Influence of the particle size of copovidone and crospovidone on tablet characteristics

Carina Hubert[1], Thorsten Cech[1], Verena Geiselhart[2], Nils Rottmann[1]

[1]European Pharma Application Lab, Pharma Solutions, BASF SE, Ludwigshafen, Germany
[2]Technical Service Europe, Pharma Solutions, BASF SE, Lampertheim, Germany

Corresponding author: nils.rottmann@basf.com

Introduction

Copovidone and crospovidone are commonly used excipients in solid oral dosage forms for many decades. Typically, copovidone is used as dry binder and crospovidone as disintegrant in tableting formulations [1]. The use of dry binder and disintegrant needs to be balanced to assure both: strong but quickly disintegrating tablets.

In this study the influence of different copovidone and crospovidone grades on the tablet's tensile strength and the ejected solid fraction (or relative density) at different compression pressures were evaluated systematically: Compactability plots (tensile strength as a function of the compression pressure), compressibility plots (ejected solid fraction as a function of the compression pressure) and bondability plots (tensile strength as a function of the ejected solid fraction) were generated to visualize the influence of the individual excipient on the tableting characteristics.

Contour plots were generated to illustrate the influence of each excipient on the tensile strength and disintegration time of the resulting tablets at different compression pressures. Potential interactions and synergies respectively between the different grades of the tested excipients were illustrated.

Materials and Methods

Blends of several filler-binder, filler-disintegrant and filler-binder-disintegrant combinations were prepared with the materials, listed in Table 1. All blends contained 0.5% magnesium stearate as lubricant.

Two grades of copovidone (a copolymer of vinyl pyrrolidone and vinyl acetate) were chosen for this study: Kollidon® VA 64 and Kollidon® VA 64 Fine. Beside differences in the morphology, Kollidon® VA 64 and Kollidon® VA 64 Fine differ mainly in their particle size distribution (Table 2).

Table 3 summarizes typical particle size distribution values of the four crospovidone grades, included in this study (Kollidon® CL, Kollidon® CL-F, Kollidon® CL-SF and Kollidon® CL-M). All grades were tested in both dry powder and a wet state. The shift of the particle size of the wetted particles, towards higher values, can be regarded as an indicator for the disintegrating properties caused by the respective excipient grade.

Table 1. List of ingredients and their individual functionality in the tabletting blends.

Ingredient [Ph. Eur.]	Functionality	Brand name (manufacturer)
Dicalcium phosphate	Filler	DI-CAFOS A150 (Chemische Fabrik Budenheim)
Copovidone	Dry binder	Kollidon® VA 64 (BASF)
Copovidone	Dry binder	Kollidon® VA 64 Fine (BASF)
Crospovidone Type A	Disintegrant	Kollidon® CL (BASF)
Crospovidone Type A	Disintegrant	Kollidon® CL-F (BASF)
Crospovidone Type B	Disintegrant	Kollidon® CL-SF (BASF)
Crospovidone Type B	–	Kollidon® CL-M (BASF)
Magnesium stearate	Lubricant	MG Siel 1 (Bärlocher)

Table 2. Characteristic values of the two copovidone grades, defining their particle size distribution (Malvern Mastersizer 2000; n=3).

Product	$d_{0.1}$	$d_{0.5}$	$d_{0.9}$	$D_{4,3}$
Kollidon® VA 64	13.3 µm	53.4 µm	139.9 µm	66.7 µm
Kollidon® VA 64 Fine	3.8 µm	13.1 µm	34.9 µm	16.9 µm

Table 3. Characteristic values of the four tested crospovidone grades, defining their particle size distribution (Malvern Mastersizer 2000; n=3).

Product	$d_{0.1}$	$d_{0.5}$	$d_{0.9}$	$D_{4,3}$
Kollidon® CL (dry)	10.8 µm	47.8 µm	166.8 µm	70.5 µm
Kollidon® CL (wet)	18.5 µm	94.0 µm	249.2 µm	116.0 µm
Kollidon® CL-F (dry)	5.8 µm	15.6 µm	45.7 µm	22.0 µm
Kollidon® CL-F (wet)	15.1 µm	28.0 µm	116.0 µm	57.1 µm
Kollidon® CL-SF (dry)	3.7 µm	10.5 µm	28.7 µm	16.5 µm
Kollidon® CL-SF (wet)	9.0 µm	31.7 µm	71.9 µm	36.7 µm
Kollidon® CL-M (dry)	0.9 µm	4.2 µm	7.8 µm	4.4 µm
Kollidon® CL-M (wet)	2.0 µm	5.3 µm	10.3 µm	5.8 µm

The particle size distribution of the copovidone and crospovidone grades was determined via laser diffraction with a Mastersizer 2000 (Malvern; n=3), equipped with a Scirocco 2000 sample handling unit.

Tabletting

The tabletting blends were prepared by passing all components through a sieve (w=0.8 mm). The main components were mixed in a Turbula® T2C tumble blender (Willy A. Backofen) for 8 minutes, subsequently followed by the incorporation of magnesium stearate for 2 minutes.

Tablets of the respective blends were directly compressed on a XP1 single punch press (Korsch) at 10, 15 and 20 kN (60 to 240 MPa) at a tableting speed of 10 tablets/min. The tablet press was equipped with a set of round, flat faced, beveled edge punches of a diameter of 10.0 mm.

Characterisation of Tablets

The disintegration time of the obtained tablets was determined in artificial gastric juice (HCl, pH 1.1) at 37°C (±1 K) (n=6) in a compendial disintegration tester (ZT74, ERWEKA).

Mass, height, diameter and crushing strength of the compressed tablets were measured with a HT100 tablet tester (Sotax; n=20). The tensile strength and density were calculated based on these values (Software: q-doc 4.00).

Taking the actual density of the tablet, divided by the true density of the respective formulation (calculated based on the values of the individual components, listed in Table 4), the ejected solid fractions were calculated. The ejected solid fraction (or relative density) delivers an indication of the amount of solid material present in the tablet.

Table 4. True density values of all components contained in one of the tabletting formulations, measured with a Micromeritics AccuPyc 1340 gas pycnometer DIN EN ISO 1183-3 [2] (mean values, n=3).

Ingredient [Ph. Eur.]	Brand name	True density
Dicalcium phosphate	DI-CAFOS A150	2.854 g/mL
Copovidone	Kollidon® VA 64	1.147 g/mL
Copovidone	Kollidon® VA 64 Fine	1.268 g/mL
Crospovidone Type A	Kollidon® CL	1.321 g/mL
Crospovidone Type A	Kollidon® CL-F	1.316 g/mL
Crospovidone Type B	Kollidon® CL-SF	1.342 g/mL
Crospovidone Type B	Kollidon® CL-M	1.225 g/mL
Magnesium stearate	MG Siel 1	1.069 g/mL

With the results obtained, the following diagrams were generated to evaluate the tabletting characteristics of the individual components:

- **Compactability plot**, representing the resulting tensile strength [N/mm²] values of the obtained tablets as function of compression pressure [MPa]. Compactability indicates the capacity of a powder to be transformed into a tablet of specific strength under the effect of compression pressure.

- **Compressibility plot**, representing the ejected solid fraction [–] of the obtained tablets as function of compression pressure [MPa]. It indicates the ability of a material to undergo a reduction in volume as a result of an applied pressure.

- **Bondability plot**, representing the resulting tensile strength [N/mm²] values of the obtained tablets as function of the ejected solid fraction [–]. Consequently, bondability is the ability of a powdered material to be transformed into tablets with strength during densification.

Using the Modde® software tool, contour plots were generated to visualize the influence of each grade on the tensile strength and disintegration time of the resulting tablets, at a predefined compression pressure.

Results and Discussion

Compactability, Compressibility and Bondability (Copovidone)

The addition of copovidone (5%) caused an increase of tensile strength at a given compression pressure. The finer grade (Kollidon® VA 64 Fine) showed a higher compactability compared to the coarser grade (Kollidon® VA 64) (Figure 1b). To understand to underlying reason compressibility and bondability plots required consideration.

Compressibility was mainly increased by the finer copovidone grade. An impact of Kollidon® VA 64 (representing the coarser grade) on the densification could not be seen when compared to the formulation without additional dry binder (Figure 1c). Favorable particles size distribution allows an inherently more compact filling of the die.

The bonding capacity was distinctively increased in blends containing either 5% Kollidon® VA 64 or 5% Kollidon® VA 64 Fine (Figure 1a). Both dry binders showed similar bondability characteristics though. Consequently the tensile strength depend on the solid fraction: the fine copovidone caused higher tensile strength values.

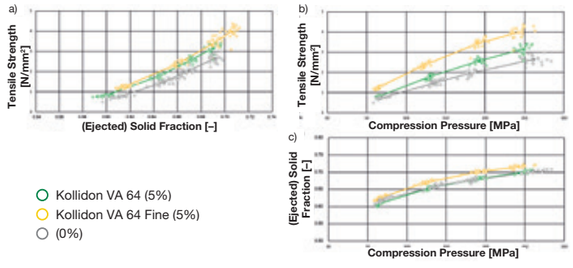

Figure 1. Bondability plot (a); Compactability plot (b); Compressibility plot (c) of Kollidon® VA 64 and Kollidon® VA 64 Fine (single values and mean value, n=20).

Compactability, Compressibility and Bondability (Crospovidone)

Fine crospovidone grades (type B) increased the tensile strength of the respective tablets at a given compression pressure. The finer the crospovidone grade, the stronger the binding capacity. The addition of 5% Kollidon® CL weakened the tablets, compared to formulations without disintegrants (Figure 2b).

Regarding their compressibility, hardly any differences between the tested crospovidone grades could be seen. Dedicated compression pressures led to similar ejected solid fraction values. In contrast the coarser crospovidone (Kollidon® CL), resulting in lower ejected solid fractions (Figure 2c).

Tablets with higher ejected solid fractions, showed in general higher tensile strength values (Figure 2a). Fine crospovidone grades, tend to deliver tablets of higher tensile strength values at a given degree of densification. A binding property of the fine crospovidone grades has been demonstrated.

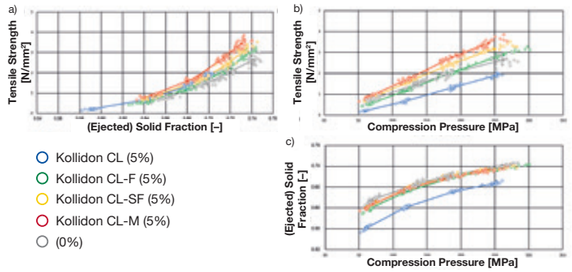

Figure 2. Bondability plot (a); Compactability plot (b); Compressibility plot (c) of Kollidon® CL, CL-F, CL-SF and CL-M (single values and mean value, n=20).

Tensile Strength (Copovidone and Crospovidone)

Within the range of compression pressures tested (60–240 MPa), higher compression pressures caused stronger tablets. This was true for all compositions in this study. (Figure 3, 4 and 5). The use of the fine copovidone grade (Kollidon® VA 64 Fine) resulted in stronger tablets, compared to the standard grade (Kollidon® VA 64).

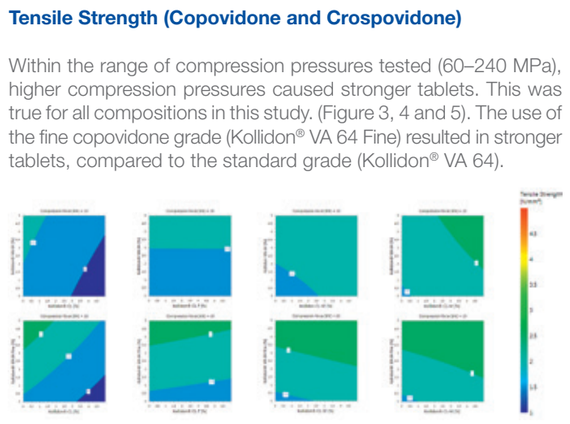

Figure 3. Contour plots: Tensile strength of tablets, compressed at 10 kN, as function of the concentration of the tested copovidone and crospovidone grades.

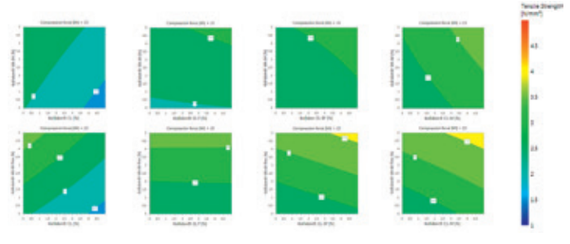

Figure 4. Contour plots: Tensile strength of tablets, compressed at 15 kN, as function of the concentration of the tested copovidone and crospovidone grades.

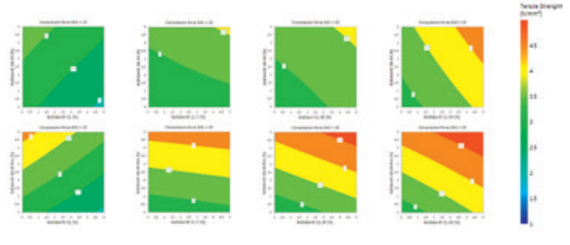

Figure 5. Contour plots: Tensile strength of tablets, compressed at 20 kN, as function of the concentration of the tested copovidone and crospovidone grades.

As previously indicated by the compactability plot (Figure 2b), the addition of the type A crospovidone (Kollidon® CL) reduced the tensile strength of the tablets obtained. In contrast, type B crospovidone grades (Kollidon® CL-SF and Kollidon® CL-M) contributed to the tablet strength (Figure 3, 4 and 5). Hardly any effect on the tensile strength could be seen with Kollidon® CL-F. Comparing the slopes of the diagrams, representing the tested crospovidone grades, the impact of the crospovidone grade is very distinct: Formulations containing Kollidon® CL, show a steeply increasing curve, while Kollidon® CL-F represents a flatter curve characteristic. Both the crospovidone type B grades show a descending curve, indicating their dominant binding effect.

All effects of the crospovidone grades in this study, on the tensile strength were concentration dependent.

Disintegration Time (Copovidone and Crospovidone)

Disintegration times were prolonged with increasing compression forces, independent of the composition tested (Figure 6, 7 and 8).

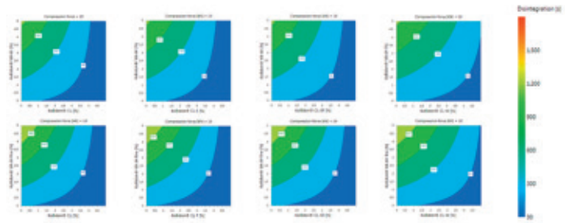

Figure 6. Contour plot: Disintegration times of tablets, compressed at 10 kN, as function of the concentration of the tested copovidone and crospovidone grades.

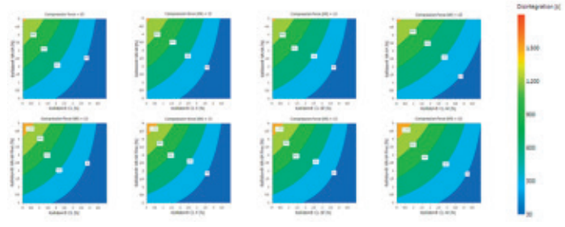

Figure 7. Contour plot: Disintegration times of tablets, compressed at 15 kN, as function of the concentration of the tested copovidone and crospovidone grades.

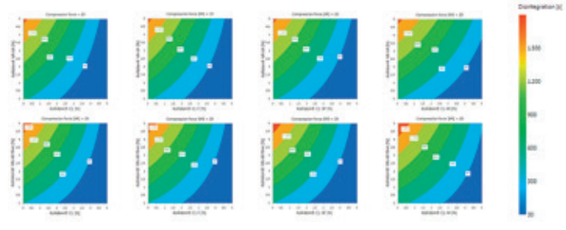

Figure 8. Contour plot: Disintegration times of tablets, compressed at 20 kN, as function of the concentration of the tested copovidone and crospovidone grades.

Prolonged disintegration times could be compensated to a certain extent by the addition of crospovidone. Increasing concentrations of crospovidone led to shorter disintegration times. Formulations, containing a certain amount of Kollidon® CL, Kollidon® CL-F

or Kollidon® CL-SF showed similar disintegrating properties at given compression conditions. Considering the fact, that tablets produced with fine crospovidone grades show higher tensile strength values, the disintegration power of these grades seems to be even higher. With dicalcium phosphate as filler, even Kollidon® CL-M showed disintegrating properties.

As anticipated, the dry binder copovidone, which increased the tablet strength, slows down the disintegration. Therefore, combinations with a “binding disintegrant” (crospovidone type B) can be recommended to achieve tablets of sufficient strength and quick disintegration at the same time.

The use of large quantities of dry binder provided the challenge of strong but poorly disintegrating tablets. Shortening the disintegration time by the addition of coarse crospovidone (type A) led typically to weaker tablets. Interestingly, this effect could be compensated by the alternative use of a fine grade crospovidone (type B). Especially, Kollidon® CL-SF contributed to the tensile strength of tablets while at the same time shortening the disintegration time. Therefore, Kollidon® CL-SF might be regarded as “binding disintegrant”.

Conclusion

Addition of copovidone resulted in tablets of higher tensile strength. The tensile strength was affected by the copovidone’s particle size and content: smaller particles and higher contents led to tablets of higher tensile strength values.

References

[1] V. Bühler; Kollidon® Polyvinylpyrrolidone – Excipients for the Pharmaceutical Industry; BASF SE, March 2008.

[2] DIN EN ISO 1183-3 (Gas-Pyknometer).

Our service offer

We are providing in-depth expertise in all steps of the production of solid and liquid oral dosage forms.
The combination of our broad portfolio of functional excipients and our expert know-how enables you to create value-adding and unique formulations.

For more information visit us on
www.pharma.basf.com

For sample requests contact us at
pharma-solutions@basf.com

BASF
We create chemistry