Croscarmellose Sodium as Pelletization Aid in Extrusion-Spheronization

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Abstract

Only few excipients are known to be suitable as pelletization aids. In this study, the potential use of croscarmellose sodium (CCS) as pelletization aid was investigated. Furthermore, the impact of cations on extrusion-spheronization (ES) of CCS was studied and different grades of CCS were tested. The influence of different cations on the swelling of CCS was investigated by laser diffraction. Mixtures of CCS with lactose monohydrate as filler with or without the inclusion of different cations were produced. The mixtures were investigated by mixer torque rheometry and consequently extruded and spheronized. Resulting pellets were analyzed by dynamic image analysis. In addition, mixtures of different CCS grades with dibasic calcium phosphate anhydrous (DP) and a mixture with praziquantel (PZQ) as filler were investigated. Calcium and magnesium cations caused a decrease of the swelling of CCS and influenced the use of CCS as pelletization aid since they needed to be included for successful ES. Aluminum, however, led to an aggregation of the CCS particles and to failure of extrusion. The inclusion of cations decreased the uptake of water by the mixtures which also reduced the liquid-to-solid-ratio (L/S) for successful ES. This was shown to be dependent on the amount of divalent cations in the mixture. With DP or PZQ as filler, no addition of cations was necessary for a successful production of pellets, however the optimal L/S for ES was dependent on the CCS grade used. In conclusion, CCS can be used as a pelletization aid.

Keywords Pelletization aid · Croscarmellose sodium · Extrusion-spheronization · Multivalent cations

Introduction

Pellets are spherical agglomerates of different mean sizes that are widely used in the pharmaceutical industry. Often a size range of approximately 0.5 to 1.5 mm is described in literature, however, also larger sized pellets (≥ 2.5 mm) can be successfully produced [1, 2]. Several advantages for pellets as multi dose units over single dose units like tablets are described, such as feed state independent gastric emptying or reduced risk of dose dumping [3]. Due to their small particle size they are also attractive as a paediatric dosage form [4]. One of the most important production techniques for the preparation of pharmaceutical pellets is the extrusion-spheronization (ES) process [5, 6]. One of the advantages of ES is the incorporation of high amounts of active pharmaceutical ingredients up to 90% [7]. The process itself can be divided into two consecutive processes: In the extrusion process a deformable mass is squeezed through a die with a defined diameter resulting in extrudates that are consequently broken down into smaller rods and rounded on a rotating friction plate of a spheronizer. For most formulations a wet extrusion is performed, however, it was shown that lipid formulations can be extruded and spheronized without the incorporation of a liquid when the temperature of the spheronizer is adjusted [8]. In the case of the wet extrusion a wetting and mixing step needs to be performed before the extrusion step unless a continuous equipment like a twin-screw extruder is used [9, 10]. In the following ES refers to a production via wet extrusion.

A pelletization aid must be included in the formulation for the preparation of pellets by ES. The purpose of the pelletization aid is to control the movement and the distribution of the wetting liquid and to adjust the rheological behavior of the wetted mass [7]. This gives the wetted mass the

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necessary properties to be successfully extruded and spheronized. For a successful spheronization the extrudates must have a sufficient strength to withstand the forces in the spheronizer yet be brittle enough to be broken down to a suitable length. A sufficient plasticity leads to the spheronization of the extrudates [7].

The excipient that is referred to as the "golden standard" is microcrystalline cellulose (MCC) [11], since it shows optimal properties for the distribution of the wetting liquid and already the incorporation of small amounts lead to pellets of good quality [12]. However, MCC shows some disadvantages such as lack of disintegration [13, 14] or incompatibility with some drugs due to degradation or absorption to the MCC fibers [15–17] and only a few other excipients are known to be used as pelletization aid as well.

An overview of excipients that were used as pelletization aids without the incorporation of MCC was given by Dukić-Ott et al. [11]. However, an additional binder needed to be included in some cases as for powdered cellulose and for starch-derivates [18, 19]. Excipients that may be suitable without MCC or an additional binder are e.g. kappa-carageenan [20, 21], crospovidone (xPVP) [22, 23], chitosan [24, 25] or pectinic acid [26, 27].

For the screening for novel pelletization aids or for a more rational development of formulations in the future, knowledge about the functionality of such pelletization aids is of high importance. For MCC different models were proposed based on its properties. Fielden et al. and Ek et al. described the MCC as a "molecular sponge" due to its ability to physically bind a high amount of water [28]. The water would then be squeezed out under compression and lead to the deformability of the wetted mass [29]. Kleinebudde on the other hand suggested the "crystallite-gel-model" [30] which is explained by the structure of the MCC. During ES the MCC is partly broken down into colloidal sized crystallites which then build up a three-dimensional network immobilizing the water distributed in the mixture. The "reversible gel" model which was developed by Lenhart combines both hypotheses since both previous described models cannot explain all observations made during ES. For example, excipients that can form gels, such as hypromellose (HPMC), should be able to be used as pelletization aids as well if only the gel-formation was of importance. However, HPMC could only be used in an insoluble state with isopropanol as liquid an hydroxyethyl cellulose as a binder [31, 32]. On the other hand the "molecular sponge" model is not able to explain why powdered cellulose (PC) cannot be used as pelletization aid in contrast to MCC, since it was shown that MCC and PC are both able to physically bind large amounts of water [32]. The "reversible gel" model describes the pelletization aid as an aggregate of microscopic and colloidal particles. The wetting liquid can be stored inside the macroscopic particles and can be distributed and taken up again during extrusion and spheronization as described by the "molecular sponge" model. When the liquid is squeezed out of the microscopic particles the "gel" network immobilizes the liquid. Plastic deformation might take place in this phase. When the liquid is taken up again the extrudates show a more brittle behavior. These models can be used as a basis for the screening of new excipients.

One of the excipients that were described as an alternative was xPVP. xPVP was selected because of different properties that might be beneficial for a pelletization aid such as water insolubility and a high capacity for water absorption and retention and it was shown that pellets could be obtained without an additional binder [22]. In contrast to MCC, the pellets from xPVP disintegrated but showed lower mechanical strength [23]. The presence of colloidal particles was also shown for xPVP [32]. Due to their insolubility and water absorption capacity other excipients that are typically used as tablet disintegrants might show suitable properties too. Croscarmellose sodium (CCS) might be a suitable candidate because it is insoluble but swellable in water. It contains non-linked, soluble carboxymethylcellulose (CMC) chains as remnants from production [33] that might act as the colloidal component as described by the "reversible gel" model [32]. CCS was already investigated for the reduction of the extruder screen pressure to produce fine spherical granules but was declared as unsuitable to obtain particles of satisfactory sphericity [34]. In this study, the use of croscarmellose sodium (CCS) as a pelletization aid for ES without the incorporation of MCC is evaluated. Since both CCS and CMC contain carboxylic acid groups which are known to interact with different divalent cations [35] a deeper look into the influence of these cations on the use of CCS is given as well.

Materials and Methods

Material

Five different CCS grades were used as received: Primellose® (PL, DFE Pharma, Germany), Ac-Di-Sol® SD-711 (ADS, IFF, USA), Solutab® A (SA, Roquette, France), Solutab® EDP (SE, Roquette, France) and Vivasol® (VS, JRS Pharma, Germany). Dibasic calcium phosphate anhydrous (DP, DI-CAFOS® A12, Budenheim, Germany), praziquantel (PZQ, Bayer AG, Germany) and lactose monohydrate (Lac, GranuLac® 200, Meggle, Germany) were used as fillers. PZQ was chosen due to its low solubility and not for the use as a model API. Sodium chloride (Na), calcium chloride dihydrate (Ca), magnesium chloride hexahydrate (Mg)

Table 1 Composition of powder mixtures with Lac as filler

	PLLac	PLLacCa7	PLLacCa2	PLLacCa1	PLLacMg9	PLLacAl11	PLLacNa3
PL (%)	50	50	50	50	50	50	50
Lac (%)	50	43.4	48	49	40.8	39.1	47.4
Ca (%)		6.6	2	1			
Mg (%)					9.2		
Al (%)						10.9	
Na (%)							2.6

Table 2 Composition of powder mixtures with DP and PZQ as insoluble fillers

	PLDP	ADSDP	SADP	SEDP	VSDP	PLPZQ
PL (%)	50					50
ADS (%)		50				
SA (%)			50			
SE (%)				50		
VS (%)					50	
DP (%)	50	50	50	50	50	
PZQ (%)						50

and aluminum chloride hexahydrate (Al) were of analytical grade.

Methods

Investigation of Supernatants of CCS-Suspensions for Colloidal Particles

The investigation of colloidal particles was performed modified according to Lenhart et al. [36]. Since it was expected that the colloidal component of CCS mainly consists of water-soluble un-crosslinked CMC chains [33], the stirring method was changed and the stirring time was reduced. PL, ADS, SA, SE and VS were suspended in demineralized water to form suspensions with a CCS content of approximately 5% (m/m). The suspensions were vortexed for 30 s at 3000 rpm. Afterwards, the suspensions were centrifuged for 2 h at 1892 g (Multifuge 1 L, Heraeus, Germany). The supernatants were transilluminated using a red laser (640–660 nm) and were visually inspected for the Tyndall effect. Pure demineralized water served as a control.

Swelling of CCS

The particle sizes of dry PL, ADS, SA, SE and VS were investigated by laser diffraction (Mastersizer 3000, Malvern, UK) using a dry dispersion unit (Aero S, Malvern Panalytical, UK). The swelling of the different CCS grades was examined by suspending 1 g of each grade in 200 g of demineralized water and stirring it for 10 min at 500 rpm on a magnetic stirrer. The suspensions were then analyzed by laser diffraction using a wet dispersion unit (Hydro MV, Malvern Panalytical, UK) for the same device using demineralized water as the dispersion medium. To investigate the influence of cations on the swelling of CCS, PL was also suspended in equimolar solutions (approx. 0.68 mol/kg) of Na, Ca, Mg and Al resulting in concentrations of 3.98%, 10%, 13.84% and 16.44% (m/m), respectively. Afterwards, the measurement was performed as described above.

Settling Volume of CCS

The settling volume of the different CCS was determined modified according to the monograph of CCS in the Ph. Eur [37]. 1.5 g of CCS was dispersed in 100 mL of demineralized water in graduated 100 mL cylinders. The dispersions were shaken and allowed to settle for 24 h. Afterwards, the settling volume was determined ($n = 2$).

The dependency of the settling volume on different salts was investigated. Therefore, 1.5 g of PL was dispersed in equimolar solutions (approx. 1.36 mmol) of Na, Ca, Mg and Al in 100 mL of demineralized water in graduated 100 mL cylinders and were treated as described above ($n = 2$). In addition to the settling volume, the redispersability of the sediments was checked by tilting the cylinders until the sediments were redispersed.

Preparation of Powder Blends

The powder blends are listed in Table 1 and 2. 200 g of each blend were prepared. All materials were blended in a laboratory scale blender (Turbula® T2C, Turbula, W.A. Bachofen AG, Switzerland) for 20 min.

Mixer Torque Rheometer Measurements

Mixer torque rheometer (MTR, Plastograph® EC Plus, Brabender, Germany) measurements were performed for all

powder blends (Table 1 and 2). 10 g of mixture was wetted and mixed at a rotational speed of 50 rpm while demineralized water was added continuously at a rate of 1 mL/min by a syringe pump (Legato 100, KD Scientific, USA) equipped with 50 mL glass syringe (SGE Analytical Science, Australia). The torque values were recorded at a frequency of 0.5 Hz at least until the suspension state was reached, visible as a decrease of the torque to the baseline. All measurements were performed in triplicate. The moving averages were calculated including nine values before each torque value to smoothen the curves.

Extrusion/Spheronization

The powder mixtures were wetted and mixed in the MTR at a rotational speed of 100 rpm while adding a specific volume of demineralized water with the syringe pump at a rate of 5 ml/min resulting in a specific liquid-to-solid-ratio (L/S). The mixing process was stopped when the measured torque reached an equilibrium. The amount of powder mixture and the optimal L/S (L/S$_{opt}$) and therefore the volume of demineralized water was dependent on the composition of the powder mixture and was determined in preliminary trials. The parameters used for each powder mixture are listed in Table 3.

The wetted material was extruded using a capillary rheometer (Malvern RH2000, Malvern, UK) equipped with a die of 15 mm length and 1 mm diameter at a speed of 200 mm/min.

Approximately 20 g of extrudate was rounded in a spheronizer (Model 120, Caleva, UK) equipped with a cross-hatched friction plate for 5 min at a tip speed of approximately 8.4 m/s.

After spheronization the pellets were dried in a fluid bed dryer (TG 1, Retsch, Germany) at a temperature of approximately 32–34 °C for 60 min. Every batch was produced once.

Table 3 Parameters for the wetting and mixing of the powder mixtures and for the analysis of the resulting pellets

Powder mixture	Amount of powder [g]	Volume of demineralized water [mL]	L/S$_{opt}$	L/S$_{max}$	Coarse particles [mm]
PLLacCa7	20	35	1.75	1.87	> 2
PLLacCa2	20	45	2.25	1.93	> 2
PLLacMg9	20	35	1.75	1.81	-
PLLacNa3	20	45	2.25	2.02	> 3.5
PLDP	15	42	2.80	2.48	> 1.6
ADSDP	15	49	3.27	2.50	> 1.6
SADP	15	37	2.47	2.18	> 1.6
SEDP	15	40	2.67	2.36	> 1.6
VSDP	15	37	2.47	2.16	> 1.6
PLPZQ	15	50	3.33	2.83	> 1.6

Microscopic Imaging of Pellets

Microscopic images of the pellets were taken with a digital microscope (VHX-7000, Keyence, Japan) at magnifications of 20x, 50x and 100x.

Dynamic Image Analysis of Pellets

Pellet sizes and shapes were analyzed using dynamic image analysis (CPA 2 − 1, Haver & Boecker, Germany) using the maximum Feret (Fe$_{max}$) as size definition. The aspect ratio (AR) was defined as the ratio of Fe$_{max}$ and the maximum width (W$_{max}$). The whole batch of each product was measured. Particles with a size below 0.63 mm were defined as fines and were excluded from the measurement by the software. The coarse fraction was defined depending on the batch (Table 3). Particles with an AR above 5 were excluded from the measurement by the software to remove artifacts. The dimensionless diameter (d) was calculated by dividing Fe$_{max}$ by the median Fe$_{max}$ of all particles of the batch. The 10%-interval (0.9 < d < 1.1) was used to characterize the width of the distribution [21]. In all cases the entire batch was measured once.

## Results and Discussion

Characterization of the Raw CCS

Tyndall-Effect

The supernatants of all CCS suspension showed a Tyndall-effect when they were transilluminated with the laser (Fig. 1). This indicates the presence of colloidal particles which play a crucial role for the functionality of MCC according to the "crystallite gel" model [30] and for insoluble pelletization aids in general according to the "reversible gel" model [32]. These colloids could either be part of the excipient as for example for MCC or can be added to the mixture e.g. in form of a water-soluble binder [18, 19]. The observation of a Tyndall-effect in the supernatants of the CCS suspensions could therefore be a first indicator for the suitability as a pelletization aid.

Swelling Behavior and Settling Volume of CCS

All CCS grades showed a particle size in a similar range with a median particle size between 41 µm and 56 µm (Fig. 2a). After suspending the materials in demineralized water, the particle size distributions of all grades showed a shift to larger particle sizes. The median particle sizes of the suspended particles ranged between 73 µm and 91 µm.

Fig. 1 From left to right: Transilluminated supernatants of PL, ADS, SA, SE, VS and demineralized water
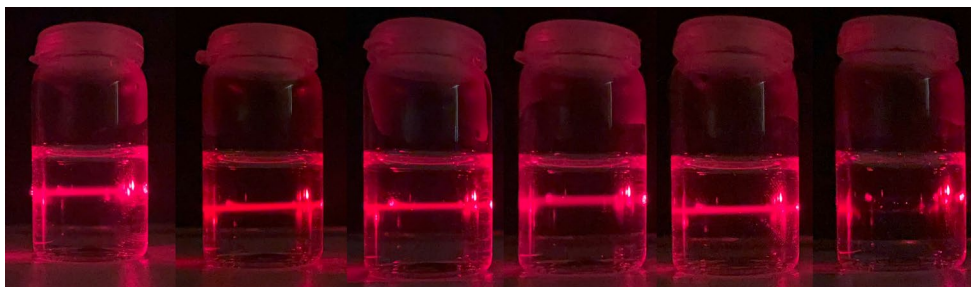
Fig. 2 Particle size distributions ($\bar{x} \pm s$) ($n = 3$); **a** dry CCS powders and suspended CCS powders in demineralized water; **b** dry PL powder and PL powder suspended in demineralized water and aqueous solutions of Na, Ca, Mg and Al
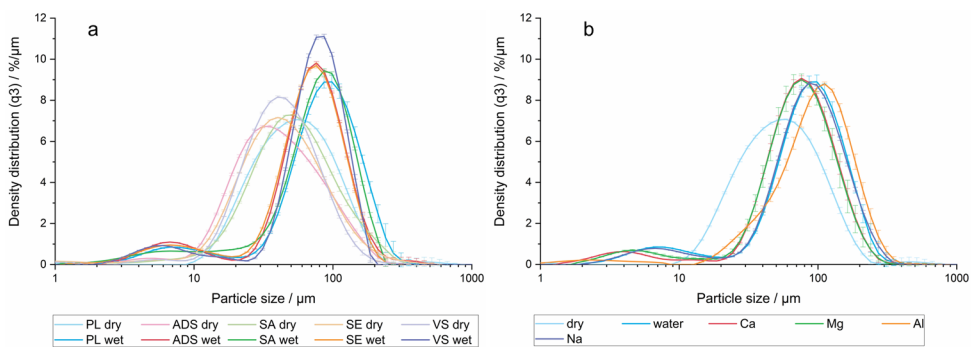
Table 4 Parameters for the wetting and mixing of the powder mixtures and for the analysis of the resulting pellets

Settling volume [mL]								
$\bar{x}$ (s)					$\bar{x}$ (s)			
PL	ADS	SA	SEDP	VS	PL_{Na}	PL_{Ca}	PL_{Mg}	PL_{Al}
18.5 (0.7)	20.0 (0.0)	18.0 (0.0)	20.0 (0.0)	16.5 (0.7)	18.5 (0.7)	13.0 (0.0)	14 (1.4)	13 (0.0)

The increase in the particle size can be explained by the swelling of the particles. The CCS molecules are insoluble in water but hydrophilic and swellable due to their cross-linking [33]. The swelling of CCS in aqueous solutions of Na, Ca, Mg and Al was done exemplary for PL (Fig. 2b). Na seemed not to decrease the swelling of the CCS significantly. Ca and Mg reduced the swelling to a similar extent. This is due to the interaction between the calcium or magnesium ions and the non-crosslinked carboxylic acid groups as described for CMC [35, 38] which can also lead to interactions between the disintegrant and cationic drugs [39]. In contrast to that the particle size of PL seems to increase with Al present. This might not indicate an increased swelling but is caused by agglomeration of the particles in the suspension. The agglomeration was already seen by the naked eye. This indicates a strong interaction between the aluminum and CCS. The influence on the swelling, however, can only be assumed by the laser diffraction data. The different CCS resulted in different settling volumes (Table 4). Differences in the settling volume might indicate differences in the uptake of water during ES, resulting in different water amounts necessary for successful ES. The presence of salts in the dispersion media indicated similar effects on the settling volume as on the particle size distributions measured by laser diffraction. Na did not affect the settling volume. Ca

and Mg led to a decrease of the settling volume. The settling volume in a solution of Al showed a similar decrease as in a solution of Ca, however there was a difference in the formation of the sediment. All sediments were easily redispersable by one tilt of the cylinder, however, the sediment in the Al solutions was not redispersable by tilting at all. This indicates a high increase of the interactions between the CCS particles caused by Al leading to agglomeration. This fits to the observations made during the laser diffraction experiments. A certain swellability for extrusion and spheronization of the pelletization aid is described as another important requirement. The pelletization aid can thereby store the wetting liquid inside its pores or between the particles. By that the liquid can be redistributed during ES. This is described by the "reversible gel" as well as by the "molecular sponge" model [29, 32]. The decrease in swelling induced by the cations might also influence the water uptake of the mixtures during wetting.

CCS and Lac as a Soluble Filler

Mixer Torque Rheometer Measurements

Figure 3a shows the MTR curves of PLLac, PLLacCa7, PLLacMg9, PLLacAl11 and PLLacNa3. The amount of

additive was chosen so that there is a similar molal concentration of cations in each dry mixture (approx. 0.45 mol/kg). The addition of Na, Ca, Mg and Al lead to a decrease of the maximum torque (T_{max}). While the effect is pronounced the most for PLLacAl11, the decrease is less pronounced for PLLacCa7 and PLLacMg9. This matches the observations seen in the swelling and settling experiments. The decrease in T_{max} can be explained by the reduced swelling and therefore by a less pronounced volume increase in the MTR chamber when Al, Ca or Mg are included. A curve shift to lower L/S can be seen for all additives as well leading to lower values for the L/S at which the maximum torque occurs (L/S_{max}). The decrease of L/S_{max} is pronounced the most for Al while L/S_{max} of Ca and Mg are in the same range which can be explained by the reduced swelling as well. According to the liquid saturation model the voids between the particles are filled with the granulation liquid, building liquid bridges between the particles. When the capillary state is reached the torque curve reaches its maximum [40]. When a material can take up some of the granulation liquid inside its pores, e.g. by swelling, more liquid is required to reach the same liquid saturation. Such behavior was shown for MCC [41]. Since the CCS swells less when Ca, Mg or Al is included in the mixture, the voids between the particles are already filled at lower L/S because less water will be absorbed by the CCS particles. However, Na led to a decrease in T_{max} and L/S_{max} as well. This does not align with the swelling and settling experiments, since no or only

low differences were found there. This might be explained by the interaction between the different cations and polyanions like CMC. For calcium cations ionic crosslinking was described before [35]. Sodium cations would not form crosslinks but would increase interactions of CMC chains by promoting hydrophobic interactions [42]. Due to the low salt concentration in the swelling and settling experiments this effect of sodium might be not pronounced significantly. The influence of the amount of additive in the mixture was investigated exemplary for Ca (Fig. 3b). Increasing the amount of Ca in the dry mixture led to a decrease of T_{max} and L/S_{max}. The more calcium ions are in the mixture, the more interactions with non-crosslinked carboxylic acid groups can occur, leading to a reduced swelling of the CCS molecules and consequently to a reduced increase of the volume. The observations are expected to have an influence on ES as well. It is described that an almost complete filling of the voids between the particles and therefore a degree of liquid saturation of almost 100% is optimal for extrusion [41], which would result in different L/S_{opt} depending on the mixtures.

Extrusion/Spheronization

Extrusion was possible for all mixtures from Table 1 except for PLLacAl11. In the latter case, the water was completely squeezed out of the wetted mixture leading to an increasing die pressure and consequently to a blocking and

Fig. 3 MTR. Moving averages ($\overline{x} \pm s$) ($n = 3$); **a** CCS/Lac with and without the incorporation of additives; **b** CCS/Lac with different amounts of Ca; **c** different CCS/DP mixtures
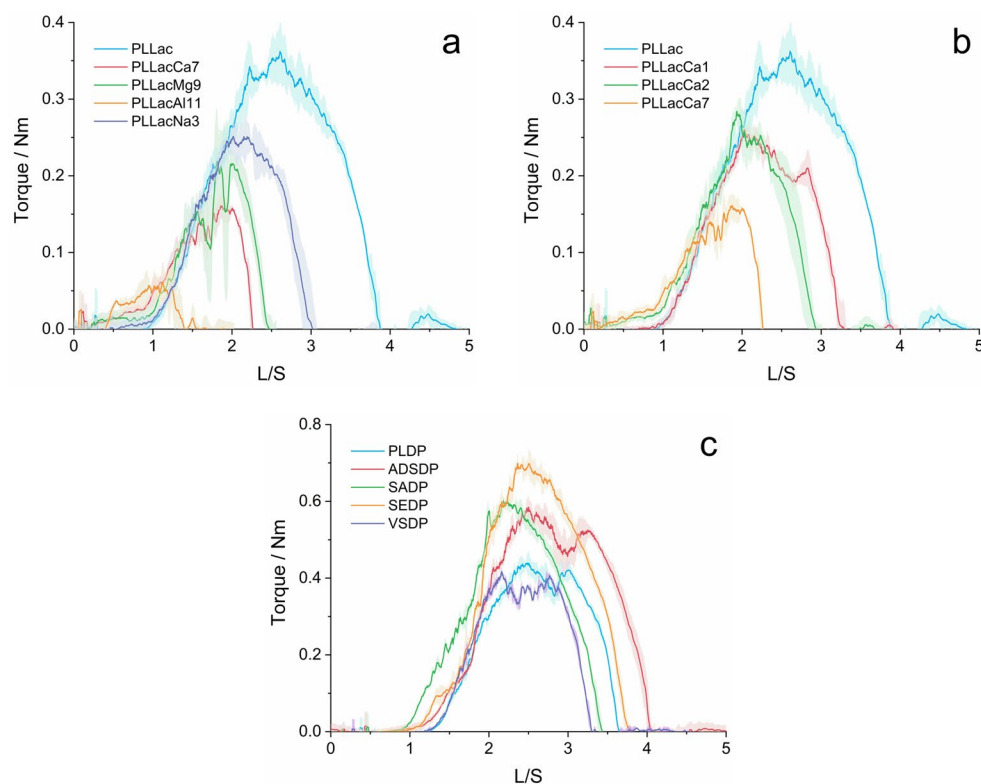
clogging of the extruder. For all other mixtures extrudates were obtained. For PLLacNa3, PLLacCa7, PLLacCa2 and PLLacMg9 spheronization led to pellets at L/S$_{opt}$ (Fig. 4a). PLLacCa7 and PLLacMg9 formed the best pellets at a similar L/S$_{opt}$ of 1.75 (Table 3). Nevertheless, the extrudates of PLLacMg9 were more sensitive to mechanical forces, as a reduction of the L/S to 1.5 already led to the grinding of the extrudates in the spheronizer (not shown). PLLacNa3 and PLLacCa2 on the other hand needed more water for successful spheronization leading to a L/S$_{opt}$ of 2.25 for both mixtures. This aligns with the results from the MTR experiments (Fig. 3a and b). PLLac and PLLacCa1 however could not be spheronized since they disintegrated during spheronization into a wet powder due to insufficient coherence. This indicates that cations play an important role in ES mechanism of CCS. The uptake of water and the mere presence of colloidal particles are not sufficient to obtain a wet mass that meets all requirements to be extruded and spheronized successfully.

Characterization of the Pellets

Figure 5a shows the pellet size distribution of PLLacNa3, PLLacCa2, PLLacCa7 and PLLacMg9. PLLacCa7 and PLLacMg9 show a similar median pellet size of 1.38 mm and 1.38 mm, respectively. However, PLLacNa3 and PLLacCa2 show lower median pellet sizes of 1.27 and 1.29 mm, respectively. This can be explained by the differences in L/S$_{opt}$ (Table III) and thereby by the shrinking of the pellets during drying [43]. PLLacNa3 and PLLacCa2 need more water for successful ES and therefore more water evaporates from the

pellets resulting in lower pellet sizes after drying. Since the quality of pharmaceutical pellets is defined by their nearly spherical shape and a narrow size distribution, the AR and d were calculated from the dynamic image analysis data. The cumulative distributions of d were used for better comparison of the widths of the distributions (Fig. 5b). An AR below 1.2 is considered acceptable, an optimal pellet is defined by an AR below 1.1 [44]. Pellets of acceptable AR could be obtained for all batches. Figure 6a shows different quantiles of the AR for the different batches. All batches showed a median AR below 1.2, whereby only PLLacCa7 showed a median AR below 1.1. For PLLacCa7 95% of the pellets had an AR below 1.2 and even 65% showed and AR below 1.1. The corresponding fractions were lower for PLacNa3, PLLacCa2 and PLLacMg9 (Table 5). All batches showed a 10%-interval above 50% (Table 5) and can be declared as "good" according to Thommes & Kleinebudde [21]. None of the pellet batches can be declared as "excellent" since the 10%-interval does not exceed 75%. However, Thommes & Kleinebudde used the mean Feret diameter instead of Fe$_{max}$ for the characterization which results in lower values for elongated pellets in general. PLLacMg9 shows a high fraction of pellets above 1.1 for the d value. This can be explained by an insufficient rounding of the extrudates which is also indicated by the 90%- and the 99%-quantile for the AR (Fig. 6a) and by the cumulative distribution of d (Fig. 5b). This might be due to the lower affinity of Mg to CMC compared to Ca [38]. This might lead to a weaker gel-network which could result in a lower plasticity of the wetted mass and therefore an insufficient rounding leading to a high variability of the batch. In this case, a change of
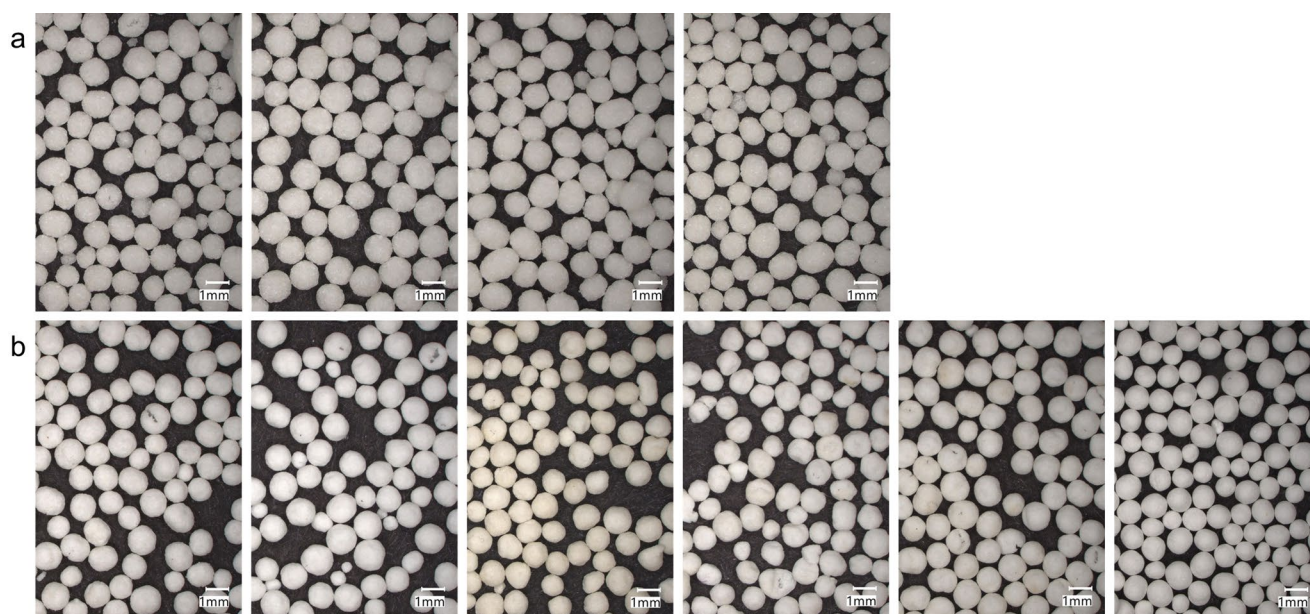

Fig. 4 **a** From left to right: Microscopic pictures of PLLacCa2, PLLacCa7, PLLacMg9 and PLLacNa3; **b** From left to right: Microscopic pictures of PLDP, ADSDP, SADP, SEDP, VSDP and PLPZQ

Fig. 5 Pellet size distributions (entire batch): **a** F_{max} of the different pellet batches containing PL, Lac and Na, Ca or Mg; **b** d of the different pellet batches containing PL, Lac and Na, Ca or Mg; **c** d of the different pellet batches containing different CCS grades and DP; d of PLPZQ
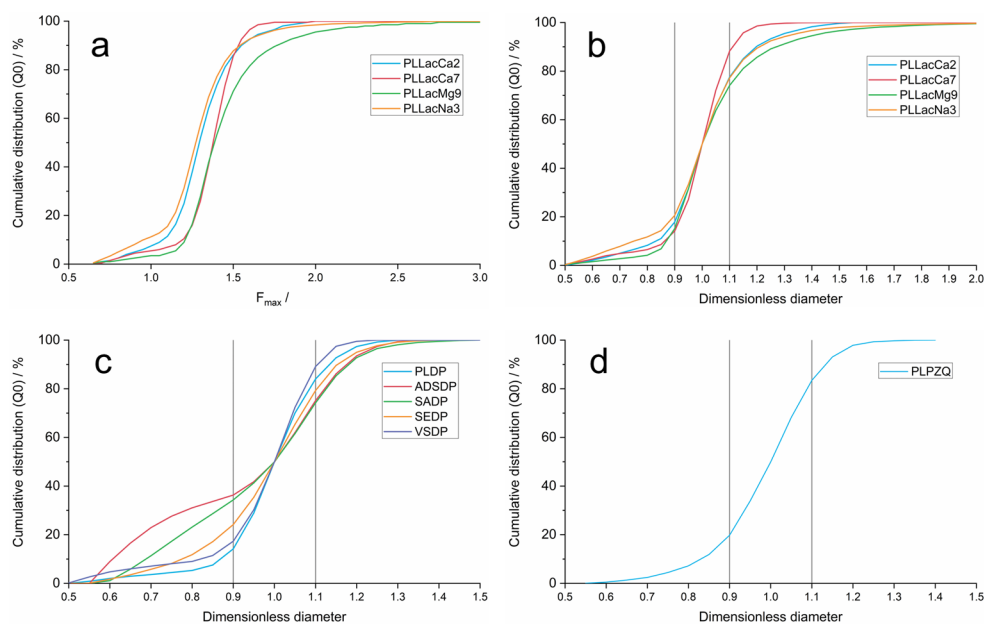
Fig. 6 AR of the different pellet batches (1%-, 10%-, 50%-, 90%- and 99% quantile, entire batch); **a** PL, Lac and Na, Ca or Mg; **b** different CCS grades and DP or PZQ
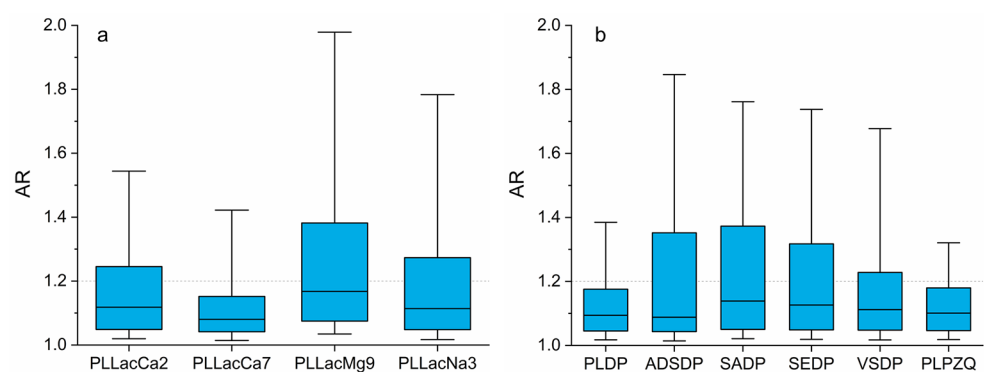
Table 5 Characteristics of the different pellet batches

Powder mixture	AR$_{Median}$	Fraction < 1.2 [%]	Fraction < 1.1 [%]	10% interval [%]
PLLacCa7	1.08	95	65	74.1
PLLacCa2	1.12	83	38	59.7
PLLacMg9	1.17	55	20	58.9
PLLacNa3	1.11	82	40	56.6
PLDP	1.09	93	53	69.9
ADSDP	1.09	80	57	38.8
SADP	1.14	69	33	39.9
SEDP	1.13	75	37	55.1
VSDP	1.11	86	41	71.8
PLPZQ	1.10	94	49	63.7

the spheronizer speed or spheronization time might lead to a better result. PLLacNa3 shows a similar behavior. It must be stated that the parameters for ES were kept constant for all pellet batches for better comparison of the mixtures in this work. Since the processability of the materials differed, the optimal process parameters might be different for each

mixture. Furthermore, the range for the optimal L/S ratio was narrow for all mixtures and only the batches with the optimal L/S found are presented. Further optimization of each batch would require more investigations.

Different CCS Types and Insoluble Fillers

Motivation for the Study

Since the presence of calcium ions in a mixture of CCS and Lac led to a successful extrusion and spheronization of the mixture, DP was tested as a filler as well. It was expected that this would make the addition of a soluble calcium salt unnecessary. Even if DP is a poorly soluble salt, parts of it might dissolve and calcium ions might act as described above. In addition, several different grades of CCS from different suppliers were tested for their processability. Since functional-related characteristics (FRCs) of CCS, such as the settling volume, the degree of substitution, the degree of crosslinking or the amount of water soluble substances might vary from grade to grade [33] differences in their behavior

during extrusion and spheronization were expected. It was shown that the differences in the FRCs have an influence on the disintegration time when CCS is used as a tablet disintegrant mainly due to differences in the degree of swelling [45]. For comparison, another insoluble substance that does not contain cations was used as a filler. PZQ was chosen due to its low solubility in water and the absence of cations.

Mixer Torque Rheometer Measurements and Extrusion/Spheronization

The MTR curves of the mixtures of DP with the different CCS grades are shown in Fig. 3c. The materials show different values for L/S_{max} (Table 3). MTR was shown to be a useful preformulation tool to find the L/S_{opt} for extrusion spheronization [46, 47]. Since extrusion of wetted masses occurs at a degree of liquid saturation close to 100% [41], it was expected that the L/S_{opt} is close to L/S_{max} which was therefore used as orientation. Pellets could be produced when DP was used as filler for all CCS grades in contrast to Lac as filler. Pictures of the resulting pellets at L/S_{opt} are depicted in Fig. 4b. However, pellets could also be obtained when PZQ was used as the insoluble filler. In this case no cations were part of the mixture. This shows that cations might not be necessary for ES of CCS when an insoluble filler is used instead of a soluble filler. It is known that the necessary amount of successful ES decreases with the increase of solubility of other components in the mixture [48] which was also considered in the screening for the L/S_{opt} for all of the investigated mixtures. However, the use of a soluble filler was not expected to completely fail ES as we described for the use of Lac. Pellets of all batches showed cracks on their surface and were sometimes burst. This might be due to the
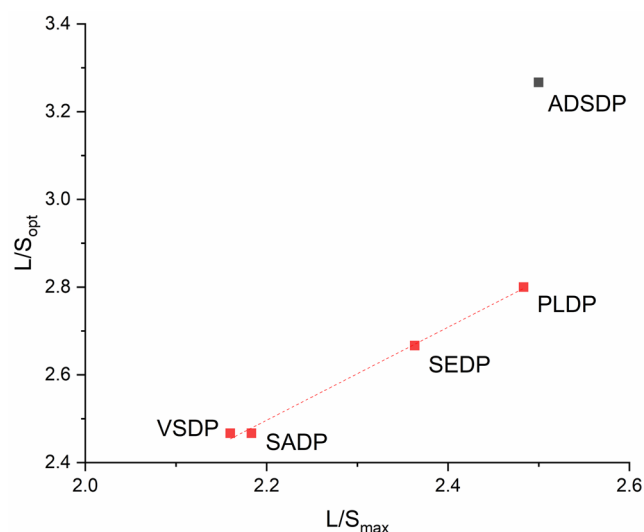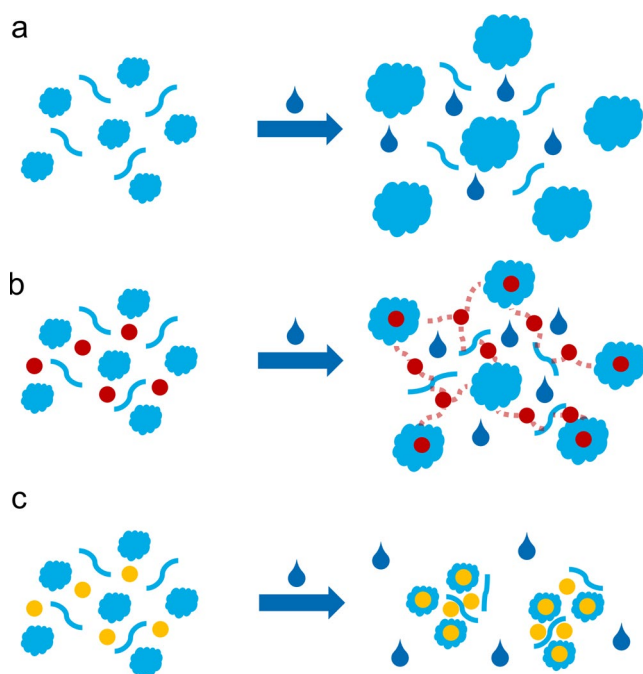
shrinking of the pellets during drying which is described for fluidized bed drying [43]. The increased amount of water needed for successful ES compared to MCC might lead to higher stresses during drying. A linear relationship between the L/S_{opt} and the L/S_{max} was found, when ADSDP was excluded (Fig. 7). According to this relationship L/S_{opt} would be underestimated for ADSDP. However, neither L/S_{opt} or L/S_{max} showed a correlation with the settling volumes. This might be due to the fact that the settling volume can be effected not only by the swelling but also by other characteristics of the CCS, such as surface properties, content of water soluble substances or packing properties of the particles [45]. L/S_{opt} was higher than L/S_{max} in all cases. This might be explained by the swelling of the CCS and by the molecular sponge model [29]. When the water uptake of the CCS is completed and the voids between the particles are filled (capillary state) the forces of the MTR might lead to squeezing out of the absorbed water from the CCS particles, resulting in an increase of the degree of liquid saturation and therefore in a decrease of the torque. However, an explanation for the remarkably increased L/S_{opt} of ADSDP was not found.

Characterization of the Pellets

All DP batches showed a median AR below 1.2 whereby PLDP and ADSDP showed a median AR below 1.1 (Fig. 6b). According to the 10%-interval only PLDP, SEDP and VSDP can be declared as "good" which is due to the narrow distribution for d as well to a reduced amount of fines and larger particles compared to the other batches. 93% of the measured particles of PLDP had an aspect ratio below 1.2 while 53% of the pellets had an aspect ratio below 1.1 (Table 5). Pellets produced from PLPZQ showed an AR of 1.10 and therefore show optimal sphericity. They as can be declared as "good" according to the 10%-interval. However, for better comparison of the different materials the parameters for ES were kept constant. For optimization it would be necessary to screen for optimal parameters for each mixture. Differences in the properties of the CCS might lead to wetted masses and extrudates of different mechanical strengths. E.g. it could be expected that ADSDP and SADP would result in less fines when the spheronizer speed is reduced. Therefore, it cannot be said that one CCS grade might be preferred.

Mechanism for the Extrusion and Spheronization of CCS

Due to the results and observations described it is proposed that cations (e.g. calcium) play an important role in the functionality of CCS for extrusion/spheronization

Fig. 7 Relationship between L/S_{opt} and L/S_{max} for the pellet batches containing different CCS grades and DP. PLDP, SADP, SEDP and VS are shown in red. ADSDP is shown in black

Fig. 8 Interactions between CCS (blue clouds), CMC (blue lines), water (drops) and cations; **a** without incorporation of cations; **b** incorporation of calcium or magnesium (red dots); **c** incorporation of aluminum (yellow dots)

especially when used in combination with a soluble filler. It is unlikely that the salts included in the mixtures reduced the solubility and thereby led to a mixture that could be successfully processed by ES since addition of salts like Ca rather increases the solubility of Lac [49]. It is more likely that bivalent cations interact with the carboxylic groups of the CCS and colloidal chains of CMC forming ionic crosslinks between the particles. Such crosslinks were already described for CMC [35]. Monovalent cations like sodium however, might increase hydrophobic interactions between CCS particles and CMC chains resulting in a stronger interaction [42]. During wetting the water can be stored inside the CCS particles and can be squeezed out during ES, as it is described for MCC by the "molecular sponge" and the "reversible gel" model [28, 29, 32]. When the water is squeezed out of the particles during ES the water needs to be immobilized between the particles, otherwise there will be liquid phase migration and therefore a separation of the liquid and the solid parts of the mass, which is especially pronounced for ram-extrusion [50]. For MCC the "crystallite gel" and the "reversible gel" hypothesis propose that a gel is formed by the colloidal particles which allows plastic deformation of the wetted mass during extrusion and spheronization [30, 32]. It is likely that the CMC chains do not form interactions strong enough to build a gel-like network (Fig. 8a) since the soluble fractions mainly consist of short chains of CMC [33]. When divalent cations are included

crosslinking between the particles might lead to a strong deformable network, making spheronization possible and on the other hand reduce the swelling leading to lower L/S$_{opt}$ depending on the concentration (Fig. 8b). Monovalent cations might have a similar effect, but most likely due to the increase of hydrophobic interactions (not shown). The inclusion of trivalent cations like aluminum however seems to induce agglomeration of the particles which leads to an enormous reduction in swelling and to a loss of the ability to hold the water between the CCS particles which makes ram-extrusion impossible (Fig. 8c). The reduced mechanical strength of the extrudates containing Mg might be explained by the interaction between magnesium cations and the carboxylic groups. It was shown that the affinity of calcium cations to CMC is higher than that of magnesium ions [38]. With an increasing amount of Ca in the mixture the amount of water needed for successful ES would be reduced due to more ionic crosslinks leading to less swelling and therefore less capacity for the uptake of water. However, when an insoluble filler is used, this leads to a higher non dissolved fraction during the ES process which might result in lower sensitivity to forces during spheronization and therefore enable successful spheronization.

Conclusion

Pellets without the incorporation of MCC by utilizing different grades of CCS as the pelletization aid were successfully prepared. Cations were necessary so that the rheological properties of CCS are sufficient for extrusion and spheronization when lactose as a soluble filler was used. When 50% DP or PZQ were used as filler, the addition of a soluble salt was not necessary. It is assumed that the cations help in building a network that can control the distribution of the water during extrusion and spheronization.

Declarations

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