Fluidized and Spouted Bed for the preparation of directly processable amorphous solid dispersions

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INTRODUCTION

One of the major challenges for modern formulation development is the increasing number of poorly water-soluble drugs. A common formulation approach to improve the solubility of those poorly soluble active ingredients is to formulate them as amorphous solid dispersions (ASDs) with a suitable polymer candidate [1].

Hot-melt extrusion (HME) and spray drying (SD) are the most frequently applied techniques for the preparation of ASDs[2]. However, HME is not applicable for thermosensitive substances and a suitable downstream operation is still needed for further processing of the extrusion products [3]. On the other hand, SD results in the formation of fine powder with poor flowability, broad particle size distribution and high sensitivity to electrostatic charge. Therefore, a further compaction step is required to obtain a freely flowable product [4].

In this study, two new techniques for the preparation of ASDs were assessed. It should be possible to fill the ASD directly into capsules without further processing. Two fluidized bed technologies were investigated. The GF3™ (Figure 1A) is a classic 6-inch Wurster Fluidized Bed (FB) equipment used for drug layering and (functional) coating of starter beads. The API containing liquid is layered on an inert core material in a batch process. In the ProCell5™ technology (Figure 1B) the API containing liquid (solution, suspension, emulsion, melt) is sprayed into the empty process chamber. Initially, fine powder is generated by spray drying, which is continuously agglomerated to seeds, and by further layering, to round pellets. The process gas enters the process chamber in the ProCell™ not through an inlet air distribution plate, but through slots in the lower part of the equipment, resulting in a spouted bed (SB) [5].

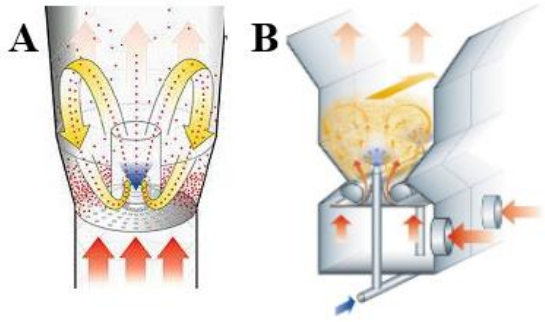

Figure 1: A: GF3™ (FB); B: ProCell5™ (SB), Glatt Ingenieurtechnik GmbH

Nifedipine (NFD) was used in this study as a model drug. NFD exhibits a very low aqueous solubility and belongs to the BCS class II. Kollidon®-VA64 (KVA64), a vinyl-pyrrolidone-vinyl-acetate-copolymer, was selected as model stabilizing polymer for the ASDs and Cellets®500, microcrystalline cellulose pellets, as inert core material.

METHODS

Manufacture of samples

NFD and KVA64 were mixed in a ratio resulting in a drug load of 40 % (w/w) and dissolved in Acetone (30 % w/w solid content).

The GF3™ was equipped with a 6''-Wurster and a Type-C bottom plate. 1.0 kg of Cellets™500 were used as a starter cores and layered with 4.0 kg of the spraying solution. The process time was appr. 3h. The final pellets had a theoretical drug load of 21.8 % (w/w).

The ProCell5™ was equipped with an air classifier (Zig-Zag-sifter) for a continuous discharge of well-sized pellets. This sifter classifies the produced pellets by their aerodynamic resistance, i.e. density and particle size. Particles which are too small and / or too low in density will be retransferred into the process chamber, the classifying air determines the resulting particle size. The SB process time was around 9h.

Based on preliminary studies, the following process parameters were adjusted (Table 1).

	Fluidized Bed	Spouted Bed
Spray rate	20 g/min	20 – 35 g/min
Product temperature	50 – 60 °C	50 – 60 °C
Process gas temp.	65 °C	80 °C
Process air flow	180 – 200 m³/h	65 – 120 m³/h
Spraying nozzle diameter	1.2 mm	1.2 mm
Spraying pressure	2.0 bar	0.5 bar

Table 1: Manufacturing parameters for FB and SB

Flowability and particle size characterization

The flowability and bulk density measurements were performed according to the standard methods of the Ph. Eur. 9.7. The flowability was performed with an ERWEKA GT (Erweka GmbH; GER) equipped with a 10 mm funnel.

The particle Size characterization was performed with a Camsizer X2 (Retsch GmbH, GER) equipped with a free fall funnel without air jet.

X-Ray-powder diffraction (XRPD)

The prepared ASDs were assessed for their crystallinity directly after preparation and after storage for two years under ambient conditions.

XRPD was performed with an X'Pert MRD Pro (PANAnalytical, NL) equipped with an X'Celerator detector and nickel filtered CuKα_1 radiation (λ = 1.5406 Å) at 45 kV and 40 mA. The scanning range used was between 5° and 45° 2θ with 0.016° measuring steps.

Dissolution

The dissolution was performed for 3 h under non-sink conditions in a USP II apparatus with 100 rpm. The temperature was set to 37° ± 0.5°C, the dissolution medium was 750.0 mL of PBS pH 6.8 R. The target concentration was set at 0.08 mg/mL which is 10 time of the equilibrium concentration.

The results were compared with a physical mixture (PM) of NFD and KVA64 (40 % w/w drug load).

RESULTS

Flowability and particle characterization

Table 2 shows the measured physical characteristics of the pellets. ASD layered particles produced by FB were more spherical (SEM images; Figure 2), had a narrow particle size distribution and better flowability compared to the SB particles. However, both techniques produced spherical pellets suitable to be directly filled into capsules.

	D_{10} [µm]	D_{50} [µm]	D_{90} [µm]	Bulk density [g/L]	Flowability [s/100g]
Fluidized Bed	823.7 ±22.5	942.5 ±12.7	1090.9 ±10.5	427	12.1
Spouted Bed	558.9 ±27.5	731.5 ±49.7	1374.4 ±409.6	280	16.2

Table 2: Particle Characterization for FB and SB particles

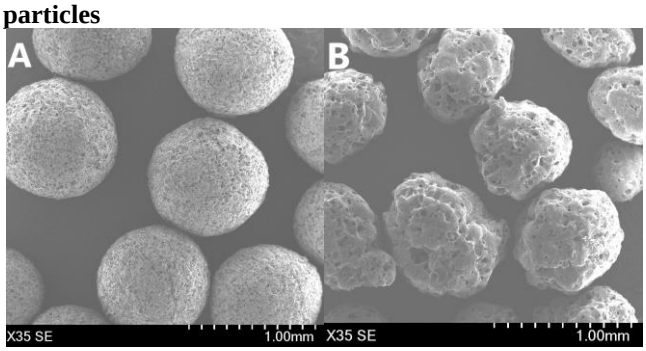

Figure 2: SEM images A: ASD layered pellets (FB); B: ASD pellets from direct pelletization (SP)

X-Ray-powder diffraction (XRPD)

The XRPD measurements showed that the produced ASDs were stable over two years stored at room temperature. No characteristic peaks of crystal NFD appeared in the scans of the produced pellets prepared by both techniques.

Dissolution

Figure 3 shows the results of the dissolution testing. Pellets obtained from both techniques achieved an appr. 2-fold higher end concentration than the PM. The FB ASD layered pellets dissolved faster compared to SB pellets from direct pelletization, resulting in a pronounced supersaturation (3-fold) and subsequent precipitation towards the 2-fold equilibrium. The SB pellets displayed a slower release rate resulting in the equilibrium supersaturation.

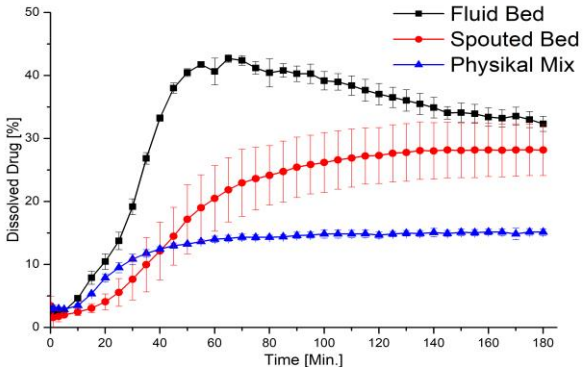

Figure 3: dissolution results

CONCLUSION

Fluidized bed and spouted bed techniques proved to be promising tools for manufacturing of stable ASDs with good flow properties for direct processing and good dissolution performances. Both techniques can be scaled up to pilot and production scale for batch or continuous manufacture of freely flowable ASDs.

REFERENCES

[1] T. Vasconcelos, B. Sarmento, and P. Costa, "Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs," *Drug Discovery Today*, vol. 12, no. 23, pp. 1068–1075, Dec. 2007.

[2] C. L.-N. Vo, C. Park, and B.-J. Lee, "Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 85, no. 3, Part B, pp. 799–813, Nov. 2013.

[3] J. Breitenbach, "Melt extrusion: from process to drug delivery technology," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 54, no. 2, pp. 107–117, Sep. 2002.

[4] I. Weuts *et al.*, "Physicochemical Properties of the Amorphous Drug, Cast Films, and Spray Dried Powders to Predict Formulation Probability of Success for Solid Dispersions: Etravirine," *Journal of Pharmaceutical Sciences*, vol. 100, no. 1, pp. 260–274, Jan. 2011.

[5] M. Jacob, "Spheronization, Granulation, Pelletization, and Agglomeration Processes," in *Microencapsulation in the Food Industry*, Elsevier, 2014, pp. 85–98.