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Note

Preliminary assessment of carrageenan as excipient for extrusion/spheronisation

Martin Bornhöft[a], Markus Thommes[b], Peter Kleinebudde[b,*]

[a]Institute of Pharmaceutics and Biopharmaceutics, Martin-Luther-University, Halle-Wittenberg, Germany
[b]Institute of Pharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany

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Abstract

The current study pursues the suitability of different types of carrageenan as a novel extrusion aid. The aim was to find out a suitable substitution to the commonly used microcrystalline cellulose (MCC). The types of κ-carrageenan were found to be the most appropriate material and the required fraction to produce acceptable pellets in the formulation was determined. The investigation showed that 5% of κ-carageenan was necessary to produce pellets without MCC. Similar formulations produced with MCC or κ-carrageenan were compared with respect to size and shape of the pellets. κ-Carrageenan required higher water content for the formation of pellets, but the formulation was more robust as the optimal range of water content was much broader. Hence, κ-Carrageenan seems to be a suitable and promising extrusion aid. The study showed that the substitution of MCC by κ-carrageenan in formulations is possible and the produced pellets were of high quality.

Keywords: Carrageenan; Microcrystalline cellulose; Extrusion/spheronisation; Pellet; Image analysis

1. Introduction

The pelletisation by extrusion/spheronisation is an established technique in the pharmaceutical industry which results in spherical particles in a typical range between 0.5 and 2 mm diameters. These particles own a high density, a small particle size distribution, and a regular shape and they are usually used for the production of multiple unit dosage forms. The extrusion/spheronisation process requires specific formulation properties. The formulation has to be rigid enough to get a coherent extrudate as well as brittle enough to ensure that the extrudate breaks into cylinders during spheronisation and plastic enough to transform the cylinders into small spheres [1].

Microcrystalline cellulose (MCC) is a standard extrusion aid and it is usually added to many formulations to achieve the desired properties. Currently, there is no other material that behaves in the same manner like MCC and possesses the same properties. However, MCC formulations show some disadvantages like the non-disintegration of the pellets [2] which will result in a prolonged, matrix type dissolution. This undesired property cannot be overcome by addition of disintegration aids [3]. Thus, the production of fast release pellets by extrusion/spheronisation using MCC is difficult. In addition, some drugs may absorb to MCC which will also alter their dissolution time [4]. For some drugs, e.g. ranitidine decomposition in presence of MCC has been reported [5]. Therefore, the search is still ongoing to find a substitution material for MCC, which can overcome the negative properties of MCC formulation but at the same time still possess the positive properties of MCC as an extrusion aid. Some alternative extrusion aids are suggested in the literature like barium sulphate and glyceryl monostearate [5] or pectinic acid [6]. However, these alternative solutions have serious disadvantages since they don't reach the universality of MCC and/or they result in poor pellet quality. Therefore, these materials are not sufficient to substitute MCC. In this study the potential of

* Corresponding author. Institute of Pharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany. Tel.: +49-211-8114220; fax: +49-211-8114251.
E-mail address: kleinebudde@uni-duesseldorf.de (P. Kleinebudde).

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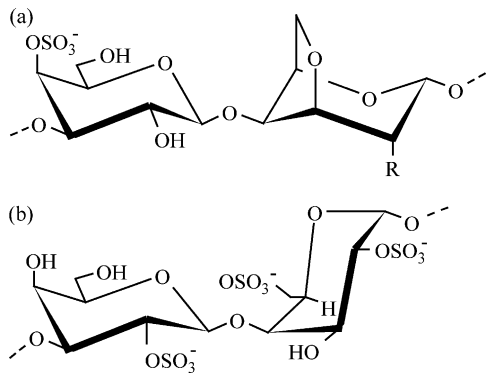

Fig. 1. (a) Dimeric repeating sequence of ι-carrageenan (R = OSO_3^-) and κ-carrageenan (R = OH): ,3)-β-D-galactose-4-sulfate (1,4) α-D-anhydro-galactose-(1, (b) Dimeric repeating sequence of λ-carrageenan: 3,)-β-D-Galactose-2-sulfate (1,4) α-D-galactose-2,6-disulfat-(1,.

carrageenan to substitute MCC in formulations for extrusion/spheronisation is evaluated. Garcia and Ghaly [7] reported about the use of carrageenan in extrusion/spheronisation. However, they used carrageenan as additive to MCC and not as a substitute for MCC.

Carrageenans are a group of acid polysaccharides which are produced from red seaweeds. Rhodophyceae like Chondrus crispus, Gigartina stellata and Euchema species are raw material for hot extraction process. After clarification, evaporation and precipitation a drying process follows [8]. Carrageenans are mainly potassium, sodium, calcium, magnesium and ammonium sulfate esters of galactose and 3,6-anhydrogalactose which are alternately linked α-1,3 and β-1,4 in the polymer (Fig. 1a and b) [9]. The commonly used types are ι-, κ- and λ-carrageenan which differ in sulfate content, in the position of the sulfate ester group in the repeating galactose units [9], and in the molecular weight. This results in different solubility and gelling properties. In the food industry carragenans are often used as a thickener, binder and stabiliser.

2. Materials and methods

2.1. Materials

Following materials were used as received: antipyrine (Caesar and Loretz, Hilden, Germany), calcium acetate (VEB Laborchemie Apolda, Germany), diprophylline (BASF, Ludwigshafen, Germany), α-lactosemonohydrate (Granulac® 200, Meggle, Wasserburg/Inn, Germany), ι-carrageenan (Gelcarin® GP-379 NF, FMC, Philadelphia, PA, USA) κ-carrageenan (Gelcarin® GP-812 NF and Gelcarin® GP 911 NF, FMC, Philadelphia, PA, USA), λ-carrageenan (Viscarin® GP-109 NF, FMC, Philadelphia, PA, USA), microcrystalline cellulose (MCC Sanaq 102 G, Phamatrans Sanaq, Basel, Switzerland) and potassium phosphate monobasic (Merck, Darmstadt, Germany).

3. Methods

3.1. Extrusion and spheronisation

After weighing the dry powder mixture was blended for 10 min in a laboratory scale blender (LM 20, Bohle, Ennigerloh, Germany) and afterwards transferred to the gravimetric powder feeder of the extruder. 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 screw speed of 100 rpm with distilled water as granulation liquid supplied by a membrane pump (Cerex EP-31, Bran and Luebbe, Norderstedt, Germany) with flow through metering device (Corimass MFC-081/K, Krohne, Duisburg, Germany). Usually, batches of 500 g wet extrudate were collected and spheronised for 5 min at 1000 rpm in a spheroniser (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) fitted with a cross-hatched rotor plate of 300 mm diameter. The drying step was carried out in a fluid bed apparatus (ST2, Aeromatic, Bubendorf, Switzerland) for 30 min with an inlet air temperature of 60 °C.

3.2. Image analysis

The pellet shape and size were determined by mean Feret diameter and aspect ratio of at least 1000 pellets of each sample using an image analysis program. Image analysis was conducted using a system consisting of a stereo microscope (SZX 9, Olympus, Hamburg, Germany), a ringlight with cold light source (Highlight 3001 with HL-VRL, Olympus, Hamburg, Germany), a digital camera (DIG1300C, Micromotion, Landshut, Germany), and a personal computer with data logging card and the software Image C (Imtronic, Berlin, Germany). For each batch, samples were obtained by using a rotary cone sample divider (Retschmühle PT, Retsch, Haan, Germany). Images of the pellets at a suitable magnification were translated into binary images. Contacting pellets were separated by a software algorithm. If the separation failed, pellets were deleted manually. For each pellet, 36 Feret diameters were determined and used to calculate the mean Feret diameter. The ratio of the maximum Feret diameter and the Feret diameter perpendicular to the maximum Feret diameter is used as the aspect ratio. Mean values for the sample were calculated using Excel 2000 (Microsoft, Unterschleissheim, Germany).

3.3. Loss on drying

To calculate the water content based on dry mass of the extrudates the loss on drying was examined at 105 °C for 24 h in a circulating air oven (Heraeus UT-6060, Kendo, Hanau, Germany) in triplicate.

4. Results and discussion

Three commercial types of different carrageenans were investigated in this study, that are ι-, κ-, and λ-carrageenan. They differ in solubility and swellability in cold water, so that different pelletising properties are expected like the brittle and elastic characteristics in spheronising. All used grades of carrageenan gave a coherent extrudate in extrusion (Table 1, formulations **1**–**4**). The κ-type, insoluble in cold water, depicted suitable plastic and brittle properties for the following spheronisation process. In contrast, the soluble ι- and λ-carrageenans resulted in extrudates, which could not be spheronised. Depending on the water content, these extrudates were either too brittle or too elastic to achieve round pellets in the spheronisation process. Preliminary trials showed that the addition of calcium, potassium and sodium ions to the granulation liquid reduced the solubility of the ι- and λ-carrageenan and, consequently, allowed successful spheronisation process. By the virtue of these findings, insoluble κ-carrageenan seems to be the most suitable type for extrusion/spheronisation and was therefore used in further investigations.

Gelcarin®GP-812 NF and Gelcarin®GP-911 NF are two commercial kinds of insoluble and swellable κ-carrageenan. The latter is partly soluble in cold water in contrast to the completely insoluble Gelcarin®GP-812 NF, which produces more solid gels with a higher level of synaeresis. Based on that, different properties in extrusion/spheronisation could be presumed and, thus, the two types were further processed in the related formulations 2 and 3 (Table 1). Both κ-carrageenan types showed similar behavior during extrusion/spheronisation. Further studies were performed using Gelcarin®GP-911 NF.

After evaluation of the different types of carrageenan, the κ-carrageenan content in a model formulation was varied in order to provide information about the suitability as extrusion aid in a broad range. Therefore, pellets with 5–98% of Gelcarin®GP-911 NF in powder mixture were produced (Table 2, formulation 5). It was possible to produce nearly round pellets in the whole ratio range of κ-carrageenan. However, a certain amount of fine particles was obtained during spheronisation. The quality of the pellets was surveyed by the shape using aspect ratio (Fig. 2). An aspect ratio lower or equal to 1.1 was considered good for pharmaceutical pellets [10]. This specification was not achieved by most of the formulations. All products were nearly spherical and the aspect ratio varied between 1.09 and 1.14. Even the addition of 5% κ-carrageenan resulted in pellets with an aspect ratio of 1.13. However, the extrusion/spheronisation process was not optimised at this stage. Changes in the water content or the spheronisation conditions might improve the result distinctly.

The optimisation of the spheronisation conditions was necessary because nearly all produced pellets had an aspect ratio higher than 1.1. The objective was to improve the shape and to reduce the fraction of fine particles by using formulation 6 containing only 10% of the extrusion aid κ-carrageenan (Table 2). First, the residence time in the spheroniser was varied from 1 to 5 min by using a constant friction plate speed of 1000 rpm. After 3 min of spheronisation the aspect ratio of the pellets was below 1.1 and remained there until the end of the spheronisation (Fig. 3). A residence time of 5 min was used for the further studies and appeared to be robust regarding the aspect ratio of the pellets.

In a second examination the influence of the friction plate speed on the pellet shape (Fig. 4a and b) was tested. For that

Table 1
Formulations of the powder mixture for screening tests for suitable carrageenan type

Substance	Formulation 1 (%)	Formulation 2 (%)	Formulation 3 (%)	Formulation 4 (%)
Diprophylline	20	20	20	20
Gelcarin® GP-379 NF	30			
Gelcarin® GP-812 NF		30		
Gelcarin® GP-911 NF			30	
Viscarin® GP-109 NF				30
α-Lactose monohydrat	50	50	50	50
loss on drying (%)	–	107	133	–

Table 2
Formulations of the powder mixture for optimising tests of Gelcarin® GP-911 NF

Substance	Formulation 5 (%)	Formulation 6 (%)	Formulation 7 (%)	Formulation 8 (%)
Antipyrine	2	2		
Gelcarin® GP-911 NF	5 to 98	10	10	
MCC 102 G				10
α-Lactosemono hydrat	93–0	88	90	90
loss on drying (%)	28–292	44	38– 61	27 to 40

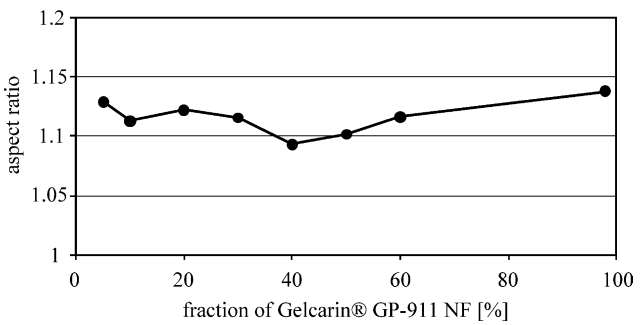

Fig. 2. Relationship between the pellet quality and κ-carrageenan content.

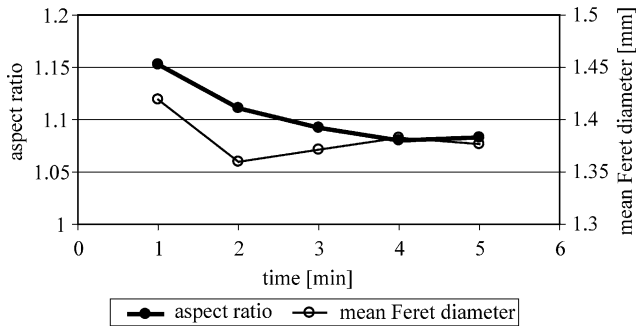

Fig. 3. Influence of the residence time in the spheroniser duration on aspect ratio and mean Feret diameter.

aim three speeds were chosen at constant residence time of 5 min. It was found that the friction plate speed of 500 rpm was too low to get spherical pellets and that the speed of 1000 rpm produced more fine fraction compared to 750 rpm. A friction plate speed of 750 rpm seemed to be the most suitable for spheronising of κ-carrageenan formulations.

It was observed that a batch size of 500 g in the spheroniser did not show the typical spheronisation movement. Therefore, the batch size was reduced from 500 to 300 g.

Further preliminary tests were performed to compare carrageenan and MCC in extrusion/spheronisation using binary mixtures with only 10% of the extrusion aid. Therefore, the two similar formulations 7 and 8 were processed (Table 2). The pellet quality was determined as a function of the water content of the extrudate (Fig. 5). Pellets were considered practically useful, if the aspect ratio and the mean Feret diameter were less than 1.1 and 1.5 mm, respectively. Thus, a practical useful range of water content

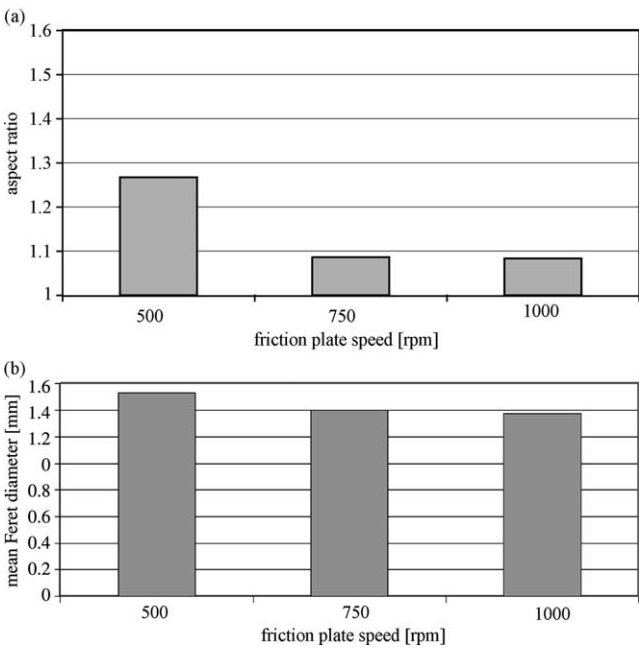

Fig. 4. (a) Influence of friction plate speed on pellet shape. (b) Influence of friction plate speed on pellet size.

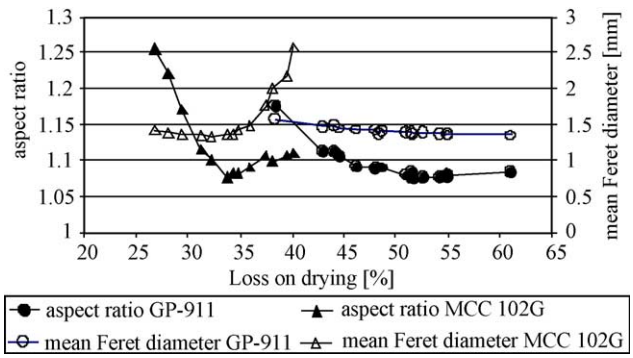

Fig. 5. Comparison of microcrystalline cellulose and κ-carrageenan.

was established for the two extrusion aids. The range of optimal water content (Fig. 5) was between 46% and more than 61% for κ-carrageenan (formulation 7), while it was 32–36% for MCC (formulation 8). Below this range the plasticity of the extrudates was insufficient and the pellets became not spherical during spheronisation. Above this range MCC was not able to bind the water in the formulation, which caused a secondary granulation in a spheronisation. This let the pellet size rose, an effect termed 'snow balling' in the literature. Using the optimal water content, κ-carrageenan und MCC pellets were produced with similar particle size and it was also possible to achieve spherical pellets. The properties of the resulted pellet using both materials were comparable but the optimal water content was different. κ-Carrageenan required a higher water content compared to MCC to produce spherical pellets. At the same time, the range of optimal water content is much broader. The new extrusion aid κ-carrageenan bound more water, which caused the disadvantages of an expensive drying process and a possible stability problem for sensitive drugs. On the other hand, the broad range of optimal water content improves the robustness of the pelletising process, because small fluctuations in powder and liquid feed rate will not affect the quality of the product. In conclusion, κ-carrageenan showed promising properties as an extrusion aid for wet extrusion/spheronisation.

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