

Melt granulation with a twin-screw extruder using Soluplus®

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Purpose

Continuous processes are gaining more and more importance in the pharmaceutical industry since they offer significant cost savings and ease of automation. Several methods for continuous wet granulation are already known and introduced [1]. However, continuous melt granulation is still quite rare although it offers the additional advantage of saving drying time and energy [2]. Thus, it is also especially feasible for moisture sensitive drugs. The recently introduced polymeric solubilizer Soluplus® and Lutrol® micro 127 were examined concerning their melt binding properties for high dosed caffeine as a model drug.

Materials

Caffeine anhydrous (BASF SE, Germany), Soluplus® (Figure 1) and Lutrol® micro 127 (both BASF SE, Germany) were used as received.

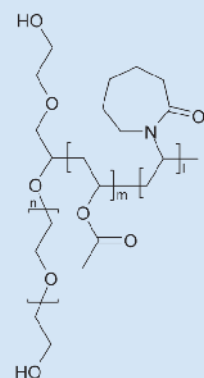


Figure 1: Chemical structure of Soluplus®

Methods

Four caffeine/polymer mixture preblends containing 80–90 % API were agglomerated using a twin-screw extruder (Polylab 16, ThermoFisher, Germany) at 1 kg/h powder feed rate and 200 rpm screw speed. Agglomeration was performed at 50 °C barrel temperature for the Lutrol® micro F 127 and 120 °C for the Soluplus® mixtures respectively. Granules were passed through an oscillating sieve (AR 400, Erweka, Germany) at 150 rpm and 1000 µm mesh size in order to remove amount of lumps.

Particle size distribution of the final granules was determined using mechanical sieving (AS 200, Retsch, Germany) for 5 minutes at amplitude of 2 mm. Bulk density was tested according to Ph. Eur [3].

Granule friability as an estimate for granule strength was detected using an air jet sieve (LPS 200 MC, Rhewum, Germany) with 125 µm mesh size. Amount of fines was removed with a flow rate of 20 m³/h for 1 minute before stressing granules for 10 minutes at 70 m³/h flow rate. Thus, only agglomerated material was considered. Friability of granules was defined as mass loss of the granule sample in % after 10 minutes [4].

Dissolution tests were conducted with a granule sieve cut (315–500 µm) containing 100 mg API. For analysis an USP apparatus 2 was used in triplicate at 50 rpm in 700 mL hydrochloric acid (0.1 molar) for 2 hours under sink conditions.

Results

It was possible to successfully produce high dosed caffeine granules with both polymers. The amount of Soluplus® could be decreased from 20 % down to 10 % without losing proper agglomeration behaviour during processing. For Lutrol® micro 127 the amount of binder could not be decreased down to 10 % since agglomeration was insufficient resulting in too large amounts of fines. Therefore, agglomeration was done applying 15 and 20 % polymeric binder.

Amount of fines (granule fraction below 125 µm) ranged from 9% for the 20% Soluplus® formulation up to 21% for the Lu-

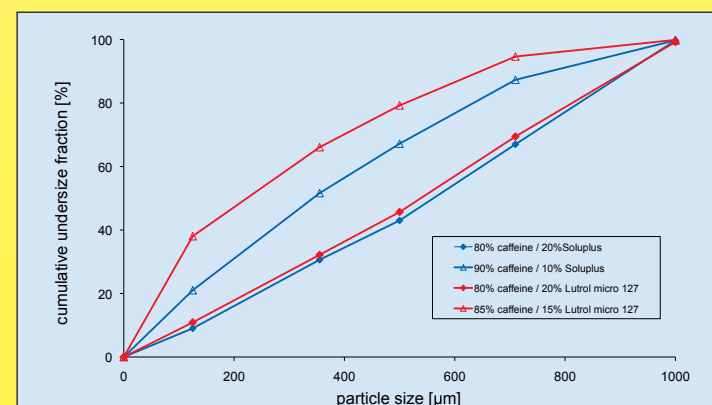


Figure 2: Particle size distribution of granule batches after sieving step through 1000 µm

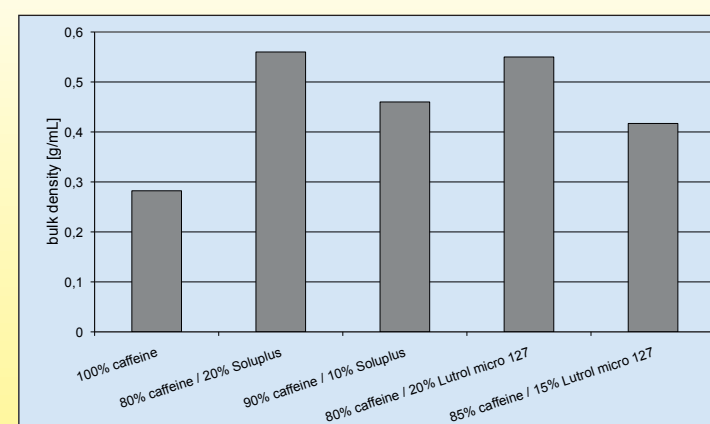


Figure 3: Bulk density of granule batches according to Ph. Eur.

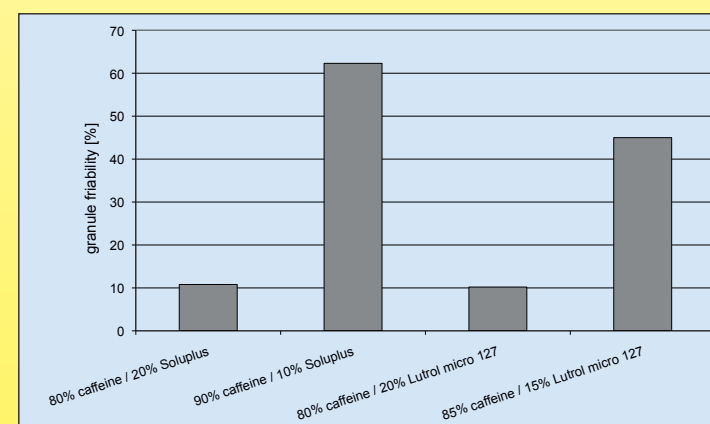


Figure 4: Granule friability of different formulation (fraction 125–1000 µm)

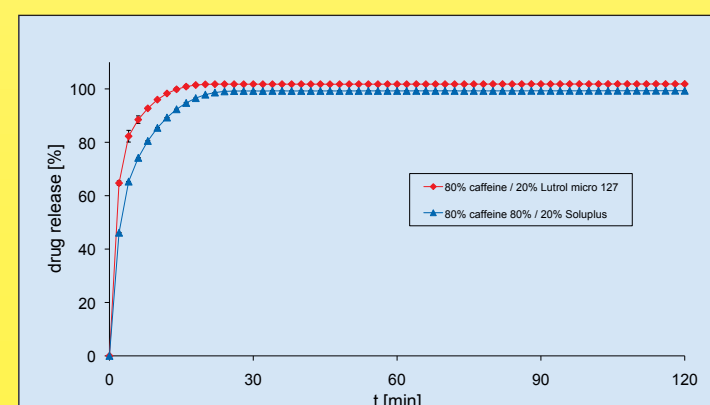


Figure 5: Drug release of granules containing 20% polymeric binder

trol® formulation with 15 % binder (Figure 2). Generally, granules with Lutrol® micro 127 showed finer particle sizes than granules produced with Soluplus®. The highest yield (granule fraction from 125 µm–1000 µm) was achieved with a 20 % Soluplus® concentration.

Bulk density could be increased for all formulations compared to raw caffeine (Figure 3). At 20 % binder concentration bulk densities were comparable whereas at lower concentration Soluplus® led to granules with slightly higher bulk density. Granule friability as a measure of granule strength was sufficient at 20 % binder concentration irrespective of the chosen binder (Figure 4). At lower binder concentrations granule strength was not sufficient resulting in high friability values. Increasing granule strength even at low binder concentrations could be possibly achieved by adapting screw configurations. Drug release out of granules was completed within the first 20 minutes for both formulations at 20 % binder concentration (Figure 5). Using Lutrol® micro 127 led to granules with a slightly faster dissolution speed.

Conclusion

- Soluplus® showed stronger melt binder properties compared to Lutrol micro 127.
- Binder concentration could be decreased down to 10% enabling high dosed caffeine granules.
- Melt granulation with polymeric solubilizers offers the possibility to agglomerate and solubilise poorly water soluble APIs as well as moisture sensitive drugs.

References

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