International Journal of Pharmaceutics 431 (2012) 84–89

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Systematic evaluations regarding interparticular mass transfer in spheronization

Martin Koester[a], Emilie Willemsen[b], Cornelia Krueger[a], Markus Thommes[a,*]

[a] Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Duesseldorf, Germany
[b] Laboratory of Pharmaceutical Technology, Ghent, Belgium

ARTICLE INFO

Article history:
Received 2 February 2012
Received in revised form 29 March 2012
Accepted 16 April 2012
Available online 23 April 2012

Keywords:
Microcrystalline cellulose
κ-Carrageenan
Wet extrusion
Spheronization
Mechanism
Mass transfer

ABSTRACT

Pellets are frequently used in pharmaceutical applications. The extrusion-spheronization process is a well-established technique used to produce pellets of a spherical shape and narrow size distribution. In this process, cylindrical extrudates are transformed into spherical pellets by spheronization. Most established mechanisms consider only breakage and deformation to explain pellet formation. An interaction between the rounding extrudates via adhesion of fine particles was not considered for many years.

This study deals with the evolution of pellet properties over time during the spheronization process in order to quantify the influence of pellet interactions on their properties. Therefore the most important pelletization aids (MCCI, MCCII and κ-carrageenan) were investigated using acetaminophen as a model drug and lactose as a filler. In the first seconds of the spheronization process, a high fine fraction was seen which decreased during the process. Simultaneously, the material transferred between the pellets increased. However the fine fraction is not high enough to explain the mass transfer; therefore a direct transfer between the pellets was assumed. The pelletization aid has a huge influence on the amount of mass transferred. Whereas κ-carrageenan leads to a quite low mass transfer of 15%, MCCI and MCCII show higher values up to 25%.

1. Introduction

In the pharmaceutical field pellets are defined as small particles (0.5–2 mm) with a spherical shape and narrow size distribution. Due to these properties pellets have a reproducible particle surface that is highly relevant for further processing, such as coating. In contrast to powders, other recognized benefits of pellets are better flowability in combination with more reproducible bulk density (Ghebre Sellassie, 1989). The outstanding properties of pellets are the lower extent of local irritations in the gastrointestinal tract as well as the lower risk of dose dumping (Bechgaard and Hegermann Nielsen, 1978). In the 1970s Conine and Reynolds first described extrusion-spheronization as a suitable technique to produce pellets from a wet mass (Conine and Hadley, 1970; Reynolds, 1970).

The pelletization mechanism was first described by Rowe in 1985. He characterized spheronization by breakage of the extrudates followed by plastic deformation and mass transfer between the formed granules (Fig. 1). The deformation was attributed to collisions of the particles with other particles, the bottom plate, or the cylindrical bin (Rowe, 1985). In 1993, Baert presented a second mechanism which includes a second breakage phase during spheronization where the dumbbell-shaped particles (Fig. 1b, 3rd step) break into nearly spherical parts (Baert et al., 1993). Recently, Liew described a new mechanism that includes a random attrition of fine particles on the pellets (Liew et al., 2007). This mechanism was further developed because an agglomeration of the fines in distinctive regions of the pellets could be seen. The fines agglomerate more in a central band around the pellet and so help to transform the 'dumbbell stage' into spherical pellets (Fig. 1c) (Koester and Thommes, 2010).

This study dealt with the influence of different pelletization aids on the evolution during spheronization under consideration of agglomeration step as mentioned above. Therefore the mass transfer fraction (MTF), the amount of fine particles during spheronization, and the pellet weight are used to explain the mass transfer over time.

Microcrystalline cellulose and κ-carrageenan were chosen as pelletization aids because of their outstanding role in pellet manufacturing. Recently, a second modification of MCC (MCC II) was promoted as a suitable pelletization aid, and is therefore included in this study. The main benefit of MCCII-based pellets over the well-described MCCI pellets is their disintegration behavior. That is to say, MCCI pellets remain intact in the presence of water (Krueger et al., 2010).

* Corresponding author at: Institute of Pharmaceutics and Biopharmaceutics, Universitaetsstrasse 1, 40225 Duesseldorf, Germany. Tel.: +49 211 8114220; fax: +49 211 8114251.
E-mail address: markus.thommes@uni-duesseldorf.de (M. Thommes).

0378-5173/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpharm.2012.04.045

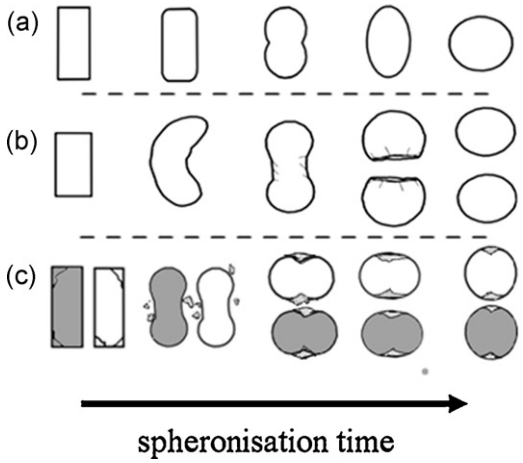

Fig. 1. Spheronization mechanisms according to (a) Rowe, (b) Baert and (c) combined deformation and agglomeration mechanism.

2. Materials and methods

2.1. Materials

The following materials were used as received: microcrystalline cellulose I (MCC 102G SANAQ®, Pharmatrans Sanaq, Basel, Switzerland), MCC II (MCC SANAQ® burst, Pharmatrans Sanaq, Basel Switzerland), α-lactose monohydrate (Granulac® 200, Meggle, Wasserburg, Germany), acetaminophen (Paracetamol BP/PH, Atabay, Istanbul, Turkey), κ-carrageenan (Gelcarin® GP 911 NF, FMC, Philadelphia, PA, USA).

2.2. Experimental plan

For each pelletization aid two different formulations were manufactured in order to investigate their behavior in the spheronizer. The two formulations were extruded separately and after a defined storage time combined in the spheronizer (Fig. 2). This storage period was necessary because it was not possible to extrude two formulations simultaneously.

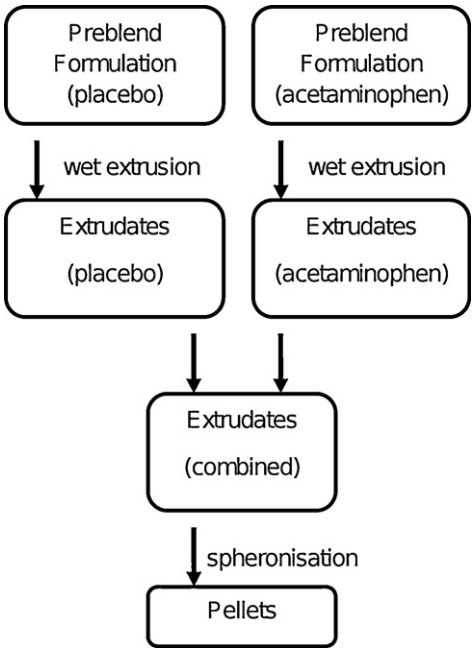

Fig. 2. Flow chart of the experimental plan for extrusion spheronization of two different formulations.

The first formulation consisted of the pelletization aid, acetaminophen as a model drug, and lactose as a filler. The second formulation is a placebo formulation in which a filler replaced acetaminophen in order to keep the content of the pelletization aids consistent (Table 1).

The spheronization step was stopped after predefined time steps and the resulting pellets dried in a fluid bed apparatus. Each of these batches was analyzed with regard to the pellets' shape, size, mass and drug content.

2.3. Pellet manufacturing

2.3.1. Blending

The powder substances were weighted and blended for 15 min in a laboratory scale blender (LM40, Bohle, Ennigerloh, Germany) at 20 rpm.

2.3.2. Extrusion

The powder blends were transferred into the gravimetric powder feeder (KT 20, K-Tron Soder, Niederlenz, Switzerland) of the extruder (Mikro 27GL-28D, Leistritz, Nuremberg, Germany) and extruded at constant screw speed of 200 rpm, a powder feed rate of 33.3 g/min and a liquid feed rate adjusted for each pelletization aid according to preliminary investigations (Fig. 3). The extruder compressed the wet mass through 23 dies of 1 mm diameter and 2.5 mm length.

2.3.3. Spheronization

150 g placebo and 150 g acetaminophen extrudates were combined (300 g total) and spheronized (RM 300, Schlueter, Neustadt/Ruebenberge, Germany). The spheronizer speed was kept constant at 750 rpm (friction plate tip speed 11.8 m/s) and the process was stopped after varied time intervals between 10 s and 8 min.

2.3.4. Drying

After spheronization the pellets were dried in a fluid bed dryer (GPCG 1.1, Glatt, Dresden, Germany). The inlet air temperature was 70 °C (volume flow of 70 m^3) and pellets were dried up to a product temperature of 45 °C. To reach this a drying time of 3 min was needed.

2.4. Analytics

2.4.1. Loss on drying

Samples of approximately 1 g were taken during extrusion to analyze the water content. These samples were dried at 65 °C under vacuum (<20 mbar) for 7 days (Thommes and Kleinebudde, 2007) (Heraeus Vacutherm, Kendo, Hanau, Germany). The water content was calculated as the amount of water ($m_{wet} - m_{dry}$) with respect to the dry mass (m_{dry}) of the extrudates (Eq. (1)). The determination was done in triplicate.

$$\text{Water content} = \frac{m_{wet} - m_{dry}}{m_{dry}} \quad (1)$$

2.4.2. Grading

The dried pellets were classified using sieve cuts. The class below 630 μm is referred to as fine fraction, the class above 2000 μm as secondary agglomerates, and the range in between as yield fraction. This yield fraction was divided into multiple samples using a rotary cone sample divider (Retschmuele PT, Retsch, Haan, Germany). Samples of approximately 500 pellets were used for further analysis.

Table 1
Design of experiment.

Formulation	Pelletization aid			API	Filler
	MCCI	MCCII	CAR	Acetaminophen	Lactose
MCCI	20%	–	–	20%	60%
	20%	–	–	–	80%
MCCII	–	20%	–	20%	60%
	–	20%	–	–	80%
CAR	–	–	20%	20%	60%
	–	–	20%	–	80%

2.4.3. Image analysis

Aspect ratio: Each of these 500 pellet samples was photographed using a stereo microscope (Leica MZ 75, Cambridge, UK), a ring light with cold light source (Leica KL 1500, Cambridge, UK) and a digital camera (Leica CS 300 F, Cambridge, UK). These images were processed with image analysis software (Qwin, Leica, Cambridge, UK) that calculated 64 feret diameters and the projected area for each pellet. The aspect ratio was calculated from the maximum feret diameter ($d_{\text{feret max}}$) and the diameter orthogonal ($d_{\text{feret 90}}$) to it (Eq. (2)).

$$\text{Aspect ratio} = \frac{d_{\text{fere max}}}{d_{\text{feret 90}}} \tag{2}$$

Equivalent diameter: The equivalent diameter is determined as the diameter of a circle with the same area as the pellets 2*d* projection taken from the image analysis.

10% interval: A 10% interval was defined to characterize the homogeneity in particle size. It describes the fraction of pellets within the interval 90% to 110% of the dimensionless diameter (Thommes and Kleinebudde, 2006).

Pellet weight: The average weight was determined by weighting 20 g of pellets of each batch and the counting them with a Camsizer® (Retsch, Haan, Germany).

2.4.4. Porosity

The helium density (ρ_{He}) was determined using a helium pycnometer (AccuPyc, Micrometrics, Moenchengladbach, Germany). The apparent density (ρ_{Hg}) was determined with a mercury porosimeter (Pascal140, Thermo Fisher, Milan, Italy) at a pressure of 0.1 MPa. The porosity (ε_p) was calculated using Eq. (3).

$$\varepsilon_p = \frac{1 - \rho_{\text{Hg}}}{\rho_{\text{He}}} \times 100\% \tag{3}$$

2.4.5. Content uniformity

To determine content uniformity, 50 pellets of each batch were weighed separately (Sartorius MC 210 P, Sartorius AG, Goettingen, Germany) and dissolved in 20.0 ml of water. After 24 h, the acetaminophen concentration was determined using a UV photometer (Lambda 20, Perkin Elmer, Germany) at a wavelength of 249 nm (USP, 2008).

2.5. Mass transfer fraction

A mass transfer fraction (MTF) was calculated (Koester and Thommes, 2012). For pellets from the placebo extrudate, the drug content (x_{pellet}) was divided by the drug content of an equal mixture of placebo (x_{placebo}) and drug powder formulation (x_{drug}) in order to obtain the MTF (Eq. (4)).

$$\text{MTF} = \frac{2\,x_{\text{pellet}}}{x_{\text{placebo}} + x_{\text{drug}}} \tag{4}$$

For the pellets from drug extrudates, the decrease in drug content must be considered (Eq. (5)).

$$\text{MTF} = \frac{2(x_{\text{drug}} - x_{\text{pellet}})}{x_{\text{placebo}} + x_{\text{drug}}} \tag{5}$$

3. Results and discussion

3.1. Preliminary studies

The water content of the extruded mass is a crucial parameter affecting the pellet shape and size (Erkoboni, 2003). Therefore an optimal water content was determined, resulting in pellets with the lowest aspect ratio, (Fig. 3). The MCCI formulation shows a decrease of the aspect ratio with an increase of the water content up to 42%. Above this water content, an increase of the aspect ratio as well as a remarkable increase in particle size was observed. According to the literature this can be explained by the characteristic properties of the wetted MCCI mass. At low water contents the mass breaks, but is then too dry to be plastically deformed in the spheronizer, resulting in short sticks or dumbbell-shaped particles. Coming closer to the optimal water content, the mass is more easily deformable, and fines can agglomerate on the wet extrudates. Increasing the water content more and exceeding the optimal range causes the particles to get stickier. Because of this, fines not only agglomerate on the particles, but multiple particles coalesce into larger particle agglomerates. This can be seen by the increase of the pellets' equivalent diameter, as well as an increase in the aspect ratio.

The MCCII-based formulation undergoes the same principle when increasing the water content. If under-wetted, the extrudates are too rigid to spheronize, but remain in a dumbbell shape. If over-wetted, the mass is too sticky and starts forming secondary agglomerates of larger size and reduced roundness. In contrast to

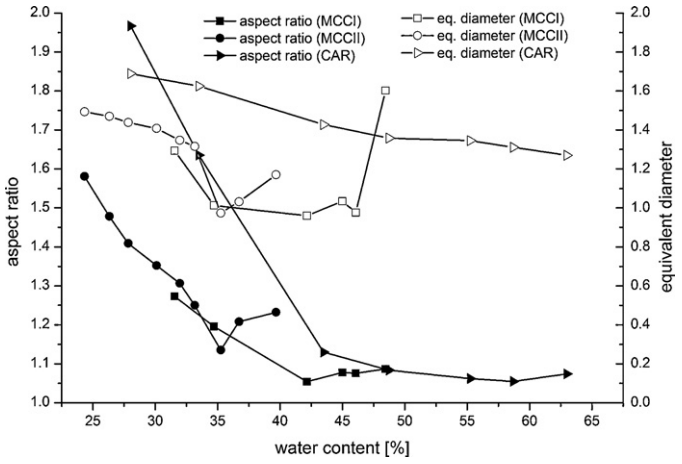

Fig. 3. Determination of the optimal water content for MCCI (square), MCCII (circle) and κ-carrageenan (triangle) formulations (Table 1) after 10 min spheronization at 750 rpm.

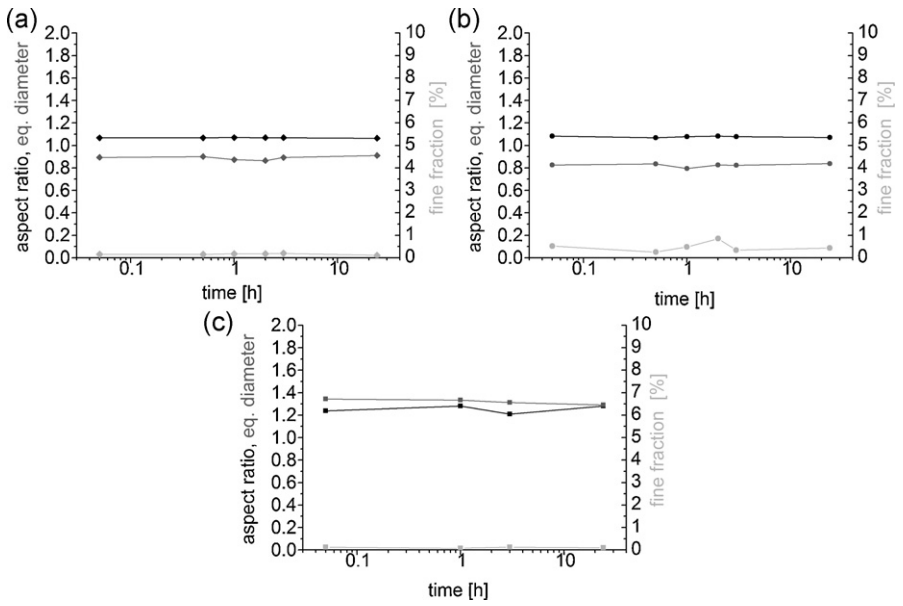

Fig. 4. Influence of storage time: aspect ratio (black), equivalent diameter (grey) and fine fraction (light grey) of MCCI (a), MCCII (b) and κ-carrageenan (c) pellets after varying extrudate's storage times.

MCCI, the optimal water content is reached at lower values (35%) and the powder formulation reacts less robustly to changes in the water content. This effect was already described by Krueger et al. (in press).

The κ-carrageenan-based formulation shows a trend similar to the MCC formulations, but at higher water contents. The aspect ratio decreases when increasing the water content. At high water contents (above 50%) κ-carrageenan behaved differently from the MCC formulations: the aspect ratio and the mean pellet diameter did not increase with an increase in water content. This indicates a missing second agglomeration phase as shown for the MCC formulations. It can be concluded, in agreement with the literature, that κ-carrageenan has a much higher water-binding capacity, and therefore reacts more robustly to changes in the water content (Thommes and Kleinebudde, 2005).

3.2. Influence of storage time

It was impossible to extrude both formulations for one spheronization batch at the same time, due to logistic issues. Therefore it was necessary to investigate the influence of the storage time of the wet extrudates on their spheronization behavior. For all formulations, extrudate samples (300 g) were stored for time periods from 5 min up to 24 h before spheronization, in order to eliminate any influence of the storage time on the pellet properties (Fig. 4). The aspect ratio and equivalent diameter did not show any change with storage time for the pellets obtained from MCCI, MCCII and κ-carrageenan. The fine fraction of the MCCI formulation showed a small increase at 2 h of storage time, but this can be disregarded since it did not influence the pellet properties. An influence of the storage time can be ruled out for the given pelletization aids and storage times up to 24 h.

3.3. Mass transfer over time

3.3.1. Microcrystalline cellulose (type 1)

In this section, the spheronization behavior of MCCI with respect to the spheronization time was investigated (Fig. 5). A formulation containing 20% MCCI as the pelletization aid, with a water content of 42%, resulted in acceptable pellets (Lindner and Kleinebudde, 1993) with an aspect ratio of 1.12 and a 10% interval of above 60% after a spheronization time of 480 s.

The aspect ratio, as a key parameter describing the pellet shape, is constantly decreasing over time. The equivalent diameter is decreasing as well, whereas the pellet weight remains constant. This increase in the pellets' density can be attributed to the pellets' porosity, which is constantly decreasing. The 10% interval increases, showing a more uniform size distribution of the pellets. The fine fraction (<630 μm) increases until reaching a maximum at 30 s; after this it decreases down to about 1% of the pellets' mass. In contrast to this the mass transferred increases constantly over the 8 min.

The spheronization of MCCI can be divided into two phases: In the first 30 s the fine fraction is increasing without a relevant change in the other pellet properties (aspect ratio, eq. diameter,

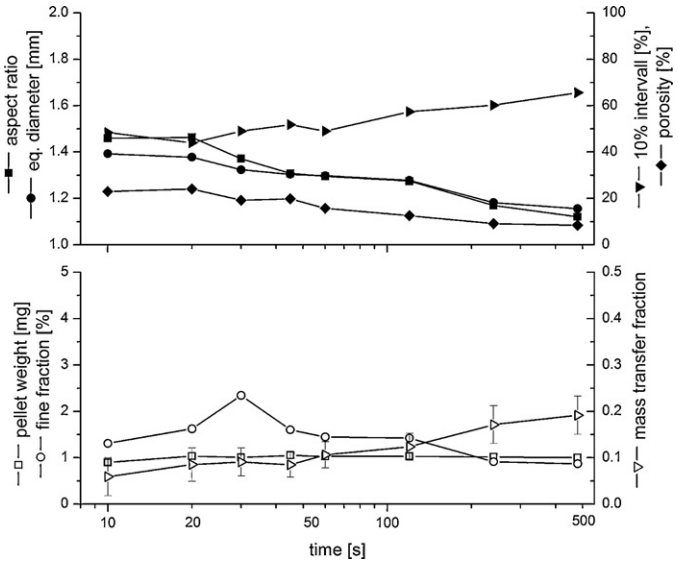

Fig. 5. pellet properties (aspect ratio (filled square), equivalent diameter (filled dot), 10% interval (filled triangle), porosity (filled diamond), pellet weight (square), fine fraction (circle) and MTF (triangle, $n = 50$, av ± ci)) for pellets made of 20% MCCI at varying spheronization times.

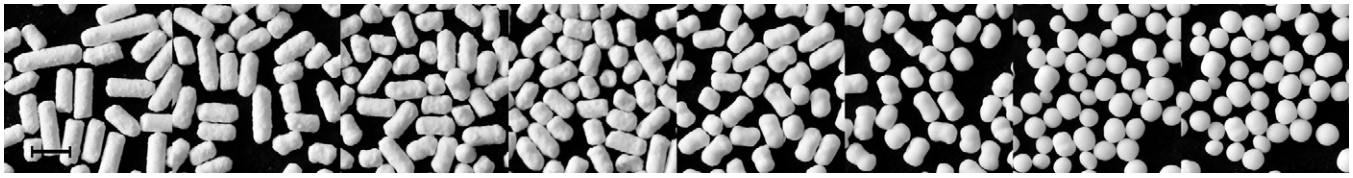

Fig. 6. Images of MCCI particles after varied spheronization times (10, 20, 30, 45, 60, 120, 240, 480 s), scale $\widehat{=}$ 2.0 mm.

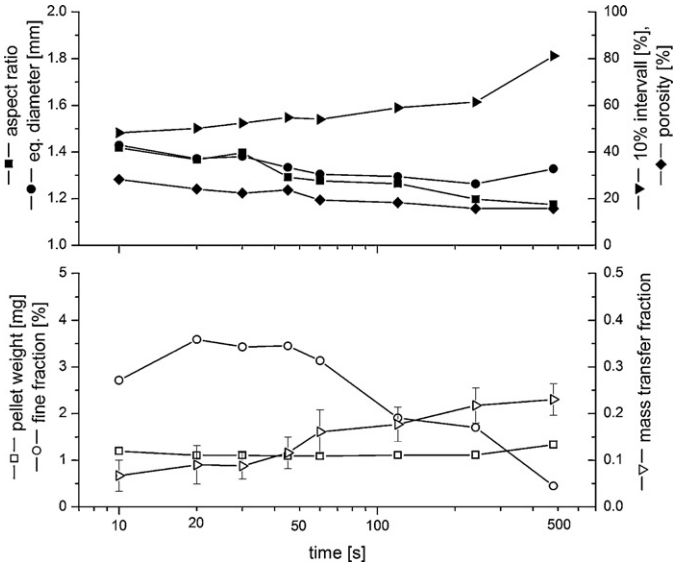

Fig. 7. Pellet properties (aspect ratio (filled square), equivalent diameter (filled dot), 10% interval (filled triangle), porosity (filled diamond), pellet weight (square), fine fraction (circle) and MTF (triangle, $n = 50$, av ± ci)) for pellets made of 20% MCCII at varying spheronization times.

weight). During this phase, fine particles start to break off the cylindrical extrudates and form a fine fraction. The plastical deformation of the cylinders does not affect the aspect ratio and the equivalent diameter (Fig. 6, 10–30 s). The second phase is dominated by a decrease of the fine fraction, the aspect ratio, the equivalent diameter, and the porosity. The fines agglomerate on the now dumbbell-shaped (Fig. 6, 120 s) particles, and together with an ongoing plastic deformation help to form spherical pellets (Fig. 6, 480 s). The simultaneous decrease of size and porosity and the constant weight are attributed to a densification of the pellets driven by the multiple impacts during spheronization.

The mass transfer increases constantly, up to a value of about 20%. In contrast to this the amount of fines reaches a maximum of no more than 2.5%, so the mass transferred cannot be explained by a simple agglomeration of fines on the bigger pellets. Instead, the additional increase in mass transfer can be attributed to two possible mechanisms. First, a steady state of breakage and agglomeration, or, second, a direct mass exchange between the pellets. A mechanism of steady breakage and agglomeration would be defined as small particles breaking off the cylindrical extrudates, dumbbells, or ellipsoids at their most stressed zone, and a coexisting agglomeration of these pieces at other zones on the particles' surface. In contrast to this, a direct mass exchange would be described as a smearing of the wet extrudates' mass while the particles are in contact. It is not clear which of these or if perhaps a combination of these two mechanisms occurs during spheronization. The important point is that this mass transfer is accountable for about 20% of the MCCI pellets' mass.

The relatively high mass transfer during the first 10 s of the spheronization can be explained by the drying step that was carried out directly after spheronization. The pellets had contacts similar to the ones during spheronization while being dried in a fluid bed apparatus. At the beginning of this drying, the pellets' mass was still wet and could be transferred, similar to the described mechanisms for the spheronization.

3.3.2. *Microcrystalline cellulose (type II)*

Using MCCII the spheronization process was different. Whereas the aspect ratio decreases similarly to MCCI, the equivalent diameter decreases at a much slower rate. This can be explained by the porosity decreasing more slowly, resulting in less dense particles. The equivalent diameter decreases to a minimum at 4 min, and then

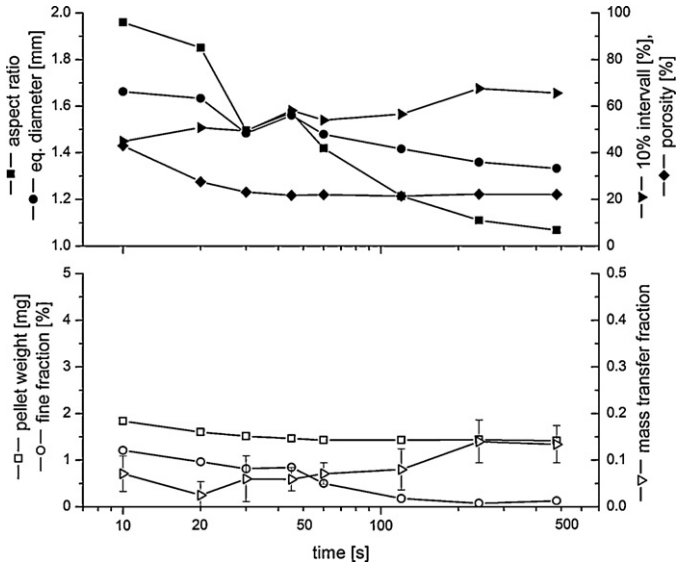

Fig. 9. Pellet properties (aspect ratio (filled square), equivalent diameter (filled dot), 10% interval (filled triangle), porosity (filled diamond), pellet weight (square), fine fraction (circle) and MTF (triangle, $n = 50$, av ± ci)) for pellets made of 20% κ-carrageenan at varying spheronization times.

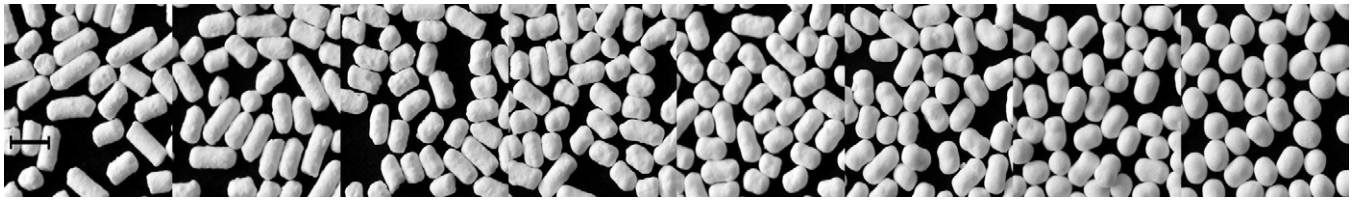

Fig. 8. Images of MCCII particles after varied spheronization times (10, 20, 30, 45, 60, 120, 240, 480 s), scale $\widehat{=}$ 2.0 mm.

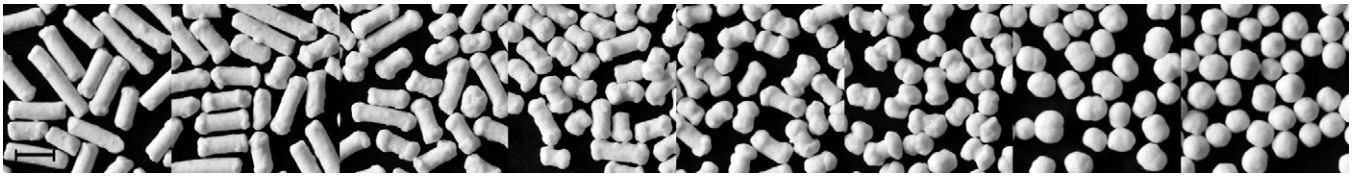

Fig. 10. Images of CAR particles after varied spheronization times (10, 20, 30, 45, 60, 120, 240, 480 s), scale $\widehat{=}$ 2.0 mm.

starts to increase again due to agglomeration on the pellets' surface. The 10% interval increases over time, indicating a homogenization of the particle size as suggested by Krueger. In contrast to Krueger the pellet weight increases more slowly. A possible explanation for this might be the slower spheronization speed, which leads to lower impact forces during spheronization. Krueger showed a significant influence of the spheronization speed on the pellet properties for MCCII (Fig. 7).

As seen for MCCI, the spheronization of MCCII can be divided into different phases as well. Within the first 20 s the fine fraction increases up to 3.5% due to abrasion on the cylindrical extrudates' surface (Fig. 8, 10–20 s). In this phase the aspect ratio and the MTF do not change. The extrudates start to deform, but not into a form that shows a reduced aspect ratio (ellipsoid or sphere). This is followed by a plateau in the fine fraction for another 30 s, until the fine fraction starts to reduce. In this phase the extrudates deform further as seen in the stronger decrease of the aspect ratio and a visible deformation (Fig. 8, 60 s). The weight remains constant, and the particles' density increases further. After about 1 min, the fines start to agglomerate on the larger particles until nearly no fines remain. As for MCCI, this fine fraction is too small to explain the mass transfer completely. The polished edges (Fig. 8, 240 s) and the higher fine fraction in contrast to MCCI make it more likely that the mass transfer is mediated through the fine fraction in a steady abrasion and agglomeration balance.

3.4. κ-Carrageenan

The behavior of κ-carrageenan formulations differed from the two MCC types. In the beginning of the spheronization process, the aspect ratio is much higher than seen for MCC. As described in the literature, the wet extrudates do not crumble into shorter particles (Fig. 10, 10 s) because of the κ-carrageenan's higher elasticity, and therefore keep a higher initial aspect ratio (Bornhoeft et al., 2005). There is only a slight change in the particles' porosity in the first 20 s of spheronization (Fig. 9), after this point no further densification occurred. The fine fraction of about 1% in the beginning decreases further until no fine fraction is left. In contrast to this the MTF increases over the whole spheronization time. The pellet weight decreases over the first 60 s. This can be attributed to further breakages of the longer extrudates in a similar fashion to the breakages that just occurred, as described by Baert, with the only difference being that this breakage occurs before, rather than after, the dumbbell stage.

It is highly probable that for κ-carrageenan the spheronization mechanism differs from the other excipients shown. The spheronization is mostly based on plastical deformation of the cylindrical extrudates, and agglomeration is not a driving force during spheronization. Here the mass transfer seen must originate from a direct pellet-to-pellet interaction. Two touching pellets smear parts of their wet mass on each other, and so transfer material during the contact.

4. Conclusion

With this study it was possible to explain the role of mass transfer and, therefore, breakage and agglomeration during spheronization. The used excipients all result in pellets of good quality, but the way these pellets are formed differs depending on the used pelletization aid. Whereas for κ-carrageenan the pelletization mechanism can be fairly well-described by initial breakage and deformation according to Rowe, for MCC-based formulations the mass transfer plays an important role. Over the whole spheronization time a substantial amount of material (20%) is transferred between the particles.

References

Baert, L., Vermeersch, H., Remon, J.P., Smeyers-Verbeke, J., Massart, D.L., 1993. Study of parameters important in the spheronisation process. Int. J. Pharm. 96, 225–229.

Bechgaard, H., Hegermann Nielsen, G., 1978. Controlled release multiple-units and single-unit doses – a literature review. Drug Dev. Ind. Pharm. 4, 53–67.

Bornhoeft, M., Thommes, M., Kleinebudde, P., 2005. Preliminary assessment of carrageenan as excipient for extrusion/spheronisation. Eur. J. Pharm. Biopharm. 59, 127–131.

Conine, J.W., Hadley, H.R., 1970. Preparation of small solid pharmaceutical spheres. Drug Cosmet. Ind. 106, 38–41.

Erkoboni, D.F., 2003. Extrusion/Spheronization. In: Ghebre Sellassie, I., Martin, C. (Eds.), Pharmaceutical Extrusion Technology. Marcel Dekker Inc., New York, pp. 277–318.

Ghebre Sellassie, I., 1989. Pellets: a general overview. In: Ghebre Sellassie, I. (Ed.), Pharmaceutical Pelletization Technology. Marcel Dekker Inc., New York, p. 1-14.

Koester, M., Thommes, M., 2010. New insights into the pelletization mechanism by extrusion/spheronization. AAPS PharmSciTech 11, 1549–1551.

Koester, M., Thommes, M., 2012. Quantification of mass transfer during spheronisation. AAPS PharmSciTech, http://dx.doi.org/10.1208/s12249-012-9770-y.

Krueger, C., Thommes, M., Kleinebudde, P., 2010. Suitability of microcrystalline cellulose II as new pelletisation aid for wet extrusion-spheronisation in comparison to microcrystalline cellulose I. J. Pharm. Innov. 5, 45–57.

Krueger, C., Thommes, M., Kleinebudde, P. Spheronisation mechanism of MCC II-based pellets. Powder Technol., http://dx.doi.org/10.1016/j.powtec.2011.12.052, in press.

Liew, V.C., Chua, S.M., Heng, P.W.S., 2007. Elucidation of spheroid formation with and without the extrusion step. AAPS PharmSciTech, 8.

Lindner, H., Kleinebudde, P., 1993. Characterization of pellets by means of autonomic image analysis. Pharmazeutische Industrie 55, 694–701.

Reynolds, A.D., 1970. A new technique for the production of spherical particles. Mfg. Chem. Aerosol News 40, 40–43.

Rowe, R.C., 1985. Spheronization: a novel pill-making process? Pharm. Int. 6, 119–123.

Thommes, M., Kleinebudde, P., 2005. Use of κ-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronisation. II. Influence of drug and filler type. Eur. J. Pharm. Biopharm. 63, 68–75.

Thommes, M., Kleinebudde, P., 2006. Use of κ-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronisation. I. Influence of type and fraction of filler. Eur. J. Pharm. Biopharm. 63, 59–67.

Thommes, M., Kleinebudde, P., 2007. Properties of pellets manufactured by wet extrusion spheronization process using κ-carrageenan: effect of process parameters. AAPS PharmSciTech 8, 95.

The United States Pharmacopeial Convention, 2008. Buffer Solutions. The United States Pharmacopeia, Rockville, USA, p. 813.