Influence of Chitosan Type on the Properties of Extruded Pellets With Low Amount of Microcrystalline Cellulose

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ABSTRACT

The purpose of this research was to study the influence of type of chitosan with different molecular weights, ie, 190 and 419 kDa, on properties of pellets prepared by extrusion/spheronization. The formulations, consisting of acetaminophen as model drug, chitosan, microcrystalline cellulose (MCC), and dibasic calcium phosphate dihydrate with/without sodium alginate, were extruded using a twin-screw extruder and water as the granulating liquid. With 30% wt/wt MCC and no added sodium alginate, spherical pellets were produced containing low and high molecular weight chitosan at a maximum amount of 60% and 40% wt/wt, respectively. With sodium alginate (2.5% wt/wt), pellets with either type of chitosan (60% wt/wt), MCC (17.5% wt/wt), and acetaminophen (20% wt/wt) could be produced indicating an improved pellet-forming ability. Type and amount of chitosan and added sodium alginate affected physical properties of pellets including size, roundness, crushing force, and drug release. Low molecular weight chitosan produced pellets with higher mean diameter, sphericity, and crushing force. Additionally, the pellets made of low molecular weight chitosan and added sodium alginate showed faster drug release in 0.1 N HCl but had slower drug release in pH 7.4 phosphate buffer. This indicated that drug release from pellets could be modified by the molecular weight of chitosan. In conclusion, the molecular weight of chitosan had a major influence on formation, physical properties, and drug release from the obtained pellets.

KEYWORDS: Chitosan, sodium alginate, pellets, extrusion/spheronization, drug release.

INTRODUCTION

Pellets have gained interest as an oral multiple-unit dosage form because they provide reproducible bioavailability, and lowered risk of side effects due to dose dumping.[1] Pellets also offer technological advantages such as better flow properties, less friable dosage form, narrow particle size distribution, and uniform packing.[2] Extrusion/spheronization is an established process used to produce pharmaceutical pellets. Extrusion methods are classified as wet extrusion and hot-melt extrusion. Wet extrusion requires granulation liquid whereas hot-melt extrusion is a solvent-free technique. The characteristics of pellets produced by the wet extrusion/spheronization process are dependent on many factors; for example, formulation composition, moisture content of the extrudate, type of granulation liquid, physical properties of the starting materials, and type of extruder.[3] Most pellets produced by wet extrusion/spheronization include microcrystalline cellulose (MCC) as an extrusion aid. The MCC-based pellets are suitable for a controlled release dosage form as they do not disintegrate and prolong drug release,[4-6] which would be a disadvantage when fast release of drug is desired. This led to the study on modification of drug release from pellets by incorporating other excipients into the formulations such as chitosan,[7-10] alginate,[10,11] and carbopol.[12,13] Some investigations are also performed to find an alternative extrusion aid to MCC, such as chitosan,[14-16] pectin,[17] and κ-carragenan.[18-20]

Chitosan, a polysaccharide obtained by N-deacetylation of chitin, has been investigated as a pharmaceutical excipient for solid dosage forms as well as a carrier for new delivery systems owing to its biocompatibility, biodegradability, and nontoxic property.[21-23] Some attempts on investigation of chitosan as an excipient in extrusion/spheronization have been made. Tapia et al[7] used chitosan (Seacure 242) solution in diluted acetic acid as the granulation liquid and prepared pellets containing 2% to 3% chitosan by ram extruder. The presence of chitosan results in sustained release of drugs from pellets in pH 7.4 phosphate buffer. Goskonda and Upadrashta[8] reported that spherical pellets with a maximum of 40% chitosan could be produced by a combination of Avicel RC-591 and different viscosity grades of chitosan (Seacure 142, 242, 342, 442) using water as the granulation liquid. The successful pelletization of chitosan in this system may be attributed to the increased binding ability brought about by the presence of sodium carboxymethyl cellulose (~11%) in Avicel RC-591. Incorporation of higher viscosity grades of chitosan slowed drug release from Avicel RC-591/chitosan

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pellets in acid media, but enhanced it in water. Santos et al[9] showed that the spherical pellets containing chitosan (0% to 16%), MCC (50%), povidone (2% to 8%), filler (38% to 16%), and diclofenac sodium (10%) could be prepared by extrusion/spheronization using a screen extruder and using ethanol/water mixtures as the granulation liquid. The achievement of extrusion/spheronization of this system was due to the addition of povidone. The pellets obtained did not disintegrate but fast release was observed. In addition, production of spherical pellets with maximum content of 16% chitosan (Seacure 252) and 50% MCC was also achieved by extrusion/spheronization with a ram extruder and using McIlvaine buffers (0.1 M citric acid and 0.2 M disodium phosphate) as the granulation liquid.[10] The pellets with chitosan from this system could disintegrate in simulated gastric fluid and addition of sodium alginate (1% to 3%) could suppress or extend disintegration of pellets. In pellet production by twin-screw extruder, chitosan (Chitoclear FG95) could be loaded to 50% when using water as the granulation liquid, and could be loaded to 100% when using diluted acetic acid as the granulation liquid.[14] Agrawal et al[15] combined chitosan with hydroxypropyl methylcellulose as a binder in the production of ethylcellulose-based pellets using water as the granulation liquid. Chitosan was loaded at a maximum amount of 20% and spherical pellets could be prepared without MCC. Recently, the use of chitosan-alginate as an alternative pelletization aid to MCC has been demonstrated.[16] The previous findings revealed differences in maximum loading of chitosan and physical characteristics, especially drug release, of chitosan-containing pellets produced by extrusion/spheronization. This was attributable to many factors, eg, type and amount of chitosan, added excipient, type of granulation liquid, and type of extruder.

As chitosan properties could be varied with its physical characteristics such as molecular weight and degree of deacetylation,[22,24] we studied the effect of these physical characteristics, especially molecular weight, on the formation and physical properties of pellets produced by extrusion/spheronization. Two types of chitosan with different molecular weights, 190 kDa and 419 kDa, were used to modify drug release from MCC-based pellets. The investigated formulations consisted of acetaminophen as model drug, chitosan, sodium alginate, MCC, and dibasic calcium phosphate dihydrate. MCC was used in a low amount and did not exceed 30% wt/wt. The extrusion/spheronization was performed using a twin-screw extruder and water as the granulating liquid. Drug release from the obtained pellets was also investigated.

Materials and Methods

Materials

Acetaminophen USP (BASF AG, Ludwigshafen, Germany) was used as the model drug. Two types of chitosan with different molecular weights (Aqua Premier Co, Chonburi, Thailand), ie, high molecular weight chitosan (chitosan HW or CSHW) and low molecular weight chitosan (chitosan LW or CSLW), and microcrystalline cellulose (MCC; Sanaq 102, Pharmatrans Sanaq, Basel, Switzerland) were used as extrusion aids. Characteristics of chitosan used are shown in Table 1. Sodium alginate (SA) (Manucol DMF, ISP alginates, UK Ltd., Strathclyde, UK) was used to form polyelectrolyte complex with chitosan. Dibasic calcium phosphate dihydrate (Dicafos, Chemische Fabrik GmbH, Budenheim, Germany) was used as filler. All other chemicals were of reagent grade.

Preparation of pellets

Two types of chitosan with different molecular weights were incorporated into the formulations containing no more than 30% wt/wt MCC. Pellet formulations consisting of acetaminophen (model drug), chitosan, MCC, dibasic calcium phosphate, and sodium alginate are shown in Table 2. The amount of chitosan and sodium alginate ranged from 0% to 60% wt/wt and 0% to 2.5% wt/wt, respectively. Demineralized water was used as the granulation liquid. Batch size for each formulation was 1200 or 1500 g. Dry powder mixtures were blended in a cone mixer (LM 20, Bohle, Ennigerloh, Germany) for 10 minutes and were then transferred to the gravimetric powder feeder of the corotating twin-screw extruder (Micro 27 GL-28D, Leistritz GmbH, Nürnberg, Germany). The axial die plate containing 23

Table 1. Physical Characteristics of Powdered Chitosan with Different Molecular Weights

Characteristics	Chitosan LW	Chitosan HW
Molecular weight*		
Mean (kDa)	190	419
Polydispersity	6.14	7.63
Particle size†		
Mean, D(v,0.5) (μm)	178	192
Span	1.86	1.75
Degree of deacetylation‡ (%)	97	93
Crystallinity index§ (%)	48	53
Viscosity‖ (mPa.s)	35.8 ± 0.6	77.4 ± 1.1
Moisture content¶ (%)	10.52 ± 0.01	9.44 ± 0.01

*Determined by gel permeation chromatography (600E, Water Corp, Milford, MA).

†Determined by laser diffraction particle size analyzer (Malvern S, Malvern Instruments, Worcestershire, UK).

‡Determined by CP-MAS ^{13}C NMR spectroscopy (AV300, Bruker AG, Fällanden, Switzerland).

§Determined by powder X-ray diffractometry (D 8 Advance Bruker, Axs GmbH, Karlsruhe, Germany).

‖Determined by Brookfield viscometer (DV II+, Brookfield, Essex, UK); conditions: spindle LV1, speed 60 rpm, 1% wt/vol chitosan in 1% wt/vol in acetic acid at 25°C.

¶Determined by thermogravimetric analyzer (TGA7, Perkin Elmer, Norwalk, CT).

Table 2. Compositions of the Pellets Containing Chitosan With Different Molecular Weights and Sodium Alginate

	Composition (% wt/wt)					
Formulation	Acetaminophen	Chitosan HW	Chitosan LW	Sodium alginate	MCC	Dibasic calcium phosphate
0%CSHW	20	0	—	0	30	50
20%CSHW	20	20	—	0	30	30
40%CSHW	20	40	—	0	30	10
60%CSHW	10	60	—	0	30	0
0%CSHW/2.5%SA	20	0	—	2.5	30	47.5
20%CSHW/2.5%SA	20	20	—	2.5	30	27.5
40%CSHW/2.5%SA	20	40	—	2.5	30	7.5
60%CSHW/2.5%SA	20	60	—	2.5	17.5	0
0%CSLW	20	—	0	0	30	50
20%CSLW	20	—	20	0	30	30
40%CSLW	20	—	40	0	30	10
60%CSLW	10	—	60	0	30	0
0%CSLW/2.5%SA	20	—	0	2.5	30	47.5
20%CSLW/2.5%SA	20	—	20	2.5	30	27.5
40%CSLW/2.5%SA	20	—	40	2.5	30	7.5
60%CSLW/2.5%SA	20	—	60	2.5	17.5	0

MCC, microcrystalline cellulose; CSHW, chitosan high molecular weight; CSLW, chitosan low molecular weight; SA, sodium alginate.

holes 1 mm in diameter and 2.5 mm in thickness was mounted directly in front of the screws.

The extruder was started after warming up at 100 rev/min^{-1} for 30 minutes. Powder feeder, water pump, data acquisition, and power control were started simultaneously. The powder feeder rate was adjusted to 33 g/min^{-1} and demineralized water 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 each formulation, different pump rates were adjusted to optimize the liquid level for production of nearly spherical pellets. The extruder was operated at a constant speed of 100 rev/min^{-1}. The experimental run was started when the power consumption reached a constant level, and then a batch of 500-g wet extrudate was continuously collected. During the extrusion process, samples of the extrudate were drawn 3 times per batch to analyze the water content. The extrudate was then spheronized immediately in a spheronizer (RM300, Schlueter, Neustadt/Ruebenberge, Germany) with a cross-hatched plate 300 mm in diameter at 1000 rpm for 5 minutes. Consequently, the pellets were transferred to a fluid-bed dryer (ST2EX, Aeromatic, Bubendorf, Switzerland) and dried at 60°C for 30 minutes.

Determination of water content of extrudate

The extrudate was collected during the extrusion process and subsequently dried at 105°C for 24 hours in a circulating hot air oven (Heraeus UT-6060, Kendo, Hanau, Germany). The water content of the extrudate was calculated in triplicate based on dry mass.

Scanning electron microscopy

Pellet morphology was observed under scanning electron microscope (SEM; Hitachi S-2360 N, Tokyo, Japan). The samples were attached to the slab surfaces with double-sided adhesive tape and then coated with gold to a thickness of ~30 nm under vacuum to make the samples conductive. Scanning electron photomicrographs were taken at appropriate magnification.

Image analysis

Pellet size and shape were determined in terms of mean Feret's diameter and roundness, respectively, using image analysis software (Image C, Imtronic, Berlin, Germany).[18] For each batch, samples were obtained using a rotary cone sample divider (Retschmuehle PT, Retsch, Haan, Germany). Before measurement, the dried pellets were separated with a 500-μm sieve. The image analyzer consisted of a stereomicroscope (SZX 9, Olympus, Hamburg, Germany), a ring-light with a 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). Images of the pellets at a suitable magnification (1 pixel = 15.2 μm) were translated into binary images. Contacting pellets were separated by a software algorithm. If the separation failed, pellets were deleted manually. The pellets were placed on a sample desk and then photographed with a video camera. Thirty-six Feret diameters were determined for each pellet and at least 500 pellets were analyzed in each batch. Mean and the coefficient of

variation were calculated for Feret's diameter and roundness (ratio of projected area to area that calculated by using mean Feret's diameter) were calculated using Excel 2000 (Microsoft, Unterschleissheim, Germany).

Determination of crushing force

A texture analyzer (TA-XT2i, Stable Microsystems, Haslemere, UK) with compression mode was used to determine the crushing force of pellets. Before measurement, the pellets of 1000- to 1100-μm sieve fraction were stored in a desiccator with saturated $Mg(NO_3)_2.6H_2O$ (55% relative humidity [RH]) at room temperature for 7 days. At least 20 pellets were measured using Texture Profile Analysis (TPA) program for the crushing force. The parameters of the texture analyzer for measuring crushing force were as follows; pretest speed 1 mm/s, test speed 1 mm/s, posttest speed 10 mm/s, and distance 50% strain. The first maximum of the force-time curve was taken as the crushing force of the pellet.

In vitro drug release study

About 100 mg of the pellets of 1000- to 1200-μm sieve fraction were accurately weighed and used for drug release study. In vitro drug release studies were performed using the paddle method at a rotation speed of 50 rpm in 900 mL of dissolution medium at 37.0 ± 0.5°C. Dissolution test media used were pH 1.2, 0.1 N hydrochloric acid and pH 7.4 phosphate buffer (USP 25). The USP dissolution apparatus 2 (PTWS3C, Pharmatest, Hainburg, Germany) was interfaced to a spectrophotometer (Lamda2, Perkin-Elmer, Wellesley, MA). The UV absorbances were measured automatically at 243 nm at each predetermined interval.

The characteristics of dissolution profiles were assessed by the mean dissolution time (MDT), which was calculated from the following equation.[25,26]

$$MDT = \frac{\sum_i \bar{t}_i \Delta M_i}{\sum_i \Delta M_i} \quad (1)$$

where $\bar{t}_i$ is the midpoint of the time period during which the fraction ΔM_i of the drug has been released from the dosage form.

To characterize the release mechanism, experimental data within the interval of $0.1 \leq M_t/M_\infty \leq 0.6$ were fitted to the power law equation.[27,28]

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

where M_t is the amount released at time t, M_∞ is the overall amount released, k is a constant, and n is the diffusion exponent.

Results and Discussion

Pellet production

Chitosan pellets were successfully prepared as shown in SEM photographs (Figure 1). Acceptable pellets were determined based on the quality of pellets in terms of uniformity of size and sphericity (roundness, 0.8 to 1.0). It was possible to produce acceptable pellets from the formulations containing 20% wt/wt acetaminophen, 0% to 40% wt/wt chitosan HW, 30% wt/wt MCC, and 50% to 10% wt/wt dibasic calcium phosphate dihydrate. Further investigation was performed by fixing the amount of MCC at 30% wt/wt and lowering the amount of drug to 10% wt/wt. Pellets still could not be produced when using chitosan HW at a level of 60% wt/wt. These formulations were difficult to extrude and the corresponding extrudate was converted to fine particles during spheronization. In chitosan LW, acceptable pellets could be produced from the formulations with 20% wt/wt acetaminophen, 0% to 40% wt/wt chitosan LW, 30% wt/wt MCC, and 50% to 10% wt/wt dibasic calcium phosphate dihydrate. The next trial on fixing MCC at 30% wt/wt and decreasing amount of drug to 10% wt/wt made it possible to produce the pellets with 60% wt/wt of chitosan LW. This implied that lower molecular weight chitosan had higher ability to form pellets by extrusion/spheronization.

Furthermore, sodium alginate was added to improve loading of chitosan into pellets. Acceptable pellets with 20% wt/wt acetaminophen, 0% to 40% wt/wt chitosan, 2.5% wt/wt sodium alginate, 30% wt/wt MCC, and 47.5% to 7.5% wt/wt dibasic calcium phosphate dihydrate could be produced. Moreover, it was possible to produce pellets containing 20% wt/wt acetaminophen, 60% wt/wt chitosan LW or chitosan HW, 2.5% wt/wt sodium alginate, and 17.5% wt/wt MCC. With the addition of sodium alginate, the production of the pellets with the amount of chitosan as high as 60% wt/wt was

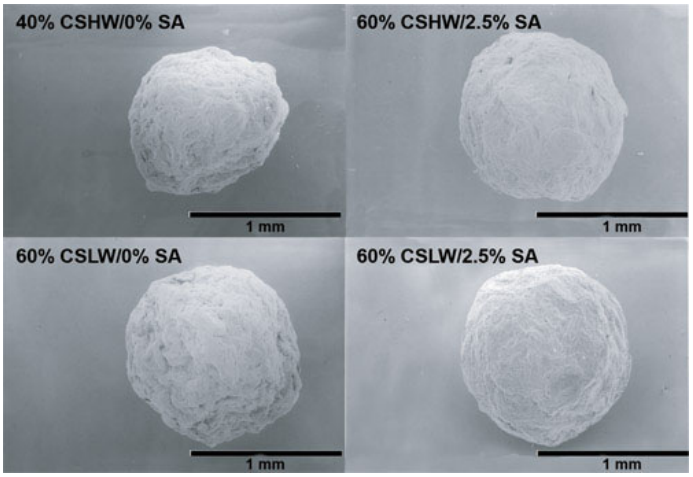

Figure 1. Scanning electron photomicrographs of the pellets containing chitosan with different molecular weights and sodium alginate.

achieved while using MCC, an essential pelletization aid, as low as 17.5% wt/wt. In a previous report, pellets could not be produced by using twin-screw extruder and water as a granulation liquid if the amount of chitosan (Chitoclear FG95) in the MCC-based formulations was greater than 50% wt/wt.[14] Sodium alginate is an anionic polymer that can form a polyelectrolyte complex with cationic polymer chitosan.[29] It was reported that the proportion of added sodium alginate (0% to 4%) had an effect on formation, physical properties, and drug release of pellets prepared by a ram extruder.[10] Recently, formation of a polyelectrolyte complex between chitosan and sodium alginate during extrusion using twin-screw extruder and water as the granulation liquid was confirmed by Fourier transform infrared spectroscopy, differential scanning calorimetry, and solid state nuclear magnetic resonance spectroscopy.[16] Thus, the improved pelletization by sodium alginate in the chitosan-containing pellets was probably due to polyelectrolyte complex formation between sodium alginate and chitosan.

Water content of the extrudate

In extrusion/spheronization, the water content of the extrudate affects the shape and size of the pellets.[30-34] Each formulation has a specific water content to produce pellets with optimal quality. The required water content of the extrudate for successful pelletization of the formulations containing chitosan of different molecular weights is shown in Figure 2. Without sodium alginate, the formulations with a higher amount of chitosan required higher water content of the extrudate to obtain round pellets. This finding agreed with that observed in extrusion/spheronization of chitosan/MCC systems by twin-screw extruder.[14] In addition, the formulations with chitosan LW required less water content than chitosan HW ($P < .05$). Addition of 2.5% wt/wt sodium alginate caused the formulations with chitosan to require less water content to produce round pellets ($P < .05$). In the formulation with 2.5% wt/wt sodium alginate, the required water content of the extrudate was also increased with increasing amount of chitosan. Furthermore, the type of chitosan used did not have a significant effect on the required water content when sodium alginate was present in the formulations. The formulations with higher molecular weight chitosan required higher water content because of its higher water uptake property.[24,35] Sodium alginate could form an insoluble polyelectrolyte complex with chitosan during extrusion,[16] thus reducing the required water content.

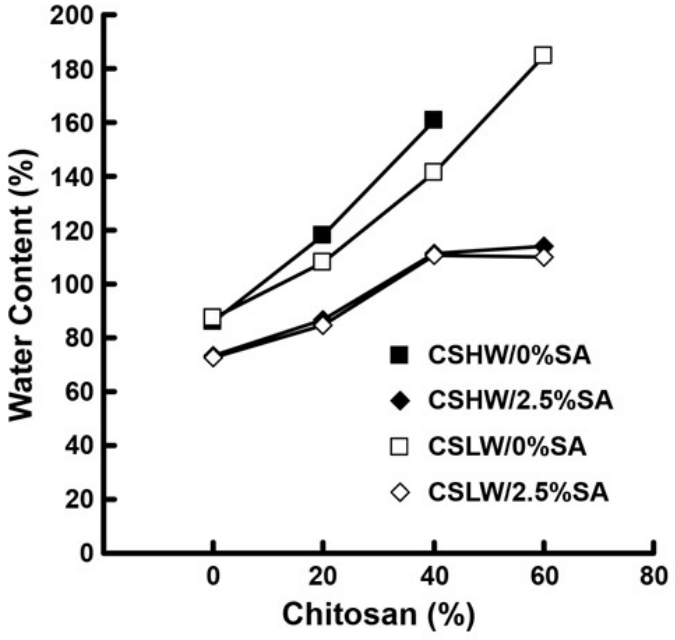

Figure 2. Effect of type of chitosan and sodium alginate on water content of the extrudate. Mean ± SD, n = 3.

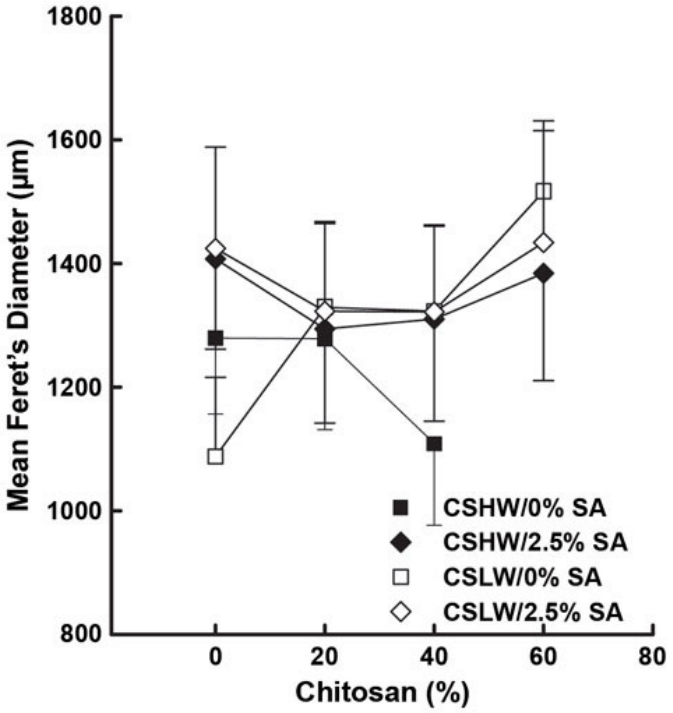

Figure 3. Effect of type of chitosan and sodium alginate on mean Feret's diameter of the pellets. Mean ± SD, n ≥ 500.

Pellet size

For chitosan/MCC pellets produced by twin-screw extruder and using water as the granulation liquid, mean Feret's diameters of pellets decreased with increasing amount of chitosan (Chitoclear FG95).[14] In this study, the mean Feret's diameters of the obtained pellets were in a range of 1.1 to 1.5 mm (Figure 3). Without sodium alginate, the pellet size tended to decrease with increasing amount of chitosan HW, whereas increasing amount of chitosan LW tended to increase the pellet size. As observed during spheronization,

addition of higher amount of high molecular weight chitosan resulted in formation of smaller agglomerates and fine particles. Moreover, the low molecular weight chitosan could provide the extrudate with sufficient plasticity, thus larger pellets were obtained at higher loading.

Addition of sodium alginate to the MCC-based formulations without chitosan at a level of 2.5% wt/wt increased the pellet size ($P < .05$). It was suggested that sodium alginate might improve the cohesive property of the extrudate mass, thus the pellets with greater size were obtained. In the formulations containing chitosan, an increase in pellet size with addition of sodium alginate was observed in the case of chitosan HW pellets but not significantly observed in chitosan LW pellets. This implied that sodium alginate was required to improve agglomeration between particles.

Pellet shape

Spherical pellets with a high level of chitosan were obtained (Figure 1). The roundness of the pellets containing chitosan with/without sodium alginate is shown in Figure 4. Without sodium alginate, the roundness of the pellets with chitosan was in the range of 0.80 to 0.85. Moreover, the pellet roundness tended to decrease as amount of chitosan HW increased but was not significantly altered with increasing amount of chitosan LW. Similar results reported that the sphericity of pellets produced by ram extruder decreased with the addition of 16% wt/wt of chitosan.[9,10] Furthermore,

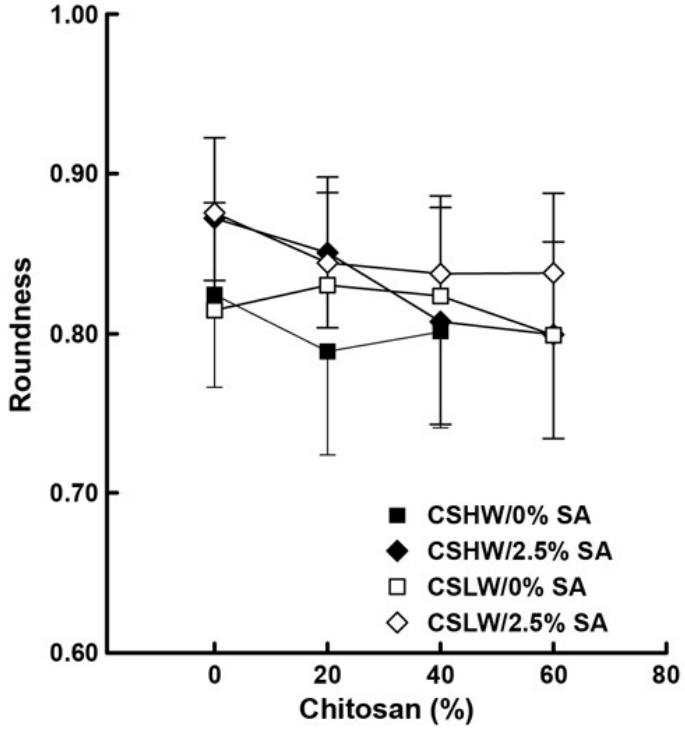

Figure 4. Effect of type of chitosan and sodium alginate on roundness of the pellets. Mean ± SD, n ≥ 500.

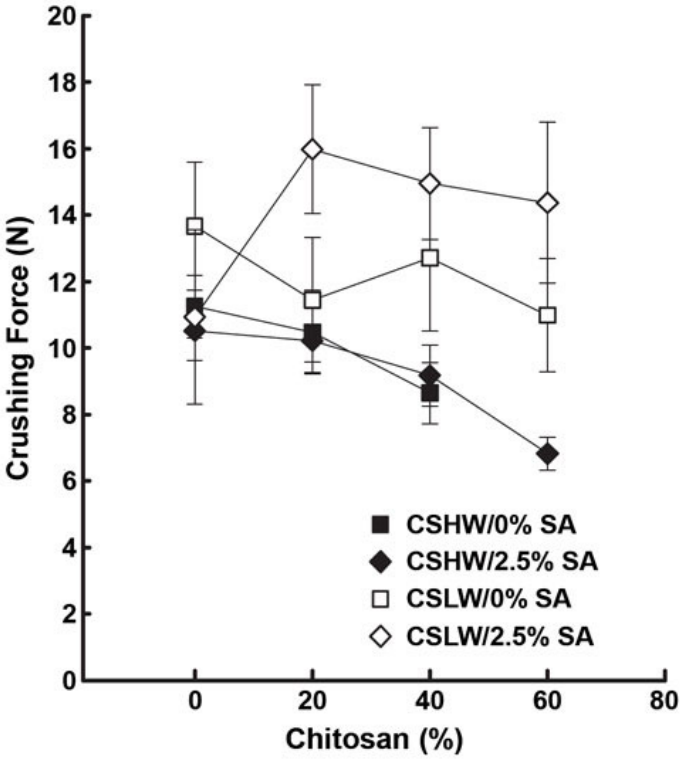

Figure 5. Effect of type of chitosan and sodium alginate on crushing force of the pellets. Mean ± SD, n ≥ 20.

chitosan HW produced pellets with less sphericity than chitosan LW ($P < .05$). Similar to the chitosan/Avicel RC-591 pellet systems, incorporation of higher viscosity grades of chitosan (Seacure 342 and Seacure 442) resulted in decrease of pellet sphericity and an increase in the surface roughness.[8]

Addition of sodium alginate did not significantly improve the roundness of the pellets with chitosan LW or chitosan HW. Similar result was reported in pellets containing chitosan (1% to 3%) and sodium alginate (3% to 1%), which were produced by ram extruder.[10] In the presence of sodium alginate, the sphericity of pellets with chitosan LW or chitosan HW tended to decrease with increasing amount of chitosan and high molecular weight chitosan could reduce the pellet sphericity to a greater extent.

Crushing force

Crushing force needed to break the pellets tended to decrease with increasing amount of chitosan when either chitosan HW or chitosan LW was used (Figure 5). A similar result was reported in chitosan/MCC pellets.[14] Moreover, chitosan LW produced stronger pellets than chitosan HW. It was indicated that low molecular weight chitosan produced harder pellets than high molecular weight chitosan ($P < .05$).

Addition of sodium alginate had a significant effect on the strength of the pellets with chitosan LW ($P < .05$), but not

those with chitosan HW. The results indicated that addition of sodium alginate at a level of 2.5% wt/wt was not sufficient to increase the strength of pellets with high molecular weight chitosan. It was explained that sodium alginate could improve binding between particles to a greater extent in the formulations containing low molecular weight chitosan, thus harder pellets were formed. This was attributable to a higher degree of polyelectrolyte complex formation of low molecular weight chitosan with sodium alginate.[16]

In vitro drug release

Disintegration of chitosan HW pellets with no added sodium alginate was observed in acidic medium within the initial 10 to 15 minutes of the dissolution test. On the other hand, it was not observed in other chitosan pellet systems in acidic medium and all chitosan pellet systems in pH 7.4 phosphate buffer; however, high molecular weight chitosan could provide the disintegrating pellets. This implied that the disintegrating property of chitosan pellets was related to the molecular weight of chitosan. Addition of sodium alginate at a level of 2.5% wt/wt could suppress disintegration of chitosan HW pellets. The findings on disintegration of chitosan pellets in acidic medium and the suppression of their disintegration by added sodium alginate have been reported previously in the pellet systems with chitosan and sodium alginate, which were produced by ram extruder.[10] However, the reason for disintegration of pellets with chitosan was not reported. It was suggested that the disintegration of chitosan HW pellets might be attributed to greater swelling of the high molecular weight chitosan.

At pH 1.2, the pellets with chitosan showed faster drug release than those with no added chitosan (Figure 6). In addition, the chitosan pellets showed different release behavior when compared with the pellets with no added chitosan. This discrepancy was remarkably observed in the chitosan HW pellets. At pH 7.4, the pellets with a different amount of chitosan gave similar dissolution profiles to the pellets with no added chitosan but had a slower drug release (Figure 7). Incomplete dissolution of acetaminophen in phosphate buffer was observed which may be due to binding of drug to the insoluble excipients.

Using either type of chitosan, the MDTs of chitosan pellets in acidic medium decreased with increasing amount of chitosan (Figure 8, left panel). As chitosan forms a gel and dissolves in 0.1 N HCl, the pellets with higher chitosan content would possess a higher amount of dissolvable components and consequently release the drug faster. Without sodium alginate, faster drug release from chitosan HW pellets was observed ($P < .05$). This was due to disintegration of chitosan HW pellets. Addition of sodium alginate caused slower drug release ($P < .05$) since the pellets with added sodium alginate did not disintegrate and remained intact during the dissolution test. Moreover, sodium alginate is water soluble but can be easily transformed into a water insoluble and swellable acid form at low pH.[36] In addition, an interpolymeric complex between chitosan and alginate could be partially formed at low pH.[37,38] Recently, the formation of a polyelectrolyte complex between chitosan and sodium alginate in pellets produced by twin-screw extruder has been confirmed.[16] These changes led to a slower drug release from the pellets containing chitosan and sodium

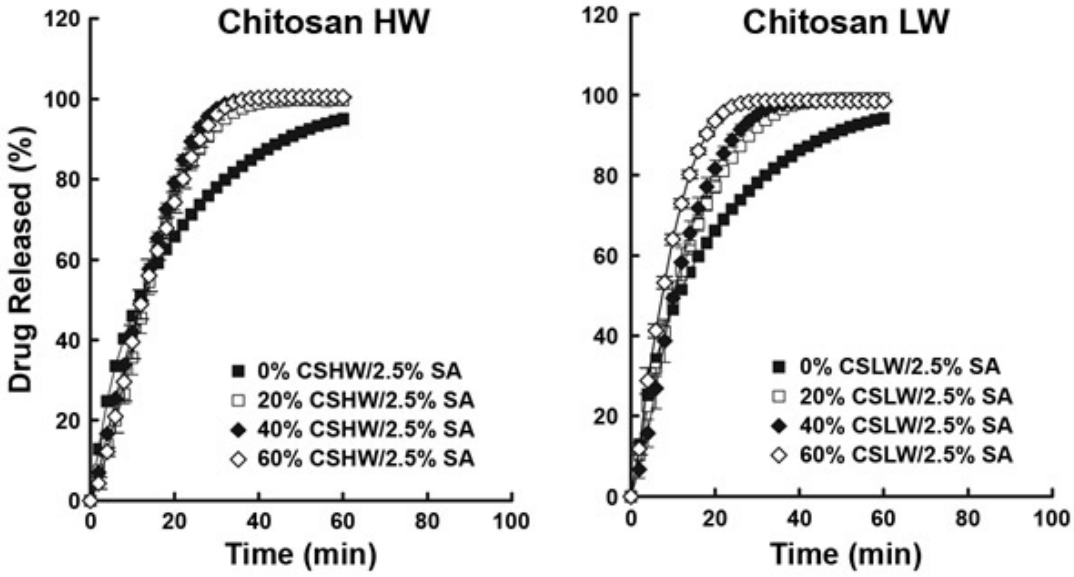

Figure 6. Dissolution profiles of the pellets containing chitosan with different molecular weights and sodium alginate in pH 1.2, 0.1 N HCl. Mean ± SD, n = 6.

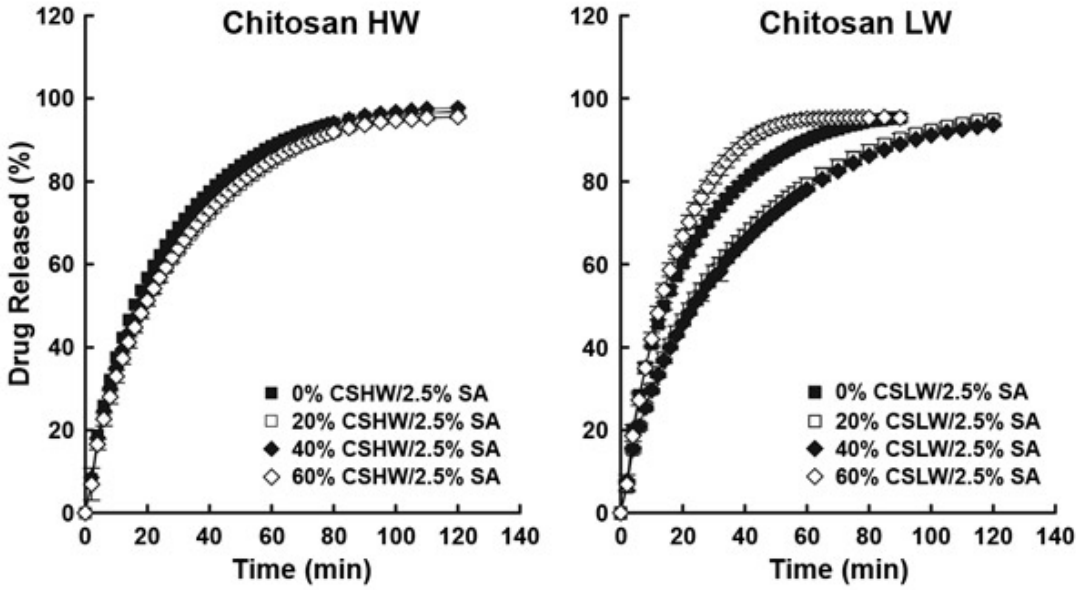

Figure 7. Dissolution profiles of the pellets containing chitosan with different molecular weights and sodium alginate in pH 7.4 phosphate buffer. Mean ± SD, n = 6.

alginate. Moreover, the chitosan HW pellets had a slower drug release than the chitosan LW. This slower drug release might be due to a formation of a more viscous barrier of high molecular weight chitosan, which could subsequently retard diffusion of drug from the pellets.

In pH 7.4 phosphate buffer, the MDT tended to increase as the amount of chitosan increased (Figure 8, right panel). Chitosan could not be dissolved in pH 7.4 phosphate buffer. Thus, the longer MDT with increasing amount of chitosan was a result of the increasing insoluble polymer content. However, the drug release from 60% chitosan LW pellets was faster and was not in the same trend. This was because the 60% chitosan LW pellets consisted of 17.5% wt/wt MCC while the 20% and 40% chitosan LW pellets contained 30% wt/wt MCC. Furthermore, addition of chitosan LW to the MCC-based formulation could decrease drug release from the pellets to a greater extent than chitosan HW. This might be attributable to a higher crushing strength of the chitosan LW pellets (Figure 5). With addition of sodium alginate, the pellets with chitosan HW had a slightly slower drug release whereas those with chitosan LW showed a faster

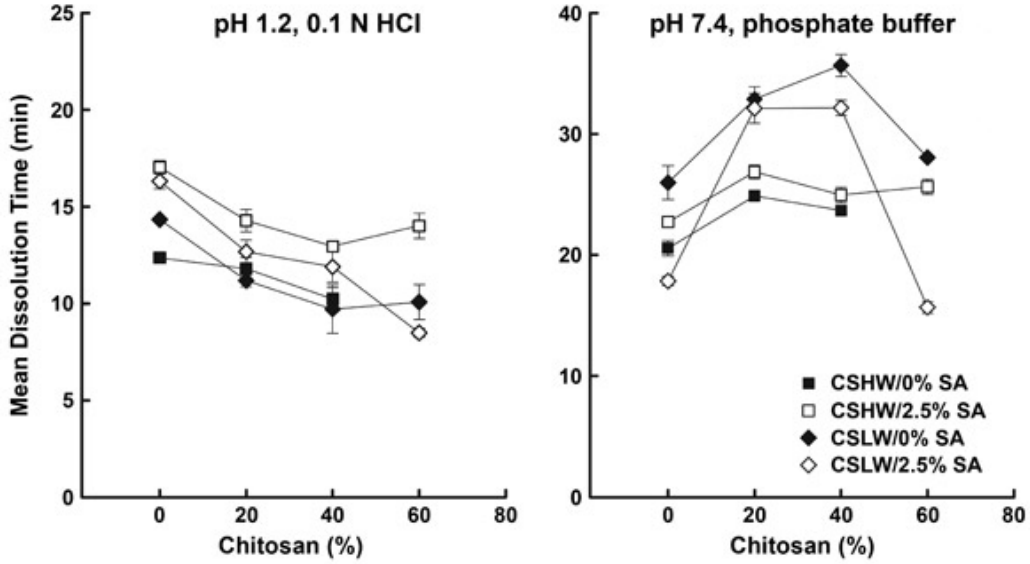

Figure 8. Mean dissolution times of the pellets containing chitosan with different molecular weights and sodium alginate in different dissolution media. Mean ± SD, n = 6.

Table 3. Drug Release Parameters for Pellets Containing Chitosan With Different Molecular Weights and Sodium Alginate Obtained From Power Law Equation

	pH 1.2, 0.1N HCl		pH 7.4 Phosphate Buffer	
Formulation	n	r^2	n	r^2
0% CSHW	0.5057	0.9812	0.5497	0.9832
20%CSHW	1.1457	0.9970	0.5350	0.9862
40%CSHW	1.0732	0.9962	0.5665	0.9865
60%CSHW	—	—	—	
0%CSHW/2.5%SA	0.5161	0.9815	0.6424	0.9891
20%CSHW/2.5%SA	1.0390	0.9950	0.6243	0.9933
40%CSHW/2.5%SA	0.9558	0.9984	0.6475	0.9938
60%CSHW/2.5%SA	0.9978	0.9914	0.6492	0.9923
0%CSLW	0.5768	0.9919	0.5182	0.9839
20%CSLW	0.8176	0.9876	0.5043	0.9831
40%CSLW	1.0686	0.9951	0.5024	0.9914
60%CSLW	0.8493	0.9905	0.4699	0.9817
0%CSLW/2.5%SA	0.6172	0.9897	0.6562	0.9704
20%CSLW/2.5%SA	0.8284	0.9929	0.6188	0.9925
40%CSLW/2.5%SA	1.1273	0.9944	0.6130	0.9945
60%CSLW/2.5%SA	0.9763	0.9907	0.8194	0.9902

CSHW, chitosan high molecular weight; CSLW, chitosan low molecular weight; SA, sodium alginate.

drug release. This discrepancy was due to concomitant complex phenomena depending on type of chitosan, water uptake, matrix swelling, and matrix erosion. Furthermore, interaction between chitosan and sodium alginate in this system may account for the drug release behavior. Moreover, sodium alginate is water soluble in pH 7.4 phosphate buffer, thus it could enhance drug release from the pellet matrix systems to some extent.

The power law equation can be used to describe the release kinetics from Fickian diffusion to non-Fickian transport. The kinetics parameters of drug release from chitosan pellets are presented in Table 3. The exponent n of power law could describe the release kinetics, depending on the geometry of the devices. For drug release from sphere; $n = 0.43$ for Fickian diffusion, $0.43 < n < 0.85$ for anomalous (non-Fickian) transport, $n = 0.85$ for case-II transport. In both media, the n value for the pellets without both chitosan and sodium alginate were in the range of 0.50 and 0.57, indicating anomalous (non-Fickian) transport. Thus, drug release from these pellets was controlled by both diffusion and swelling of polymer. As the n values were slightly higher than 0.43, the drug release from these pellets was mainly diffusion controlled. When sodium alginate was incorporated, the pellets with no added chitosan had a slightly higher n value of drug release in both media. However, drug release kinetics was still anomalous transport. Drug release from the pellets with added sodium alginate was controlled by swelling to a greater extent.

The n value of chitosan HW pellets and chitosan HW/sodium alginate pellets in acidic medium were in the range of 0.95 to 1.04, indicating super case-II transport. This indicated swelling of controlled drug release that was nearly close to zero-order release kinetics. The n value of drug release from the chitosan LW pellets indicated case-II transport and super case-II transport. These results revealed zero-order release kinetics via swelling controlled mechanism. The swelling process of polymer occurring upon water uptake into the system is the rate-controlling step. It was expected that in acidic medium, the chitosan pellets could swell upon water uptake during the initial period and a hydrated viscous layer around pellets was formed and then eroded. The drug subsequently diffuses through the hydrated viscous layer. It was observed from the dissolution profiles that the chitosan pellets showed an initial slower drug release and a subsequent faster drug release than the pellets with no added chitosan. Additionally, the higher molecular weight chitosan showed such an effect at a greater extent.

In pH 7.4 phosphate buffer, both types of chitosan produced pellets with similar release kinetics. The drug release from chitosan pellets was anomalous transport, indicating superposition of 2 apparently independent mechanisms of drug transport, a Fickian diffusion and a case-II transport. It could be described that drug release was controlled by a coupling of swelling and diffusion. The n values of chitosan pellets with no added sodium alginate were closer to 0.43 than those of chitosan pellets with added sodium alginate. Thus, drug release from the chitosan pellets with no added chitosan was dominantly controlled by diffusion and swelling took part in controlling drug release to a greater extent in the chitosan pellets with added sodium alginate.

The results indicate that drug release from the pellets containing chitosan is pH dependent and related to physical

characteristics of chitosan, eg, molecular weight, and the added excipients in the formulations.

CONCLUSION

The present study demonstrated that it was possible to produce pellets containing chitosan at a maximum amount of 60% wt/wt by extrusion/spheronization with no more than 30% wt/wt of MCC using a twin-screw extruder and water as the granulation liquid. The physical properties and drug release of the obtained pellets depended on type and amount of chitosan, added sodium alginate, and dissolution media. Moreover, molecular weight of chitosan showed a major effect on formation and characteristics of the obtained pellets and the low molecular weight chitosan had a better pellet-forming property.

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REFERENCES

1. Bechgaard H, Nielsen GH. Controlled release multiple units and single-unit doses. *Drug Dev Ind Pharm.* 1978;4:53–67.

2. Reynolds AD. A new technique for the production of spherical particles. *Mfg Chem Aerosol News.* 1970;41:40–43.

3. Vervaet C, Baert L, Remon JP. Extrusion-spheronisation: a literature review. *Int J Pharm.* 1995;116:131–146.

4. O'Conner RE, Schwartz JB. Spheronization II: drug release from drug-diluent mixture. *Drug Dev Ind Pharm.* 1985;11:1837–1857.

5. Schröder M, Kleinebudde P. Development of disintegrating pellets obtained from extrusion/spheronization. *J Pharm Sci.* 1995; 1:415–418.

6. Zimm KR, Schwartz JB, O'Connor RE. Drug release from a multiparticulate pellet system. *Pharm Dev Technol.* 1996;1:37–42.

7. Tapia C, Buckton G, Newton JM. Factors influencing the mechanism of release from sustained release matrix pellets, produced by extrusion/spheronisation. *Int J Pharm.* 1993;92:211–218.

8. Goskonda SR, Upadrashta SM. Avicel RC-591/chitosan beads by extrusion-spheronization technology. *Drug Dev Ind Pharm.* 1993;19:915–927.

9. Santos H, Veiga F, Pina M, Podczeck F, Sousa J. Physical properties of chitosan pellets produced by extrusion-spheronisation: influence of formulation variables. *Int J Pharm.* 2002;246:153–169.

10. Chatchawalsaisin J, Podczeck F, Newton JM. The influence of chitosan and sodium alginate and formulation variables on the formation and drug release from pellets prepared by extrusion/spheronisation. *Int J Pharm.* 2004;275:41–60.

11. Sriamornsak P, Nunthanid J, Luangtana-anan M, Puttipipatkhachorn S. Alginate-based pellets prepared by extrusion/spheronization: a preliminary study on the effect of additive in granulating liquid. *Eur J Pharm Biopharm.* 2007;67:227–235.

12. Neau SH, Chow MY, Durrani MJ. Fabrication and characterization of extruded and spheronized beads containing Carbopol 974P. *Int J Pharm.* 1996;131:47–55.

13. Bommareddy GS, Paker-Leggs S, Saaripella KK, Neau SH. Extruded and spheronized beads containing Carbopol® 974P to deliver nonelectrolytes and salts of weakly basic drugs. *Int J Pharm.* 2006;321:62–71.

14. Steckel H, Mindermann-Nogly F. Production of chitosan pellets by extrusion/spheronization. *Eur J Pharm Biopharm.* 2004;57:107–114.

15. Agrawal AM, Howard MA, Neau SH. Extruded and spheronized beads containing no microcrystalline cellulose: influence of formulation and process variables. *Pharm Dev Technol.* 2004;9:197–217.

16. Charoenthai N, Kleinebudde P, Puttipipatkhachorn S. Use of chitosan-alginate as alternative pelletization aid to microcrystalline cellulose in extrusion/spheronization. *J Pharm Sci.* 2007;96: 2469–2484.

17. Tho I, Sande SA, Kleinebudde P. Disintegrating pellets from a water-insoluble pectin derivative produced by extrusion/spheronisation. *Eur J Pharm Biopharm.* 2003;56:371–380.

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

19. Thommes M, Kleinebudde P. 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.* 2006;63:59–67.

20. Thommes M, Kleinebudde P. 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.* 2006;63:68–75.

21. Felt O, Buri P, Gurny R. Chitosan: a unique polysaccharide for drug delivery. *Drug Dev Ind Pharm.* 1998;24:979–993.

22. Ilium L. Chitosan and its use as a pharmaceutical excipient. *Pharm Res.* 1998;15:1326–1331.

23. Paul W, Sharma CP. Chitosan, a drug carrier for the 21st century: a review. *STP Pharma Sci.* 2000;10:5–22.

24. Nunthanid J, Puttipipatkhachorn S, Yamamoto K, Peck GE. Physical properties and molecular behavior of chitosan films. *Drug Dev Ind Pharm.* 2001;27:143–157.

25. Voegele D, Brockmeier D, Von Hattingberg HM, Lippold BC. Mean dissolution time - a parameter for testing release condition comparability. *Acta Pharm Technol.* 1983;29:167–174.

26. Costa FO, Sousa JJS, Pais AACC, Formosinho SJ. Comparison of dissolution profiles of ibuprofen pellets. *J Control Release.* 2003;89:199–212.

27. Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. *Int J Pharm.* 1983;15:25–35.

28. Ritger PL, Peppas NA. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. *J Control Release.* 1987;5:37–42.

29. Takahashi T, Takayama K, Machida Y, Nagai T. Characteristics of polyion complexes of chitosan with sodium alginate and sodium polyacrylate. *Int J Pharm.* 1990;61:35–41.

30. Baert L, Fanara D, Debaets P, Remon JP. Instrumentation of a gravity feed extruder and the influence of the composition of binary

and ternary mixtures on the extrusion force. *J Pharm Pharmacol.* 1991;43:745–749.

31. Fielden KE, Newton JM, Rowe RC. The influence of moisture content on spheronization of extrudate processed by a ram extruder. *Int J Pharm.* 1993;97:79–92.

32. Kleinebudde P, Lindner H. Experiments with an instrumented twin-screw extruder using a single-step granulation extrusion process. *Int J Pharm.* 1993;94:49–58.

33. Lustig-Gustafsson C, Kaur Johal H, Podczeck F, Newton JM. The influence of water content and drug solubility on the formulation of pellets by extrusion and spheronization. *Eur J Pharm Sci.* 1999;8:147–152.

34. Wan LSC, Heng PWS, Liew CV. Spheronization conditions on spheroid shape and size. *Int J Pharm.* 1993;96:59–65.

35. Blair HS, Guthrie J, Law T, Turkington P. Chitosan and modified chitosan membranes I: preparation and characterization. *J Appl Polym Sci.* 1987;33:641–645.

36. Hodsdon AC, Mitchell JR, Davies MC, Melia CD. Structure and behaviour in hydrophilic matrix sustained release dosage forms 3: the influence of pH on the sustained-release performance and internal gel structure of sodium alginate matrices. *J Control Release.* 1995;33:143–152.

37. Fernández-Hervás M, Holgado M, Fini A, Fell JT. In vitro evaluation of alginate beads of diclofenac salt. *Int J Pharm.* 1998; 163:23–34.

38. Murata Y, Miyamoto E, Kawashima S. Additive effect of chondroitin sulfate and chitosan on drug release from chitosan-induced alginate gel beads. *J Control Release.* 1996;38:101–108.