The Role of Different Binary Binder Systems on Ibuprofen-Tablets by Dry Granulation (Roller Compaction)

Patrick Müsse, Hochschule Fresenius University of Applied Sciences, Idstein, Germany / **Dr. Mahmud Yunis,** BIOGRUND GmbH, Huenstetten, Germany

Introduction

Dry granulation (roller compaction) as a continuous process becomes more important for the pharmaceutical and related industries. That is the reason why the interest of different materials and their processing is growing. One negative aspect of the roller compaction is the work hardening effect. The term work hardening effect refers to the effect that granules often show a reduced tensile strength compared to direct compression. With CompactCel®, a dry binding agent, it is possible to improve the mechanical properties and lower the work hardening effect.

The present study investigates the suitability of CompactCel® based on Hydroxypropyl cellulose (HPC), CompactCel® based on low-substituted Hydroxypropyl cellulose (L-HPC) and a Reference, which is a binary binder system of Kollidon® (Vinylpyrrolidone-vinyl acetate copolymers) and microcrystalline cellulose (MCC), in the dry granulation.

Materials and Methods

The investigated formulations contain maize starch, Ibuprofen, magnesium stearate and the different binding agents. Furthermore, the disintegration time of formulations with croscarmellose sodium were compared with the disintegration time of the other formulations. The formulation details are listed in table 1.

A roller compactor WP 120 Pharma (Alexanderwerk AG) was used for dry granulation. All experiments were conducted at a compaction force of 3.5 MPa, a roll speed of 3.5 rpm and a gap width of 2 mm. The gap was controlled by adjusting feeding speed. Subsequently the ribbons were milled to the targeted particle size of 0.63 mm by an integrated size reduction unit. The 600 mg tablets were compressed on a Pressima rotary press (IMA Kilian GmbH & Co. KG). The punches were flat-faced and had a diameter of 12 mm. The rotation speed was set to 10 rpm. The granules were compressed using compaction pressures of 15, 20 and 25 kN. To assess the suitability of the different binding agents, the angle of repose (measured according to Ph. Eur. 2.9.36) and the bulk density (measured according to Ph. Eur. 2.9.34) of the granules are compared as well as the tensile strength (measured according to Ph. Eur. 2.9.8), the friability (measured according to Ph. Eur. 2.9.7) and the disintegration time (measured according to Ph. Eur. 2.9.1) of the tablets. Furthermore, the particle size distribution of the granules was measured via dynamic image analysis. The used devices and methods are listed in table 2.

Table 1: **Investigated formulations/Materials**

Ingredients and Excipients	Abbreviation	w/w in %	
Lycatab® C (partially pregelatinized maize starch, Roquette)	–	18.5	16.5
Different binding agents: 1 CompactCel® based on HPC SSL SFP (NISSO Chemical Europe GmbH) 2 CompactCel® based on L-HPC LH-31 (Shin-Etsu Chemical Co., Ltd.) 3 Comprecel® MCC (Mingtai) + Kollidon® VA 64 F (BASF)	–	15	
Ibuprofen 50 (BASF)	Ibp	66	
Magnesium stearate (Applichem)	Mg-St	0.5	
Croscarmellose sodium (JRS Pharma)	NaCmC-Cl	0	2
Tablet mass	–	100	

Table 2: **Used Devices/Methods**

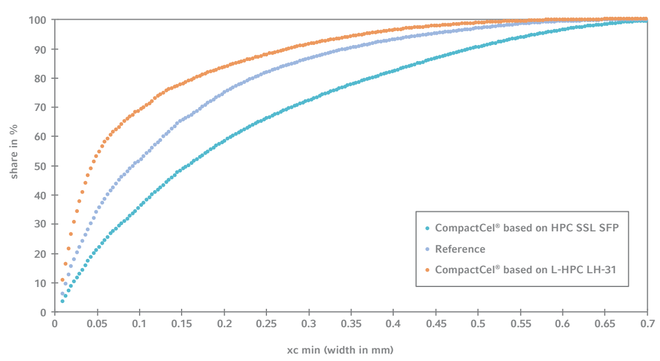
Methods	Device	Manufacturer
Dry granulation + milling	WP 120 Pharma	Alexanderwerk AG
Compression	Pressima	IMA Kilian GmbH & Co. KG
Particle size distribution	Camsizer XT	Retsch Technology GmbH
Angle of repose	BEP 2	Copley Scientific Ltd.
Tablet hardness	TBH 325	Erweka GmbH
Tablet friability	TAR 120	Erweka GmbH
Disintegration time	ZTM 322	Erweka GmbH

Results and Discussion

The results of the comparison are shown in table 3 and figure 1–4.

The influence of the different binding agents on the granulation characteristics was determined by the resulting particle size of granules. The largest particle sizes and the lowest amount of fines resulted from formulations with CompactCel® based on HPC SSL SFP. Formulations granulated with CompactCel® based on L-HPC LH-31 or the Reference had a median particle size distribution of 44.5 µm and 93.3 µm respectively, whereas the formulation with CompactCel® based on HPC SSL SFP had a median particle size distribution of 158.4 µm.

Figure 1: **Particle size distribution of granules with various binding agents**

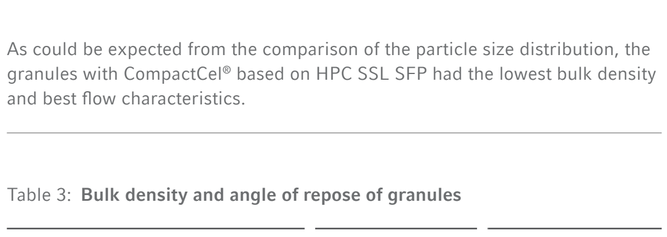


As could be expected from the comparison of the particle size distribution, the granules with CompactCel® based on HPC SSL SFP had the lowest bulk density and best flow characteristics.

Table 3: **Bulk density and angle of repose of granules**

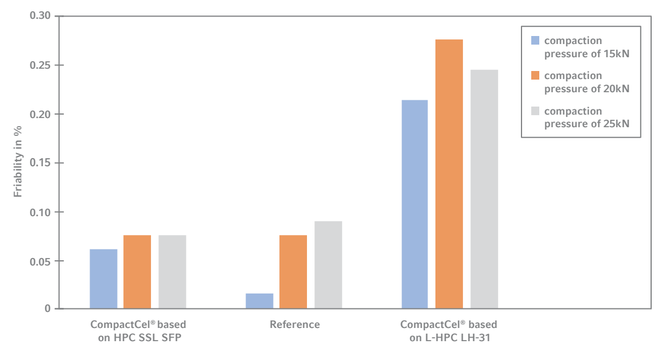
Granules with binding agent	Bulk density in g/cm³	Angle of repose in °
CompactCel® based on HPC SSL SFP	0.48	39.16
Reference (Kollidon® VA 64 F + Comprecel® MCC)	0.50	40.56
CompactCel® based on L-HPC LH-31	0.53	45.77

Figure 2: **Comparison of tensile strength with various binding agents and different compaction pressures (n=10)**



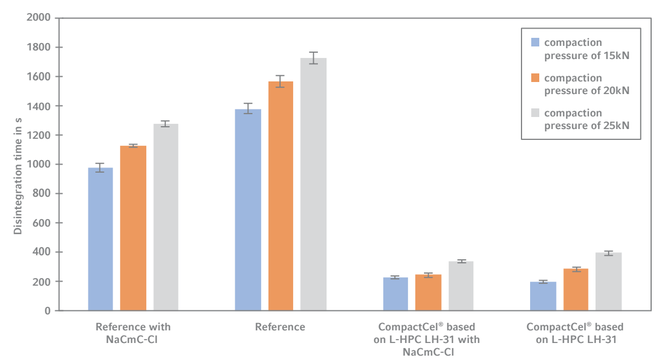
The different binders used for granulation have a high impact on tensile strength. The formulation with CompactCel® based on HPC SSL SFP creates stronger tablets in comparison to the formulations with the other two binding agents.

Figure 3: **Comparison of tablet friability with various binding agents and compaction pressures**



All formulations show excellent friability below 0.3 % (USP and EP accept a max. loss of 1.0% of the tablet). The friability of the formulation with CompactCel® based on HPC-SSL SFP is not influenced by the compaction pressure and the tablets show the best mechanical stability. For the Reference, the different compaction forces have a great influence on the friability. CompactCel® based on L-HPC LH-31 shows the highest friability at all pressures.

Figure 4: **Tablet disintegration time with various binding agents and different compaction pressures (n=6)**



When the disintegration time is considered, only the results of the CompactCel® formulation based on L-HPC LH-31 and the Reference are compared with each other, since the disintegration times for all tablets of the CompactCel® formulation based on HPC SSL SFP was higher than 30 minutes, also with croscarmellose. Due to the hydrophobic character of L-HPC LH-31, which is associated with the low degree of substitution, the formulation with CompactCel® based on L-HPC LH-31 has the shortest disintegration time.

Conclusion

The study shows that the process of dry granulation needs a careful selection of the binder and disintegrant. The tablets with CompactCel® based on HPC SSL SFP as a binding agent are the most mechanically stable and are recommended for active pharmaceutical ingredients (API) which need a strong binder. The tablets with CompactCel® based on L-HPC LH-31 as a binding agent component have the lowest mechanical stability, whereas the two possible applications of L-HPC LH-31 are well-established during the trials. In addition to the use as a binder, L-HPC LH-31 is suitable as a swelling agent and the need of a disintegrant in the tablet is redundant. Depending on the API and desired dissolution, CompactCel® can be formulated with a disintegrant as well.

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