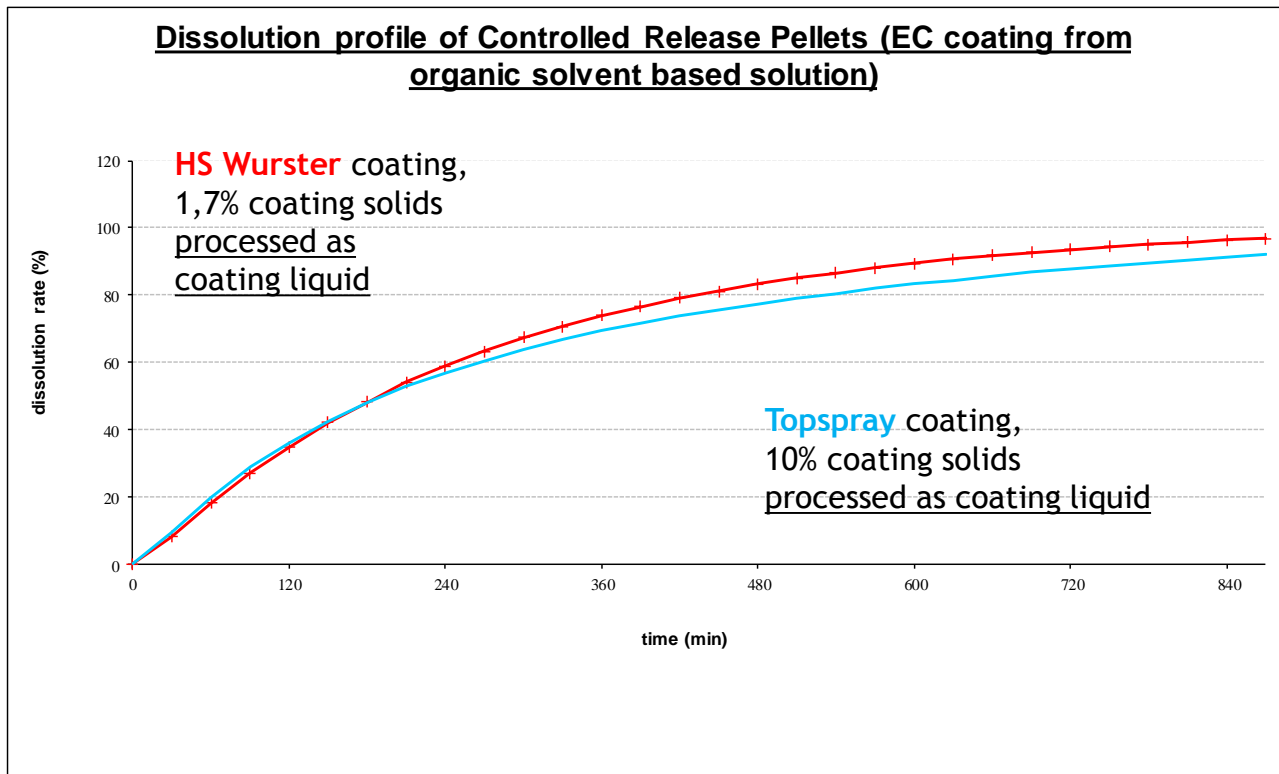




Pellet Manufacturing Methods

Wurster bottom spray process

Case Study V: Wurster or Top spray technology for pellet coating?

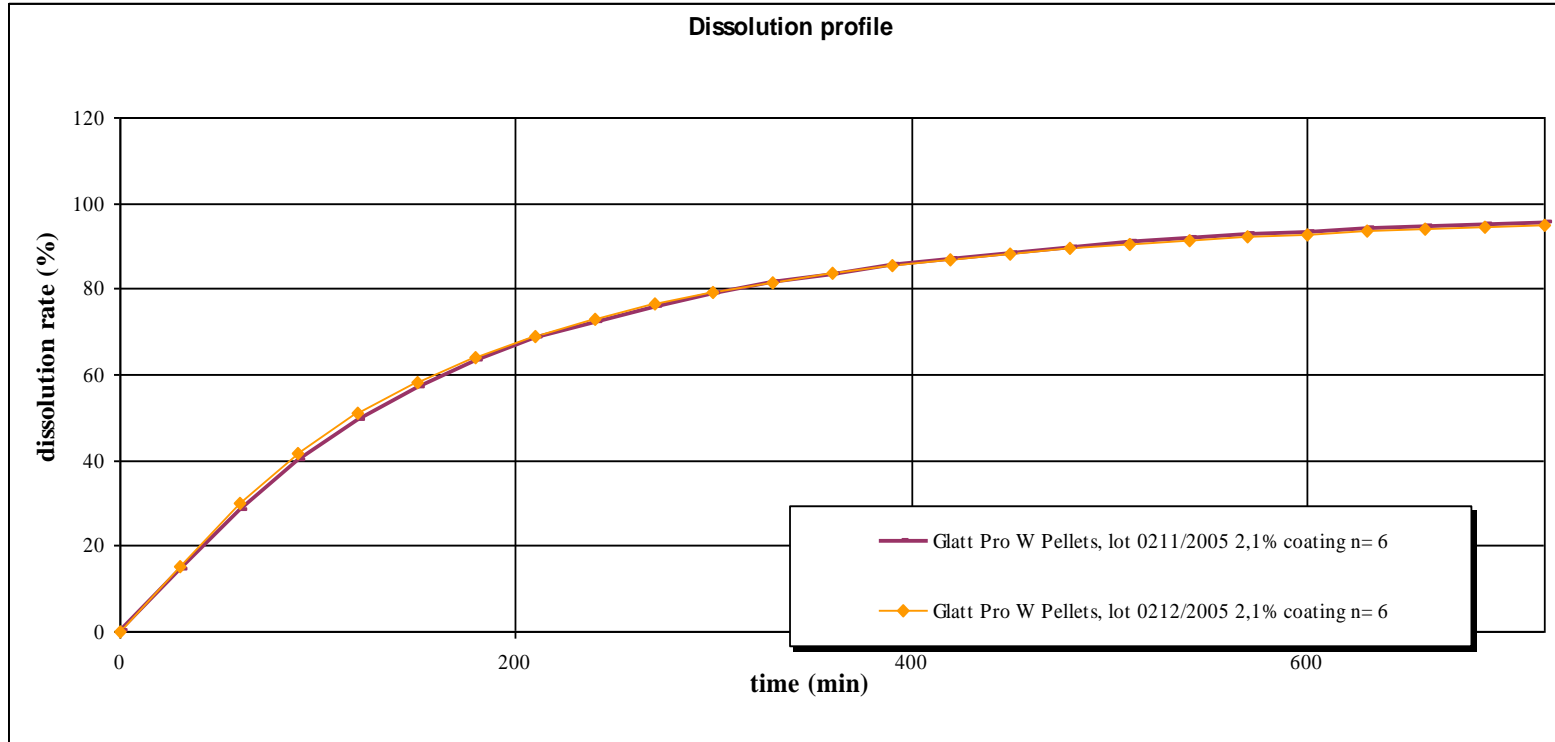




Pellet Manufacturing Methods

Wurster bottom spray process

Case Study V: Wurster or Top spray technology for pellet coating?



Wurster bottom spray process

Wurster or Top spray technology for pellet coating?

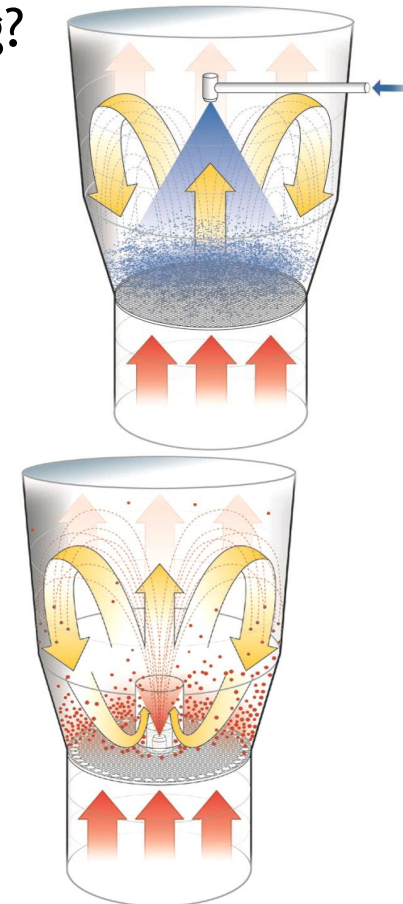
- **Final Statement**

Top spray:

- Well-established granulation technology

Bottom spray:

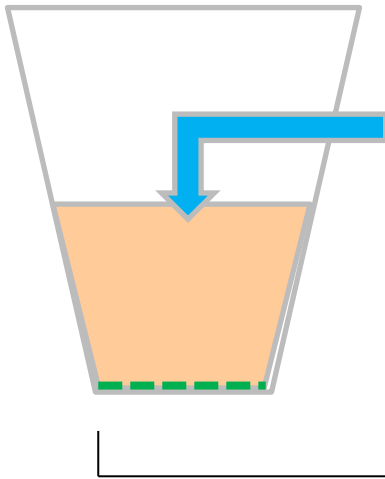
- Concurrent spraying
→ ideal technology for particle layering
and coating
- Optimal yields + perfect film quality
- Minimal agglomeration rate
- Very efficient process due to HS-Wurster system



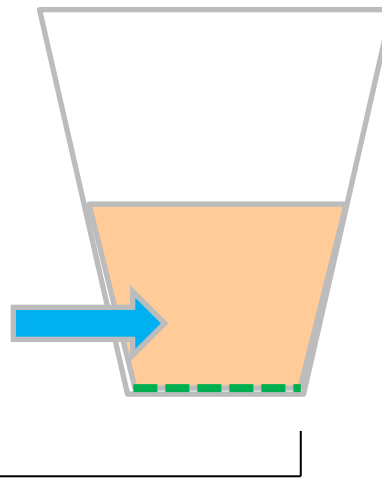
Pellet Layering and Coating Methods

Spray nozzle positions

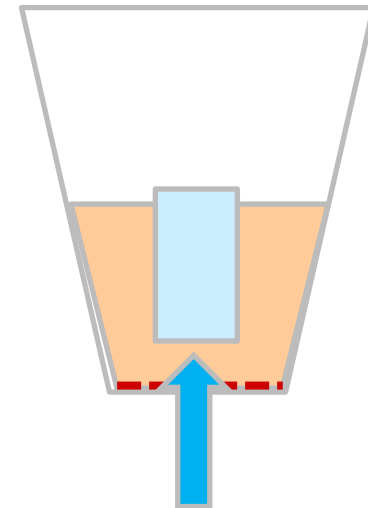
topspray



tangential spray



bottomspray
(Wurster)



granulation



Pellet Manufacturing Methods

Pellet Layering and Coating Methods

HP Tangential spraying system

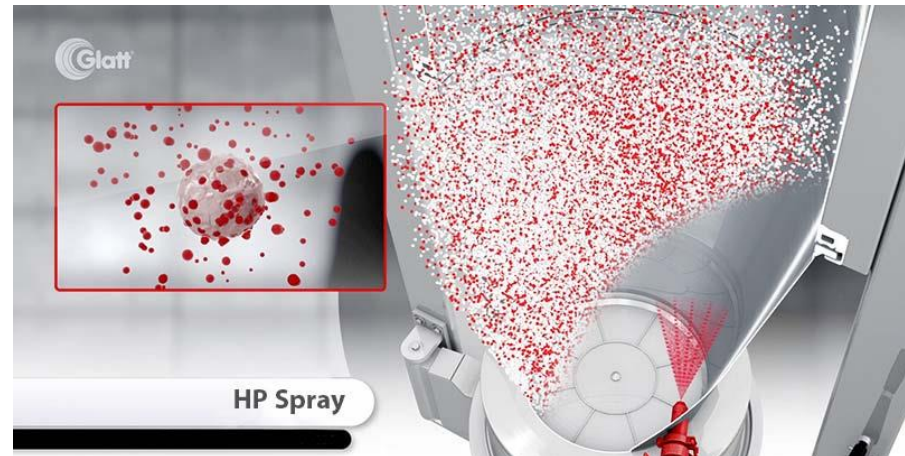


Granulation:

- Segmented Conidur bottom

Coating:

- Segmented Conidur bottom





Pellet Manufacturing Methods

Pellet Layering and Coating Methods

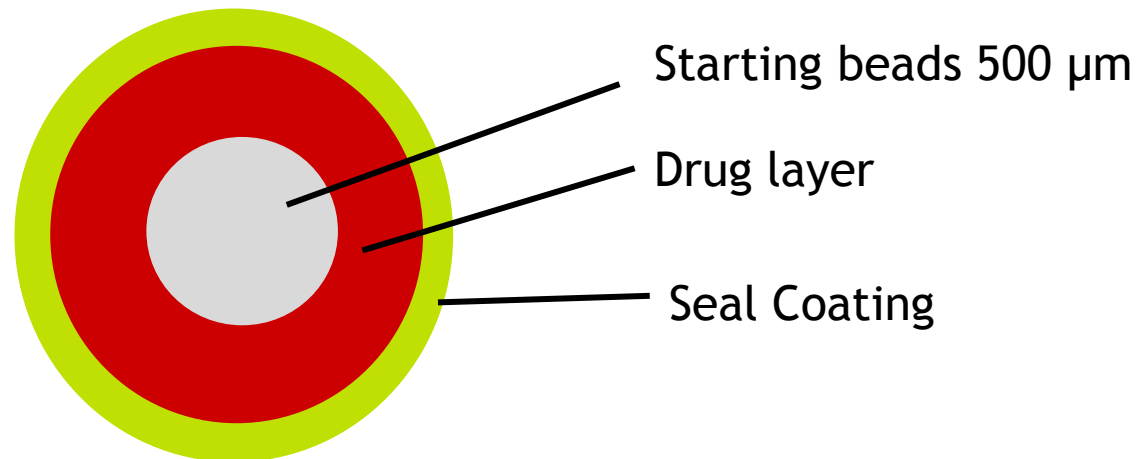
HP Tangential spraying system

[Tangential_Process.pptx](#)

Pellet Layering and Coating Methods

Case Study VI: Wurster or Tangential spraying technology for pellet layering and coating?

Formulation:





Pellet Manufacturing Methods

Pellet Layering and Coating Methods

Case Study VI: Wurster or Tangential spraying technology for pellet layering and coating?

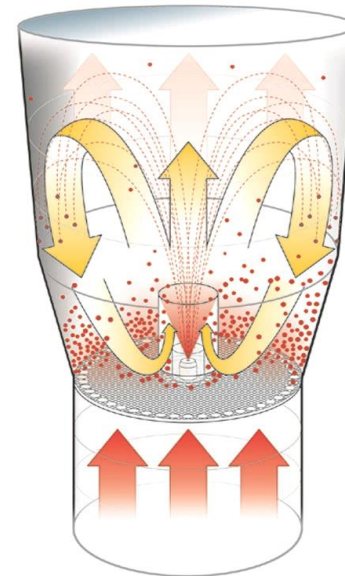
- **Scenario:** Impact of fluid bed configuration on layering / coating performance
- Application of drug layer onto sugar beads with an aqueous based solution
- Yields and target drug content should be achieved
 - comparison of film quality and yields (overall weight gains)
- **Target:** Selection of feasible layering and coating technology for scale up and industrial process (**Tangential / Wurster**)

Pellet Layering and Coating Methods

Case Study VI: Wurster or Tangential spraying technology for pellet layering and coating?



Tangential
spraying (HP)



Bottom spray
(Wurster)

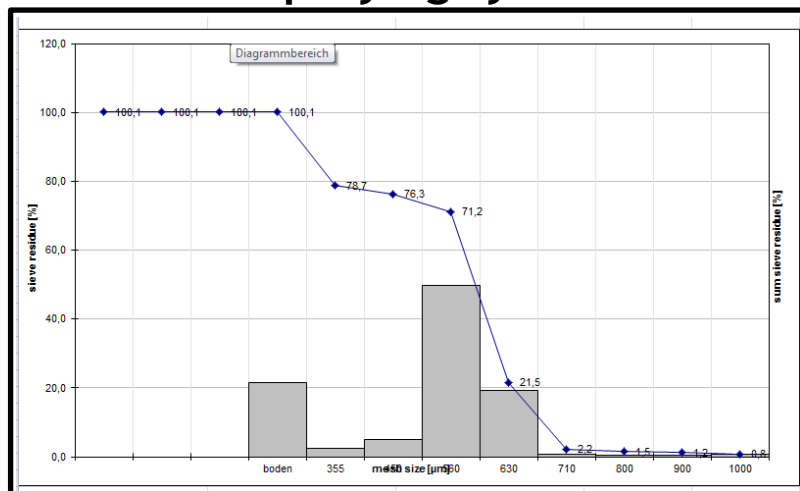
Pellet Layering and Coating Methods

Case Study VI: Wurster or Tangential spraying technology for pellet layering and coating?

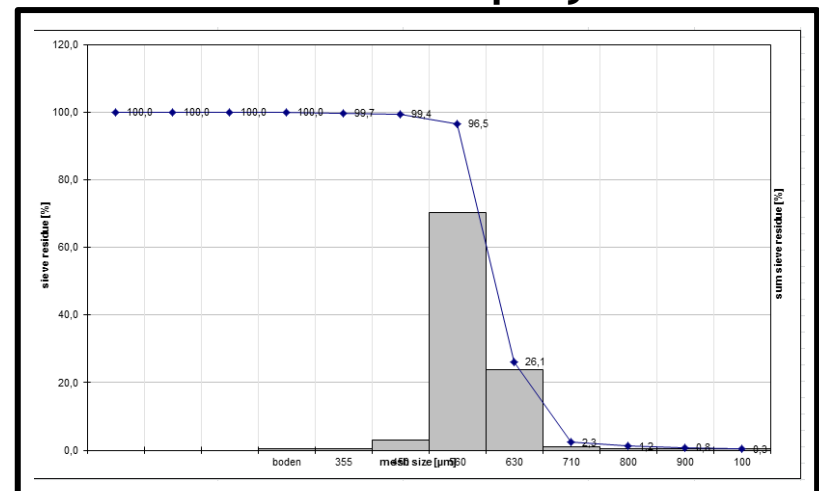
Comparable process parameters applied in both systems

(Product temperature, Atomisation Air Pressure, Spray rate, total spraying time)

Results: HP spraying system



Wurster bottom spray





Pellet Manufacturing Methods

Pellet Layering and Coating Methods

Case Study VI: Wurster or Tangential spraying technology for pellet layering and coating?

- HP system:**
- solids from spraying liquid could not be fixed on pellet surface
 - agglomeration and formation of fines < 400 μm
 - process needs to be optimized for this certain formulation

- Wurster system:**
- no agglomeration
 - perfect yield



Pellet Manufacturing Methods

Pellet Layering and Coating Methods

Case Study VI: Wurster or Tangential spraying technology for pellet layering and coating?

HP system:

- appropriate granulation technology for dense granules
- layering and coating application for this certain formulation not possible

Wurster system:

- concurrent spraying
- ideal technology for particle layering and coating
- optimal yields + perfect film quality
- minimal agglomeration rate
- very efficient process due to HS-Wurster system

The Wurster is clearly recommended for processing this formulation (drug layering and seal coating)



Pellet Manufacturing Methods

Wurster bottom spray process: Summary and Conclusion

- The WURSTER fluid bed technology is a feasible process for highly efficient and reproducible pellet processing.
- It is a complex, but very logical and comprehensive process technology which provides stable conditions for particle coating (of pellets, micropellets, crystals ...).
- The understanding of potential interactions of fluid bed equipment configuration and processing parameters is a prerequisite in order to achieve stable processes in development and industrial production.
- Development is ongoing in order to improve efficiency, stability and safety of processes - PAT (Process Analytical Technology).



Pellet Manufacturing Methods

Summary and Conclusion

- New pellet technologies in addition to established technologies (completion, no replacement)
- New possibilities for drug product development
 - Options for unmet biopharmaceutical demands
 - Potential for line-extensions / life cycle management (NCE's)
 - Enable by-passing of existing specific patent landscape (generics)



Thank you!

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