Influence of the Granulation Step on Pellets Prepared by Extrusion/Spheronization

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Pellets were prepared by granulation/extrusion/spheronization. Four different procedures applying different amounts of shear were used for granulation: planetary mixer, high-shear mixer and twin-screw extruder with two different screw assemblies. Extrusion was performed on a rotary ring die press. Pellet properties were rated by size, shape, release behaviour and different mechanical characteristics like crushing strength or porosity. The study revealed that different granulation methods affected pellet properties by the application of different shear forces. The application of higher shear forces during granulation resulted in a higher water content necessary for successful pelletization. This finding is in contrast to conventional granulation and was explained by the crystallite-gel-model. The difference in water content of the extrudate influenced the extent of shrinking during drying, which was responsible for the different mechanical characteristics of the pellets. The release rate for paracetamol was higher for pellets with lower porosity. This is explained by the presence of drug crystals on the surface of these pellets due to the higher extent of shrinking during drying.

Key words pellet; extrusion/spheronization; ring die press; granulation; shrinking; porosity

Every single step in the process of pelletization by extrusion/spheronization affects the properties of the resulting pellets. Pharmaceutical scientists originally directed their focus to extrusion, spheronization and drying which can be seen from the literature.[1)] Only a few authors reported investigations concerning the impact of the granulation step. Baert *et al*.[2)] investigated ternary mixtures of microcrystalline cellulose (MCC), a drug substitute and water on a planetary mixer and a high-shear mixer. Granulation time on the high-shear mixer was then varied. Granulation in the high shear mixer resulted in higher extrusion forces for the same composition blends. But these results were not further evaluated. Increasing granulation time also resulted in higher extrusion forces, but this was attributed exclusively to an increased loss of water. Vervaet and Remon[3)] worked *inter alia* on the influence of granulation time, mixing speed and type of mixing arm of a planetary mixer on the quality of pellets made of MCC, ibuprofen and water. They concluded that the extrusion step superimposed the effect of variations in granulation.

These experiences show that studies on the isolated influence of the granulation process have to be performed under the following conditions. Firstly, the changes in granulation have to be distinct enough to result in perceptible effects. Secondly, the subsequent steps that can influence the product also have to be chosen carefully. Additional excessive treatment of the granules that would level existing differences should be avoided.

The aim of this study was to meet those requirements by the utilization of suitable equipment. For that purpose a planetary mixer and a high-shear mixer were used as well as a twin-screw extruder with two different screw designs for granulation. Extrusion was performed on a rotary ring die press, an intrument which is known to work with less compression force and shear rate[4)] than other extruders. The resulting pellets were evaluated with regard to their size, shape, porosity, release behaviour and other properties.

Experimental

Materials Pellets were prepared from a binary mixture of paracetamol (Rhodapap dense and fine powder, Rhone Poulenc, Frankfurt, Germany) and MCC (Avicel PH 101, FMC, Cork, Ireland) at a ratio of 20 : 80. Demineralized water was used as granulation liquid. Table 1 summarises the characterization of excipients.

Pellet Preparation Granulation: After sufficient blending the dry excipients were granulated with demineralized water by four different procedures. A planetary mixer (A200, Hobart GmbH, Offenburg, Germany) was used for low shear granulation (G1). Granulation liquid was added manually over 45 s. High shear granulation was performed on a SP1 (G2) (Aeromatic-Fielder, Eastleigh, UK). A previously described twin-screw extruder (Berstorff ZE 25×18 D, Berstorff GmbH, Hannover, Germany)[5)] was used for granulation by removing the die plate and collecting the exceeding material. The screws were assembled without (G3) and with mixing and kneading elements (G4) again in order to apply different amounts of shear (Fig. 1) . For details see Table 2.

The moisture content (MC) of granules was measured for two samples per batch and was calculated by the loss of drying at 105 °C for 24 h on dry base (m/m). Calculations of the formulations were based on dry substances.

Extrusion/Spheronization/Drying: Extrusion and spheronization of all granules was performed on a rotary ring die press PP-127 and a RM-300 spheronizer (Schlüter Maschinenfabrik GmbH & Co. KG, Neustadt a. Rbge., Germany). Process conditions were kept constant for all trials as described.[6,7)] The shear stress exerted on the granule and the compression of the granule was adjusted by the width of the gap between press roll and ring

Table 1. Characteristics of Utilized Excipients

Excipient	Particle size (μm) d(v, 0.1)	d(v, 0.5)	d(v, 0.9)	Moisture content	ρ_t (g/cm^3)
Microcrystalline cellulose	23	63	143	4.7%	1.60
Rhodapap dense powder	8	49	209	0.2%	1.30
Rhodapap fine powder	3	15	58	0.2%	1.30

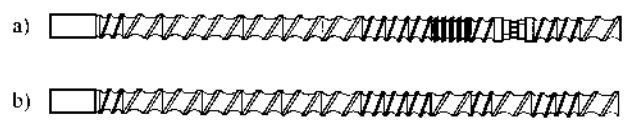

Fig. 1. Screw Design of Twin-Screw Extruder

a) With mixing and kneading elements (G4), b) without mixing and kneading elements (G3).

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Table 2. Process Parameters of 4 Different Granulation Procedures Using Two Qualities of Paracetamol

#	Paracetamol	Granulation equipment	Rotational speed (rpm)	Wet massing time (min)	Max. temp. (°C)	Net power consumption
G1	Coarse	Planetary mixer	177	5	Room	—
G2		High-shear mixer	1000	10	53	—
G3		Twin-screw extruder without mixing/ kneading elements	60	Approx. 1	23	32 W
G4		Twin-screw extruder with mixing/ kneading elements	60	Approx. 1	32	115 W
G1*	Fine	Planetary mixer	177	5	Room	—
G2*		High-shear mixer	1000	10	56	—

die. The small roll gap that was used during this trial (0.3 mm) and the fixed speed ratio of the ring die and the press roll prevented excessive mechanical treatment of the mass. The pellets were dried in a fluid bed dryer (MP1, Aeromatic-Fielder, Eastleigh, UK) at 50 °C for 30 min.

Experimental Design Formulations containing coarse paracetamol were processed with each granulation method (G1, G2, G3, G4) by preparing several batches with various amounts of water. For each series of trials the moisture content was determined which resulted in optimal pellets in terms of size and shape. Those optimal pellet batches were further investigated. Trials with optimal conditions identified for coarse paracetamol on the planetary and the high-shear mixer were repeated twice with fine paracetamol (G1*, G2*).

Analytical Methods Particle Size Distribution: Particle size of the excipients was measured with a Helos particle sizer in combination with a Rodos Aerodispersion unit (Sympatec GmbH, Goslar, Germany). Two samples per batch were analysed and the mean particle diameters in volume of 10, 50 and 90% cumulative percentage were determined (d(v, 0.1), d(v, 0.5), d(v, 0.9)).

Image Analysis and Scanning Electron Microscopy (SEM)-Photographs: Size and shape of the pellets were determined as mentioned earlier.[6,7] The size was characterised by the mean equivalent diameter (D_{eq}) and the shape by the mean aspect ratio (AR) of about 400 pellets per batch.

For preparation of SEM-photographs 6 pellets per batch from the 900—1000 μm fraction were viewed with a Phillips XL20 (Phillips, Eindhoven, The Netherlands) scanning electron microscope. Magnification was adjusted to give an overview of the whole pellet (70×) or an impression of surface structure (550×), respectively.

Dissolution Testing: Dissolution studies were performed according to paddle method USP XXIII, apparatus 2 (Sotax AT7, Sotax AG, Basel, Switzerland) fitted with a peristaltic pump and flow cells for online UV-absorption measurement. At least 5 samples per batch of the 900—1000 μm fraction were tested in demineralized water under sink conditions at a temperature of 37 °C and a stirring speed of 100 rpm. Absorption was recorded every 2 or 3 min up to 180 min at a wavelength of 243 nm. The following parameters were calculated from the dissolution data on the basis of statistical moment analysis[8]: mean dissolution time (*MDT*), variance of dissolution time (*VDT*) and relative dispersion (*RDC*). For details see Eqs. 1—3.

$$MDT=\frac{m_1}{M_0}=\frac{ABC}{M_0}=\frac{\int_0^t t\cdot f(t)\cdot dt}{M_0} \quad (1)$$

$$VDT=m_2-MDT^2=\int_0^t t^2\cdot f(t)\cdot dt-MDT^2 \quad (2)$$

$$RDC=\frac{VDT}{MDT^2} \quad (3)$$

where m_1 is first statistical moment; m_2 is second statistical moment; *ABC* is area between the curves (dissolution curve and *y*-axis); M_0 is amount of drug finally dissolved.

Crushing Strength: A texture analyser (TA-XT2, Stable Micro Systems, Haslemere, GB) was used for determination of crushing strength. Preceding the measurement pellets of the 900—1000 μm fraction were stored for at least 7 d under constant condition (55% rel. humidity). More than 50 pellets per batch were analysed.

Density and Porosity: True density (ρ_t) of pellets and excipients was measured with a helium pycnometer (Accupyc 1330, Micromeritics GmbH, Mönchengladbach, Germany) for two samples per batch. Values for the true density of pellets were lower than expected from calculations considering amount and true density of excipients. These findings implied the existence of closed intraparticular pores, and consequently these density values have to be considered as apparent densities (ρ_a) according to the literature.[9] Thus, pellets were crushed and true density was measured again for the pulverised material. Due to electrostatic effects, parts of paracetamol remained on the pestle and mortar and the correct true density of the pellets could not be determined by this method. Calculated values for the mixtures from the true densities of the individual components were subsequently used instead. The amount of closed intraparticular pores (*CIP*) of the pellets that could not be perceived by helium pycnometry was calculated according to Eq. 4.

$$CIP=\left(1-\frac{\rho_a}{\rho_t}\right)\times 100\% \quad (4)$$

Effective density (ρ_e) and pore size distribution were measured by mercury pycnometry or intrusion, respectively. For effective density and macropores measurement (pore radius: 5—55 μm) a Pascal 140 (CE Instruments, Rodano, Italy) was used. Micropores (pore radius: 0.005—5 μm) were determined in a Porosimeter 2000 (Carlo Erba Instruments, Milano, Italy). The pore size corresponding to the intrusion pressures was calculated by an external PC with the Milestone 200 software (CE Instruments, Rodano, Italy). Calculations were based on circular pore openings, a surface tension for mercury of 480 mN/m and a contact angle between material and mercury of about 142°. Porosity was calculated according to Eq. 5.

$$\varepsilon=\left(1-\frac{\rho_e}{\rho_t}\right)\times 100\% \quad (5)$$

From the combined data of the macro- and micropore units, an average pore radius was determined. For that purpose the total cumulative volume of pores was considered. The 50% cumulative percentage was evaluated and the corresponding radius was calculated. Two samples per batch were analyzed.

Results

Moisture Content, Pellet Shape and Size Moisture content had the most considerable effect on pellet shape and size. Figure 2 shows that variations in moisture content influenced AR and D_{eq} as mentioned earlier.[6] Formulations with low amounts of granulation liquid could not be spheronized sufficiently. Pellets remained oblong and AR values were comparably high. An increase of moisture content improved the plastic deformability of the extrudates and spheronization resulted in rounder pellets with lower AR values. Up to that water content D_{eq} had not changed distinctly since it was mainly determined by the die diameter. After reaching an optimal low AR value further addition of granulation liquid led to the beginning of uncontrolled agglomeration of extrudates during spheronization. This was indicated by a rapid increase of the D_{eq} while the AR values remained nearly constant. The moisture content that corresponds to the optimal AR is therefore called optimal moisture content. Similar observations were made for trials granulated on the mixer granulators (Fig. 3).

Whereas the general relation between moisture content and pellet size and shape was independent of granulation method, the optimal moisture content values differed significantly on different granulation equipment. The required moisture content for preparation of optimal pellets was, in general, lower when granulated with lower shear (Table 3). Comparing planetary and high-shear mixer (Fig. 3) the value for optimal moisture content increased from 99% up to 123% (G1, G2). These differences were established for fine paracetamol where trials performed with 96% (G1*) or 120% (G2*) moisture content resulted as well in pellets of acceptable quality (Fig. 3). The inclusion of mixing and kneading elements in the twin-screw extruder (G3, G4) (Fig. 2) also resulted in a higher optimal moisture content (106%→127%). It must be underlined that the high differences for the same formulation can only be attributed to the granulation method.

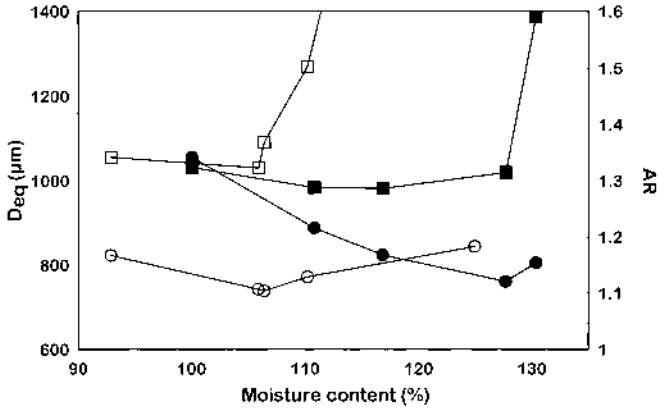

Fig. 2. Comparison between Extruder Screws without (G3) and with Mixing and Kneading Elements (G4)

Results of image analysis: □■, D_{eq}; ○●, AR; □○, G3; ■●, G4.

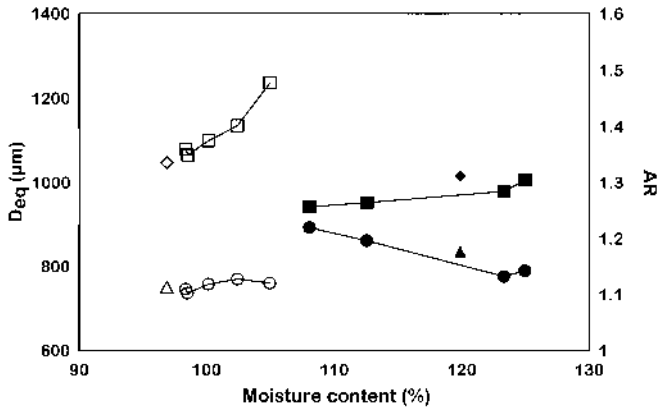

Fig. 3. Comparison between Low (G1, G1*) and High Shear Mixer (G2, G2*)

Results of image analysis: □■, D_{eq}; ○●, AR; □○, G1; ■●, G2.

The shape of pellets was better using low shear granulation. AR values were lower as well as the corresponding standard deviations. The opposite relation must be noted for pellet size. Pellets granulated with the planetary mixer had a higher D_{eq} compared to those with the high-shear mixer (1065→979 μm). This observation was independent of the utilised paracetamol (1075→991 μm) and was supported by the trials on the twin-screw extruder (1092→1020 μm).

Crushing Strength, Density, Porosity and Pore Size Distribution Crushing strength was in general higher for pellets prepared with higher shear during granulation with one exception. Utilization of mixing and kneading elements in the twin-screw extruder did not result in significant changes of crushing strength (Table 4). In contrast, porosity and amount of *CIP* were generally lower for high-shear granulated pellets. Usage of fine paracetamol led to an additional decrease of those values in both investigated granulation processes.

The size distribution measurement revealed differences in pore structure for planetary and high-shear mixer. Lower shear during granulation (G1, G1*) shifted the mean pore radius to higher values (11→18 nm; 9→25 nm), while the usage of the twin-screw extruder led to the opposite effect. Lower shear resulted in lower pore radii (24→14 nm).

Release Behaviour The *MDT* was generally low (<30 min) (Table 3). Nevertheless, differences between the granulation methods were detected. G1, G1*, and G3 representing the low-shear granulation methods showed a slower release than their high-shear counterparts G2, G2*, and G4. Figures 4—6 show the corresponding release profiles. The differences were similar using fine paracetamol (21.2→27.7 min) compared to the coarse quality (21.6→27.0 min). *MDT* values for the twin-screw extruder trials differed comparably less (24.3→26.7 min). Similar observations were made for *VDT* while *RDC* did not diverge significantly.

Table 3. Overview of Results for Optimal Moisture Content, Image Analysis and Dissolution Testing with Corresponding Standard Deviation

#	MC (%)	AR	D_{eq} (μm)	*MDT* (min)	*VDT* (min^2)	*RDC*
G1	99	1.10±0.06	1065±70	27.0±0.42	893±12	1.2±0.02
G2	123	1.13±0.07	979±72	21.6±0.44	529±10	1.1±0.04
G3	106	1.10±0.07	1092±83	26.7±0.69	781±19	1.1±0.04
G4	128	1.12±0.08	1020±84	24.3±0.16	593±14	1.2±0.03
G1*	96	1.10±0.07	1074±72	27.7±0.41	871±42	1.1±0.03
G2*	120	1.16±0.08	1018±71	21.2±0.24	494±10	1.1±0.01

Table 4. Overview of Results for Densities, Porosity and Pore Size Distribution

#	Crushing strength (N)	ρ_t (g/cm^3)	ρ_a (g/cm^3)	ρ_e (g/cm^3)	ε (%)	*CIP* (%)	Mean pore radius (nm)
G1	14.4±3.4	1.50	1.41	1.38	8.1	6.0	18
G2	22.8±5.2	1.51	1.45	1.41	6.3	4.0	11
G3	15.6±4.7	1.51	1.42	1.38	8.5	8.4	14
G4	15.4±2.6	1.50	1.44	1.41	7.1	4.5	24
G1*	15.6±3.8	1.50	1.43	1.40	7.0	5.1	25
G2*	22.0±3.4	1.50	1.45	1.42	4.9	3.0	9

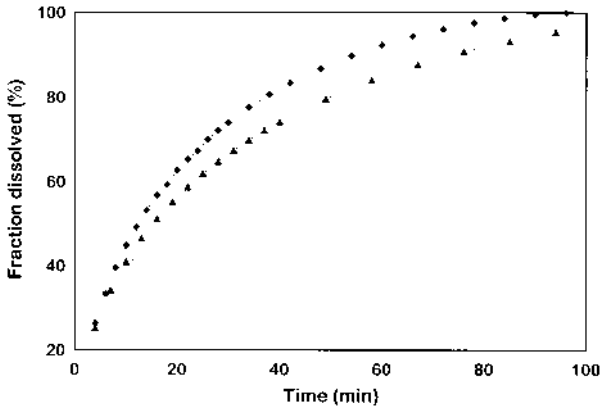

Fig. 4. Comparison between Low (G1) and High-Shear Mixer (G2)

Results of dissolution tests for trials with coarse paracetamol (mean of 5 samples): ▲, G1; ◆, G2.

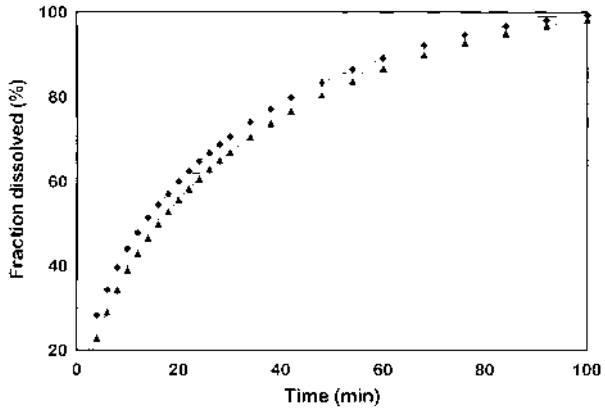

Fig. 5. Comparison between Extruder Screws without (G3) and with Mixing and Kneading Elements (G4)

Results of dissolution tests (mean of 5 samples): ▲, G3; ◆, G4.

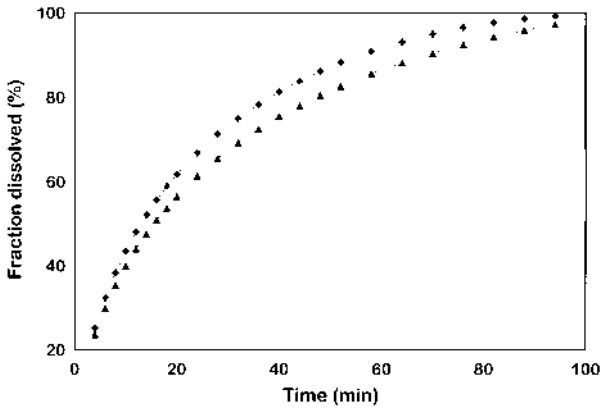

Fig. 6. Comparison between Low (G1*) and High-Shear Mixer (G2*)

Results of dissolution tests for trials with fine paracetamol (mean of 5 samples): ▲, G1*; ◆, G2*.

Discussion

Granulation Methods Planetary mixers and SP1 represent typical low- and high-shear mixer that are already well-known in classical granulation. Process and formulation variables have been well studied as is described in the literature.[9,10] The density of granules is known to increase when the agitation during wet-massing is increased or prolonged. The liquid saturation changes and less granulation liquid is required for successful granulation. Particle size and size distribution of raw materials affect the packing density and the ease by which dense packings are achieved. These effects are further influenced by the intensity of agitation. Moreover, granule structure, rated by porosity and binder distribution, alters with variations in the granulation method.

In contrast, the employment of a twin-screw extruder for granulation is unusual. No explicit statements concerning a twin-screw granulator or even similar devices could be found in the literature. Thus, granulation behaviour must be assessed on the basis of the well-known extrusion characteristics. Hicks and Freese[4] divided the screw-extruder into three major zones that are defined by the mechanical operation that is performed: feed zone, transport and compression zone, and extrusion zone. The feed and transport zones are not affected by the present extruder setup. The removal of the die plate and the exchange of mixing and kneading elements has certain impacts on the functionality of the compression and extrusion zones. Without the die plate the extrusion zone is missing as is the mechanical resistance of the die plate against the forwarded material. Independent of the screw design, pressure inside the barrel is lowered and compression is less effective.

Comparing screw designs with and without mixing and kneading elements (Fig. 1) it is obvious that assembly a) (G4) provided more mechanical treatment to the wet mass than b) (G3). In addition to the higher shear forces that occurred in a), the kneading elements in particular functioned as resistance inside the barrel. This led to a higher compression in a) compared to b). These considerations are reflected by the different net power consumption and the higher temperature that were recorded during the trials (Table 2).

The comparison between mixer granulator and twin-screw granulator must be drawn carefully, since too little information about the twin-screw granulator is available. Nonetheless, one difference can be stated: wet massing time is considerably lower inside the extruder barrel (Table 2).

Moisture Content Moisture content is one of the most important influence factors as well as yield factors in pelletization. Several authors reported on varying process parameters or pellet characteristics by altering moisture content (*e.g.* ref. 2, 5, 8, 11—17). Our previous studies[6,7] revealed different optimal moisture contents as a consequence of different process and formulation parameters. Besides particle size and solubility of additional ingredients or spheronizing conditions the type of the granulation/extrusion equipment was stated as critical. The influence of granulation/extrusion method was attributed to different amounts of applied shear stress during this process. On the basis of a recently published model for the role of MCC in pelletization by extrusion/spheronization (the "crystallite-gel-model"),[18] it was assumed that different amounts of shear led to changes in the structure of the MCC matrix. According to that model, MCC particles are ultimately comminuted to single crystallites that are able to form a gel-network. The higher the applied shear the more delicate the network and the more water can be immobilized resulting in granules with the same extrusion properties.

Another model showing the function of MCC to be sponge-like[19] was recently controversely discussed with the

crystallite-gel-model.[20] MCC as sponge is thought to hold water inside intraparticular pores and interparticular voids. During extrusion/spheronization water is squeezed out to the surface of particles where it can act as lubricant or plasticiser. The need for different amounts of moisture content in different extruders is also explained by different shear forces. Shear forces influence the extent of water that is squeezed out or held inside the pores and voids, respectively. But in contrast to the crystallite-gel-model MCC particles are assumed to remain intact during the process.

Comparing G1/G2 and G3/G4 application of higher shear during granulation resulted in the need for higher moisture content. This is in contrast to conventional granulation where the application of higher shear results in a decrease of required granulation liquid.[10] Moreover, these results seem to support the assumptions of the crystallite-gel-model. The supposed comminution of MCC particles is not restricted to the extrusion process and could even take place during granulation. In contrast, the sponge-model offers no explanation of how the interaction of water with intact MCC particles can be modified solely by more intensive agitation in granulation. Higher shear forces and higher densification during wet massing should actually lead to a lower amount of adhered water due to the reduction of interparticular voids.

Pellet Size and Shape With a constant die diameter pellet size is mainly dependent on the rate of shrinking during the drying process. With a given drying method shrinking is more pronounced the higher is the initial moisture content or loss of water, respectively.[21]

Comparing the planetary and high-shear mixers and the two screw designs results in mutual agreement with those findings. Pellets prepared with lower shear and lower moisture content (G1, G1*, G3) had a higher D_{eq} compared to the corresponding high-shear granulation process (G2, G2*, G4). However, pellets granulated on the twin-screw extruder were generally larger in spite of the higher moisture content when compared to mixer granulated pellets. One possible reason could be an overwetting of the granules that would result in slight agglomeration of the wet pellets during spheronization.

Crushing Strength, Density, Porosity and Pore Size Distribution Looking at the differences in pellet properties of planetary (G1, G1*) and high-shear mixers (G2, G2*) a uniform relationship can be seen (Table 2). Starting with the already discussed different moisture contents all observations can be attributed to the shrinking phenomenon. The higher densification during the drying process led to lower porosity, less closed intraparticular pores and smaller mean pore radii. Due to a higher contact area between MCC particles in more densified, pellets crushing strength is higher for those batches, too. The generally lower porosity and *CIP* with a smaller particle size of paracetamol can be explained by an easier densification during the granulation.

The properties of pellets that were granulated in the twin-screw extruder (G3, G4) showed some exceptions to that reasoning. Whereas porosity and *CIP* were again lower for pellets prepared with higher shear forces (G4), the mean pore radius was found to higher. Crushing strength was nearly constant on a comparably low level, although moisture content differed significantly for the two screw designs. The

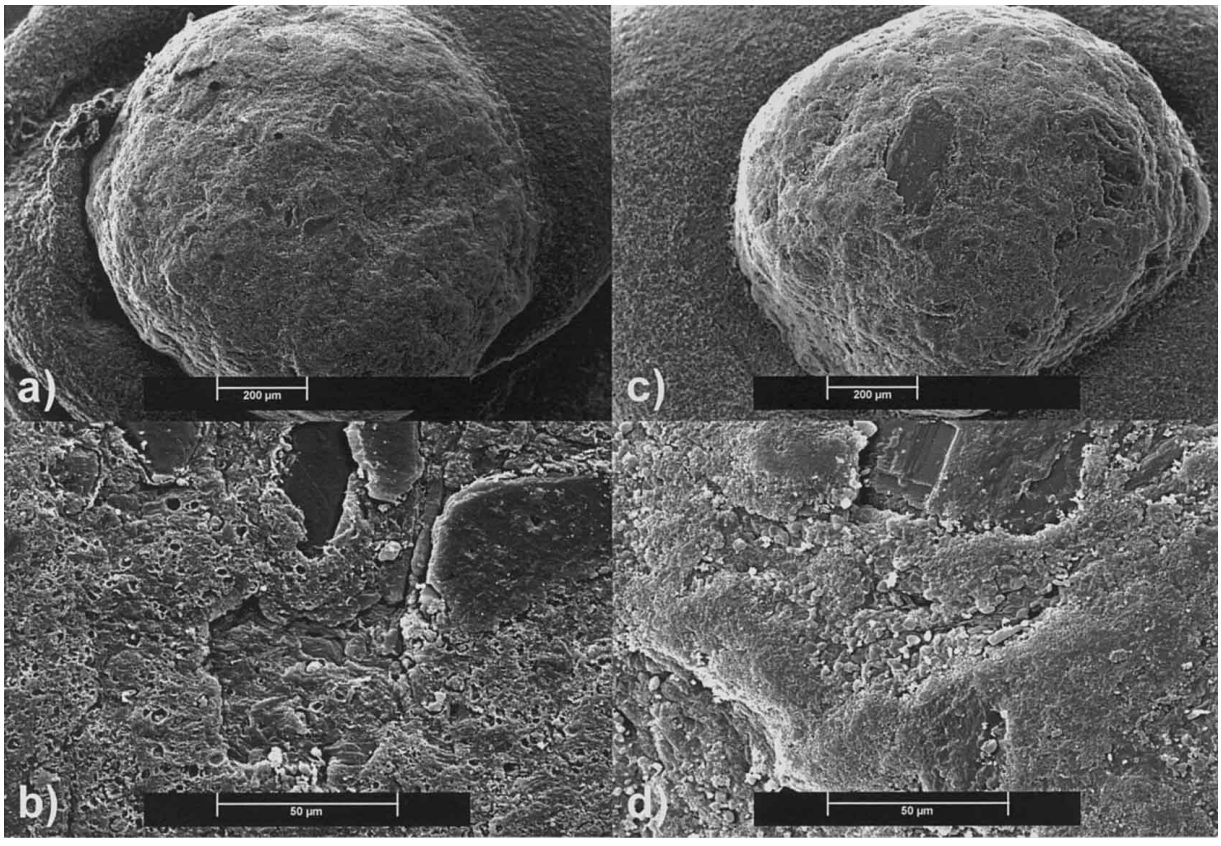

Fig. 7. SEM-Photographs of One Pellet per Batch, Representative of 6 Analysed Pellets

a), b): G1. c), d): G2. For identification see Table 2.

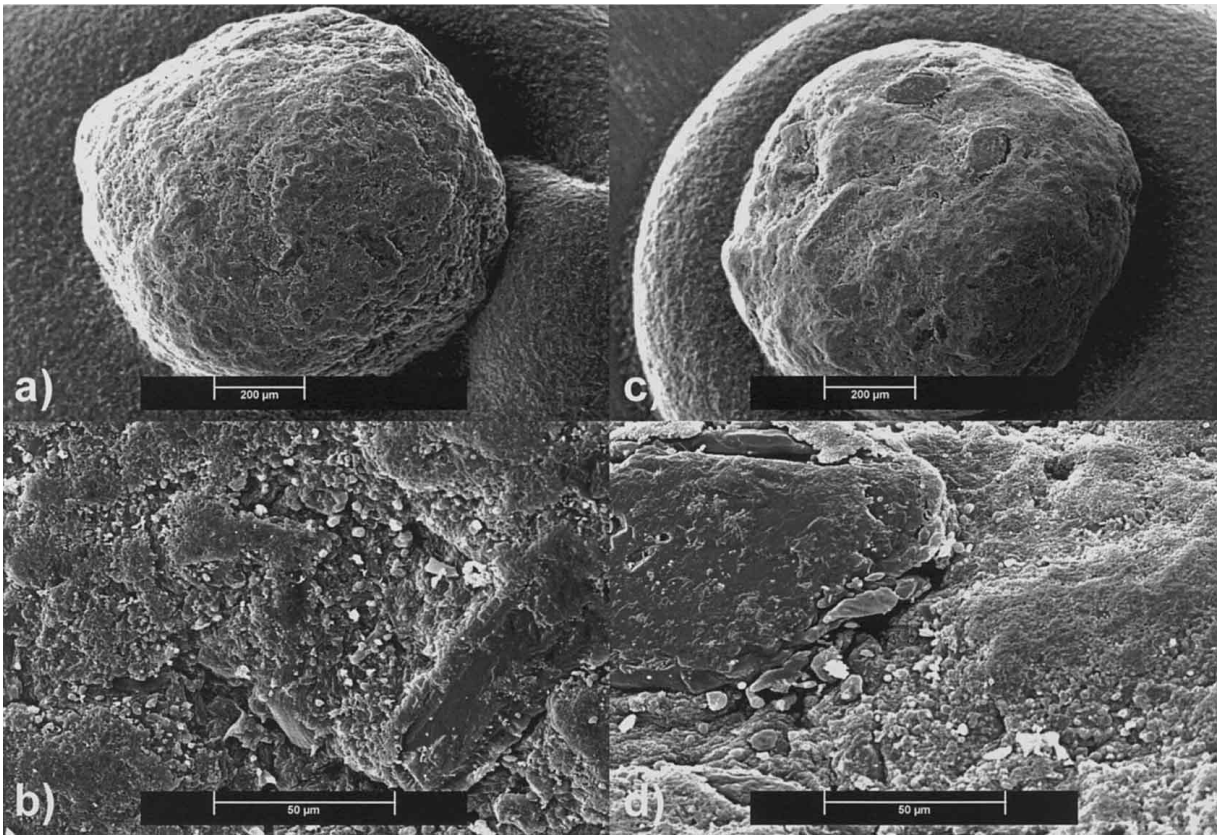

Fig. 8. SEM-Photographs of One Pellet per Batch, Representative of 6 Analysed Pellets
a), b): G3. c), d): G4. For identification see Table 2.

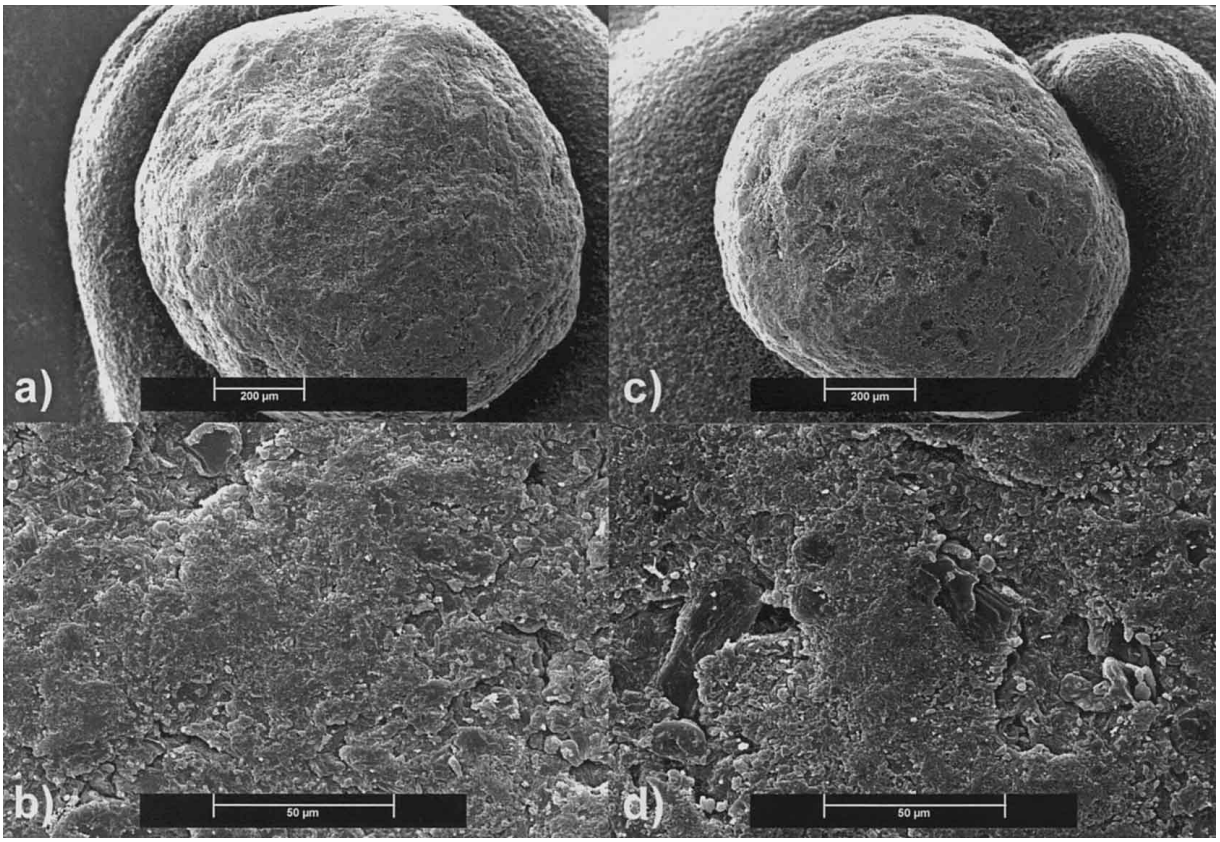

Fig. 9. SEM-Photographs of One Pellet per Batch, Representative of 6 Analysed Pellets
a), b): G1*. c), d): G2*. For identification see Table 2.

mean pore radius, on the contrary, was even higher for pellets prepared with mixing and kneading elements (G4). These findings have not yet been explained and should be confirmed in further trials.

Release Behaviour From theoretical considerations it was expected that changes in the MCC matrix would alter the release rate. Higher shear forces during granulation should lead to a more dense structure and consequently to slower release rate and *vice versa*.

The opposite was found for the present trials as *MDT* and *VDT* values increased when lower shear forces were used and pellets of less density were obtained. One explanation is the different pellet morphology as shown in the SEM-photographs (Figs. 7—9). It is apparent that pellets prepared by granulation G1, G1*, G3 show a uniform surface, whereas the surface of pellets from G2, G2*, G4 is penetrated by paracetamol crystals. This might be caused by the different extent of densification of the MCC matrix during the drying process. When the MCC matrix loses water and shrinks, paracetamol particles are not affected by this phenomenon. The distances between single paracetamol particles will be shortened. In the case of higher water contents the MCC matrix is densified to a higher extent and paracetamol crystals literally grow to the outside; their location on the surface means they will dissolve faster than crystals within the MCC matrix. Thus, two cases must be considered when release behaviour is rated (marked as area A and area B in Fig. 10). Case A is valid when pellets are mantled by MCC, and in this case drug release is mainly determined by porosity and other properties that describe the internal structure of the matrix. This is visualized by G1, G1*, G3 that show slower release with lower porosity. In case B when size is reduced over a certain extent the pellet surfaces are perforated by drug particles. Therefore, higher surface areas of the paracetamol located on the outside that were caused by smaller drug particles (G2→G2*) or a greater extent of shrinking (G4→G2) consequently led to faster drug release.

The *RDC* was nearly constant in all trials. According to the literature,[22] *RDC* serves as indicator for the width of a distribution and is related to the model dissolution behaviour that did not vary in the study.

Several authors worked on the influence of process and formulation variables on the release behaviour of pellets prepared by extrusion/spheronization. A selection will be reviewed briefly in order to find support or contradiction for the present findings.

Baert and Remon[14] reported lower release rates for pellets prepared with higher amounts of water. From the provided SEM-photographs pellet surface appears to be uniform without any defects like case A pellets. This could either be due to agglomeration and varying pellet size or due to enhanced densification during drying. Dyer *et al*.[23] investigated the influence of drying method on release properties of pellets. Fluid-bed dried pellets showed a slightly slower release compared to tray-dried, despite the fact that tensile properties indicate a less dense structure of pellets. Varshosaz *et al*.[17] showed that an increase of granulation liquid led to a decrease in porosity as well as to amount of drug released within 30 min regardless of type and level of the utilized binder. Sousa *et al*.[8] worked *inter alia* on the effect of moisture content and drying method (fluid-bed and tray oven) and their interaction on several pellet properties. They reported that crushing strength increased with increased moisture content. Porosity was not affected by the influence variables but only by the raw materials. Drug release was faster for larger pellets with higher moisture content.

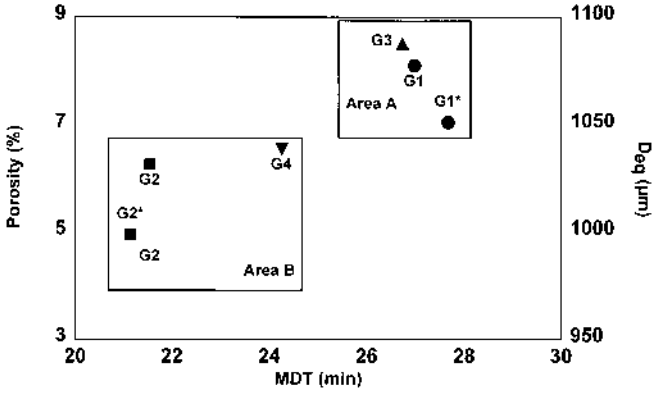

Fig. 10. Relation between Dissolution Rate (MDT), Porosity and Pellet Size (D_{eq}) for Different Granulation methods

●: G1, G1*; ■: G2, G2*; ▲: G3; ▼: G4. Open symbols: D_{eq}; closed symbols: porosity.

This overview indicates that the relation between drug release, physical properties and preparation procedures is quite complex. A comparison of these studies is difficult because of missing information or great variation in experimental conditions.

Conclusions

This study demonstrated that the granulation method affects pellet properties. However, there are still areas of uncertainty concerning the mechanism of interaction. Especially, the role of morphology and solubility of a drug substance should be further investigated.

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