Accessing amorphous solid dispersions for improved Solubility and Bioavailability in paediatric applications

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Introduction

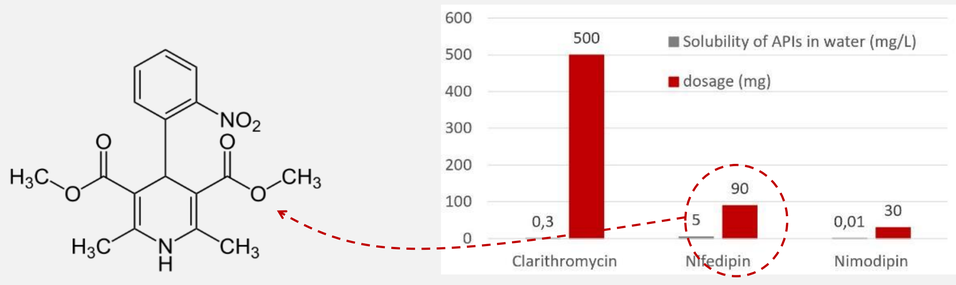
- BCS class II drugs show a low solubility. Modern paediatric formulations are needed to obtain high acceptance of patients at recommended daily doses
- Hot-melt extrusion (HME) and Spray Drying (SD) are the standard preparation techniques for ASD formulation attempts [1]
- Both products are not direct processable to capsules and need further preparation [2,3]

Objectives

- Investigating two alternative fluid bed systems for the preparation of a free-flowing product for further processing (e.g., filling into capsules)
  - Layering an ASD on beads in a Fluid-Bed-Wurster
  - In-situ SD and agglomeration in a Spouted Bed

Materials

- 40 % (w/w) **Nifedipine** as model BCS Class II drug
- 60 % (w/w) **Kollidon VA64**, a Vinyl-pyrrolidone/vinyl-acetate copolymer
- Solvent: **Acetone**
- Manufactured in a **Glatt Wurster-System** and **ProCell-Labsystem** (Glatt Ingenieurtechnik GmbH, Germany)



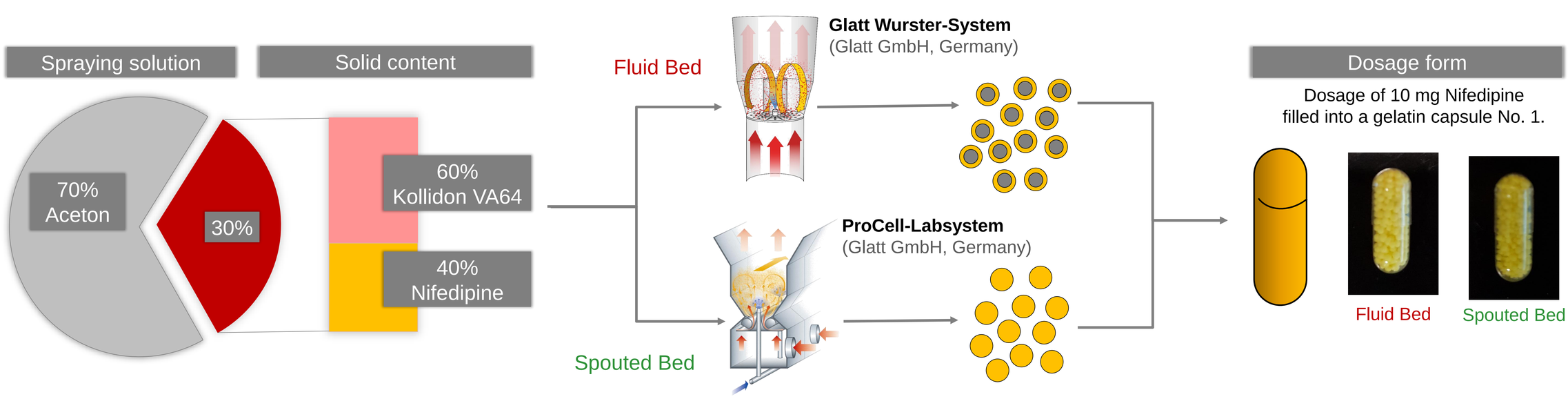


Figure 1: Illustration of the manufacturing process for layered ASD pellets produced in the Fluid Bed and for ASD pellets from direct pelletization in the Spouted Bed.

Characterization of the ASDs

	D_{10} [µm]	D_{50} [µm]	D_{90} [µm]	Bulk density [g/L]	Flow time [s/100g]	Angle of response [°]	Flowability [1)]	Specific Surface Area [m²/g]
Fluid Bed	823.7 ± 22.5	942.5 ± 12.7	1090.9 ± 10.5	427	12.1	11.4°	Excellent	0.731
Spouted Bed	558.9 ± 27.5	731.5 ± 49.7	1374.4 ± 409.6	280	16.2	25.1°	Excellent	0.203

Table 1: Particle characteristics for Fluid Bed and Spouted Bed particles. [1)] Characterization after Carr et al.

SEM Images

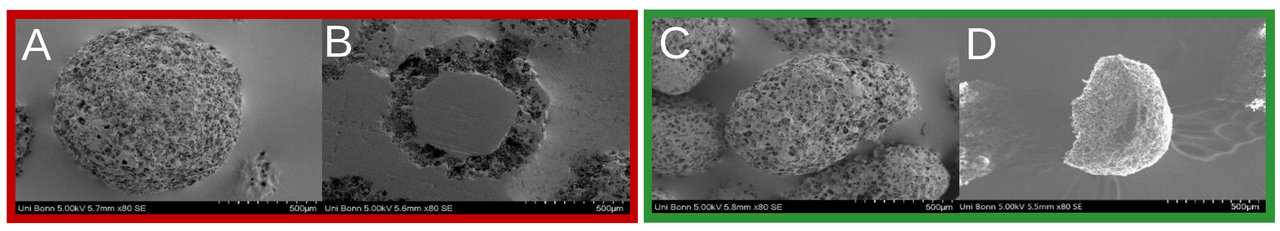


Figure 2: SEM images A: ASD layered pellet (Fluid Bed) B: cut trough ASD layered pellet (Fluid Bed) C: ASD pellet from direct pelletization (Spouted Bed) D: cut trough ASD pellet from Spouted Bed.

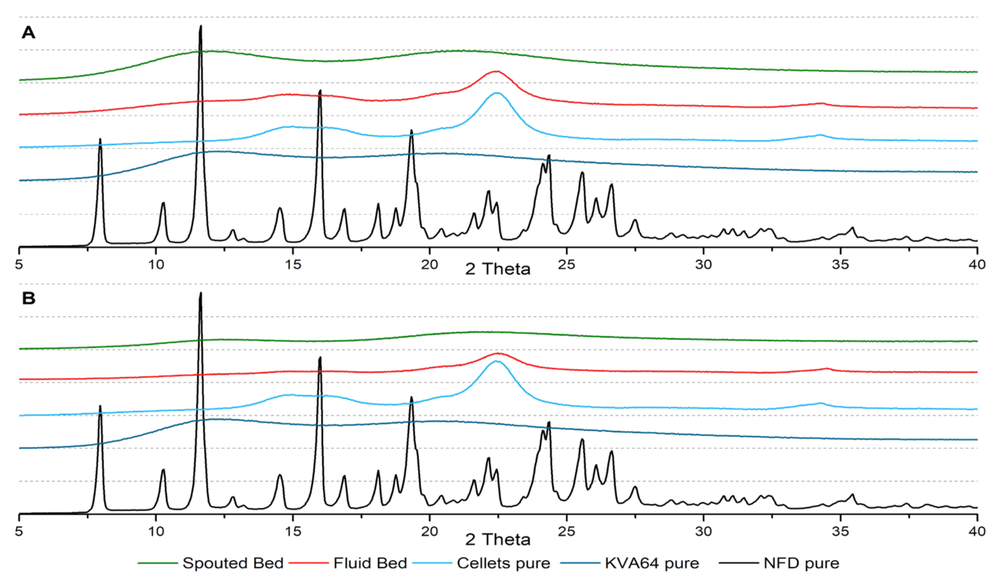


Figure 3: Results of XRPD measurements
A) made directly after production
B) made after two years of storage under ambient conditions

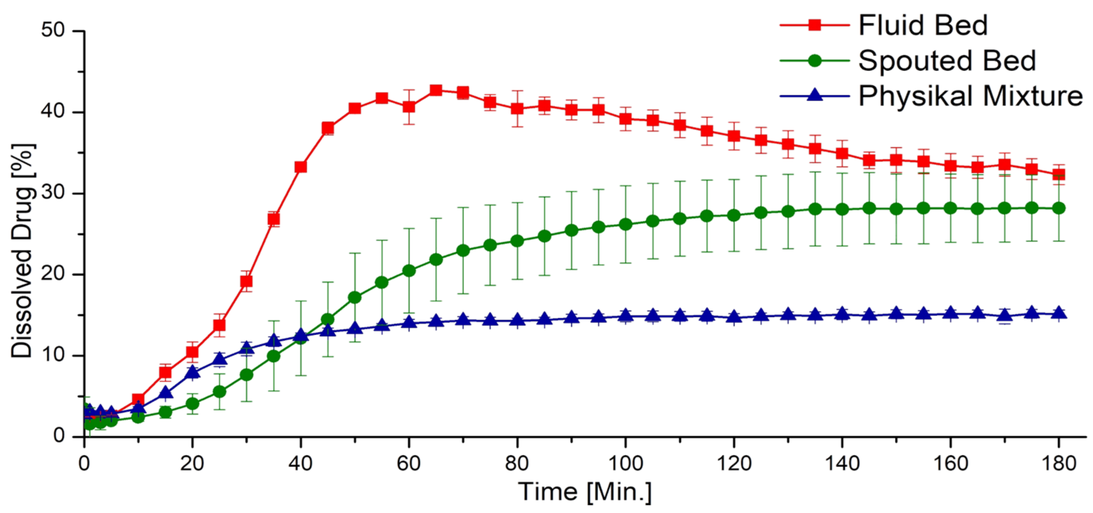


Figure 4: Dissolution results of the prepared pellets in 750 ml PBS pH 6.5 observed over 3h; Temperature: 37°C ± 0.5 °C; Paddle speed: 100 rpm; c(100%) = 80 µg/mL

Conclusion

- Both techniques proved to be promising tools for the development and manufacturing of ASDs
  - Stable over a long time (up to 2 yrs.)
  - Good flow properties for further processing to e.g. capsules
  - Good dissolution performance
- Up-scaling to pilot or production scale possible
- Suitable for batch and continuous process design

References

[1] T. Vasconcelos, et al, Drug Discov. Today, 12 (23) 1068–1075, 2007.
[2] J. Breitenbach, Eur J Pharm Biopharm, 54 (2) 107–117, 2002.
[3] I. Weuts, et al., J. Pharm. Sci, 100 (1) 260–274, 2011.

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