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ORIGINAL ARTICLE

Use of crospovidone as pelletization aid as alternative to microcrystalline cellulose: effects on pellet properties

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Abstract

Background: Microcrystalline cellulose (MCC) is the most important pelletization aid in extrusion/spheronization. Because of known disadvantages, the search for substitutes is ongoing. In this context, crospovidone has proven to offer substantial advantages as pelletization aid because of its ability to turn low-soluble active ingredients into fast-dissolving stable pellets. *Method*: Pellets from crospovidone with different amounts of paracetamol, hydrochlorothiazide, and spironolactone as model drugs were prepared by extrusion/spheronization. For comparison, pellets with MCC as extrusion aid were also produced. The pellets of different formulations were evaluated in terms of yield, aspect ratio, mean Feret diameter, 10% interval fraction, tensile strength, disintegration, and drug release profile. *Results*: Only crospovidone types exhibiting small particle sizes are suitable as pelletization aid. While maintaining the pharmaceutical quality aspects, it was possible to incorporate up to 60% (w/w) active pharmaceutical ingredients (API) into pellets with crospovidone. The most distinguished differences between pellets based on crospovidone and MCC are the disintegration and drug release behavior. The pellets containing binary mixtures of the low-soluble APIs and crospovidone resulted in fast release in contrast to the pellets with MCC as pelletization aid, which exhibited a slow release. *Conclusion*: Crospovidone shows an excellent behavior as pelletization aid and produces fast-releasing pellets even with low-soluble APIs.

Key words: *Crospovidone; disintegration; dissolution; extrusion/spheronization; pellets; pelletization aid*

Introduction

To date, microcrystalline cellulose (MCC) remains the most frequently used excipient for the production of pellets by wet extrusion and spheronization. Such excipients are called pelletization aids because they assist both extrusion and spheronization. The manufactured pellets are particularly characterized by a narrow particle size distribution, a high sphericity, and suitable mechanical properties. However, with regard to low-soluble drugs, MCC-based pellets show a tendency to have a prolonged drug release profile because of a lack of disintegration. Other negative impacts of MCC are reported to be drug decomposition in the presence of MCC as well as drug adsorption to the surface of MCC fibers[1–3].

To overcome these disadvantages, various approaches were investigated[4]. Recently, Dukic-Ott et al.[5] gave a critical overview of the actual status of those alternatives. A number of materials have been proposed as alternatives to MCC. However, a perfect pelletization aid is not available. One promising alternative might be crospovidone, but up to now data for pellets containing active pharmaceutical ingredients (APIs) are missing. Crospovidone was first introduced by Liew et al.[6] They examined the properties of some proposed substances with regard to whether they possessed superior features in comparison with MCC when used as a pelletization aid. The authors ascertained that features of particular significance for an improved product quality are low water solubility, high water absorption, and retention ability for optimized rheological conditions for extrusion and spheronization; the binding capacity; a sufficiently large surface for the interaction with water, and the ability to improve the release behavior.

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They concluded that crospovidone possesses many features that support the use of this substance as a pelletization aid. It was possible to produce pellets with crospovidone as pelletization aid. However, in this study only placebo formulations without any API were tested. Mixer torque rheometry revealed that the consistency of crospovidone/lactose mixtures is of lower magnitude compared with MCC/lactose mixtures. Because of their lower cohesiveness, the extrudates formulated with crospovidone could not withstand higher shear forces. Unfortunately, information about some essential parameters for a product intended for extrusion/spheronization is missing: information about the mechanical properties and disintegration of crospovidone pellets is not available. Furthermore, it is not clear whether drugs with different properties can be included and to what extent this is possible. Consequently, data about dissolution profiles are missing.

Crospovidone is a cross-linked insoluble polyvinylpyrrolidon polymer. The cross-linking in the popcorn polymer (Figure 1) is essentially of a physical nature[7]. Several types with different particle size are commercially available. The main advantages of crospovidone compared with MCC arise from the different chemical properties. Crospovidone is a synthetic polymer and more stable with well-defined physicochemical attributes compared with MCC of natural origin with its inherent variations of qualities[6]. The main disadvantage of using crospovidone instead of MCC is the relatively higher cost.

Based on the approach of Liew et al.[6], investigations were carried out to identify the effects of crospovidone as pelletization aid on properties of pellets with some active pharmaceutical ingredients of low solubility. The pellet properties were compared with pellets with MCC as pelletization aid.

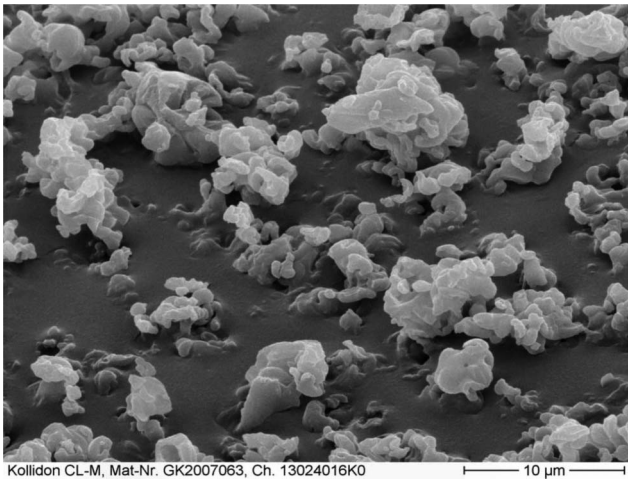

Figure 1. Popcorn structure of Kollidon CL-M®.

Materials and methods

Materials

For the formulations, two qualities of crospovidone (Kollidon CL-SF® and Kollidon CL-M®; BASF, Ludwigshafen, Germany) were used. MCC (Avicel PH 101; FMC BioPolymer/Wallingstown Little Island, FMC International, Wallingstown, Little Island, Co. Cork, Ireland) was used for comparison.

Three different active ingredients with very different solubility in water were selected for the trials:

- paracetamol (Rhodia, Roussilion, France) with a solubility of 14 g/L at 20°C and pH 6[8];
- hydrochlorothiazide [IPCA Laboratories, Kandivali (West), Mumbai, India] with a solubility of 0.722 g/L[9];
- spironolactone (Diapharma Francis Srl, Barazate, Italy) with a solubility of 0.028 g/L[10].

Methods

Experimental plan

All tests were carried out in binary systems consisting of an API and either crospovidone or MCC as pelletization aid. As a first step, the maximum loads of active ingredient in the pellets with crospovidone were identified. The water content was adjusted based on preliminary pelletization tests.

Pellet production

Binary systems with fractions of 10–90% active pharmaceutical ingredient in batches of 500 g dry powder mass were used for pelletization. The wet massing was carried out in a kneading machine (Kenwood, Seligenstadt, Germany) using an appropriate amount of water. The extrusion of the wet mass was conducted in a basket extruder (NICA E 140; GEA Process Engineering Ltd., Hampshire, UK). The wetted material was extruded through a radial screen fitted with circular dice of 1.0 mm diameter and 1.0 mm thickness. The feeding was performed at 16 rpm; the impeller run at 18 rpm.

Spheronization was performed in a NICA S 450 (GEA Process Engineering Ltd.) at 480 rpm for 8.5 minutes using a 450-mm frictional plate with a cross-hatched surface.

For the optimal water content, the spheronization process is characterized by a roping action of the wet mass. Over- and under-wetting resulted in a high amount of fines or in a residual mass on the rotating disk.

The drying was done in a conventional circulating drying oven at 65°C for 6–8 hours.

Loss on drying

Samples of extrudate were taken from each batch after the extrusion process for the determination of water

content. The samples were dried at 105°C for 24 hours using a circulating air oven. The water content was calculated based on the dry mass.

Yield

Each batch was sieved from 0.71 to 1.4 mm. This fraction was determined as a yield. Both fractions outside the limits were also determined. Samples of appropriate size were obtained from the yield fraction by using a Fritsch Analysette 3 Pro (Idar-Oberstein, Germany) with 1 mm amplitude for 10 minutes. The samples were used for further analysis.

Image analysis

Image analysis was conducted by using a system consisting of a stereomicroscope (Leica MZ 75, Wetzlar, Germany), a digital camera (Leica DC 300 F), and a computer using specific imaging software (Q-win version 2.8). Images of approximately 500 pellets of each sample were translated into binary images. Contacting pellets were separated by the software algorithm. If the system failed, pellets were deleted manually. The system was used to characterize the pellet size and shape by the mean Feret diameter, the aspect ratio, and the circularity.

The mean Feret diameter is the mean of 36 measured Feret diameters for one particle. Aspect ratio (Equation 1) is defined as the ratio of the maximum Feret diameter ($D_{\text{Fer.max}}$) and the Feret diameter perpendicular to the maximum Feret diameter ($D_{\text{Fer.90°}}$). Circularity is defined according to Equation (2) by using the area (A) and the perimeter (P) of the pellet.

$$\text{Aspect ratio} = \frac{D_{\text{Fer.max}}}{D_{\text{Fer.90°}}} \tag{1}$$

$$\text{Circularity} = 4\pi\frac{A}{P^2}. \tag{2}$$

The distribution of the particle size was determined by the fraction within the 10% interval[11] $0.9<\text{dd}<1.1$ (dd=dimensionless diameter=$d/d50$). The distribution was rated as good when the 10% interval exceeded 50% and was rated excellent with a value above 75%.

Friability

The friability was determined using the apparatus Friabimat GTA 120 (ERWEKA, Heusenstamm, Germany) according to the procedures specified in the European Pharmacopoeia[12].

Fracture force and tensile strength

The mechanical stability of pellets was tested by using a texture analyzer (TA.XT2i; Stable Micro Systems, Goldalmig, UK). The fracture force (F) and the diameter (d) in crushing direction of 50 pellets per batch of each formulation were determined.

The calculation of the tensile strength was based on Equation (3):

$$\delta = \frac{1.6F}{\pi d^2}. \tag{3}$$

Pellet disintegration

The pellet disintegration in water was evaluated by a tablet disintegration tester using special transparent tubes of 10 mm diameter and 15 mm length. Sieves of 710 µm were placed on the top and the bottom of the described tube. After filling 100 mg pellets in each tube, they were placed into the standard tablet disintegration tester (ERWEKA ZT 304). The disintegration time of six samples was determined in purified water. The tester was running with a speed of 30 dips per minute. The maximal disintegration time is given as a result.

Dissolution

The tests were performed according to the monographs 'Acetaminophenon tablets', 'Hydrochlorothiazide tablets', and 'Spironolactone tablets' of the U.S. Pharmacopoeia[13] by using the apparatus 2 at 50 rpm. All drug release tests were performed by using an automated dissolution tester (ERWEKA DT 700). To avoid a scum forming of the test solution because of the lauryl sulfate content, samples of spironolactone were only taken every 5 minutes. The interval for the other two APIs was 2 minutes.

Stability of the pellets

The stability of paracetamol and HCT and spironolactone pellets was checked after a storage period of 6 months at room temperature and ambient humidity. The parameters friability, disintegration, and drug release profile were evaluated.

Results and discussion

Selection of the suitable crospovidone type

Liew et al.[6] evaluated different crospovidone types in relation to a possible substitution of MCC as a pelletization aid in their study. They proposed to use the finer grades of Polyplasdone XL-10® and INF-10®, which showed great potential in functioning as effective pelletization aid.

In this study, crospovidone grades from another supplier are used, namely Kollidon CL-SF® and Kollidon CL-M®. A comparison of the physical parameters of the different crospovidone grades is summarized in Table 1.

When comparing Kollidon CL-SF® and Kollidon CL–M® as basis of the binary system, it was not possible to prepare pellets with Kollidon CL-SF®. Regardless of the amount of water used, it was not possible to spheronize the rope of the wetted mass. This type of crospovidone presented too large particles, whereas the type Kollidon CL–M® matched all the requirements for successful extrusion/spheronization. Because of these results, all further investigations were carried out using the Kollidon CL-M® quality. The results confirm the findings of Liew et al.[6] that only crospovidone types with smaller particle sizes are suitable as pelletization aid. However, Polyplasdone INF-10, which was successful in the study of Liew et al.[6], has a similar particle size as Kollidon CL-SF®, which failed in this study. Generally, smaller particle sizes seem to be more suitable, but the absolute particle size might depend on the properties of crospovidone produced by different suppliers or the equipment used for extrusion/spheronization. Polyplasdone types were not included in this study.

Water content for pelletization

With increasing fraction of API, the required water content for pelletization was lower (Figure 2). Furthermore, with increasing solubility of the API, less water (%) was needed for pelletization. This is in agreement with findings for other pelletization aids, especially MCC[14]. Generally, the water content at the same fraction of API is higher with lower solubility of the API. Compared to pellets with MCC the formulations with crospovidone required generally higher amount of water. Looking at the surface of the different pellets (Figure 3a–c), it can be stated that the MCC pellets showed a higher degree of sphericity and a smoother surface. With regard to the pellets based on Kollidon CL-M® impressions can be seen. Furthermore, all pellets containing a high fraction of crospovidone (i.e., pellets with 10% API and 90% crospovidone) appear to be mat.

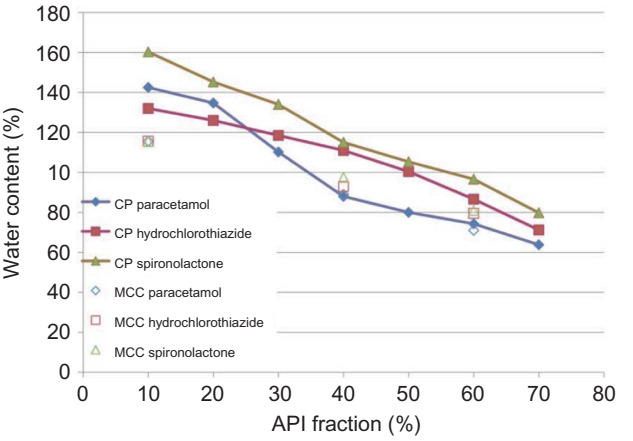

Figure 2. Required water content-based on dry mass (w/w) for pelletization.

Yield

Some properties of the pellets are summarized in Table 2. The data demonstrate that crospovidone as a pelletization aid enables a formulation to generate acceptable yield levels. For pellets with 10–60% of paracetamol the yield varied between 78% and 94%, for pellets with hydrochlorothiazide between 75% and 91%, and for spironolactone from 70% to 90%.

Pellets with 10%, 40%, and 60% MCC resulted in yield values from 88% to 95%. For paracetamol the yields show no significant differences between MCC and crospovidone. For hydrochlorothiazide and spironolactone the yield for pellets with MCC is higher than for pellets with crospovidone.

It was not possible to produce pellets with 80% of API. Pellets with 70% of API could be produced, but the yield and other pellet properties were insufficient. Thus, only the results for pellets up to 60% of API were included in this study. The achievable drug load is lower for crospovidone compared with MCC, which is a restriction for the use of crospovidone.

Table 1. Physical characterization of crospovidone grades.

Crospovidone grade	Polyplasdone XL-10[a]	Polyplasdone INF-10[a]	Kollidon CL-SF[b]	Kollidon CL-M[b]
Mean size (µm)	31.3	19.7	17.0	5.4
Span	1.68	1.48	2.4	1.6
Bulk density (g/mL)	0.28	0.30	0.14	0.20
Tapped density (g/mLl)	0.43	0.48	0.21	0.27
Hausner ratio	1.54	1.60	1.50	1.35

[a]Liew et al.[6]; [b]Bühler[7].

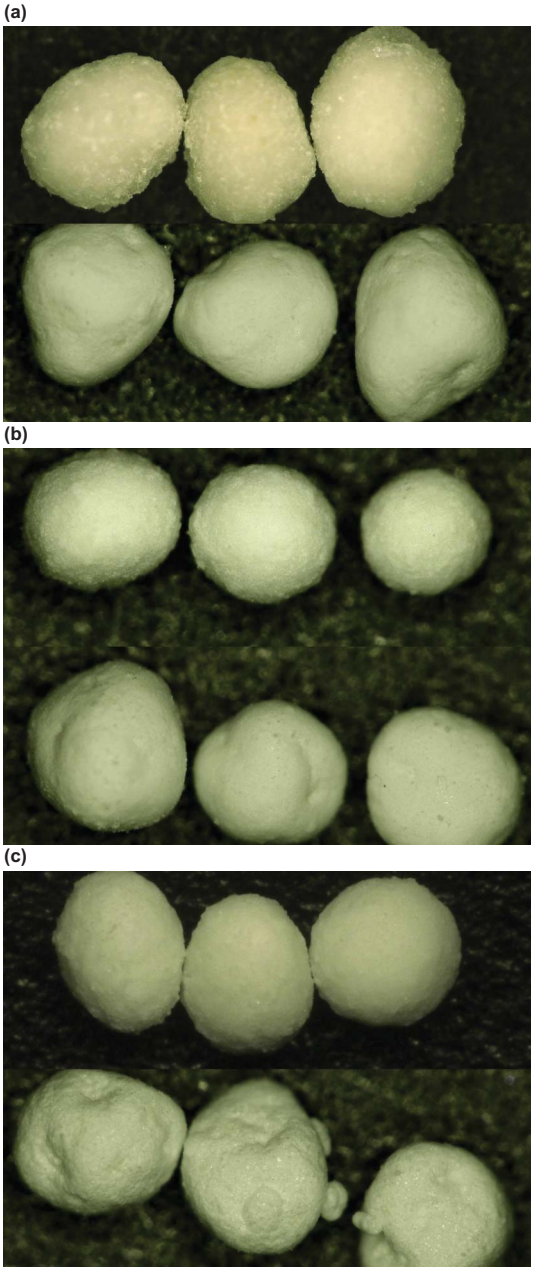

Figure 3. (a) Pellets with 10% paracetamol. Top part, MCC; bottom part crospovidone. (b) Pellets with 40% spironolactone. Top part, MCC; bottom part, crospovidone. (c) Pellets with 60% hydrochlorothiazide. Top part, MCC; bottom part, crospovidone.

Image analysis

The results for mean Feret diameter, aspect ratio, circularity, and 10% interval obtained from image analysis are summarized in Table 3. The aspect ratio is rated as acceptable in the range of 1.1–1.2. Pellets from all three APIs were within this range.

The optimal value for the circularity is 1.0. Numbers between 0.8 and 1.0 were considered as acceptable values. All values of spironolactone and paracetamol matched with this requirement, whereas HCT was on the borderline with an API concentration above 50%. The borderline values might be a result of adhesion of fine particles on the surface as can be seen in Figure 3c. Concerning the size distribution determined by the 10% interval, all evaluated formulations lay well within the requirements range for being good. The dimensionless particle size distributions are shown in Figure 4a–d.

Looking at the particle size distribution, it is obvious that the MCC formulations have a different pattern than the crospovidone preparations. MCC pellets have a small portion of pellet fines and a greater portion of coarser pellets with all three APIs.

Crospovidone pellets present a higher percentage of fine particles and a significantly lower volume of coarser particles for all APIs. This leads to the conclusion that there is a higher binding effect with MCC than with crospovidone. Regarding the disintegration and drug release profile, the higher binding forces of MCC-based pellets prohibit a fast disintegration and a fast dissolving system.

Friability

The range of friability is 0.1–1.4% for pellets with paracetamol, 0.2–2.1% for hydrochlorothiazide pellets, and 0.1–0.4% for spironolactone pellets. The variation for repeated batches of the same formulation is of the same magnitude than for different formulations of the same API. Friability of all formulations is generally low, and therefore it can be expected that all pellets of the different formulations show sufficient mechanical properties (Table 2). Spironolactone pellets show similar friability when using crospovidone or MCC as pelletization aid. However, for paracetamol or hydrochlorothiazide, the friability of pellets based on crospovidone is higher than for pellets based on MCC.

Pellet fracture force and tensile strength

With regard to the following process steps such as drying in a fluidized bed, coating using the Wurster process, or integrating into a blend for tabletting, a high degree of mechanical stability of the extruded pellets is important. The mean fracture force values of paracetamol and hydrochlorothiazide pellets were in the same magnitude of approximately 3 N (Figure 5). For spironolactone pellets the crushing force declines with increasing API content. The drop from around 3 to 1.7 N (60% API) had no real impact to the friability behavior. The corresponding friability value had only a value of 0.2%.

A tensile strength between 0.5 and 1.0 MPa is regarded as sufficient for further processing steps. All

Table 2. Physical properties of the manufactured pellets.

	Paracetamol			Hydrochlorothiazide			Spironolactone		
API fraction (%)	Yield (%)	Friability (%)	Disintegration (seconds)	Yield (%)	Friability (%)	Disintegration (seconds)	Yield (%)	Friability (%)	Disintegration (seconds)
Crospovidone									
10	89.4	0.4	13	85.4	0.2	11	79.3	0.1	11
	78.4	1.0	73	75.5	2.1	30	70.1	0.3	26
	93.4	1.1	70	77.6	1.3	30	69.5	0.4	43
20	90.1	0.3	13	80.3	0.3	28	84.2	0.1	8
30	93.3	0.2	13	91.3	0.3	21	86.3	0.1	9
40	94.0	0.4	15	89.2	0.4	37	87.7	0.2	40
	89.7	1.4	60	82.0	0.6	20	75.3	0.2	40
	88.8	1.2	32	82.2	0.6	13	72.6	0.3	36
50	92.1	0.1	6	88.7	1.0	14	88.7	0.1	9
60	94.2	0.6	18	87.4	0.2	30	90.1	0.2	68
	90.8	1.2	15	79.5	0.8	15	82.4	0.3	
	92.4	1.2	20	77.0	0.8	15	84.9	0.3	
MCC									
10	87.8	0.2	—	89.3	0.3	—	94.3	0.4	—
40	93.5	0.1	—	88.6	0.4	—	92.7	0.3	—
60	94.1	0.2	—	92.1	0.1	—	89.7	0.3	—

Table 3. Results of image analysis.

	Paracetamol				Hydrochlorothiazide				Spironolactone			
API fraction (%)	$D_{Fer.av}$ (μm)	AR	Circularity	10% interval	$D_{Fer.av}$ (μm)	AR	Circularity	10% interval	$D_{Fer.av}$ (μm)	AR	Circularity	10% interval
Crospovidone												
10	956	1.16	0.82	63.0	990	1.14	0.80	54.0	868	1.20	0.82	80.2
20	989	1.19	0.82	61.2	931	1.19	0.83	74.4	867	1.17	0.81	64.0
30	1008	1.18	0.82	63.6	946	1.18	0.83	59.4	918	1.17	0.83	67.2
40	1026	1.19	0.80	70.0	994	1.19	0.81	61.6	928	1.15	0.82	52.0
50	1031	1.17	0.82	65.8	1029	1.22	0.79	61.2	993	1.16	0.84	71.6
60	1082	1.20	0.83	71.0	1002	1.20	0.78	52.6	966	1.16	0.84	67.6
MCC												
10	944	1.18	0.81	55.4	857	1.16	0.82	50.4	891	1.16	0.82	54.8
40	929	1.13	0.83	68.2	923	1.14	0.82	64.6	906	1.16	0.83	52.0
60	849	1.13	0.82	43.2	905	1.14	0.83	55.4	1003	1.18	0.83	64.2

results obtained showed that pellets with crospovidone as pelletization aid matched this range. Based on the literature, MCC pellets obtained values of tensile strength being clearly higher. The high mechanical stability of MCC pellets is linked to the high binding forces of MCC and the known shrinking process during the drying process that results in a decrease of porosity[14].

Disintegration

The disintegration values display that pellets of all APIs showed a very fast disintegrating behavior (Table 3). Based on this behavior, crospovidone is an ideal pelletization aid for fast dissolving formulations[6]. Using the standard method for disintegration of MCC- and crospovidone-based pellets, it was not surprising that none of the MCC formulations disintegrated at all.

Drug release

The drug release profiles for pellets containing the two pelletization aids and the three APIs are shown in Figure 6a–c. There are important differences in the release from pellets based on the two pelletization aids. Although the drug release is fast for all pellets with crospovidone, the drug release is strongly dependent on the solubility of the API in case of MCC-based pellets. In all cases, the MCC pellets show a matrix type of release because of the missing disintegration. As the drug solubility is one important parameter in the Higuchi equation, it can be expected that the dissolution

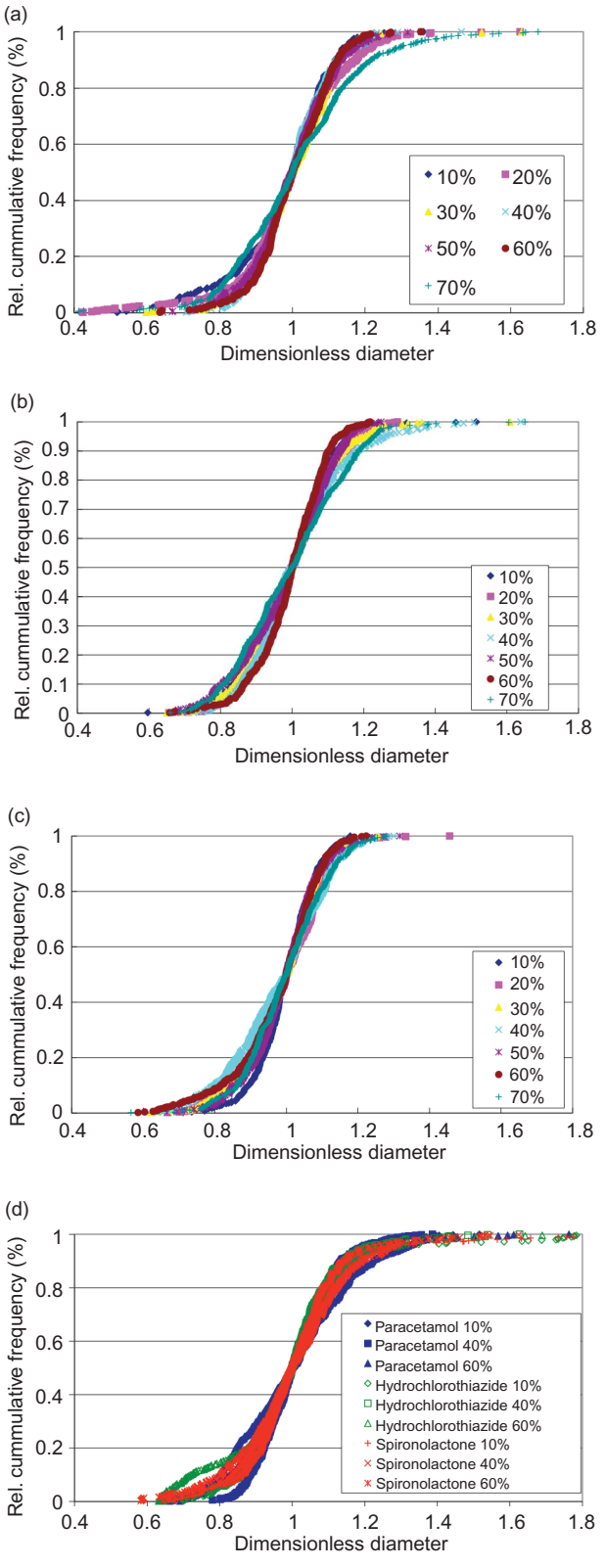

Figure 4. (a) Dimensionless particle size distribution of crospovidone/paracetamol pellets. (b) Dimensionless particle size distribution of crospovidone/hydrochlorothiazide pellets; (c) Dimensionless particle size distribution of crospovidone/spironolactone pellets; (d) Dimensionless particle size distribution of MCC pellets.

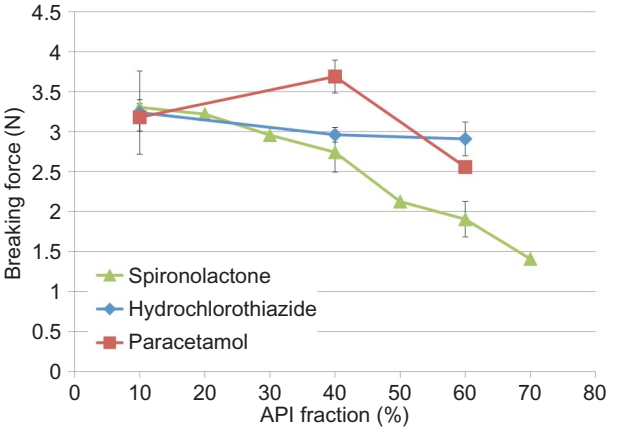

Figure 5. Comparison of pellet-breaking force of pellets containing the three APIs (three batches for 10%, 40%, and 60% API, mean ± SD).

is slower for lower soluble drugs. In the case of crospovidone pellets, the fast disintegration and sufficient wetting leaves the individual drug particles suspended. The dissolution profile depends on the saturation solubility of the drug particles. Besides the solubility, the particle size is of importance because smaller particles result in a higher specific surface area, which enhances the dissolution rate.

The advantage of a fast drug release for crospovidone-based pellets is clearly more pronounced for lower soluble drugs (Figure 6a–c). All pellet formulations of the three APIs demonstrated a drug release profile for fast-releasing pellets. Based on these results, it can be stated that the advantages of crospovidone as pelletization aid are more relevant for low-soluble APIs.

Because of the missing disintegration of MCC-based pellets, it has been expected that the drug release profile will not result in a fast release of the low-soluble APIs. These results indicate that MCC is not a choice for pellet formulations of low-soluble APIs such as hydrochlorothiazide or spironolactone.

Stability of the pellets

The parameters disintegration, dissolution, and friability of the pellets with crospovidone were tested after 6 months. Friability and disintegration time were higher after storage, but the values were still around 1% for friability and below 100 seconds for the maximal disintegration time. The dissolution profiles were similar to those obtained from freshly prepared pellets. However, the dissolution from pellets with 50% or 60% spironolactone was slightly delayed, and complete dissolution was observed within 30 minutes. In future studies, the effects

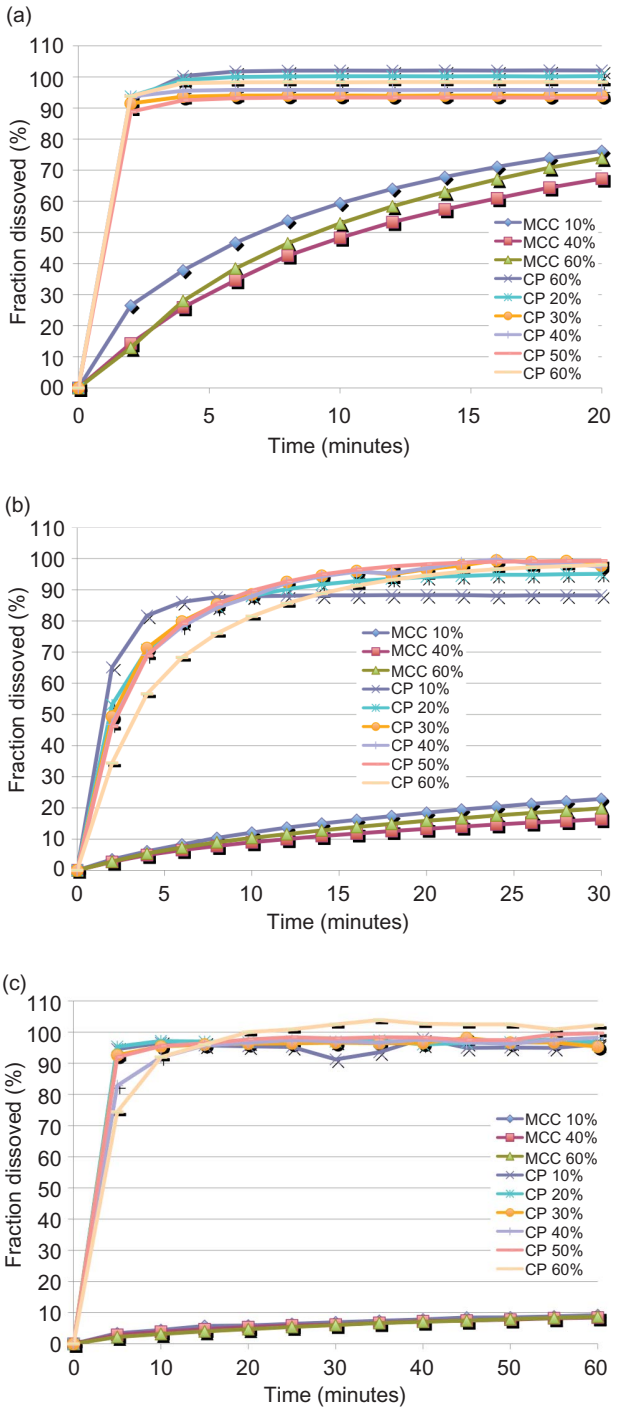

Figure 6. (a) Release profiles for pellets containing paracetamol; the legend gives the pelletization aid and the fraction of paracetamol. (b) Release profiles for pellets containing hydrochlorothiazide; the legend gives the pelletization aid and the fraction of hydrochlorothiazide. (c) Release profiles for pellets containing spironolactone; the legend gives the pelletization aid and the fraction of spironolactone.

of storage temperature and relative humidity on the pellet properties should be investigated more systematically. However, it has to be kept in mind that the pellets usually will be coated to achieve certain functionality like gastric resistance or prolonged release and not stored without a coating for a longer time.

Conclusion

It was possible to produce acceptable pellets using a fine crospovidone grade (Kollidon CL-M®) as a pelletization aid with an active substance concentration of up to 60%. All pellets showed a fast disintegration resulting in a fast dissolution of incorporated APIs. This was demonstrated by using three model substances with highly different solubility.

The comparable formulations with the conventional pelletization aid MCC instead of crospovidone (Kollidon CL-M®) demonstrated the weakness of MCC formulations when using low-soluble active ingredients. Neither the disintegration nor the drug release profile matched the requirements of fast-dissolving and fast-releasing pellet systems. It can be concluded that crospovidone is a promising pelletization aid with high potential.

Declaration of interest: The authors report no conflicts of interest.

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