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Rapid Communication

New Insights into the Pelletization Mechanism by Extrusion/Spheronization

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Abstract. Pellet manufacturing by extrusion/spheronization is quite common in the pharmaceutical field because the obtained product is characterized by a high sphericity as well as a narrow particle size distribution. The established mechanisms only consider deformation of the initially fractured particles but do not account for mass transfer between the particles as a factor in achieving spherical particles. This study dealt with the visualization of mass transfer during spheronization. Therefore, two common pelletization aids, microcrystalline cellulose and kappa-carrageenan, were used alone as well as in combination with lactose as a filler. This study proves that mass transfer between particles must be considered in addition to plastic deformation in order to capture the spheronization mechanism. Moreover, it is evident that there are regional distinctions in the amount of mass transfer at the particle surface. Therefore, the commonly espoused pelletization mechanisms need to be extended to account for material transfer between pellet particles, which has not been considered before.

KEY WORDS: agglomeration; carrageenan; MCC; pelletization; spheronization; wet extrusion.

INTRODUCTION

Since extrusion/spheronization was suggested by Conine and Reynolds in 1970 (1,2), it has been developed as common technology in bead manufacturing in the pharmaceutical area. In the last few years, several efforts were made to analyze and characterize the spheronization process. However, most studies focus on an empirical description of the spheronization process (3–5). Consequently, there has been a lack of fundamental understanding of the spheronization process until now.

Two pelletization mechanisms are discussed in terms of extrusion/spheronization. The first one was suggested by Rowe in 1985 (6) and describes the actual rounding as a consequence of collision of the particles. Based on this, he identified different stages of spheronization (shown in Fig. 1), which were attributed to plastic deformation. This first mechanism was extended by Baert in 1993 (7). He introduced a particle breakage of dumbbell-like particles into two oblate spheres during the spheronization process. These particles are also plastically deformed into spheres afterwards. Both mechanisms are currently used to describe the spheronization process (8).

Extrusion and spheronization both require certain rheological properties from the formulation, such as an adequate relationship of brittleness to plasticity (9). These properties are usually realized by the addition of pelletization aids to the formulation such as microcrystalline cellulose (MCC) or kappa-carrageenan (10). There are a few models that attempt to explain the outstanding pelletization properties of MCC (11,12). However, this study focused on the macroscopic scale of the particle interaction. Therefore, these models were not considered.

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MATERIALS AND METHODS

Materials

The following materials were used as received: kappa-carrageenan (Gelcarin® GP 911 NF, FMC, Philadelphia, PA, USA), lactose (Granulac 200, Meggle, Wasserburg, Germany), MCC 102 (Pharmatrans Sanaq, Basel, Switzerland), Sicovit red (BASF, Ludwigshafen, Germany), Sicovit green (BASF, Ludwigshafen, Germany), and titanium dioxide (Gruessing GmbH, Filsum, Germany).

Methods

Experimental Plan

In this study, two common pelletization aids (MCC and kappa-carrageenan) were used. Additionally, the powder formulation was varied using lactose as filler. Each powder formulation was colored using one of three different pigments (Sicovit red, green, and titanium dioxide, Table I). The water content in the extrusion was optimized for each formulation in preliminary investigations and fixed in extrusion at certain levels, which are given in the manuscript. Differently colored extrudates (3×100 g) were spheronized simultaneously and a color change occurred which was visually observed. The color change of the extrudate was attributed to mass transfer since insoluble pigments were used for coloring. It was assumed

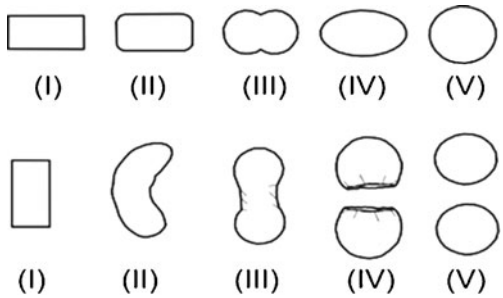

Fig. 1. Different pelletization mechanisms according to Rowe (*upper row*: *I*, cylinder; *II*, rounded edges; *III*, dumbbell; *IV*, ellipse; *V*, sphere) and Baert (*lower row*: *I*, cylinder; *II*, rope; *III*, dumbbell; *IV*, sphere a cavity; *V*, spheres)

that the influence of the pigments on the pelletization behavior was negligible.

Powder Blending

A pelletization aid and a filler (1,500 g) were weighed and blended for 15 min in a laboratory scale blender (LM40, Bohle, Ennigerloh, Germany) at 25 rpm. Afterward, the powder was divided into three equal parts and blended again (15 min) with one of three different pigments (Sicovit red, green, and titanium dioxide).

Extrusion

Each powder blend was transferred into the gravimetric powder feeder (KT 20, K-Tron Soder, Niederlenz, Switzerland) of the extruder. The twin-screw extruder (Mikro 27GL-28D, Leistritz, Nuremberg, Germany) was equipped with an axial screen with dies of 1 mm diameter and 2.5 mm length. Extrusion took place at a constant powder feed rate of 35 g/min, with suitable liquid feed rates (given in the text). Batches of 100 g wet extrudate were collected, sealed, and stored until spheronization.

Spheronization

Three hundred grams of extrudates of three different colors (100 g each) were spheronized (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) simultaneously at 11.7 m/s tip speed. The differently colored extrudates had the same water content, and it was assumed that the pelletization properties would be similar. The drying step was carried out in a fluid bed apparatus (GPCG 1.1, Glatt, Dresden, Germany) for 10 min with an inlet air temperature of 65°C.

Table I. Powder Formulations Using MCC or CAR as Pelletization Aid and Sicovit Red, Sicovit Green, and Titanium Dioxide as Pigments

	White		Red		Green	
MCC or CAR	50	100	50	100	50	100
Lactose	50		50		50	
Sicovit red			0.5	0.5		
Sicovit green					0.5	0.5
Titanium dioxide	0.5	0.5				

MCC microcrystalline cellulose, *CAR* kappa-carrageenan

Fig. 2. Pellets obtained from MCC (*left*, water content 151%) and MCC–lactose (*right*, water content, 74%) after 5 min spheronization

Imaging

Images of pellets were taken with a digital camera (Nikon D300, Nikon Corporation, Tokyo, Japan) using a resolution of at least 100 pixels per pellet diameter. The images were then post-processed to reduce brightness variability and to adjust the contrast of the image in relation to the background.

RESULTS AND DISCUSSION

Concept of Mass Transfer in Spheronization

All four tested formulations (Table I) showed an adequate pelletization behavior (9). Pellets of a spherical shape and a narrow size distribution were obtained regardless of the pelletization aid and amount of filler. The size and shape of pellets of one formulation and one color was similar to the size and shape of pellets formed by the other colors and formulations (Figs. 2 and 3). Therefore, images from representative single particles are given throughout the manuscript.

It is remarkable that the aspect ratio of the particles increases from the green, to the red, and then, to the white particles. This is related to the storage time between extrusion and spheronization because the differently colored formulations were extruded one after the other. The storage resulted in different rheological properties, affecting the pellet shape. This might be attributed to a drying of the extrudates. The differences in particle size of the differently colored pellets were also attributed to this effect.

The images from the different MCC and kappa-carrageenan formulations (Figs. 2a, b and 3a, b) show that all pellets which were initially white became colored during spheronization. Obviously, material was transferred from the colored pellets to the surfaces of the white pellets.

Fig. 3. Pellets obtained from CAR (*left*, water content, 312%) and CAR–lactose (*right*, water content, 152%) after 5 min spheronization

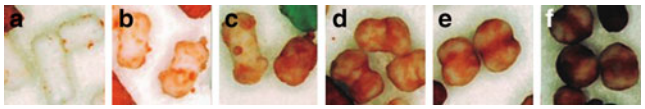

Fig. 4. Images of pellets (pure MCC) at the beginning (*left*, **a**), after 10, 30, 60, 120, and 240 s (*right*, **f**) spheronization, using a water content 151%

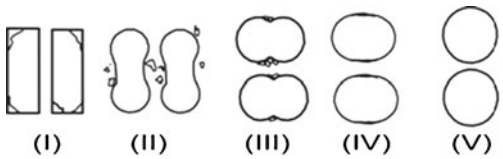

Fig. 5. Combined pelletization and agglomeration mechanism (*upper row*: *I*, cylinder; *II*, rounded edges and fractured fines; *III*, dumbbell with agglomerated fines; *IV*, ellipse; *V*, sphere)

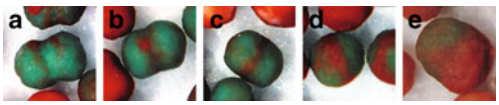

Fig. 6. Images of pellets (pure MCC) using different water contents 124% (*left*, **a**), 137%, 151%, 164%, and 177% (*right*, **e**) after 5 min spheronization

Fig. 7. Images of pellets (pure CAR) using different water contents 240% (*left*, **a**), 264%, 288%, 312%, and 336% (*right*, **e**) after 5 min spheronization

Mechanism of Mass Transfer

In further investigations, mass transfer was investigated with respect to spheronization duration for the pure MCC formulation. In the initial phase of spheronization, the long cylindrical extrudates broke into shorter cylinders (Fig. 4a) and were plastically transformed to spherical pellets (Fig. 4b–f) according to Rowe (6). In the initial phase of spheronization, fine fragments from differently colored pellets attached to the surface of larger particles. During the plastic deformation of the pellets, the smaller, differently colored particles at the pellet surface consolidate with the larger pellet.

Moreover, the material transferred between pellets by fine particles occurs in certain regions of the pellets. The fine particles prefer to attach to pellet regions subjected to lower mechanical stress during spheronization (Fig. 5). Therefore, a waist region is characterized by a more intensive coloring of the pellets (Fig. 4e, f).

Water Content and Mass Transfer

Since the water content of the extrudates is a crucial parameter in spheronization (4), its influence on this mechanism was investigated further. For each formulation, five different levels of water content were spheronized. Figure 6 shows images of pellets after drying. These pellets were made from a formulation of pure MCC colored red, white, and green, and are shown after 5 min of spheronization.

Mass transfer between pellets was observed for all water contents. The extent of the mass transfer increased in correlation with an increasing amount of water used. The pellets produced with the highest amount of water seem to be a mixture of green and red. It was impossible to determine whether the initial particle was white, green, or red. The higher extent of the mass transfer is also demonstrated by the larger pellet diameter because smaller pellets disappeared in the fine fraction and combined with larger particles, provoking pellet growth.

Using carrageenan (Fig. 7), the influence of water content to the mass transfer between pellet particles during spheronization is similar to MCC. A higher mass transfer was found for higher water contents, which could be explained with lower rigidity of the extrudates. This results in a higher fine fraction and higher capillary forces, which attach more fine particles to the surface of the pellets.

CONCLUSION

The mass transfer between particles must be considered in addition to plastic deformation in order to capture the spheronization mechanism. A material transfer between pellet particles was observed for all four formulations using MCC and carrageenan as pelletization aid. Moreover, regional distinctions in the amount of mass transfer as well as an influence of the water content were observed.

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