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Research paper

Production of chitosan pellets by extrusion/spheronization

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Abstract

Chitosan pellets were successfully prepared using the extrusion/spheronization technology. Microcrystalline cellulose was used as additive in concentrations from 70 to 0%. The powder mixtures were extruded using water and diluted acetic acid solution in different powder to liquid ratios. The effects on bead formation using water and different acetic acid concentrations and solution quantities were analysed. Also, the morphological and mechanical characteristics of the obtained beads were investigated. With demineralized water as granulation fluid, pellets with a maximum of 50% (m/m) of chitosan could be produced. The mass fraction of chitosan within the pellets could be increased to 100% by using diluted acetic acid for the granulation step.

Keywords: Pellet; Extrusion/spheronization; Chitosan; Microcrystalline cellulose; Porosity

1. Introduction

Chitosan is obtained by *N*-deacetylation from chitin, the second most common natural polymer. *N*-deacetylation of chitin leads to a cationic polymer, which shows pH-dependent solubility in water. Whereas chitosan is soluble in acidic media it shows no solubility in neutral and alkaline aqueous solutions. This is in contrast to a lot of other high molecular weight polymers showing neutral or anionic character, which makes them soluble in neutral and alkaline aqueous solutions. Chitosan is of pharmaceutical interest because of its biological compatibility, bio-degradation and non-toxic properties [1]. Chitosan is also said to have wound-healing effects as well as anti-acidic, anti-ulcer and cholesterol-lowering properties. Because of its favourable properties and effects chitosan has so far been used for numerous delivery systems. For oral application, several scientific papers deal with the production of tablets, microparticles and beads [2–5].

The focus of the present study was to produce pellets as a multi-particulate delivery system, because of its advantage over monolithic dosage forms. Particles less than 2–3 mm rapidly pass the pylorus regardless of the filling level of the stomach as well as on size and density of chyme [6]. Also, gastrointestinal irritations are limited by spreading in the intestine. A burst effect has so far not been noticed with multi-particulate systems. Furthermore, incompatible drugs processed separately and mixed later, or pellets with different release mechanisms can be mixed to give a new modified release profile. So far, microcrystalline cellulose (MCC) has been used as a universal filler and binder for the extrusion/spheronization process. However, alternative materials are being investigated for the purpose to substitute MCC. Chitosan as an alternative filler/binder offers the following advantages: It is as well-analysed as MCC and it is a biodegradable compound from a natural source that has been established in the pharmaceutical and cosmetic industry. Furthermore, chitosan has the potential to be degraded by the colon microflora and could therefore be used for a colon-targeted delivery of the drugs incorporated in enteric-coated pellets. Finally, it is assumed that the drug release from chitosan pellets differs from that of MCC pellets and, hence, offers new approaches for drug delivery.

For the preparation of chitosan pellets several techniques have been used up to now. Chitosan beads were produced by dissolving chitosan in an acidic medium and adding a salt-containing solution to precipitate chitosan pellets [7]. Another method is described by Hoffmann et al. [8], who dropped a solution or dispersion of chitosan into a cooled

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non-solvent, obtaining cryo-pellets. Another approach to produce heterogeneous pellets is to coat cores with a chitosan solution thus obtaining a release-controlling polymer film [9]. Spheres containing small portions of chitosan were also made by extrusion/spheronization. Tapia et al. [10] dissolved chitosan in diluted acetic acid and added it as granulation liquid to the powder mixture. The mass was pressed through a ram extruder and afterwards spheronized to pellets. The chitosan fraction in the resulting pellets was as low as 2–3 (m/m)%. Goskonda et al. [11] described the production of chitosan pellets using the extrusion/spheronization with colloidal MCC which is a spray-dried mixture of 89% microcrystalline cellulose and 11% carboxymethylcellulose-sodium. The amount of chitosan in the pellets did not exceed 40% of the total solid content. They also noticed that the production of pellets with pure MCC was not possible with the extrusion/spheronization technique. Chatchawalsaisin et al. [12] produced pellets with the same technique by using a ram extruder. The maximum content of chitosan in the formulations was 16%. Santos et al. [13] characterized chitosan pellets with a maximum content of 16% chitosan, 50% MCC and different types of filler using a screen extruder for production.

The aim of this study was to produce chitosan pellets with little or no further excipients using the extrusion/spheronization technology. The physicochemical properties of the pellets in relation to various process parameters were studied.

2. Materials and methods

2.1. Materials

The following materials were used as matrix forming materials: chitosan (Chitoclear FG 95, Primex, Norway) and microcrystalline cellulose (Avicel PH 101, FMC Corporation, USA). Acetic acid (Merck, Germany) was used as granulation fluid for the extrusion step. All reagents and solvents used were of analytical grade. Water was always used in demineralized quality.

2.2. Methods

2.2.1. Preparation of the pellets

Chitosan/MCC powder blends with different amounts of chitosan (30, 50, 70 and 100%) were studied initially. The powders were blended in a Turbula T 10 (W.A. Bachofen AG, Switzerland) for 30 min. The blend was fed by means of a screw feeder to the extruder with a rate of 15 g/min. The mixtures were extruded with a power consumption controlled twin screw extruder (ZE 25, Berstorff, Hannover, Germany) at fixed power consumption levels of 200, 180 and 150 W, respectively. A detailed description of the power consumption controlled extruder is given by Lindner et al. [14]. Demineralized water as well as 0.1 and 0.5 N acetic acid were used as granulation liquid for the extrusion process.

Four hundred grams of extrudate per batch were collected and spheronized in a Nica spheronizer (Type S-320, Nica, Moelndal, Sweden) with cross-hatched plate at 800 rpm for 5 min. The products were dried in a fluid-bed dryer, type Glatt TR 2 (Glatt GmbH, Binzen, Germany) at 65 °C for 30 min.

2.2.2. Analytical methods

2.2.2.1. Moisture content. During extrusion three samples of about 8–10 g were taken and dried at 75 °C over 36 h in a hot air oven (Heraeus T6, Kendro, Hanau, Germany). The moisture content (MC) (%) of the extrudate was calculated according to the Eq. (1), where m_d is the dried mass and m_w is the wet mass:

$$\mathrm{MC}\ (\%) = \frac{m_w - m_d}{m_d} \times 100 \quad (1)$$

2.2.2.2. Image analysis. The fine content was removed by sieving with a 500-μm sieve. The size and shape of pellets > 500 μm were determined individually by an image analysis system (Leco 2001, Leco, Germany). The average size is calculated as the mean of eight measured Feret diameters of one single pellet. The aspect ratio is defined as the ratio of length to width of the pellets. A detailed description of the test conditions used for pellet analysis is given by Lindner et al. [15].

2.2.2.3. SEM pictures. Additionally, beads were examined by scanning electron microscopy (SEM) (Phillips XL20, Eindhoven, The Netherlands) to determine their size, shape and surface characteristics.

2.2.2.4. Porosity. The porosity of the pellets was calculated using Eq. (2), where ε is the porosity, ρ_e is the effective density and ρ_a is the apparent density.

$$\varepsilon = 100 \times \left(1 - \frac{\rho_e}{\rho_a}\right) \quad (2)$$

The apparent density (ρ_a) was determined using a helium pycnometer (AccuPyc 1330, Micromeretics, USA). The effective density (ρ_e) was determined using mercury intrusion porosimetry (Pascal 140, Fisons, Italy). Measurements of the apparent density were carried out in duplicate.

2.2.2.5. Crushing strength. To investigate the crushing strength, 50 pellets in a range of 900–1100 μm of each batch were crushed with a texture analyser TAXT2 (Stable Micro Systems, UK). The punch was moved with a speed of 1 mm/s down onto the pellet. After contact the strain was 50% of the height while measuring the force. The arithmetic mean of the force was used as the crushing strength in the study.

2.2.2.6. Friability. The friability of the pellets was determined by using a friability tester described by Schultz et al. [16]. For the test the particle fraction < 710 μm of each batch was removed by sieving. Per batch, 8.000 g (m_1) was whirled in a stream of air with 450 l/min for 16 min. Abrasion was removed with the air. The pellets were weighed after the test (m_2) and the abrasion (F) calculated from Eq. (3):

$$F = \frac{m_1 - m_2}{m_1} \times 100\% \quad (3)$$

3. Results and discussion

3.1. Preparation of chitosan pellets

As shown in Table 1 an extrusion of chitosan and MCC in a maximum ratio of 1 to 1 was possible using demineralized water. With all chosen power levels a stable process was achieved, with exception of the 50% mixture at a power level of 150 W where an unstable process resulted as indicated by the high standard deviation of the average power. Replacing the water by a 0.1 N acetic acid solution enabled the production of chitosan pellets with a chitosan content of up to 70%. However, at 200 W a blocking of the die was observed due to a lack of extrusion liquid. For the extrusion of pure chitosan it was necessary to raise the acidic power to a 0.2 N acetic acid solution. The process could not be carried out using the chosen levels of 200 and 180 W because of the increasing need of liquid to extrude the powder. An extrusion with 0.5 N acetic acid solutions was not possible. As a result of this high acid concentration the extrudate stuck together and could not be spheronized.

Table 1
Pellet compositions, granulation liquid and chosen power levels resulting in a stable process

Chitosan/MCC ratio	Extrusion liquid	Power level	
		Average	SD
30:70	Water	201.8	5.5
30:70	Water	184.0	4.4
30:70	Water	150.2	4.3
50:50	Water	201.7	3.8
50:50	Water	185.9	3.6
50:50	Water	148.6	17.4
30:70	0.1 N acetic acid	202.4	4.8
30:70	0.1 N acetic acid	182.8	6.6
30:70	0.1 N acetic acid	149.4	5.5
50:50	0.1 N acetic acid	209.1	4.7
50:50	0.1 N acetic acid	180.1	5.2
50:50	0.1 N acetic acid	149.3	8.9
70:30	0.1 N acetic acid	183.9	6.8
70:30	0.1 N acetic acid	151.3	8.8
70:30	0.1 N acetic acid	129.4	5.5
100:0	0.2 N acetic acid	148.3	7.5

In Fig. 1 the moisture content depending on the chitosan/MCC ratio, power level and chosen solution is summarized. With increasing chitosan concentration a higher amount of liquid is necessary to extrude at the chosen power level, e.g. at 180 W the acetic acid quantity in the extrudate increases from 170 to 210% when the concentration of chitosan is increased from 30 to 70%. During the spheronization process the water-extruded batches at 150 W led to an uncontrolled agglomeration of the mass. Similarly, the extrudates with 70% chitosan extruded with 0.1 acetic acid solution at 130 W stuck together and formed large agglomerates. However, it was possible to produce pellets which contained chitosan with microcrystalline cellulose. This is in contrast to what is described previously in the literature [11]. Pellets with a maximum content of 50% chitosan could be produced with demineralized. water. In order to obtain a stable extrusion process, at least some plasticity of the wet mass in the extruder is needed. While processing MCC gives the wet mass good plastic formability, the chitosan remains undissolved. In the case of a surplus of MCC the chitosan particles are dispersed within the MCC matrix and the mass can be pressed through the die of the extruder. If the chitosan fraction is greater than 50% it determines the behaviour of the wet mass in the extruder, leading to insufficient plastic formability and blocking of the die.

With aqueous acetic acid solution it was possible to produce pure chitosan pellets. Initially, it was expected that chitosan would be dissolved in the acid medium resulting in a gel-like behaviour. However, depending on the acetic acid concentration the chitosan particles are only partially dissolved giving sufficient plastic formability to the wet mass, so that it can be extruded. It is assumed that the particles become flexible due to the partial dissolution of chitosan at the surface of the particles. Also, the cohesiveness is enhanced. A low amount of fluid and low acid concentration leads to a less adhesive extrudate, so that after breaking and the following spheronization process smaller pellets are formed. A further reduction of granulation liquid leads to a block of the extruder die. This is the reason for the unprocessability of the batches containing 70% chitosan at 200 W with 0.1 N acetic acid. For extruding higher amounts of chitosan or pure chitosan at a level of 200 and 180 W the use of a larger quantity of extrusion liquid and higher acid concentration is necessary. An excess of liquid and a high acid concentration results in more chitosan being dissolved at the surface and leads to higher elastic and sticky extrudates. Thus, the tendency of breaking the extrudates in the spheronizer is limited and also the agglomeration of particles gets out of control.

3.2. Morphological characteristics

The mean Feret diameter of the pellets is expected to be 0.9–1.1 mm due to the diameter of the die. This Feret

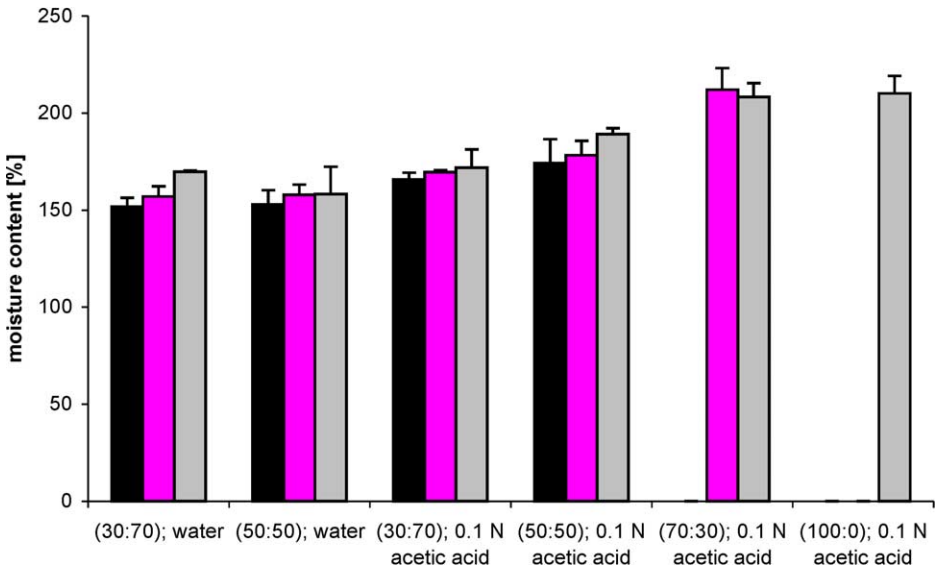

Fig. 1. The moisture content of the different chitosan/MCC pellets extruded at various power levels with water and acetic acid. Black bars, 200 W; dark grey bars, 180 W; light grey bars, 150 W.

diameter was obtained for all batches containing 30% chitosan (Fig. 2). Extrusion at 200 W power with water and a chitosan fraction of 50% produced beads with a mean diameter of 0.7 mm as a result of the loss of cohesiveness of the particles caused by the small amount of liquid. A similar trend is noticed with pellets extruded with acetic acid. The particle size of the pellet batches containing 50% chitosan increases from 0.87 to 1.0 mm with increasing liquid quantity. It is also shown that with an increasing amount of chitosan the quantity of liquid must be increased. At the same time, the particle size decreases with increasing chitosan quantity when the powder is extruded with the same acid concentration and with constant power (180 W).

In Fig. 3, SEM-pictures of typical pellets made under the described conditions are shown. Independent from the used extrusion liquid and extrusion force, all pellets show nearly the same surface texture. The appearance of the pellets is determined by the chitosan particles, which have a flake-like character. This supports the theory that the chitosan particles are partly dissolved in the solution and stuck to pellets. It is also obvious that an unfavourable solution

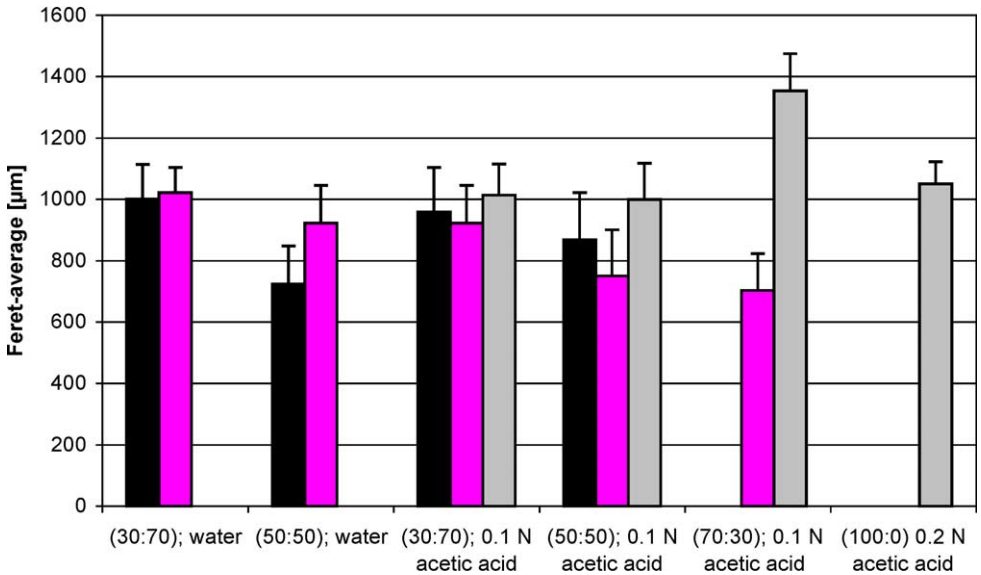

Fig. 2. The Feret diameter of the different chitosan/MCC pellets produced at various power levels with water and acetic acid. Black bars, 200 W; dark grey bars, 180 W; light grey bars, 150 W.

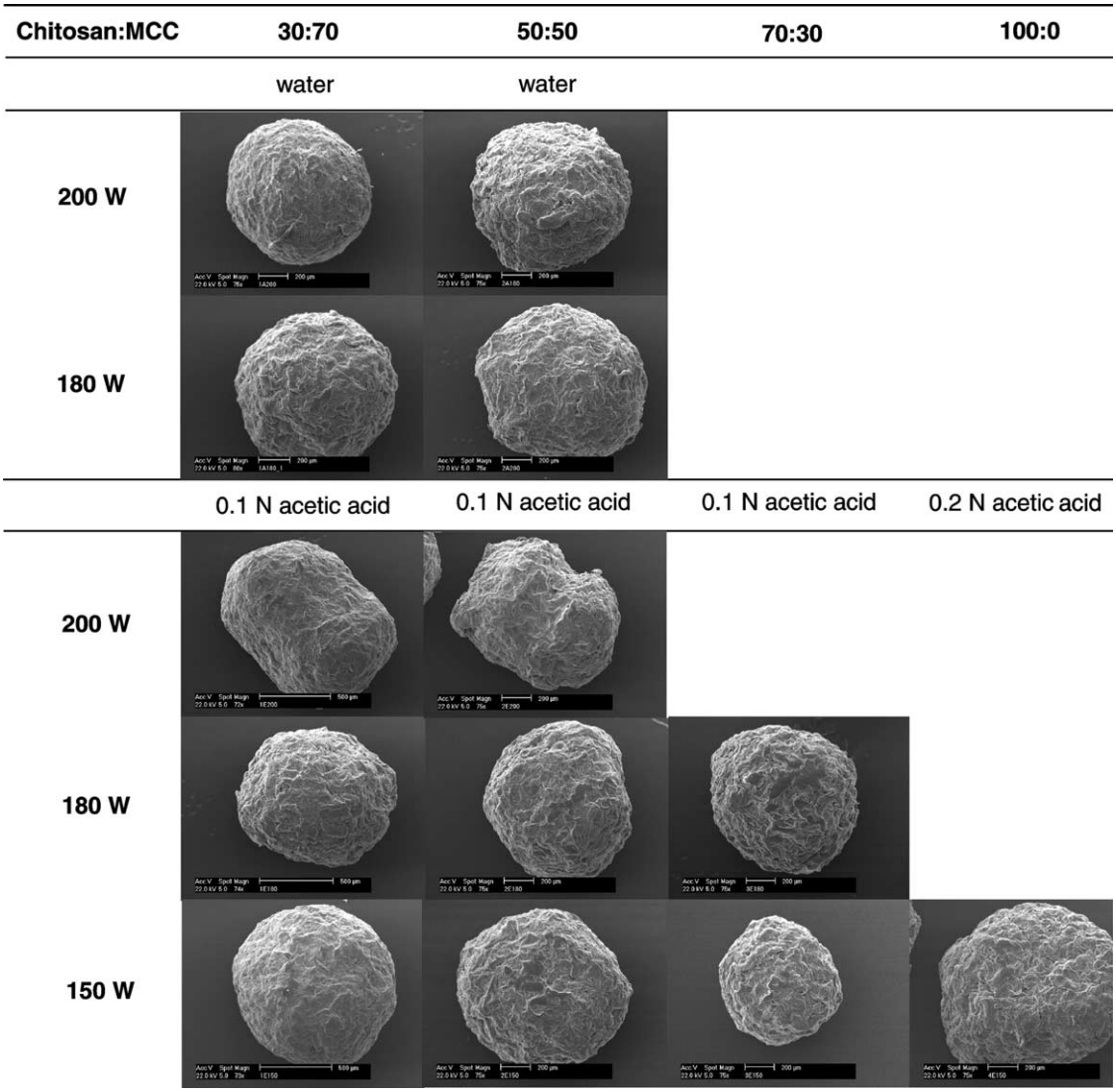

Fig. 3. Scanning electron microscopy images made from the obtained chitosan pellets.

quantity and acid concentration leads to pellets with a more irregular form; e.g. pellets containing 30 or 50% chitosan produced with 0.1 N acetic acid at 200 W have a rod-like shape.

Accordingly, the quantity of liquid also has an effect on the roundness of the spheres. The aspect ratio describes the length to width ratio. An ideal round sphere would give a value of 1.0. The use of a sub-optimal quantity of liquid leads to an increase of the aspect ratio. All batches extruded at 200 W show a higher aspect ratio than the batches extruded at lower power levels because of the lacking plasticity of the mass (Fig. 4). In consequence, the mass is squeezed at higher pressure which leads to a higher compaction. The extrudate breaks on the hatched plate in the spheronizer into non-uniform particles and is not completely rounded.

3.3. Mechanical properties

3.3.1. Friability

The mechanical properties of pellets are important for processing. In the case of a subsequent coating process it is desirable to have pellets with low friability. The friability of chitosan-MCC pellets increases with an increase of chitosan content when water is used as granulation liquid. As an example of this, abrasion rises from 0.6 to 2.9% when the chitosan quantity is increased from 30 to 50% and extrusion is performed at a power level of 200% (Fig. 5). An enhanced abrasion (from 0.7 to 1.3%) can also be observed with increasing chitosan content and extrusion at a power level of 180 W and 0.1 N acetic acid as granulation liquid. The abrasion decreases when the mass is extruded at lower power levels. It can be concluded that a low abrasion is achieved

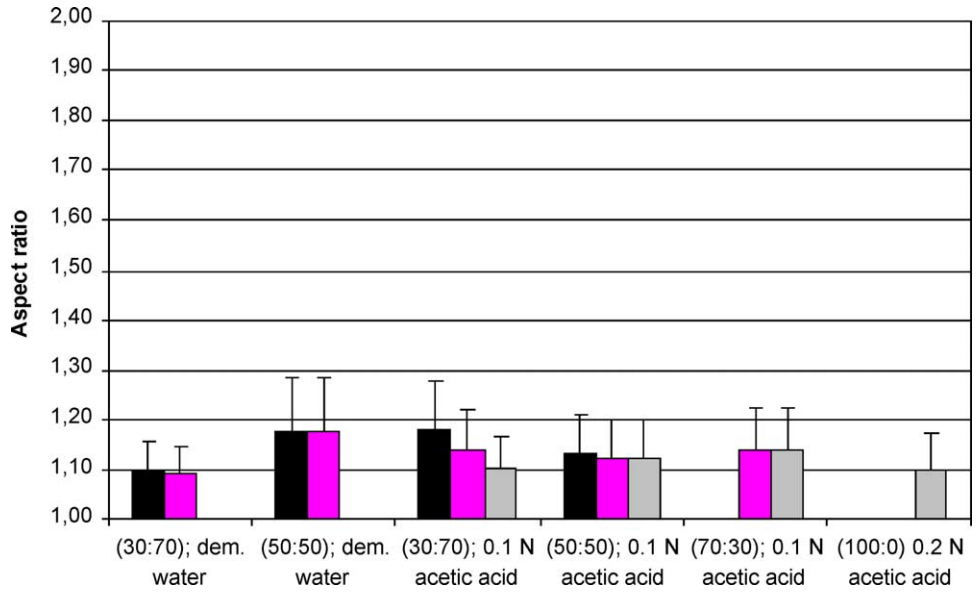

Fig. 4. The aspect ratio of the different chitosan/MCC pellets extruded at various power levels with water and acetic acid. Black bars, 200 W; dark grey bars, 180 W; light grey bars, 150 W.

when the acid concentration and the quantity of granulation liquid is adjusted to the higher amount of chitosan.

3.3.2. Crushing strength

The same mechanisms that influence the size and shape of the extruded pellets also affect the strength of the pellets; for instance, an increase of the chitosan content in pellets extruded with water tends to result in a decrease of crushing strength. But also, using 0.1 N acetic acid reduces the crushing strength with increasing chitosan content, probably due to the lower quantity of chitosan that is dissolved by the acid. Thus less chitosan molecules can form cohesive bonds, resulting in less adhesion between chitosan particles. As a result, a lower force is needed to crush the pellets. In this case the crushing strength decreases from 20.8 to 17.6 N at a power level of 150 W when the chitosan amount is increased from 30 to 70% (Fig. 6). As before, the quantity of granulation liquid has an effect. There is a tendency of a decreasing tensile strength with decreasing liquid quantity in proportion to the powder. To keep the crushing strength at a constant level it is necessary to adjust the acid concentration and the liquid quantity to the higher chitosan content.

3.3.3. Porosity

Independent from the condition of granulation liquid, it is observed that the porosity increases with an increase of

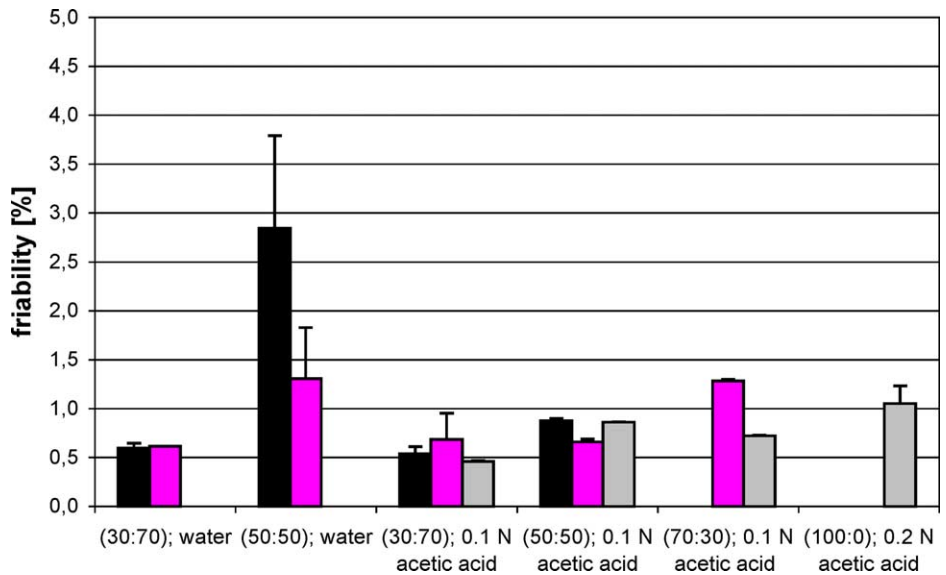

Fig. 5. The friability of the different chitosan MCC pellets extruding at various power levels with water and acetic acid. Black bars, 200 W; dark grey bars, 180 W; light grey bars, 150 W.

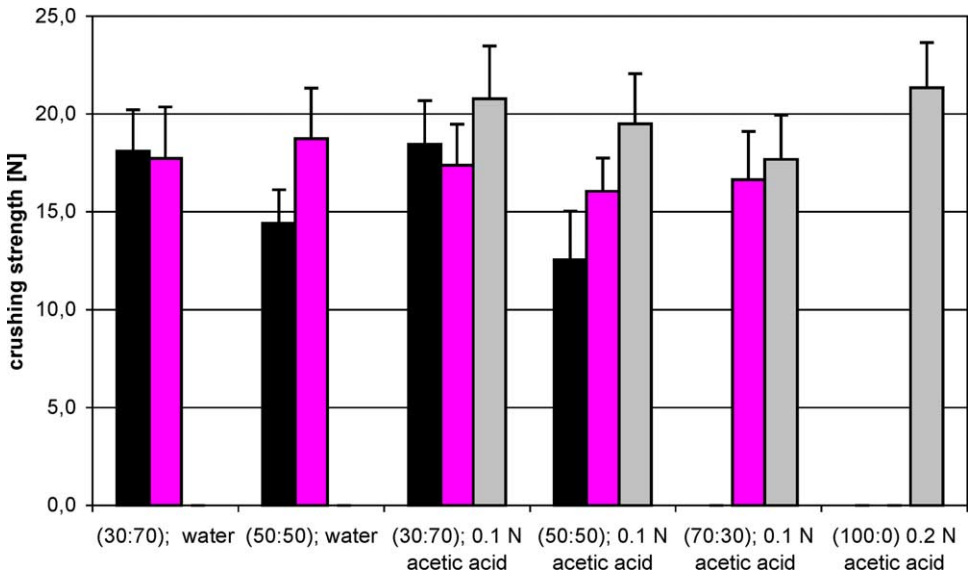

Fig. 6. The crushing strength of the different chitosan MCC pellets at various power levels with water and acetic acid. Black bars, 200 W; dark grey bars, 180 W; light grey bars, 150 W.

chitosan amount. However, the solution quantity and acid concentration affects the extent of porosity. In Fig. 7 it is shown that the porosity rises from 1.6 to 9.5% (extrusion at 180 W) while the porosity is only 7.1% with an amount of 70% chitosan when extruded at 150 W. With 0.2 N acetic acid the pure chitosan pellets have a porosity of 11%. In aqueous solutions microcrystalline cellulose loses its particulate appearance after extrusion, resulting in a low porosity because of the shrinkage during drying [17]. The SEM-pictures (Fig. 3) show a flake-like appearance of the chitosan particles forming the pellet. Thus it can be assumed that by association of the particles, larger pore spaces remain.

4. Conclusions

It is possible to produce morphologically and mechanically satisfying pellets by extrusion/spheronization technology with a maximum content of 50% chitosan with no other excipients than microcrystalline cellulose, using demineralized water as granulation liquid. This is in contrast to the observation of Goskonda et al. [11]. Switching from demineralized water to diluted acetic acid as granulation fluid enabled the processability of pure chitosan powder in a twin screw extruder with no other excipients. With an increasing amount of chitosan in a powder mixture it is necessary to raise the quantity of granulation liquid and

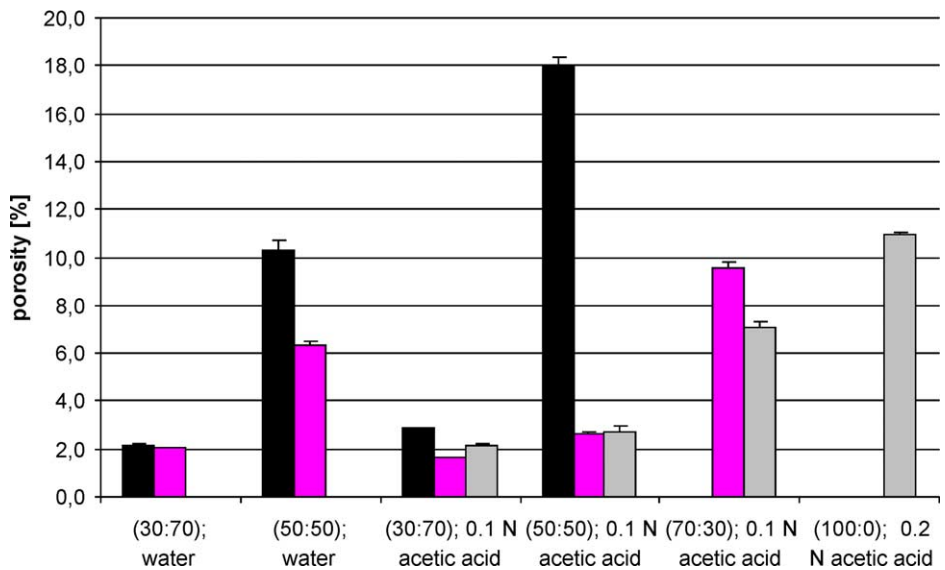

Fig. 7. The porosity of the different chitosan MCC pellets extruding at various power levels with water and acetic acid. Black bars, 200 W; dark grey bars, 180 W; light grey bars, 150 W.

the acid concentration to obtain pellets with good sphericity, tight particle size distribution, low abrasion and an adequate tensile strength. Due to the shape of the used particles an increase of the chitosan proportion leads to a higher porosity in the resulting pellets. Increasing the acetic acid concentration to > 0.2 N acetic acid leads to a sticky extrudate or pellets with a rod-like appearance.

References

[1] S. Hirano, H. Seino, Y. Akiyama, I. Nonaka, Chitosan: A biocompatible material for oral and intravenous administrations, Progress in Biomedical Polymers, Plenum, New York, 1990, pp. 283–290.
[2] P. He, S.S. Davis, L. Illum, Chitosan microspheres prepared by spray drying, Int. J. Pharm. 187 (1999) 53–65.
[3] R. Hejazi, M. Amiji, Stomach-specific anti-*H. pylori* therapy. I: preparation and characterisation of tetracycline-loaded chitosan microspheres, Int. J. Pharm. 235 (2002) 87–94.
[4] N. Inoyatov, N. Celebi, F. Acarturk, Preparation and evaluation of a prolonged release pentoxyphyllin tablet with chitosan, Pharm. Ind. 60 (5) (1998) 472–475.
[5] M. Säkkinen, U. Seppälä, P. Heinänen, M. Marvola, In vitro evaluation of microcrystalline chitosan as gel-forming excipient in matrix granules, Eur. J. Pharm. Biopharm. 54 (2002) 33–40.
[6] N. Follonier, E. Doelker, Biopharmaceutical comparison of an oral multiple-unit and single-unit sustained-release dosage forms, STP Pharma Sci. 2 (1992) 141–158.
[7] A. Berthold, K. Cremer, J. Kreuter, Preparation and characterisation of chitosan microspheres as drug carrier for prednisolone sodium phosphate as model for anti-inflammatory drugs, J. Controlled Release 39 (1996) 17–25.
[8] H.-R. Hoffmann, B, Asmussen, Schnellzerfallende Pellets auf der Basis von Chitosan, Patent DE 199/40795 A1, 1999
[9] N. Shimono, M. Mori, Y. Higashi, Solid preparations containing chitosan powder and process for producing the same, Patent WO 01/10467, 1999
[10] C. Tapia, G. Buckton, J.M. Newton, Factors influencing the mechanism of release from sustained release matrix pellets, produced by extrusion/spheronization, Int. J. Pharm. 92 (1993) 211–218.
[11] S.R. Goskonda, S.M. Upadrashta, Avicel RC-591/Chitosan beads by extrusion-spheronization technology, Drug Dev. Ind. Pharm. 19 (8) (1993) 915–927.
[12] J. Chatchawalsaisin, F. Podczeck, J.M. Newton, The influence of chitosan, sodium alginate and formulation variables on the formulation and drug release from pellets, 3rd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Berlin, 2000.
[13] H. Santos, F. Veiga, M. Pina, F. Podczeck, J. Sousa, Physical properties of chitosan pellets produced by extrusion-spheronisation: influence of formulation variables, Int. J. Pharm. 246 (2002) 153–169.
[14] H. Lindner, Entwicklung eines leistungsgeregelten Zweischneckenextruders zur Herstellung pharmazeutischer Pellets. Dissertation, Kiel University, Kiel, 1993.
[15] H. Lindner, P. Kleinebudde, Anwendung der automatischen Bildanalyse zur Charakterisiserung von Pellets, Pharm. Ind. 55 (1993) 694–701.
[16] P. Schultz, P. Kleinebudde, Development of a new pellet friability tester, Pharm. Ind. 57 (1994) 323–328.
[17] L. Nymo, M. Schröder, P. Schultz, B. Müller, T. Waaler, P. Kleinebudde, Properties of extruded pellets made from binary mixtures, Proc. 1st World Meeting, APGI/APV, 1995, pp. 367–368.