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Spray-Dried Chitosan as a Direct Compression Tableting Excipient

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The objective of this study was to prepare and evaluate a novel spray-dried tableting excipient using a mixture of chitosan and lactose. Three different grades of chitosan (low-, medium-, and high-molecular-weight) were used for this study. Propranolol hydrochloride was used as a model drug. A specific amount of chitosan (1, 1.9, and 2.5 g, respectively) was dissolved in 50 mL of an aqueous solution of citric acid (1%) and later mixed with 50 mL of an aqueous solution containing lactose (20, 19.1, and 18.5 g, respectively) and propanolol (2.2 g). The resultant solution was sprayed through a laboratory spray drier at 1.4 mL/min. The granules were evaluated for bulk density, tap density, Carr index, particle size distribution, surface morphology, thermal properties, and tableting properties. Bulk density of the granules decreased from 0.16 to 0.13 g/mL when the granules were prepared using medium- or high-molecular-weight chitosan compared with the low-molecular-weight chitosan. The relative proportion of chitosan also showed a significant effect on the bulk density. The granules prepared with 1 g of low-molecular-weight chitosan showed the minimum Carr index (11.1%) indicating the best flow properties among all five formulations. All three granules prepared with 1 g chitosan, irrespective of their molecular weight, showed excellent flow properties. Floating tablets prepared by direct compression of these granules with sodium bicarbonate showed 50% drug release between 30 and 35 min. In conclusion, the spray-dried granules prepared with chitosan and lactose showed excellent flow properties and were suitable for tableting.

Keywords chitosan; direct compression; tablets; granulation; spray drying

INTRODUCTION

Chitosan is a cationic natural polymer derived from chitin. It is insoluble in water, in aqueous alkaline solutions at pH above 6.5, or in organic solvents. It dissolves readily in dilute solutions of several organic acids including formic, acetic, tartaric, citric, and lactic (Felt, Buri, & Gurny, 1998; Illum, 1998; LeHoux & Grondin, 1993). Ormrod et al. studied the effect of chitosan following oral administration in mouse model. The results of their study showed that chitosan was not hydrolyzed by human digestive enzymes (Ormrod, Holmes, & Miller, 1998). Several investigators have also evaluated chitosan for its toxicity effect on cilia beat frequency in guinea pigs after 28 days' application (Aspden et al., 1997), effect on mucociliary clearance rates on the frog palate and human nasal tissue (Aspden, Adler, Davis, Skaugrud, & Illum, 1995; Aspden, Illum, & Skaugrud, 1997), and effect on nasal membranes in rats (Aspden, Illum, & Skaugrud, 1996). In all cases the toxicity of chitosan was not significant. Commercial grade chitosan is available in different forms. However, chitosan most commonly used as pharmaceutical excipient is either low-molecular-weight (viscosity, 20–200 cP), medium-molecular-weight (viscosity, 200–800 cP), or high-molecular-weight (viscosity, 800–2000 cP). Because of the wide range of viscosity, chitosan has been successfully used in the preparation of various controlled-release drug delivery systems (Agnihotri & Aminabhavi, 2007; Aspden et al., 1995; Calvo, Vila-Jato, & Alonso, 1997; Karlsen, 1991; Kotze et al., 1997; Sezer & Akbuga, 1995; Takeuchi, Yamamoto, Niwa, Hino, & Kawashima, 1996; Tarimci & Ermis, 1997) including matrix tablets (Nunthanid et al., 2004). Upadrashta, Katikaneni, & Nuessle (1992) evaluated chitosan as a tablet binder. In comparison with other commonly used tablet binders, the binding efficiency of chitosan was between hydroxypropyl methyl cellulose and methyl cellulose. Ritthidej, Chomto, Pummangura, & Menasveta (1994) evaluated chitosan as a tablet disintegrating agent. Disintegration time for matrix tablets containing 7% chitosan was significantly faster than those containing corn starch and microcrystalline cellulose, and slower than those containing sodium starch glycolate and croscarmellose sodium. Chitosan has also been evaluated as a direct compression excipient for tablets (Knapczyk, 1993). The fluidity and compressibility of a mixture of chitosan and lactose were studied by Sawayanagi, Nambu, & Nagai (1982a). The fluidity of the powder mixture was higher than that of the mixture of crystalline cellulose and lactose. It was also reported that the mixture of chitosan and lactose showed friction-lowering properties. Similar observations were also reported for a mixture of chitosan and mannitol (Sawayanagi, Nambu, & Nagai, 1982b).

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Direct compression excipients are preferred over regular excipients in tableting because the former does not require granulation before tableting. However, to qualify for direct compression the excipients must show good flow properties. In an attempt to improve the powder flow properties of hydrolyzed gelatin, a spray-dried mixture of chitosan and hydrolyzed gelatin was prepared (Kokil, Patil, Mahadik, & Paradkar, 2005). The results of this investigation showed that spray-dried preparation of chitosan and hydrolyzed gelatin resulted in free-flowing powder with improved compressibility and compactability. He, Davis, & Illum (1999) developed chitosan microspheres by a spray-drying technique using the H_2-antagonist, cimetidine. The size of these particles was between 2 and 10 μm and dissolution of these particles was very fast. Rege, Garmis, & Block (2003) have studied the tableting properties of a mixture of spray-dried granules, tetracycline, and magnesium stearate. The results suggested that spray drying improved the binding functionality of chitosan. Although, these findings suggest that spray-dried chitosan possess good tableting properties, all these formulations were prepared using additional excipients like magnesium stearate as flow aid. Spray-dried composite particles containing lactose and alginate–chitosan complex was also prepared to develop dry coated acetaminophen tablets (Takeuchi, Yasuji, Yamamoto, & Kawashima, 1999). A comparison between the composite particles prepared with lactose and preformed alginate–chitosan and composite particles prepared by concomitant spray drying of a mixture of lactose, alginate, and chitosan showed significant difference in tableting properties. These particles showed controlled-release properties.

The objective of this study was to prepare and evaluate a novel spray-dried direct compression tableting excipient using a mixture of chitosan and lactose. Commercially available spray-dried lactose is one of the very commonly used direct compression excipient because of its excellent tableting properties. We hypothesized that spray-dried granules prepared with a mixture of lactose and chitosan will possess excellent flow as well as dissolution properties.

MATERIALS AND METHODS

Materials

Low (viscosity, 20–200 cP, 1% in 1% acetic acid)-, medium (viscosity, 200–800 cP, 1% in 1% acetic acid)-, and high (viscosity, 800–2000 cP, 1% in 1% acetic acid)-molecular-weight chitosan were purchased from Sigma-Aldrich (St. Louis, MO, USA). Citric acid (99.5%) monohydrate, sodium bicarbonate USP and the model drug, propranolol HCl, were also purchased from Sigma-Aldrich (St. Louis, MO, USA).

Experimental Design

The effect of molecular weight of chitosan was studied at three levels, low, medium, and high. The effect of the amount of chitosan was also studied at three levels (1, 1.9, and 2.5 g) for only the low-molecular-weight chitosan, because the viscosities of the medium- and high-molecular-weight chitosan were too high to spray through the spray nozzle. The amount of lactose was also adjusted accordingly to maintain a constant weight. The compositions of the various formulations of the lactose/chitosan granules are listed in Table 1.

TABLE 1
Composition of the Lactose/Chitosan Granules

Formulation	Chitosan MW	Amount of Chitosan (g)	Amount of Lactose (g)	Amount of Propranolol (g)
A	Low	1.0	20.0	2.2
B	Medium	1.0	20.0	2.2
C	High	1.0	20.0	2.2
D	Low	1.9	19.1	2.2
E	Low	2.5	18.5	2.2

Spray-Dried Granules

A specific amount of chitosan (1, 1.9, and 2.5 g, respectively) was dissolved in 50 mL of a 1% citric acid solution and later mixed with 50 mL of an aqueous solution of lactose (containing 20, 19.1, and 18.5 g, respectively) and propanolol (2.2 g) (Table 1). The resultant solution was sprayed through a Büchi B191 Mini Spray Dryer (Flawil, Switzerland), with a standard 0.7-mm nozzle. The inlet air temperature, aspirator, liquid flow, and compressed spray air flow were set at 140°C, 75%, 1.4 mL/min, and 400 L/h, respectively. When the resultant solution was fed to the nozzle with a peristaltic pump, atomization occurred by the force of the compressed air, disrupting the emulsion into small droplets. The droplets, together with hot air, were blown into a chamber where the solvent was evaporated and discharged through an exhaust tube. The fine granules that accumulated into the glass collection chamber were collected and freeze-dried (–20°C; 10×10^{-4} mbar; FreeZone 6, Labconco Corporation, Kansas City, MO, USA) for 24 h for complete removal of any residual solvent. The granules were evaluated for particle size and morphology, bulk density, tap density, and Carr index. Differential scanning calorimetry (DSC) was used to determine the effect of spray drying on chitosan and lactose.

Particle Size and Morphology

Particle size distribution was measured using dynamic laser scattering on a Malvern Mastersizer 2000 (Malvern Instruments Ltd., Malvern, UK) using a Scirocco 2000 dry powder sampling accessory fitted with a microvolume feeder. Measurement parameters included a 10 s measurement time utilizing 10,000 measurement snaps, a feed rate of 81%, and a dispersive air pressure of 1.625 bar. A 5-g sample of granules

was used for each measurement. Each measurement was performed in triplicate.

The surface morphology of the granules was examined by a Hitachi 3000N variable pressure scanning electron microscope (SEM) (Hitachi, Gaithersburg, MD, USA) following mounting of samples on metal stubs. The analytical parameters included an accelerating voltage of 10 keV, a working distance of 13.5 mm, and a vacuum of 40 Pa in variable pressure mode. Because the samples were analyzed in variable pressure mode, the backscatter detector BSE2 was used.

Thermal Characterization

Thermal analysis of the granules was performed using a DSC (TA 2920) fitted with a refrigeration unit (TA Instruments, New Castle, DE, USA). Low-molecular-weight chitosan, lactose, and spray-dried granules were used for thermal characterization. About 5 mg of a sample was weighed, crimped into an aluminum pan and analyzed at a scanning rate of 5°C/min. The temperature at the peak of endotherms was calculated using TA universal analysis software.

Density Measurement

The bulk and tap densities were measured in a 10-mL glass cylinder and the sample weights were maintained at 10 g. For bulk density measurement, the sample was placed into the graduated cylinder and the sides were tapped slightly to achieve uniform horizontal level. The same sample was tapped 100 times prior to the tap density measurement.

Preparation of Direct Compression Tablets

To evaluate the tableting properties of the spray-dried lactose/chitosan granules, 1 g of the granules was mixed thoroughly with 54 mg of sodium bicarbonate and compressed into tablets. The tablets were prepared by manually feeding the mixture into a tablet die of a hydraulic press (Carver Inc., Wabash, IN, USA). The tablets were compressed at 5,000 lb force using a flat-faced tablet punch and die with a flat steel plate as a lower retainer.

Dissolution Study

The dissolution rates of the tablets were monitored using a Varian Automated dissolution apparatus fitted with a Cary-50 Tablet Spectrophotometer (Model VK 7000, Varian Inc., Palo Alto, CA, USA). A volume of 900 mL of double-distilled water was used as the dissolution medium and the temperature was maintained at 37 ± 1°C. The USP II rotating paddle dissolution method was used at a rotation speed of 50 rpm. A specific volume of the dissolution medium was withdrawn automatically at a preset time and analyzed spectrophotometrically in-line at a wavelength of 296 nm.

Statistical Analysis

Statistical analysis was performed using the GraphPad Prism, version 5.0 software package (GraphPad Software, Inc, San Diego, CA, USA). The bulk density, tap density, average particle size, and dissolution data were reported as mean and standard deviation of three measurements. The bulk density and tap density were compared separately using one-way analysis of variance (ANOVA). Cochran's test was used to determine the homogeneity of variance of the data. A p value of $<.05$ was considered as evidence of a significant difference. In the event of a significant difference, the mean values were further compared using Student–Newman–Keul's multiple range test (SNK) to determine which formulation was significantly different from the others.

RESULTS AND DISCUSSION

The physical properties of the granules are listed in Table 2. A comparison of the particle size of the granules showed that the particles were heterogeneous in size with a range between 18 and 1,538 μm. The granules prepared with the low-molecular-weight chitosan (A, D, E) showed relatively smaller median particle size (422, 153, 499 μm, respectively) compared with the medium- and high-molecular-weight chitosan (788 and 683 μm). Despite slight differences in the median particle sizes, all five granules showed no practical differences in granules size ranges. A comparison of the SEM pictures of the granules showed that all five formulations showed similar surface morphology (Figure 1).

TABLE 2
Physical Characteristics of the Lactose/Chitosan Granules

Formulation	Bulk Density (g/cc) (±*SD*)	Results of SNK[a] Test	Tap Density (g/cc) (±*SD*)	Results of SNK[a] Test	Carr Index	Particle Size (μm) (80% Range)
A	0.16 (0.005)	A > B = C > D >E	0.18 (0.008)	A > B = C > D >E	11.1	422 (42–1,060)
B	0.13 (0.002)		0.15 (0.008)		13.3	788 (43–1,538)
C	0.13 (0.004)		0.15 (0.006)		13.3	683 (21–1,489)
D	0.12 (0.006)		0.14 (0.005)		14.3	153 (18–520)
E	0.10 (0.004)		0.12 (0.008)		16.7	400 (41–1,353)

[a]Student–Newman–Keul's multiple range.

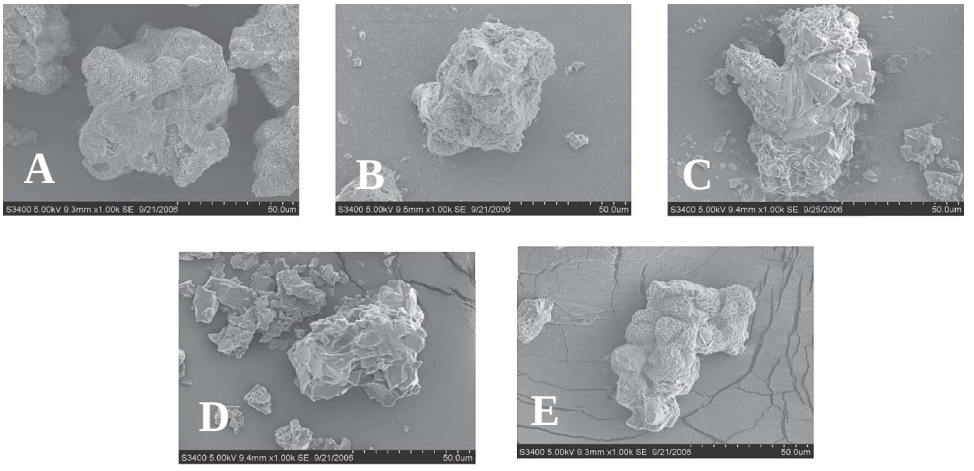

FIGURE 1. SEM photographs of spray-dried chitosan/lactose granules.

DSC is a valuable tool in the detection of changes that might occur during processing. Thermal characterization of the granules after spray drying, and comparing the results with the thermograms of lactose and chitosan before processing, can help determine the effect of spray drying on these adjuvants. Because the effect would be most pronounced at the highest concentrations, and the concentration of the lactose solution was essentially the same for all batches, DSC was conducted on the granules containing the highest concentration of chitosan (Formulation E; prepared by using the solution containing 2.5% low-molecular-weight chitosan) and compared with the thermograms of each of lactose and chitosan alone, as shown in Figure 2. DSC of lactose was characteristic of α-lactose monohydrate as evidenced by a dehydration endotherm peaking at approximately 145°C and a melting endotherm peaking at approximately 218°C. DSC of chitosan shows only a broad endotherm in the vicinity of 100°C and which corresponds to water removal as reported by Mladenovska et al. (2007). Spray-dried lactose has been reported to be amorphous, and upon heating recrystallizes at about 172°C to form α-lactose with a melting endotherm at approximately 217°C (Corrigan, Healy, & Corrigan, 2002). The DSC thermograms of the granules showed that lactose was in the amorphous form and did not recrystallize upon heating as evidenced by the absence of the characteristic melting endotherm at 217°C and the absence of a recrystallization exotherm at 172°C. Based on these findings, lactose and chitosan appear to be in the form of a molecular dispersion, which prevents the recrystallization of lactose upon heating.

As seen in Figure 3, the melting peak of propranolol was absent in the thermograms of the granules, and new peaks in the range between 180 and 200°C appeared in the granules containing the lower amounts of chitosan (1 and 1.9%). The intensities of these new peaks were reduced upon increasing

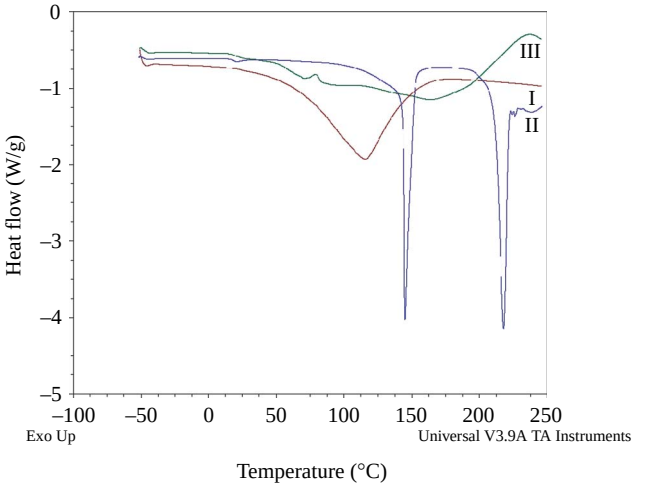

FIGURE 2. DSC thermograms of chitosan (I), lactose (II), and spray-dried granules (III).

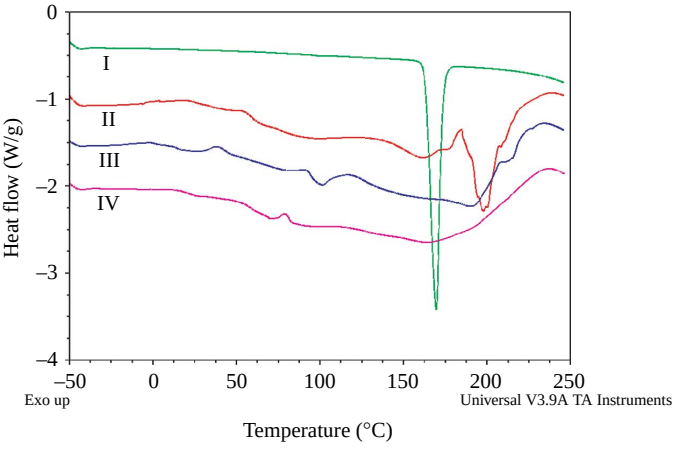

FIGURE 3. DSC thermograms of propranolol (I), granules containing low-molecular-weight chitosan 1% (II), 1.9% (III), and 2.5% (IV).

the amount of chitosan from 1 to 1.9%, and disappeared at the higher 2.5% concentration. The disappearance of the melting peak of propranolol could be attributed either to the presence of propranolol in the form of a solid solution in the particles, or to its interaction with lactose, or both. Gerber and Lotter (1993) have attributed the appearance of the new peaks between 180 and 200°C in a physical mixture of propranolol and lactose to an amine reaction between propranolol and lactose. Therefore, the decrease in the intensity of these peaks upon increasing the amount of chitosan could be attributed to one of the following: (1) increasing the amount of chitosan resulted in dissolution of the propranolol/lactose product to form a solid solution, or (2) chitosan reduced the interaction between propranolol and lactose, and a large amount of chitosan (2.5%) prevented the interaction from occurring. However, the identification of the exact mechanism of what is occurring requires further studies and is beyond the scope of this work.

A comparison of the bulk density of the granules revealed that when the amount of chitosan was constant (1 g), the bulk density of the granules was dependent on the molecular weight of the chitosan. The low-molecular-weight chitosan showed the highest bulk density (0.16 g/cc) compared with the medium- and the high-molecular-weight chitosan (Table 2). No significant differences ($p > .05$) were observed between the medium- and high-molecular-weight chitosan granules. The bulk density of the granules was further decreased when the amount of low-molecular-weight chitosan was increased to 1.9 and 2.5 g, respectively. Similar studies were not conducted for the medium- and high-molecular-weight chitosan because the amount of the medium- and high-molecular weight chitosan could not be increased due to their high viscosity at these concentrations. Similar observations were also recorded during the comparison of the tap densities (Table 2). Both bulk density and tap density are important to measure the flow properties of granules. The flow property is generally referred to as the Carr index. The values of Carr index of the various batches of granules were calculated by using the following equation:

$$\text{Carr index (\%)} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100.$$

The Carr index is an indication of the flowability of a powder. A Carr index greater than 25% is considered to be an indication of poor flowability, and a Carr index below 15% of excellent flowability (Wells, 2002). The granules prepared with 1 g of low-molecular-weight chitosan showed the minimum Carr index (11.1%) indicating the best flow properties among all five formulations. All three batches of granules prepared with 1 g of chitosan, irrespective of their molecular weight, showed excellent flow properties (Carr index < 15%). An increase in the amount of low-molecular-weight chitosan to 1.9 and 2.5 g, reduced the flow properties from excellent (Carr index 11.1%) to good (14.3 and 16.7%, respectively).

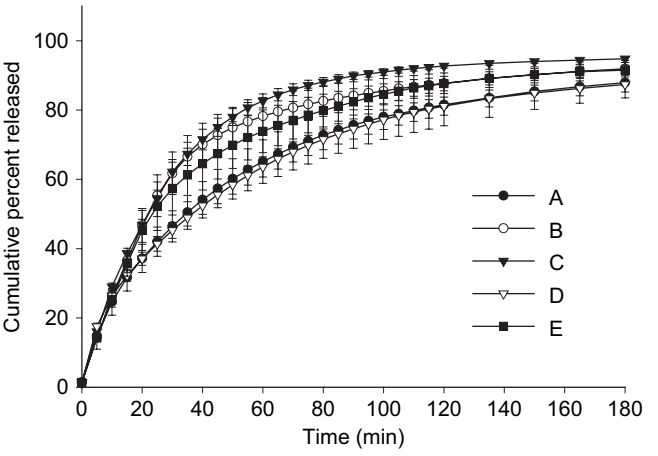

FIGURE 4. Dissolution profiles of the tablets prepared with various granule formulations.

Figure 4 shows the dissolution profiles of the tablets. The purpose of bicarbonate in the formulation mixture was to provide an effervescent action after reaction with the citric acid that was used to dissolve chitosan. During dissolution, the evolved carbon dioxide introduced buoyancy in the wet tablet, and the tablets were floating at the top of the dissolution vessels throughout the dissolution study. Irrespective of the molecular weight and the amount of chitosan, the floating behavior was observed in all the formulations. A comparison of the dissolution rates showed that all five formulations showed very fast drug release with 50% or more drug released within 60 min. The drug release from all five formulations was not significantly different for up to the first 15 min, and the dissolution rates thereafter showed a rank order correlation (Formulations A, B, and C; $p < .05$) with the molecular weight of chitosan. The high-molecular-weight chitosan (Formulation C) showed the fastest drug release followed by the medium- (Formulation B) and low- (Formulation A) molecular-weight chitosan. The trend continues throughout the dissolution study. An increase in the amount of low-molecular-weight chitosan from 1 to 1.9 g (Formulation D), did not show any significant difference in dissolution. However, when the amount of low-molecular-weight chitosan was increased to 2.5 g (Formulation E), the dissolution rate also increased and showed similar dissolution pattern with the formulation prepared with 1 g medium-molecular-weight chitosan (Formulation B). In summary, the use of higher molecular weight or higher amount of chitosan significantly increased the dissolution rate.

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