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Research Article

Quantification of Mass Transfer During Spheronisation

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Abstract. Spherical granules (pellets) are quite useful in many pharmaceutical applications. The extrusion spheronisation technique is well established as a method of producing pellets of a spherical shape and narrow size distribution. After the extrusion, the cylindrical extrudates are transformed to spherical pellets by spheronisation. The frequently used models consider deformation and breakage during this process. However, the adhesion of fine particles has been neglected as a mechanism in spheronisation for many years. This study quantifies the mass transfer between pellets during spheronisation. During the investigation, the pelletisation aids (microcrystalline cellulose and kappa-carrageenan), the drug (acetaminophen and ibuprofen) and water content were varied systematically. A novel parameter, namely, the "mass transfer fraction" (MTF), was defined to quantify the mass transfer between the pellets. All four investigated formulations had an MTF between 0.10 and 0.52 that implies that up to 50 % of the final pellet weight was involved in mass transfer. Both pelletisation aids showed similar MTF, independent of the drug used. Furthermore, an increase of the MTF, with respect to an increase of the water content, was found for microcrystalline cellulose formulations. In conclusion, the mass transfer between the pellets has to be considered as a mechanism for spheronisation.

KEY WORDS: carrageenan; MCC; mechanism; pellets; spheronisation.

INTRODUCTION

Spherical agglomerates (pellets) are widely used in pharmaceutics because their distinctive properties (*i.e.* spherical shape and narrow size distribution) make them particularly useful for processes like coating and encapsulation. Furthermore, pellets have a low risk of intoxication and fewer side effects related to local irritations (1). Pellets are often prepared by extrusion spheronisation as introduced by Conine and Reynolds in 1970 (2,3).

Extrusion spheronisation is a two-step process: During the extrusion step, the wet mass is pressed through circular dies, and cylindrical extrudates are obtained. These are transferred to a spheroniser consisting of a cylindrical bin and a rotating bottom plate. The spheronisation process transforms the cylindrical extrudates into spherical pellets (4). This process requires particular properties of the wet mass: To form cylindrical extrudates, the mass must be cohesive and rigid, but it must also be brittle and plastically deformable to form spheres (5). These requirements are usually met by the addition of pelletisation aids to the formulation (6). Several pelletisation aids have been suggested in the last few years (7–10). Other investigations deal with the influence of various process variables over pellet properties (11–15). Until now, there have been just a few suggestions regarding the pellet formation mechanism: In 1985, Rowe (16) attributed spheronisation to breakage and collision. In the initial phase of spheronisation, the cylindrical extrudates break in shorter cylinders, which are plastically deformed by collision with each other as well as the spheroniser. This leads to different interim stages of deformation (Fig. 1a). Baert (17) extended this mechanism by an additional breakage in 1993. The dumb-bell-shaped particles break in two and are rounded into spherical particles afterwards (Fig. 1b). Both mechanisms share their focus on the plastic deformation as a driving force in pellet formation. In 2007, Liew (18) described a third mechanism, whereby fine particles break off the extrudates and agglomerate randomly on the larger particles.

Recently, Liew's approach was refined because an agglomeration of fines in distinctive regions of the pellets was found (Fig. 1c) (19). Due to the lower mechanical stress at the central band of the pellets, the fine particles tend to accumulate in this pellet region.

In this study, the mass transfer between pellets was quantified for the two most common pelletisation aids [microcrystalline cellulose (MCC) and kappa-carrageenan]. Acetaminophen and ibuprofen were used as model drugs that were chosen based on their aqueous solubility because an effect on the mass transfer was expected (20). Acetaminophen was considered as representative of drugs with high solubility, whereas ibuprofen represented drugs with low solubility. Lactose is a common filler in extrusion spheronisation and was used for that purpose (20–22). The water content was varied because it is a crucial process parameter that affects the pellet properties. High water content, for example, can change the pelletisation mechanism to secondary agglomeration, called "snowballing" (22).

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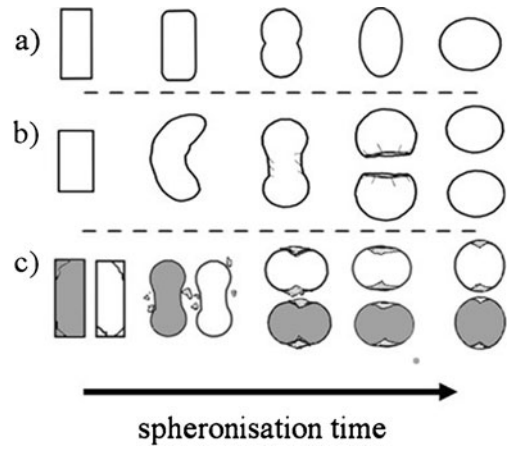

Fig. 1. Different pelletisation mechanisms according to **a** Rowe, **b** Baert and **c** the combined pelletisation and agglomeration mechanism

MATERIALS AND METHODS

Materials

The following materials were used as received: κ-carrageenan (Gelcarin® GP 911 NF, FMC, Philadelphia, PA, USA), alpha lactose monohydrate (Granulac 200, Meggle, Wasserburg, Germany), microcrystalline cellulose (MCC Sanaq 102G, Pharmatrans Sanaq, Basel, Switzerland), acetaminophen (Paracetamol BP/PH, Atabay, Istanbul, Turkey) and ibuprofen (Ibuprofen 50 FF, Losan Pharma GmbH, Neuenburg, Germany). All substances were pharmaceutical grades, according to the pharmacopoeias.

Methods

Powder Blending

The powder substances were weighed and blended for 15 min in a laboratory scale blender (LM40, Bohle, Ennigerloh, Germany) at 25 rpm and transferred into the gravimetric powder feeder (KT 20, K-Tron Soder, Niederlenz, Switzerland) of the extruder.

Extrusion/Spheronisation

The twin-screw extruder (Mikro 27GL-28D, Leistritz, Nuremberg, Germany) was equipped with an axial screen with 23 dies of 1 mm diameter and 2.5 mm length. The extrusion took place at a constant powder feed rate of 30 g/min, with suitable liquid feed rate. Two hundred fifty grams of wet extrudate was collected, sealed and stored until spheronisation. Two hundred fifty grams of extrudate with and without drug (500 g total) were combined and spheronised (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) at 11.7 m/s tip speed for 5 min. Afterwards, 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 55 °C.

Loss on Drying

Samples of 1 g were taken to analyse the water content. The samples were dried at 65 °C under vacuum (<20 mbar) for 7 days (23) (Heraeus Vacutherm, Kendo, Hanau, Germany). The water content was calculated with respect to the dry mass of the extrudates. The determination was done in triplicate.

Image Analysis

The pellets were sieved with sieves of 0.8 and 2 mm apertures, respectively. Statistically representative samples were obtained from the yield fraction using a rotary cone sample divider (Retschmuele PT, Retsch, Haan, Germany). Image analysis software (Qwin, Leica, Cambridge, UK) was used to analyse images which were obtained using a system consisting of 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). Images of at least 500 pellets from each sample were recorded at a suitable magnification (1 pixel, 17.5 μm) and converted into binary images. Contacting pellets were separated by a software algorithm. If the automatic separation failed, the pellets were deleted manually. For each pellet, 64 feret diameters and the projected area were determined (24). A dimensionless aspect ratio (AR) was calculated from the feret diameter (d_{feret}) and the orthogonal feret diameter (d_{90}) (Eq. 1). The projected area was used to calculate the equivalent diameter to which is referred as diameter throughout the text.

$$AR = d_{feret}/d_{90} \tag{1}$$

Drug Assay

Fifty pellets each were weighed (Sartorius MC 210 P, Sartorius AG, Goettingen, Germany) separately from each other and dissolved in 20.0 ml medium afterwards. Water was used for acetaminophen, while phosphate buffer (pH 7.2) (25) was chosen for ibuprofen. The drug concentration was quantified using an UV photometer (Lambda 20, Perkin Elmer, Germany) at a wavelength of 249 nm (acetaminophen) or 221 nm (ibuprofen).

Calculation of the Mass Transfer Fraction

To describe the amount of mass exchanged between the pellets during spheronisation, the mass transfer fraction (MTF) was introduced. The MTF has to be defined differently for pellets originating from placebo extrudate rather than from drug extrudate. For the pellets from placebo extrudate, the drug content (x_{pellet}) is divided by the drug content of an equal mixture [$(x_{placebo}+x_{drug})/2$) of placebo ($x_{placebo}$) and drug powder formulation (x_{drug}) in order to obtain the MTF (Eq. 2).

$$MTF = \frac{2 \cdot x_{pellet}}{x_{placebo} + x_{drug}}. \tag{2}$$

Table I. Powder Formulations Used

	MCC	CAR	Acetaminophen	Ibuprofen	Lactose
MCCACE	50		25		25
	50				50
MCCIBU	50			25	25
	50				50
CARACE		50	25		25
		50			50
CARIBU		50		25	25
		50			50

For the pellets from drug extrudates, the decrease in drug content has to be considered (Eq. 3).

$$\mathrm{MTF} = \frac{2 \cdot (x_{\mathrm{drug}} - x_{\mathrm{pellet}})}{x_{\mathrm{placebo}} + x_{\mathrm{drug}}}. \tag{3}$$

RESULTS AND DISCUSSION

Pellet Shape and Size

Previous investigations used different coloured extrudates that were combined in the spheronisation process and the colour change was investigated (19). In this study, extrudates with different amounts of drug (0 and 25 %) were combined during spheronisation in order to quantify the mass transfer. Four different formulations varying the pelletisation aid and the drug were considered (Table I) in order to demonstrate the relevance of the observations.

The four formulations were pelletised using various water contents because the influence of the water content on pellet shape and size is well known and frequently used to describe the pelletisation behaviour of a formulation (Fig. 2) (20). All formulations had adequate pelletisation behaviour with respect to the aspect ratio (<1.2) (24).

There is no effect of the drug on the pellet's shape and size beyond that which can be explained with the low amount of drug (25 %) compared to the high amount of pelletisation aid (50 %). The carrageenan formulations require higher water contents than MCC formulations to realise pellets of a spherical shape. This observation is consistent with the literature (22) since the water-binding capacity of carrageenan is higher (26). Moreover, the carrageenan formulations are less sensitive to differences in the water content, which was also seen in prior investigations (27).

Mass Transfer

The mass transfer was investigated for all formulations by determining the drug content of individual pellets (Fig. 3). Since the drug content in single pellets was evaluated, the variability is quite high. However, a bimodal distribution of the drug content was found for all water contents regardless of the formulation. If the pelletisation is based on breakage and deformation as described by Rowe and Baert, the pellets with the full drug load and with no drug at all, should be obtained. The deviating results can be explained by the mass transfer between pellets, which increased the drug content of pellets without drug and decreased the drug content of those containing drug. Drug content of more than 25 % can be attributed to an increase of the drug content during storage due to drying, since MCC and kappa-carrageenan show significant water adsorption (26).

Mass Transfer Fraction

The MTF was introduced as a parameter to quantify the mass transfer between pellets. An MTF of 0 indicates no mass transfer between the pellets, while 1 characterises pellets that

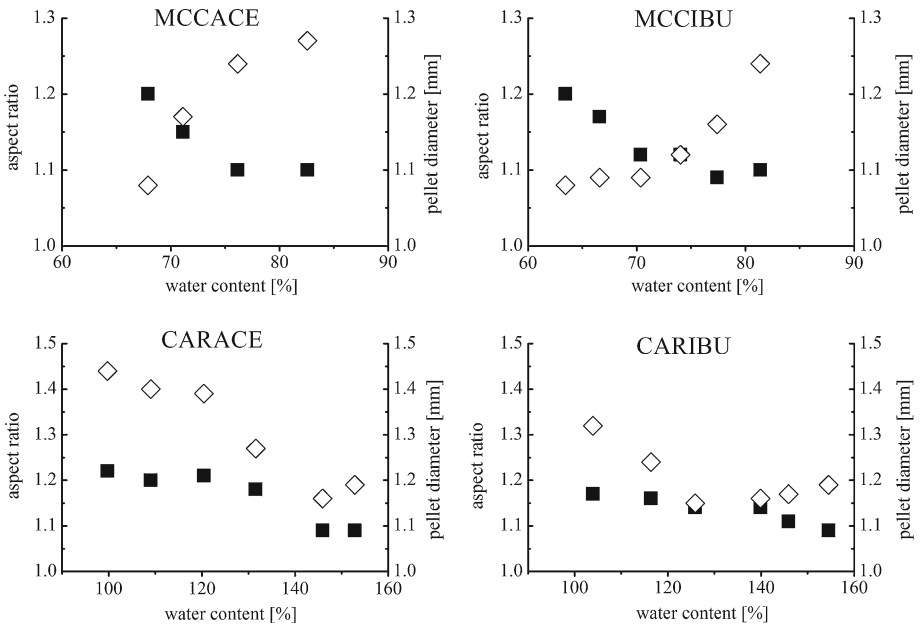

Fig. 2. Aspect ratio and pellet diameter in correlation to the water content (*diamond* pellet diameter, *square* aspect ratio)

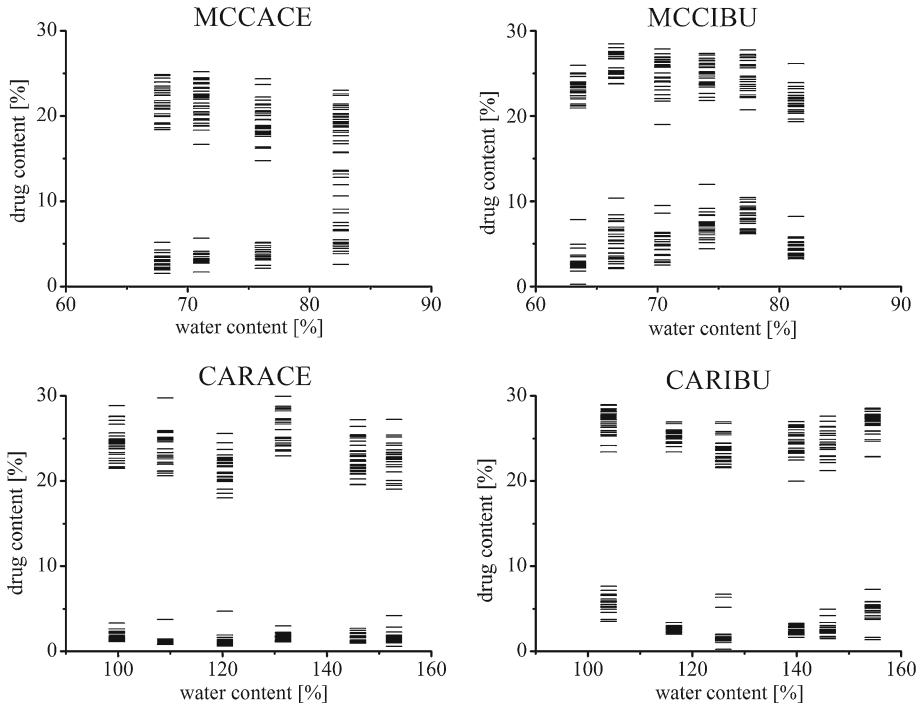

Fig. 3. Drug content in relation to the water content for each batch (n=50 pellets)

originate entirely from mass transfer (Eqs. 2 and 3). It seems likely that the pellets consist of a core and a shell. The shell contains a mixture of drug-free and drug-containing particles. The core includes no drug or full drug load with respect to whether the core originates from a placebo or drug-containing extrudate. Based on previous observations, the thickness of the shell should be different depending on the positions on the pellet (19).

The MTF did not differ with respect to the drug. This observation was unexpected, but the mass transfer seems to be attributed to a transfer of solid particles rather than a transfer of dissolved materials. This might be related to an immobilisation of the liquid phase. MCC and carrageenan had a remarkable MTF because more than 10 % of the pellet's mass can be attributed to mass transfer. Values up to 50 % were obtained. Based on this, mass transfer must be considered when explaining the spheronisation process.

The MCC formulations have higher MTF than those made with carrageenan. Furthermore, an increase of the MTF with respect to the water content was observed for MCC (p<0.001) (Fig. 4). The extrudates became more fragile at higher water contents because the solid fraction decreased. This leads to a higher intermediate fine fraction that is attracted to the particles (secondary agglomeration) (20). Because of this, an increase of the pellet size is also observed for MCC formulations (Fig. 2a, b). The MCCACE formulation with the highest water content showed a higher secondary agglomeration than the others. Therefore, the pellet diameter (Fig. 2) and the mass transfer were increased up to a point where the two parts of the bimodal distribution were closer (Fig. 3). Carrageenan does not show secondary agglomeration in the spheronisation process (22). Therefore, no effect of the water content to the mass transfer was observed.

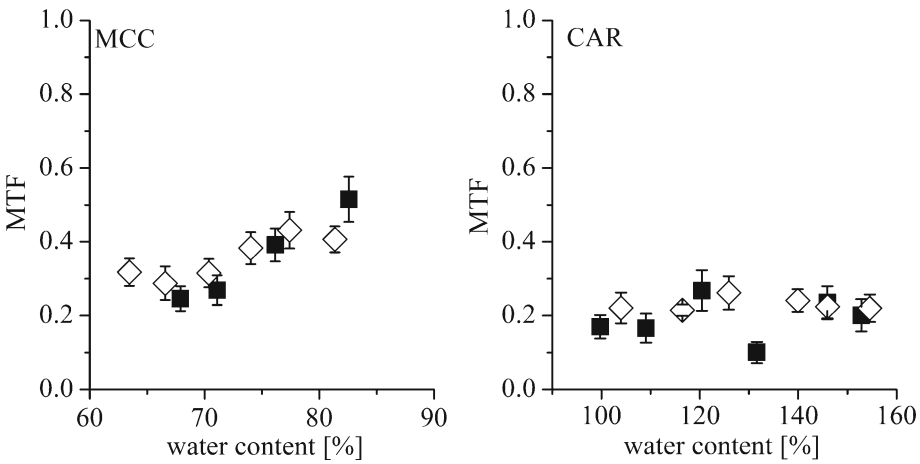

Fig. 4. MTF for microcrystalline cellulose and kappa-carrageenan, AV ± CI (*square* acetaminophen, *diamond* ibuprofen)

CONCLUSION

The mass transfer between the pellets was investigated in this study using different formulations and various water contents. The MTF was introduced as a novel parameter for quantification. All formulations had a significant MTF that ranged from 10 to 52 %. Due to this fact, it is indispensable to consider mass transfer as one major pelletisation mechanism. A correlation between the water content and the amount of mass transferred could be observed for microcrystalline cellulose, which was attributed to secondary agglomeration.

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