Combining directly compressible Ibuprofen DC 85 W with different caffeine grades and investigating the impact of particle size on processability and content uniformity

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Introduction

Ibuprofen is a very challenging product in direct compression. Due to its low melting point and unfavourable particle-shape, there are many problems (e.g. sticking) that might occur during tabletting. However, Ibuprofen DC 85 W as a pre-processed formulation is available offering a distinctively improve processability.

Over-the-counter cold remedies frequently carry more than one active pharmaceutical ingredient, supporting the relief of various symptoms at the same time. Since, at least one component is a painkiller (e.g. Ibuprofen) the doses of other potential actives are typically much lower, causing an inherent risk for inhomogeneity.

The aim of this study was, to investigate the impact of particle size of Caffeine (added to Ibuprofen DC 85 W) on the processability of the tabletting blend and the content uniformity of the final tablets.

Materials and Methods

Ibuprofen DC 85 W (BASF) is a pre-formulated, directly compressible, granulated material. It contains a binder (microcrystalline cellulose), a disintegrant (croscarmellose sodium) and merely requires the customised incorporation of some standard lubricant (e.g. magnesium stearate or stearic acid) to be ready for tabletting. Alternatively, external lubrication can be employed to convert Ibuprofen DC 85 W into a ready-to-use tabletting formulation.

The product was specifically developed to simplify the production of Ibuprofen tablets and to overcome the inherent sticking problem of Ibuprofen (caused by its low melting point) by coating the granules with nanoparticles (fumed silica) (Figure 1) [1].

Three different anhydrous Caffeine grades: fine powder, granules 0.2/0.5, and granules 0.5/1.0 (all Siegfried), varying distinctly in particle size (Table 1) were added to Ibuprofen DC 85 W in such a concentration that the final tablets carried an Ibuprofen dose of 400 mg and a Caffeine dose of 25 mg.

Figure 1. Scanning electron microscopy (SEM) image of cetirizine HCl (SE, 5 kV).

The tabletting blend was prepared in a tumble blender (Turbula® T2C). Caffeine and Ibuprofen DC 85 W were mixed for 8 minutes, followed by an additional 2 minutes after adding 0.5% magnesium stearate (Bärlocher). Prior to blending, all formulation components were passed through a sieve (granules: w=2.0 mm, powders: w=0.8 mm).

Tabletting was conducted with a Korsch XP 1 excenter single punch press using round, flat faced, bevelled edge punches with a diameter of 12.0 mm. Compression forces of 4, 7, 10, and 15 kN (33 to 133 MPa) were applied at a tabletting speed of 15 tablets per minute.

At each compression pressure, samples were tested of each formulation to determine height, diameter, and crushing strength of the tablets. Based on these results, the following diagrams were generated to evaluate the tabletting characteristics [2–4]:

- Compactability plot, indicating the resulting tensile strength [N/mm^2] values of the tablets as function of compression pressure [MPa].
- Compressibility plot, indicating the porosity [–] of the tablets as function of compression pressure [MPa].
- Bondability plot, indicating the resulting tensile strength [N/mm^2] values of the tablets as function of the porosity [–].

Tablet characterisation

The tablets were characterised (n=20) using a multi-tester (HT100, Sotax) equipped with q-doc 2.06 software. Disintegration time was tested for each sample (n=6) using a compendial disintegration tester (Erweka ZT74). Phospate buffer (pH 7.2) was used as a testing medium (37°C ±1 K).

True density

After vacuum drying (10 mbar) for 12 hours, the samples were transferred under nitrogen gas into a gas pycnometer with a volume of approximately 10 cm³ (Micromeritics, AccuPyc 1340). The true density of the granules (n=3) was determined at a temperature of 23.0°C ±0.1 K and a filling pressure of 19.5 psig. The measurement was stopped at 0.020 psig/min [5]. The true density was determined for each single component in the formulation (Table 2).

Table 2. True density values of all components contained in the tabletting formulation.

Product	True density
Ibuprofen DC 85 W	1.177 g/mL
Caffeine (Anhydrous)	1.444 g/mL
Magnesium Stearate	1.069 g/mL

Particle size distribution

The particle size distribution (n=3) was determined via laser diffraction with a Mastersizer 2000 (Malvern), equipped with a Scirocco 2000 sample handling unit. The particle characterisation, the following settings were applied: measuring time/snaps: 5/5000 s, background time/snaps: 5/5000 s, dispersive air pressure: 2.0 bar, calculation mode: Frauenhofer.

Results and Discussion

An inherent risk in tabletting is the segregation of one formulation component of the tabletting blend during feeding. Typically, this is mainly ascribed to distinct differences in the ingredient's particle size distribution and/or density. A distinct number of cold remedies combine comparatively high-dosed Ibuprofen with an additional low-dose active ingredient. In the present study, pre-formulated Ibuprofen granules (Ibuprofen DC 85 W) and Caffeine was chosen to investigate the tabletting characteristics, the mechanical properties of the final tablets, and the content uniformity of the two active ingredients. In order to examine the influence of the particle size distribution of the low-dose API onto the described features, Caffeine with different particle size distributions was used (Table 1).

Table 1. Characteristic values of all main components defining their particle size distribution.

Product	$d_{0.1}$	$d_{0.5}$	$d_{0.9}$	$D_{4,3}$
Ibuprofen DC 85 W	50.5 µm	572.9 µm	1,278.1 µm	633.7 µm
Caffeine (Anhydrous) Fine Powder	1.2 µm	6.1 µm	36.7 µm	12.9 µm
Caffeine (Anhydrous) Granules 0.2/0.5	17.9 µm	264.7 µm	527.0 µm	272.2 µm
Caffeine (Anhydrous) Granules 0.5/1.0	36.6 µm	492.8 µm	1,032.7 µm	523.6 µm

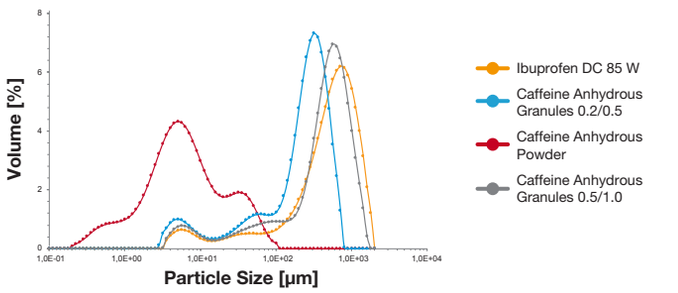

Figure 2. Particle size distribution of Ibuprofen DC 85 W and the different Caffeine grades, determined via laser diffraction (mean values, n=3).

Ibuprofen DC 85 W, which is a pre-processed agglomerate, has quite coarse particles, providing an excellent powder flow. Caffeine (anhydrous) granules 0.5/1.0 present a particle size distribution just slightly below the one of Ibuprofen DC 85 W, and can therefore be regarded as quite comparable. Caffeine (anhydrous) granules 0.2/0.5 offers a decisively smaller particle size distribution, with characteristic values of more than 50% below the previously two products. Markedly smaller are the particles of Caffeine (anhydrous) fine powder (Table 1, Figure 2).

The flow characteristics of all three Ibuprofen/Caffeine blends were excellent. Consequently, tablet mass hardly showed any variability, with a relative standard deviation of 0.7–0.8% for all batches (Figures 8–10) and easily fulfilled the requirements of uniformity of mass of single-dose preparations.

Both formulations containing coarse Caffeine grades had almost identical tabletting features, resulting in tablets of 2.0 N/mm² at compression pressures of 130 MPa. A similar result was obtained in a previous study, for tablets containing Ibuprofen DC 85 W only [1]. Tablets containing very fine Caffeine merely reached a tensile strength of 1.7 N/mm² at the same compression pressure (Figure 3). Even though the compressibility of all three formulations was identical (Figure 4), fine Caffeine caused poorer bondability leading to a distinctly lower tensile strength values (Figure 5), for this formulation, at all compression pressures.

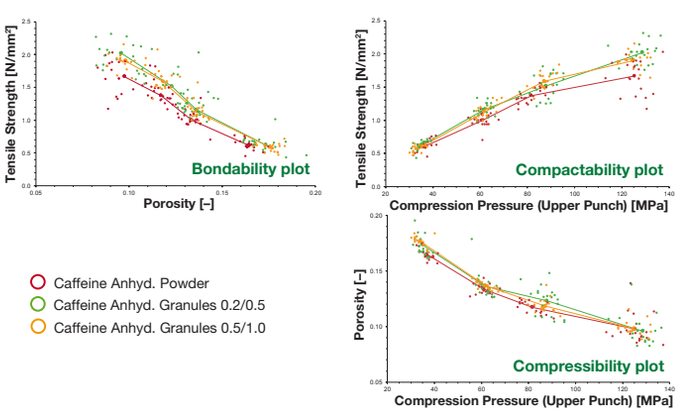

Figure 3. Compactability plot: tensile strength as function of compression pressure (single values and mean value, each compression pressure: n=20).

Figure 4. Compressibility plot: porosity as function of compression pressure (single values and mean value, each compression pressure: n=20).

Figure 5. Bondability plot: tensile strength as function of tablet density (single values and mean value, each compression pressure: n=20).

Disintegration time was strongly affected (prolonged) by an increasing tensile strength of the tablets (Figure 6). In particular, for Ibuprofen formulations, this is a frequently observed dependency and is rooted in the low melting point of Ibuprofen. High compaction pressures lead to a more intensive solidification,

yet result in a sintering of Ibuprofen in addition. As a result, porosity of the tablet becomes that low, that water needs more time to migrate into the tablet and starts to interact with the disintegrant. Thus, disintegration time gets prolonged (Figure 7) [1].

However, the particle size distribution of the different Caffeine grades hardly had an impact on the disintegration characteristics of the tablets.

The uniformity of content was excellent for Ibuprofen (Figures 11–13), whereas an increasing particle size resulted in a rising relative standard deviation of the Caffeine content (Figures 14–16). The reason being that the Caffeine dose was low and eventually got increasingly affected by the exact number of particles dosed. However, all three formulations fulfilled the requirements of the acceptance value test.

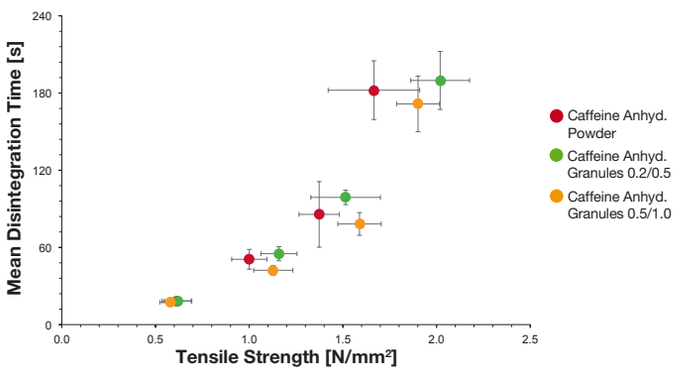

Figure 6. Disintegration time as function of tensile strength (mean values ±SD, n_x=20, n_y=6).

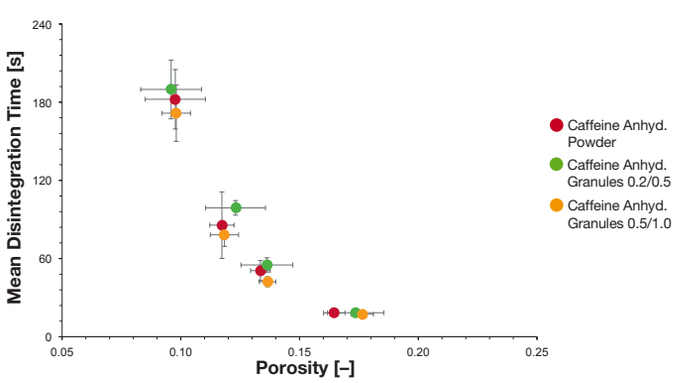

Figure 7. Disintegration time as function of porosity (mean values ±SD, n_x=20, n_y=6).

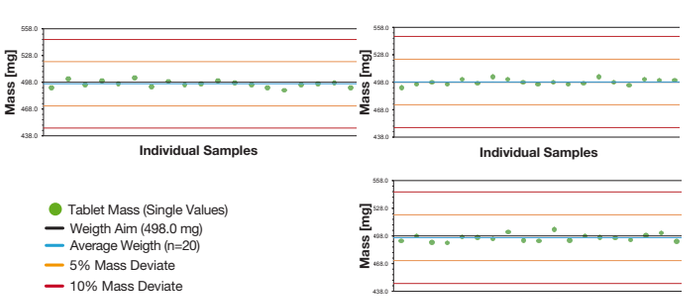

Figure 8 (upper left). Uniformity of mass of single-dose preparations, formulation containing Caffeine anhydrous fine powder.

Figure 9 (upper right). Uniformity of mass of single-dose preparations, formulation containing Caffeine anhydrous granules 0.2/0.5.

Figure 10 (lower right). Uniformity of mass of single-dose preparations, formulation containing Caffeine anhydrous granules 0.5/1.0.

Conclusion

The results show that the Ibuprofen DC 85 W formulation was quite robust and content uniformity of the low-dose Caffeine hardly got affected by its respective particle size distribution.

In terms of processing, both course Caffeine grades were similar in their performance, and resulted in very strong tablets. The Caffeine fine grade led to comparatively lower tensile strength values especially at high compression pressures. This effect was caused by a lower bondability for this formulation.

Regarding disintegration and the uniformity of mass features, all three formulations were the same. Caffeine fine showed advantages in the uniformity of content test, though. However, all formulations passed the acceptance value test.

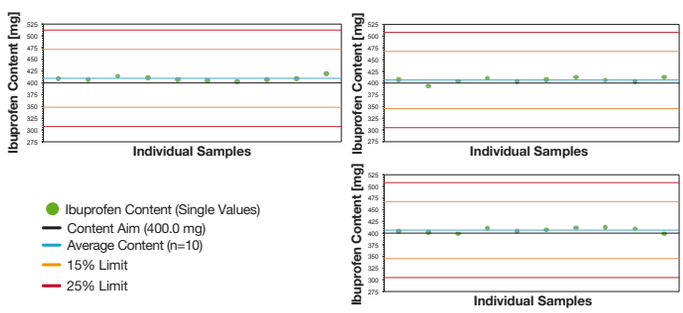

Figure 11 (upper left). Uniformity of content (Ibuprofen) of single-dose preparations, formulation containing Caffeine anhydrous fine powder.

Figure 12 (upper right). Uniformity of content (Ibuprofen) of single-dose preparations, formulation containing Caffeine anhydrous granules 0.2/0.5.

Figure 13 (lower right). Uniformity of content (Ibuprofen) of single-dose preparations, formulation containing Caffeine anhydrous granules 0.5/1.0.

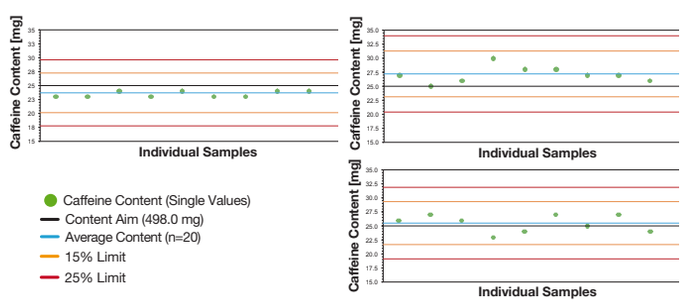

Figure 14 (upper left). Uniformity of content (Caffeine) of single-dose preparations, formulation containing Caffeine anhydrous fine powder.

Figure 15 (upper right). Uniformity of content (Caffeine) of single-dose preparations, formulation containing Caffeine anhydrous granules 0.2/0.5.

Figure 16 (lower right). Uniformity of content (Caffeine) of single-dose preparations, formulation containing Caffeine anhydrous granules 0.5/1.0.

References

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[4] Piazza, D.; Cech, Th.; Geiselhart, V.; How to evaluate the tabletting characteristics of a powder blend; 1st Industry Meets Academia; UCL School of Pharmacy; April 13–14, 2016; London, UK.

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