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Properties of Pellets Manufactured by Wet Extrusion/Spheronization Process Using κ-Carrageenan: Effect of Process Parameters

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ABSTRACT

The aim of this study was to systematically evaluate the pelletization process parameters of κ-carrageenan-containing formulations. The study dealt with the effect of 4 process parameters—screw speed, number of die holes, friction plate speed, and spheronizer temperature—on the pellet properties of shape, size, size distribution, tensile strength, and drug release. These parameters were varied systematically in a 2^4 full factorial design. In addition, 4 drugs—phenacetin, chloramphenicol, dimenhydrinate, and lidocaine hydrochloride—were investigated under constant process conditions. The most spherical pellets were achieved in a high yield by using a large number of die holes and a high spheronizer speed. There was no relevant influence of the investigated process parameters on the size distribution, mechanical stability, and drug release. The poorly soluble drugs, phenacetin and chloramphenicol, resulted in pellets with adequate shape, size, and tensile strength and a fast drug release. The salts of dimenhydrinate and lidocaine affected pellet shape, mechanical stability, and the drug release properties using an aqueous solution of pH 3 as a granulation liquid. In the case of dimenhydrinate, this was attributed to the ionic interactions with κ-carrageenan, resulting in a stable matrix during dissolution that did not disintegrate. The effect of lidocaine is comparable to the effect of sodium ions, which suppress the gelling of carrageenan, resulting in pellets with fast disintegration and drug release characteristics. The pellet properties are affected by the process parameters and the active pharmaceutical ingredient used.

KEYWORDS: Pellets, carrageenan, extrusion, spheronization, process parameters, experimental design.

INTRODUCTION

Pellets are spherical beads that are between 0.5 and 2 mm in mean diameter and have a narrow size distribution. Their reproducible particle surface is ideal for coating. Therefore, pellets have gained considerable attention in the development of modified-release dosage forms. Further advantages of pellets are improvement of bioavailability, reduction of the risk of dose dumping, and decrease of local irritations in the gastrointestinal tract.[1]

κ-Carrageenan extracted from cell walls of red seaweeds is a pelletization aid for the wet extrusion/spheronization process. It is able to replace the commonly used microcrystalline cellulose in various formulations to achieve pellets of an adequate quality with a fast drug release.[2,3]

Pellet preparation by wet extrusion/spheronization is based on 3 different processes: extrusion, spheronization, and fluid bed drying. The final pellet properties are determined by many process parameters, such as the water content of the extrudate, the residence time of spheronization, and the temperature of fluid bed drying. Some of these parameters were evaluated in previous studies.[4,5]

Four process parameters that were not previously systematically evaluated for pellets based on κ-carrageenan were chosen for the 2^4 factorial design. Two extrusion parameters (screw speed and number of die holes) and 2 spheronization parameters (spheronizer speed and spheronizer temperature) were chosen. A second objective was to test formulations with high loads of different drugs to challenge the pelletization aid. Two sparingly soluble drugs and 2 drugs in a salt form were included in the study. The granulation liquid for the salts was adjusted below the pK_a of the salt.

MATERIALS

The following materials were used as received: calcium hydroxide (Acros, Geel, Belgium), κ-carrageenan (Gelcarin GP 911 NF, FMC, Philadelphia, PA), chloramphenicol (Northeast General Pharmaceutical Factory, Tiexi, China), dimenhydrinate (ion pair of diphenhydramine [+] and 8-chlorotheophyllinate [–], Recordati, Milan, Italy), formic acid (Riedel-de Haen, Seelze, Germany), lidocaine hydrochloride (Moehs Catalana, Barcelona, Spain), and phenacetin (Hubei Zenith Airbeck Pharmaceutical, Xiangfan, China).

METHODS

Experimental Design

The 4 pelletization parameters—screw speed, number of die holes, spheronizer speed, and spheronizer temperature—were

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Table 1. Overview of Factors and Levels

	Level		
	–1	0	+1
Screw speed	50 rpm	125 rpm	200 rpm
Number of die holes	3	13	23
Spheronizer speed	500 rpm	750 rpm	1000 rpm
Spheronizer temperature	15°C	30°C	45°C

evaluated in a full 2^4 factorial design. In addition, 3 experiments were performed at the center point. An overview of the factors and levels is given in Table 1. The factor levels were selected according to the limits of the equipment to ensure a reproducible manufacturing process. For example, the condensation of water in the spheronizer below 15°C prevented reproducible pellet movement. Temperatures above 45°C blocked the pellet discharge mechanism of the spheronizer mechanically. Only temperatures between these 2 limits were used in the design. A formulation containing 80% phenacetin as model drug and 20% κ-carrageenan as pelletization aid was used. Several pellet properties, such as shape, size, yield, mechanical stability, and drug release, were determined as responses.

Further experiments dealt with the other actives, chloramphenicol, dimenhydrinate, and lidocaine (Table 2). The formulations with the different drugs were manufactured under center point conditions according to the first part of this study.

Extrusion and Spheronization

The dry powders were weighed and blended for 10 minutes in a laboratory-scale blender (LM40, Bohle, Ennigerloh, Germany) and then 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. The extrusion took place at a constant powder feed rate of 33 g/min and a suitable liquid feed rate. Deionized water was used as the granulation liquid and was supplied by a membrane pump (Cerex EP-31, Bran and Luebbe, Norderstedt, Germany) with a flow-through metering device (Corimass MFC-081/K, Krohne, Duisburg, Germany). For the extrusion of dimenhydrinate and lidocaine hydrochloride, the pH of the water was adjusted to 3 with formic acid. Batches of 300 g wet extrudate were collected and spheronized for 5 minutes in a spheronizer (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) fitted with a cross-hatched rotor plate of 300 mm diameter. The drying step was performed in a fluid bed apparatus (GPCG 1.1, Glatt, Dresden, Germany) for 10 minutes with an inlet air temperature of 60°C.

Loss on Drying

For each batch, 3 samples of extrudates were taken during extrusion for the determination of the extrudate water content. The samples were dried at 70°C for 14 days in a vacuum oven (Heraeus VT 6060 M, Kendo, Hanau, Germany). The water content of the extrudates was calculated in % (wt/wt) based on dry mass.

Image Analysis

Each batch was sieved with sieves of 0.63 mm and 2.0 mm aperture. The fraction between 0.63 and 2.0 mm is denoted as yield. Samples of a suitable amount from the yield fraction were obtained by using a rotary cone sample divider (Retschmuele PT, Retsch, Haan, Germany).

Image analysis was conducted by 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), a digital camera (Leica CS 300 F, Cambridge, UK), and image-analyzing software (Qwin, Leica, Cambridge, UK). Images of at least 500 pellets of each sample at a suitable magnification (1 pixel ≅ 17.5 μm) were translated into binary images. Contacting pellets were separated by a software algorithm. If the automatic separation failed, pellets were deleted manually. For each pellet, 36 Feret diameters and the projected area were determined. The ratio of the maximum

Table 2. Formulation of Powder Mixture, Humidities, Yield, and Pellet Size (arithmetic mean ± standard deviation)

	Phenacetin	Chloramphenicol	Dimenhydrinate	Lidocaine
Phenacetin	80			
Chloramphenicol		80		
Dimenhydrinate			80	
Lidocaine				80
Gelcarin GP 911 NF	20	20	20	20
Loss on drying (%)	90.7 ± 0.26	85.5 ± 1.41	102.3 ± 4.81	47.7 ± 0.41
10% interval	62.6	69.8	30.2	42.0
Equivalent diameter (mm)	1.31 ± 0.15	1.31 ± 0.14	1.09 ± 0.25	1.23 ± 0.24

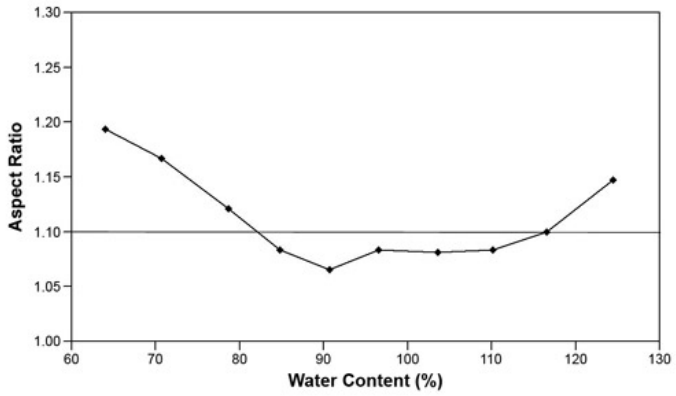

Figure 1. Effect of water content on pellet shape.

Feret diameter and the Feret diameter perpendicular to the maximum Feret diameter was used as the aspect ratio. The pellet size and shape were characterized by equivalent diameter and aspect ratio, respectively.

The dimensionless particle size was calculated from Equation 1:

$$d = \frac{d_{eq}}{d_{eq50}} \tag{1}$$

with dimensionless diameter (d), equivalent diameter (d_{eq}), and median of all equivalent diameters (d_{eq50}). The distribution of the particle size is characterized as a 10% interval by the fraction of the particles in the interval $0.9 < d < 1.1$.[2] Fine particles are defined as the fraction of particles with $d < 0.8$, and coarse particles as the fraction of particles with $d > 1.2$.

Tensile Strength

The mechanical characteristics of pellets were investigated using a texture analyzer (TA.XT2i, Stable Micro Systems, Godalming, UK) after equilibrating the pellets at 20°C and 60% relative humidity for at least 48 hours. The fracture force (F) of 50 pellets per batch at a loading rate of 0.1 mm/s was determined. To calculate the tensile strength (σ), the diameter (d) of each pellet in the crushing direction was considered (Equation 2)[6]:

$$\sigma = \frac{1.6 * F}{\pi * d^2} \tag{2}$$

Drug Release

A basket apparatus (100 rpm) was used for all dissolution tests. The tests were performed according to the monographs for chloramphenicol capsules and dimenhydrinate tablets in United States Pharmacopeia (USP) *28*. Lidocaine was tested in 0.1N hydrochloric acid. Phenacetin hydrolyses in acid or basic pH. Thus, water was chosen as the dissolution medium. Six samples of each pellet batch were tested in a randomized order. The drug concentration in the release medium was determined 3 times per minute for 60 minutes. The measurement was performed at the wavelength of maximal UV absorption (phenacetin 245 nm, chloramphenicol 278 nm, dimenhydrinate 278 nm, lidocaine 262 nm) in a photometer (Lambda 2, Perkin-Elmer, Überlingen, Germany). The mean dissolution time was calculated from the dissolution profile by Equation 3[7]:

$$MDT = \frac{\sum_{i=0}^{\infty}\left[(c_{i+1} - c_i)\left(\frac{t_i + t_{i+1}}{2}\right)\right]}{c_\infty} \tag{3}$$

where MDT is mean dissolution time.

Results and Discussion

Evaluation of Process Parameters

Preliminary Tests

Several process parameters that affect the pellet properties,[8-13] such as the water content of extrusion and the spheronizer duration, were kept constant. Sufficient levels for these parameters were evaluated in preliminary tests (Figures 1, 2). Good pharmaceutical pellets have an aspect ratio below 1.1.[14,15] Thus, the appropriate water content for obtaining pellets with an aspect ratio below 1.1 needed to be determined. For this purpose, experiments were performed under center point conditions (Figure 1). Water contents between 81% and 117% resulted in pellets with aspect ratios below the required value of 1.1. The most spherical pellets were achieved at a water content of 91%. For a robust manufacturing process, this water content should be used. However, for the current experimental design, a water content of only 81% was selected. At the optimal water content of 91%, further

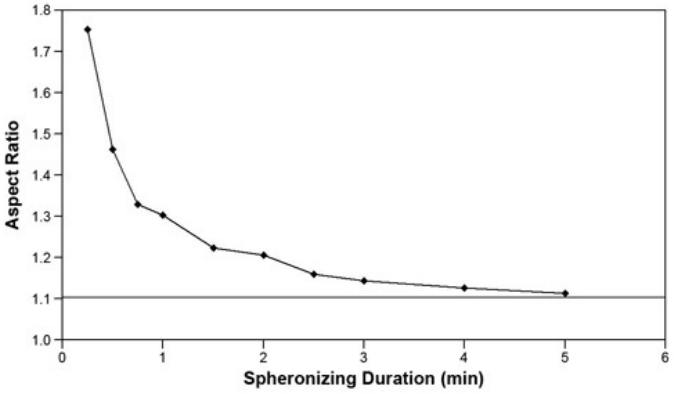

Figure 2. Effect of spheronizing duration on pellet shape.

Table 3. Results From the Experimental Design*

Experiment	Screw Speed (rpm)	Number of Die Holes	Spheronizer Speed (rpm)	Spheronizer Temperature (°C)	Aspect Ratio	Equivalent Diameter (mm)	10% Interval (%)	Coarse Fraction (%)	Fine Fraction (%)	Tensile Strength (MPa)	MDT (min)
N01	50	3	500	15	1.24	1.54	65.6	0.6	5.0	0.59	7.98
N02	200	3	500	15	1.13	1.51	67.8	1.2	2.6	0.58	7.90
N03	50	23	500	15	1.56	1.47	52.2	9.0	6.4	0.74	6.62
N04	200	23	500	15	1.52	1.47	49.8	7.6	9.0	0.85	6.12
N05	50	3	1000	15	1.07	1.39	57.0	0.4	14.8	0.63	7.66
N06	200	3	1000	15	1.06	1.32	63.6	1.4	8.2	0.62	7.03
N07	50	23	1000	15	1.07	1.22	55.6	4.6	8.4	0.48	6.35
N08	200	23	1000	15	1.08	1.26	63.8	1.4	7.0	0.65	7.60
N09	50	3	500	45	1.24	1.55	63.0	1.8	5.4	0.57	7.45
N10	200	3	500	45	1.09	1.48	65.2	1.4	6.8	0.54	8.05
N11	50	23	500	45	1.54	1.49	50.0	10.8	6.0	0.95	6.76
N12	200	23	500	45	1.52	1.50	46.2	8.8	9.8	0.94	6.48
N13	50	3	1000	45	1.07	1.25	40.2	10.0	19.6	0.56	6.94
N14	200	3	1000	45	1.08	1.24	28.8	9.6	31.8	0.64	6.99
N15	50	23	1000	45	1.06	1.26	54.8	1.6	13.2	0.64	6.75
N16	200	23	1000	45	1.07	1.27	65.2	1.2	5.4	0.66	6.78
N17	125	13	750	30	1.13	1.36	68.2	0.2	4.2	0.54	7.31
N18	125	13	750	30	1.08	1.34	62.0	1.2	8.6	0.58	7.35
N19	125	13	750	30	1.08	1.34	65.6	1.8	6.0	0.55	7.51

*MDT indicates mean dissolution time.

improvements of aspect ratio caused by the factor-level combinations of the experimental plan could not be detected. Thus, a water content of 81% was expected to be better able to discriminate among the effects of the evaluated factors than the optimal water content of 91%. The water content of 81% resulted in pellets with an aspect ratio of 1.1, but a suitable spheronizer residence time should be evaluated. In these experiments, a water content of 81% and center point conditions were used. Increasing the spheronizer residence time improved the pellet shape (Figure 2). Above 5 minutes there was no benefit for the pellet shape from a practical standpoint and the spheronization process was considered to be complete.

Power of Model

The first evaluation of the experimental results (Table 3) focused on the search for a sufficient model. For the first investigations, a model was developed that included the 4 factors and their 6 binary interactions. This model should be simplified by a backward regression. The insignificant ($P > .05$) factors and binary factor interactions were dropped out stepwise. This process was performed for each response regardless of the others. Two factors and 1 binary interaction were significant in the optimizations: number of die holes (NuHo), spheronizer speed (SpSp), and the binary interaction of number of die holes and spheronizer speed (NuHo*SpSp). A simple model using only the 3 terms was fitted (Equation 4):

$$y = b_0 + b_{NuHo}x_{NuHo} + b_{SpSp}x_{SpSp} + b_{NuHo*SpSp}x_{NuHo}x_{SpSp} \quad (4)$$

The power of this model was evaluated by the parameters given in Table 4. A model has no lack of fit when a sufficiently low model error is obtained compared with the replicate error (pure error). The level of significance for the

Table 4. Power of the Model*

	Aspect Ratio	Equivalent Diameter	10% Interval	Coarse Fraction	Fine Fraction	Tensile Strength	MDT
R^2	0.9178	0.8992	0.4359	0.5460	0.5184	0.7249	0.6760
Q^2	0.8857	0.8356	0.0910	0.2722	0.1952	0.5745	0.4618
P (lack of fit)	.146	.061	.107	.067	.150	.079	.074
Coefficient of variation (%)	2.29	0.79	4.77	75.8	35.3	4.17	1.42

*MDT indicates mean dissolution time.

lack of fit, determined by analysis of variance, should exceed $P = .05$. In addition, the coefficient of variation is given: the ratio of standard deviation and the arithmetic mean given in percent.

The power of the model was evaluated for each response (Table 4). It was adequate for aspect ratio, pellet size, and tensile strength because all 4 parameters of these responses were in a sufficient range. The 10% interval and the mean dissolution time were not sufficiently described by this model because the Q^2 values were below the required value of $Q^2 = 0.5$.[16]

The Q^2 value for the 10% interval was 0.09. This might have been caused by the fact that changes in both the coarse fraction and the fine fraction affect the 10% interval. Thus, the coarse fraction and the fine fraction were evaluated separately. Both single fractions were also poorly described by this model because the quality of prediction (Q^2) was too low, although results were better than they had been for the 10% interval. The high coefficients of variation of these responses were attributed to a low mean average for the coarse and fine fractions and were an artifact of the method.

The effect of the remaining factors, number of die holes and spheronizer speed, and their interaction on the responses are given in coefficient plots (Figure 3).

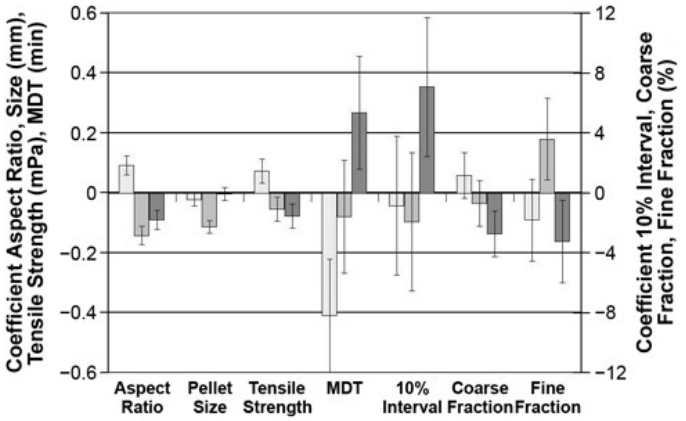

Figure 3. Pellet properties depending on number of die holes, spheronizer speed, and interaction between number of die holes and spheronizer speed (coefficient, confidence interval, $\alpha = 0.05$, n = 19). MDT indicates mean dissolution time.

Pellet Shape and Size

A spherical shape is the most characteristic property of pellets and is evaluated by the aspect ratio. Both factors of the model, number of die holes and spheronizer speed, and their interaction influence the pellet shape significantly (Figure 3).

Increasing the number of die holes will reduce the speed of the mass in the dies, and consequently the shear force during extrusion will decrease. High shear forces are able to degrade the κ-carrageenan structure.[17] In contrast, lower shear forces obtained by using a higher number of die holes will have less of an effect on the κ-carrageenan structure and result in a higher rigidity of the extrudates. A higher spheronizer speed transfers more energy to the pellet batch. This allows more breaking in the first phase and more subsequent plastic deformation.

The highest aspect ratio values were found for the combination of high number of die holes and low spheronization speed. The extrudates were too rigid to sufficiently break during the low energy input at the low spheronizer speed. Decreasing the number of holes and using a low spheronization speed resulted in pellets with a lower aspect ratio, because of the lower rigidity of the extrudates. At high spheronization speed, all values for the aspect ratio were low. The energy input was sufficient to spheronize the extrudate regardless of rigidity.

A high number of die holes and a high spheronizer speed resulted in pellets of a low aspect ratio. This effect was related to the lower plasticity of the extrudate caused by a high number of die holes. In addition, the higher spheronizer speed gave more energy to the pellet batch, which compensated for the lower plasticity of the extrudates. The effects of the number of die holes and the spheronizer speed on the pellet shape are summarized in a surface plot (Figure 4). Based on the results of aspect ratio tests, the combination of a high number of die holes and a low spheronization speed should be avoided.

The pellet size was mainly determined by the spheronizer speed. Increasing the spheronizer speed decreases the pellet size. In the first phase of the spheronization process, long extrudates break into short cylinders, which are then spheronized to form beads. The breaking of extrudates was probably affected by the spheronizer speed. A higher speed gave more energy to the extrudate and resulted in shorter cylinders and, consequently, in pellets of smaller size during spheronization.

Coarse Fraction, Fine Fraction, and 10% Interval

The pellet size distribution, characterized by the 10% interval, coarse fraction, and fine fraction, was poorly described by the model (Figure 3). High values for the 10% interval were achieved if both factors were either at their high or at their low levels (Table 3). This is indicated by the high value for the interaction.

A high number of die holes and a higher spheronizer speed resulted in a higher 10% interval, which meant a more narrow size distribution. This effect could be attributed to a lower plasticity of the extrudates, which was caused by a high number of die holes and more energy during spheronizing. The

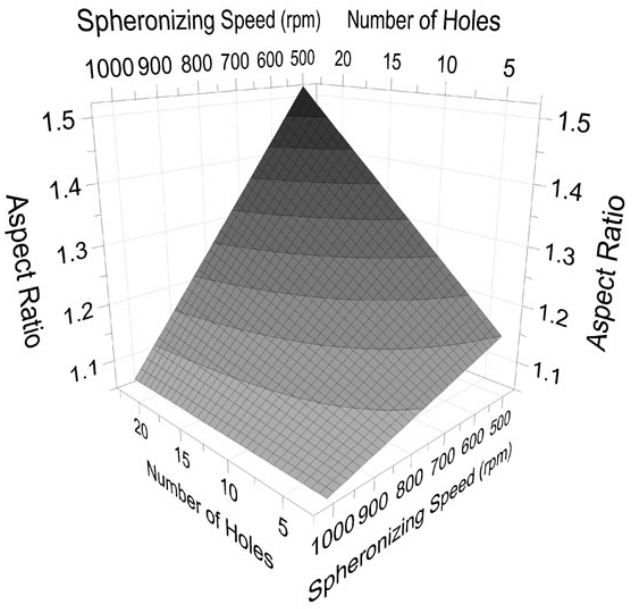

Figure 4. Effect of number of die holes and spheronizer speed on pellet shape (predicted surface plot).

combination of low plasticity and high spheronizer speed caused the extrudates to break into segments of equal size. Similarly, a low number of die holes and a low spheronization speed resulted in a high 10% interval. The lower rigidity of the extrudate required a lower energy input for breaking into particles of similar sizes.

A low spheronizer speed in combination with a high number of die holes resulted in the highest fraction of fines, whereas a high spheronization speed in combination with a low number of die holes led to the highest coarse fraction.

Based on the results of aspect ratio and 10% interval tests, a high number of holes together with a high spheronizer speed are recommended for the production of pellets with adequate aspect ratio and 10% interval values.

Tensile Strength and Mean Dissolution Time

A high mechanical stability of pellets is important for further process steps such as drying, coating, and tableting. The mechanical properties of the pellets were characterized by the tensile strength. The effect of the number of die holes, the spheronizer speed, and the interaction of both on the tensile strength was qualitatively similar to the effect of the aspect ratio. Since the evaluation of the tensile strength is based on a spherical pellet shape (Equation 2), calculation of the tensile strength of nonspherical pellets is not appropriate. Therefore, the 4-pellet batches with an aspect ratio above 1.5 were excluded from the calculation. For that reason, the number of die holes, the spheronizer speed, and their interaction became insignificant ($P > .05$). Thus, the tensile strength was not determined by the investigated process parameter of extrusion and spheronization. The effects shown in Figure 3 were artifacts and could be attributed to the high aspect ratio from 4 experiments within the design of experiments (DOE).

Since the drug release from the pellets is a crucial property, the effect of the process parameters on the drug release was evaluated by mean dissolution time. The differences in mean dissolution time were quite low (6.12-8.05 minutes) and irrelevant from a practical standpoint, so a detailed investigation was not performed.

Evaluation of Different Actives

In the first part of this study, the formulation was constant and the production parameters during extrusion/spheronization were varied. In the second part, different model drugs using the same process parameters were tested, to evaluate the portability of the results from the first part to further actives. Three additional model drugs (chloramphenicol, dimenhydrinate, and lidocaine hydrochloride) were chosen according to their chemical properties, such as high chemical stability and sufficient UV absorption. The drug concentrations used in pellets were for research purposes only and are pharmacologically or pharmaceutically irrelevant. Phenacetin and chloramphenicol were chosen because of their low solubility, 0.8 g/L and 2.5 g/L, respectively,[18] whereas dimenhydrinate and lidocaine hydrochloride were chosen because of their salt form. The main advantage of κ-carrageenan compared with the standard pelletization aid microcrystalline cellulose (MCC) is the fast pellet disintegration, which is an important property for low-solubility drugs like phenacetin and chloramphenicol.[3] However, because of the presence of acid sulfate ester groups in κ-carrageenan, an interaction of the κ-carrageenan and an alkaline drug was expected. Dimenhydrinate and lidocaine were chosen because of their pK_a values of 9.1 and 7.8[19] and pelletized with an aqueous solution adjusted to pH 3 with formic acid as a granulation liquid. The drugs are dissociated, and an interaction with κ-carrageenan is possible. All experiments were performed under center point conditions of the DOE from the upper part.

Water Content and 10% Interval

The water content that resulted in pellets of a low aspect ratio was evaluated by varying the liquid feed rate (Table 2). The sparingly soluble drugs, phenacetin and chloramphenicol, required water contents similar to those required by other insoluble drugs in similar formulations.[3] The resulting pellets offered a similar and high 10% interval. The salts dimenhydrinate and lidocaine had required water contents different from those of the low-solubility phenacetin and chloramphenicol. The required water content was higher for dimenhydrinate and lower for lidocaine hydrochloride, respectively.

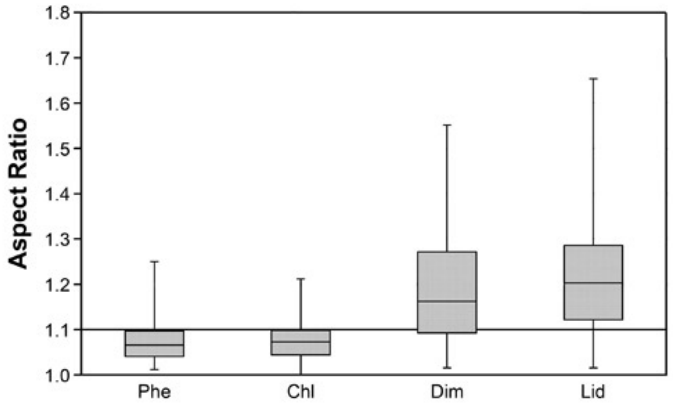

Figure 5. Pellet shape of different formulations (x_1, x_{10}, x_{50}, x_{90}, x_{99}, n > 500). Phe indicates phenacetin; Chl, chloramphenicol; Dim, dimenhydrinate; Lid, lidocaine.

Different interactions of the drugs and the carrageenan were assumed. The 10% interval of the formulations including the 2 drugs was clearly low.

Pellet Shape and Size Distribution

The shape of phenacetin and chloramphenicol pellets described by the aspect ratio was sufficient, as the median of the distribution was below the required value of 1.1 (Figure 5).[14] The size distributions of both formulations were similar, which indicates a similar pelletization mechanism.[20] The size distributions of pellets with dimenhydrinate and lidocaine were much broader than the size distribution of pellets with the low-solubility drugs (Figure 6). Different pelletizing mechanisms were assumed to be caused by an interaction of drug with κ-carrageenan. The pellet shape of lidocaine was insufficient; the median of the aspect ratio was above 1.2. Dimenhydrinate pellets had a sufficient shape, but they were not regarded as good.[14]

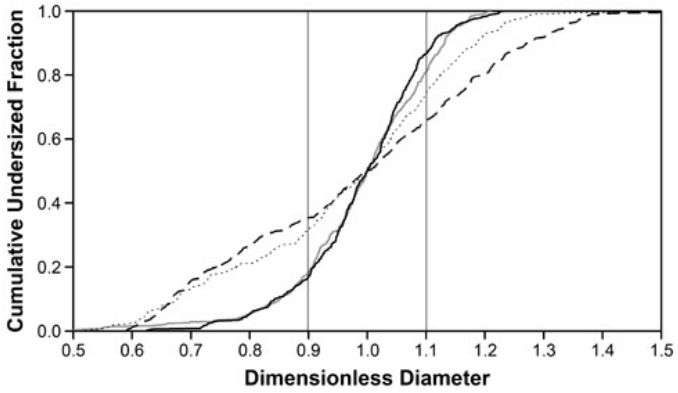

Figure 6. Pellet size distribution of the formulations: phenacetin, chloramphenicol, dimenhydrinate, lidocaine (n = 500).

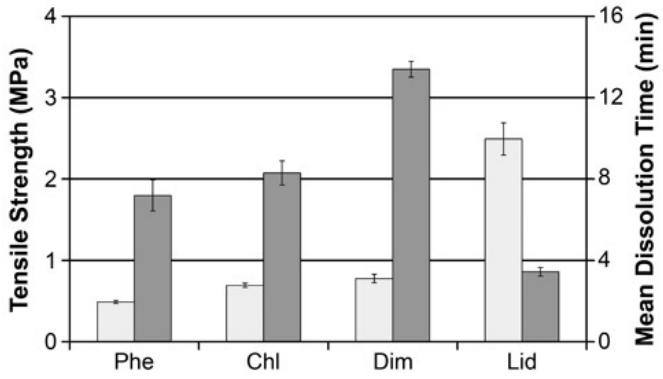

Figure 7. Mechanical stability and drug release of the different formulations: tensile strength (arithmetic mean, confidence interval, $\alpha = 0.05$, n = 50), mean dissolution time (arithmetic mean, confidence interval, $\alpha = 0.05$, n = 6). Phe indicates phenacetin; Chl, chloramphenicol; Dim, dimenhydrinate; Lid, lidocaine.

Mechanical Stability and Drug Release

The tensile strength and the drug release of the phenacetin and chloramphenicol were comparable to those from earlier studies[3] (Figure 7). A tensile strength of 0.5 to 1.0 MPa is lower than that of MCC pellets, but there was no mechanical instability during fluid bed drying and handling.

Although the drug release from dimenhydrinate pellets reached a plateau within 1 hour, the pellets did not disintegrate in the dissolution medium even after 24 hours (Figure 8a, 8b). In addition, a drug recovery of less than 90% in the dissolution medium was observed. Hence, an ionic interaction between diphenhydramine (the cationic part of the drug) and κ-carrageenan was assumed.

After completion of the dissolution test, the dimenhydrinate pellets were transferred into water and dispersed by ultrasonic sound. After filtration, a high amount of diphenhydramine was determined to be in the water by UV spectroscopy. However, chlortheophylline was almost not detectable. This

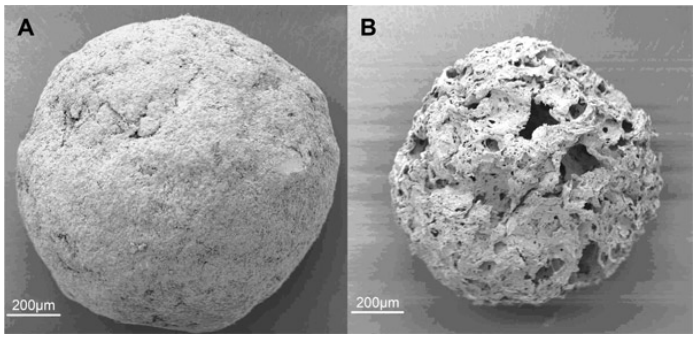

Figure 8. Scanning electron microscopy image of dimenhydrinate (a) before dissolution and (b) 24 hours after dissolution.

supports the hypothesis of an ionic interaction of diphenhydramine with κ-carrageenan.

This interaction was caused by using aqueous formic acid (pH 3) as the granulation liquid. Using aqueous calcium hydroxide solution (pH 12) in the dimenhydrinate formulation resulted in pellets of a good median aspect ratio (1.08) that were able to disintegrate. The changing of the dimenhydrinate pellet properties using aqueous calcium hydroxide solution could be attributed to a lower dissociation of the drug at higher pH and the gel-amplifying properties of calcium ions.[21]

The behavior of the lidocaine hydrochloride extrusion/spheronization process was completely different from that of the low-solubility drugs, phenacetin and chloramphenicol, and from that of dimenhydrinate. Lidocaine pellets disintegrated during the dissolution test very quickly and had the lowest mean dissolution time of all the formulations. The low amounts of water during the pelletization resulted in a high tensile strength.[22] The behavior of lidocaine hydrochloride in extrusion/spheronization is comparable to that of sodium salts of drugs like sodium benzoate. This sodium salt also requires a low amount of water (42%) and results in pellets with a high aspect ratio (1.3). Sodium ions hinder the κ-carrageenan gelling,[23] and sticky extrudates are achieved using low water content. Such gelling suppression probably causes the pelletization behavior of lidocaine hydrochloride.

Conclusion

Two of the 4 investigated process parameters affected the pellet properties. The most spherical pellets were achieved in a high yield by using a high number of die holes and a high spheronizer speed. There was no relevant influence of the investigated process parameters on the size distribution, mechanical stability, and drug release characteristics. Using different drugs affected the pellet properties as well.

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