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Spray-dried chitinosans Part II: in vitro drug release from tablets made from spray-dried chitinosans

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Abstract

Purpose: Application of spray-dried chitinosans as excipients for use in drug delivery systems was explored. *Methods*: Spray- and tray-dried chitinosans previously *N*-deacetylated and depolymerized were used. Directly compressed tablets (200 mg) containing tetracycline, chitinosan, and magnesium stearate were prepared. The tablets were characterized for dimensions, weight, friability, crushing strengths, disintegration, and dissolution. *Results*: The tablet weights, thickness, and diameters were not affected by the chitinosan selected ($P > 0.05$). Friability of tablets containing tray-dried chitinosans was generally higher (and crushing strengths were lower) than tablets containing spray-dried chitinosans. Chitinosan molecular weight, degree of *N*-deacetylation, and drying method used, significantly affected crushing strengths ($P < 0.0001$). Disintegration times were affected only by the type of chitinosan ($P < 0.0001$) but not by the drying method used ($P > 0.9$). Dissolution from tablets was significantly affected by the chitinosan type ($P < 0.025$), but not affected by the drying method ($P > 0.5$). *Conclusions*: Spray drying improved binding functionality of chitinosans, thereby enhancing the tablet crushing strength; however, friability, disintegration, and dissolution profiles were not significantly affected. The data obtained from this study support the usefulness of spray-dried chitinosans as excipients for use in drug delivery systems.

Keywords: Chitinosan; Chitosan; Chitin; Drug release; Polyelectrolyte

1. Introduction

Tetracycline, a semisynthetically produced antibiotic, is a drug that is available commercially for peroral administration for the treatment of bacterial infections. The gastric effects (i.e. gastrointestinal distress, nausea, and vomiting) of perorally administered tetracycline may be alleviated, to some extent, by inhibiting its release in the gastric region (Kapusnik-Uner et al., 1996). When used in a matrix-type tablet formulation, chitinosan (Block, 1997)—a cationic biopolymer—forms a gel-barrier in an acid environment that can modulate or constrain drug release (Sawayanagi et al., 1982; Acartürk, 1989a; Machida and Nagai, 1989). Furthermore, at acidic pHs, chitinosan's amines are protonated and, therefore, can interact with oppositely charged drug ions, and in this manner serve as excipients for modified release drug delivery systems (Akbuga, 1995). Miyazaki et al. (1981) evaluated the suitability of

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this biopolymer for use as vehicle for sustained release of indomethcin and papavarine hydrochloride. Zero-order drug release was obtained from chitinosan films. Sawayanagi et al. (1982) evaluated the fluidity, compressibility, and disintegration behavior of tablets made from powder blends of chitinosan with lactose, potato starch, or mannitol and compared them with crystalline cellulose. Fluidity of chitinosan powder blends was higher than that for crystalline cellulose and tablet crushing strength increased with increasing polymer concentration. In another study, diclofenac sodium release was prolonged from chitin and chitinosan matrices (Acartürk, 1989a,b), where an increase of chitinosan content in the tablets provided sustained diclofenac sodium release. Knapczyk (1993) used chitinosans (with 49 and 66% degree of *N*-deacetylation) in tablet formulations and evaluated the usefulness of this excipient after long-term tablet storage. Chitinosan met the standard requirements for auxiliary substances used in direct compression, and behaved as a disintegrant when present above 50% of tablet mass.

Chitinosans have been evaluated as directly compressible tablet excipients, but virtually all formulations developed necessitated the addition of other ingredients to facilitate compression. However, papers indicating to the use of this biopolymer as a directly compressible tablet excipient (Sabnis et al., 1997; Shukla et al., 1998; Rege et al., 1999) are also available in the literature. Although these papers suggest the possibility of chitinosan use as a directly compressible agent, the compressibility of chitinosan needs to be improved in order to make it acceptable to the formulator.

Spray drying has been successfully used in the pharmaceutical industry to process powders, since it offers a means for obtaining powders of predetermined particle size and shape (Broadhead et al., 1992; Rankell et al., 1991). Furthermore, spray-dried lactose is one of the most commonly encountered pharmaceutical excipients, and has been commercially available for many years. Its main advantage is that it is directly compressible.

Insofar as the chitinosans are concerned, their spray drying and the characterization of the spray-dried products have been reported earlier.

In this study, we explored the use of spray- and tray-dried chitinosans in directly compressed tablets containing tetracycline as a model drug. Tetracycline release, as a function of time, from the chitinosan-containing tablets, was evaluated as a function of dissolution medium pH.

2. Materials and methods

Commercial chitinosans, deacetylated, depolymerized, and subsequently spray dried or tray dried (Table 1) using the procedures reported in Part I of this series were evaluated as direct compression binders in this study.

2.1. Development of an analytical method for tetracycline

The acidic pH (1.2) was obtained using a 0.1N hydrochloric acid solution, whereas the basic buffer employed 0.2 M sodium triphosphate salt solution. These buffer solutions were prepared in accordance with USP guidelines (USP 24/NF 19, 2000). Standard solutions of tetracycline were prepared by dissolving the drug in 0.1N HCl or in a solvent mixture containing 75% 0.1N HCl: 25% 0.2 M sodium triphosphate. Calibration plots for subsequent UV analysis of tetracycline (concentration range = 0–30 μg/ml) were generated for both solvent systems. The analyses were conducted

Table 1
Degrees of *N*-deacetylation and molecular weights of chitinosans used in this study

Chitinosan	Degree of *N*-deacetylation (%)[a]	Molecular weight (kDa)[a]
FLMW spray dried	88.9 ± 0.2	280.3 ± 10.2
FLMW tray dried	86.0 ± 0.5	287.3 ± 10.1
FHMW spray dried	85.3 ± 0.2	522.1 ± 12.6
FHMW tray dried	87.3 ± 0.5	519.6 ± 10.5
SP spray dried	66.7 ± 0.9	–
SP tray dried	65.9 ± 0.3	–
SP12 spray dried	82.2 ± 0.7	2.0 ± 0.9
SP12 tray dried	81.4 ± 0.5	1.8 ± 0.1
SP21 spray dried	86.3 ± 0.1	15.8 ± 0.4
SP21 tray dried	86.6 ± 0.2	16.6 ± 0.5
SF11 spray dried	82.5 ± 0.5	6.5 ± 0.3
SF11 tray dried	81.7 ± 0.4	6.7 ± 0.1
SF22 spray dried	85.7 ± 0.6	5.0 ± 0.1
SF22 tray dried	85.8 ± 0.5	4.9 ± 0.2

[a] Mean ± S.D.; $n = 3$.

at wavelengths (λ_{max}) of 268 and 276 nm, respectively, using a Perkin-Elmer UV-Vis spectrophotometer (Model λ-4A, UV-Vis Spectrophotometer, Perkin Elmer, Norwalk, CT).

2.2. Preparation of tetracycline–chitinosan tablets

Directly compressed tablets (200 mg) were prepared from admixtures containing tetracycline (12.5%), chitinosan (86.5%), and magnesium stearate (1 mg). The tablets were compressed using a Carver hydraulic press (Model C, Fred S. Carver, Menomonee Falls, WI) fitted with 3/8-in. flat-faced tooling. The total compaction time was 5–7 s, during which pressure was applied for the first 2–3 s and then maintained at 5000 psig for the rest of the time.

2.3. Tablet characterization

2.3.1. Determination of physical characteristics

Tablet diameter, thickness, and crushing strength of 10 tablets from each batch were determined using a Pharma Test™ tablet tester (Model PTB 311, Scientific Instruments and Technology Corp., NJ). The friability of 10 tablets from each batch was determined using an Erweka friability tester (Model TA3, Erweka Apparatebau GmbH., Heusenstamm, Germany).

2.3.2. Evaluation of disintegration times of the tablets

Disintegration times (USP XXIV method, with disks) of the tablets in pH 1.2 hydrochloric acid buffer were determined using a VanderKamp disintegration tester (VanKel Industries Inc., Edison, NJ). The buffer solution was maintained at $37 \pm 0.5\,^{\circ}C$ in a constant-temperature bath (Precision water bath, Model 183, VanKel Industries Inc., Edison, NJ). Three tablets from each batch were evaluated for their disintegration times.

2.3.3. Study of in vitro drug dissolution

In vitro drug dissolution studies were performed using an USP Type 2 dissolution apparatus (VanderKamp 600, VanKel Industries Inc., Edison, NJ). The dissolution study was conducted in accordance with USP XXIV guidelines for extended release drug dosage forms. Dissolution was evaluated at $37 \pm 0.5\,^{\circ}C$, at a stirring speed of 50 rpm, from 0 to 5 h. The release study employed 750 ml of 0.1N HCl (pH ∼ 1.2) for a period of 2 h, following which 250 ml portions of 0.2 M sodium triphosphate buffer (Reagents, indicators, and solutions, 1999) were added and the pH adjusted to 6.8. The dissolution was then continued in this medium for additional 3 h. Three replicates from each batch were tested. Dissolution medium samples (3 ml) were withdrawn at predetermined time intervals (i.e. 0.25, 0.5, 1.0, 2.0, 3.5, and 5.0 h), filtered through a 5 μm nylon filter and analyzed for drug content by UV spectrophotometry. The sample volume was replaced with fresh dissolution medium and a correction factor was used to account for the change in the dissolution medium volume after the addition of the basic buffer.

2.4. Experimental design

2.4.1. Effect of chitinosan drying methods on the physical characteristics of tetracycline–chitinosan tablets

A full factorial analysis of variance procedure was used to evaluate the effect of the chitinosan drying method on the physical properties of the tetracycline–chitinosan tablets. The *independent* variables were the chitinosans used ($n = 7$), the drying process (spray drying or tray drying), and the replicate measurements. The *dependent* variables used were the tablet crushing strengths and the disintegration times.

2.4.2. Effect of spray-dried chitinosans on tetracycline release

A $7 \times 2 \times 3$ full factorial analysis of variance procedure was used to evaluate the effect of chitinosans and the drying process on tetracycline release. The *independent* variables were the chitinosans used ($n = 7$), the drying process (spray drying or tray drying), and the replicate measurements ($n = 3$). The *dependent* variable used was the release rate of tetracycline (milligrams per hour) from chitinosan tablets. All data were analyzed using Statview (v. 5.0, SAS Institute, Inc., Cary, NC) and JMP (v.3.1.5, SAS Institute, Inc., Cary, NC).

3. Results and discussions

The chitinosans used in this study were deacetylated and/or depolymerized in accordance with procedures reported by Rege and Block (1999). The chitinosans

Table 2
Physical properties of tetracycline–chitinosan tablets

Lot	Drying method used[a]	Weight (mg)[b]	Thickness (mm)[b]	Diameter (mm)[b]	Crushing strength (kp)[b]	Friability (% loss)[c]	Disintegration time (min)[d]
FLMW	SD	201.4 ± 3.2	2.3 ± 0.1	10.4 ± 0.1	3.2 ± 1.1	0.71	180.9 ± 2.5
	TD	200.4 ± 2.2	2.1 ± 0.2	10.2 ± 0.2	1.1 ± 0.5	–	179.9 ± 6.5
FHMW	SD	200.6 ± 2.7	2.1 ± 0.1	10.3 ± 0.2	3.9 ± 0.5	0.85	191.1 ± 6.1
	TD	199.6 ± 2.7	2.4 ± 0.1	10.4 ± 0.1	1.7 ± 0.2	–	243.2 ± 2.6
SP	SD	200.8 ± 2.6	1.9 ± 0.1	10.0 ± 0.1	4.1 ± 0.4	0.43	8.7 ± 0.6
	TD	202.6 ± 2.1	2.1 ± 0.1	10.3 ± 0.1	4.1 ± 0.9	0.49	18.9 ± 0.6
SP12	SD	200.0 ± 2.2	2.1 ± 0.1	10.5 ± 0.1	7.4 ± 0.9	0.32	6.6 ± 0.4
	TD	200.4 ± 1.8	2.0 ± 0.2	10.4 ± 0.1	3.1 ± 0.5	0.28	3.7 ± 0.3
SP21	SD	199.2 ± 3.0	1.9 ± 0.1	10.3 ± 0.1	18.6 ± 1.7	0.23	14.9 ± 0.2
	TD	200.8 ± 2.8	2.1 ± 0.1	10.3 ± 0.1	1.4 ± 0.2	1.08	4.7 ± 0.8
SF11	SD	198.8 ± 1.8	2.0 ± 0.1	10.3 ± 0.1	16.9 ± 1.4	0.05	34.1 ± 4.0
	TD	199.4 ± 2.4	2.1 ± 0.1	10.3 ± 0.1	2.46 ± 0.2	0.2	6.8 ± 1.0
SF22	SD	200.4 ± 1.8	2.0 ± 0.1	10.3 ± 0.1	4.7 ± 0.7	0.35	31.2 ± 3.0
	TD	200.8 ± 0.13	2.2 ± 0.1	10.4 ± 0.1	0.3 ± 0.2	–	7.4 ± 1.2

[a] SD, spray drying; TD, tray drying.
[b] Mean ± S.D.; $n = 5$ tablets.
[c] $n = 5$ tablets.
[d] $n = 3$ tablets.

purchased from Sigma Chemical Co. (i.e. lots SP and SF) were deacetylated and depolymerized, using the procedures described above to yield lots SP12, SP21, SF11, and SF22. The deacetylated and depolymerized chitinosans were subsequently either spray dried or tray dried. Although, lots SP and SF (labeled as chitins) were used as starting materials to prepare the "treated" batches, only one chitin sample (lot SP) was further characterized, as a in the drug release study. The chitinosans purchased from Fluka Chemie (i.e. lots FLMW and FHMW) were not chemically treated (i.e. deacetylated or depolymerized).

3.1. Physical characteristics of tetracycline–chitinosan tablets

The physical properties of the tetracycline–chitinosan tablets are listed in Table 2. The weights, thicknesses, and diameters of the tablets were not affected by the specific chitinosan used in the tablet formulation ($P > 0.05$). However, the friability of tablets containing *tray-dried* chitinosans was generally higher than the corresponding tablets containing *spray-dried* chitinosans; tablet chipping and breakage was observed for tray-dried chitinosan batches FLMW, FHMW, and SF22. The crushing strengths of the tablets containing spray-dried chitinosans were generally higher than the tablets containing tray-dried chitinosans. Chitinosan molecular weight and degree of *N*-deacetylation, as well as the drying method used during chitinosan manufacture, significantly affected tablet crushing strengths ($P < 0.0001$). The ANOVA outcome is shown in Table 3.

Surprisingly, disintegration times of tablets were affected only by the type of chitinosan ($P < 0.0001$) but not by the drying method used in chitinosan manufacture, i.e. tablets containing either spray- or tray-dried chitinosans had similar disintegration times ($P > 0.9$). The ANOVA is shown in Table 4.

Table 3
ANOVA outcome, dependent variable: tablet crushing strengths

Source	d.f.	SSQ	*F*-ratio	*P*-value
Chitinosan	6	654.2	8.9	<0.0001
Drying method	1	723.8	59.5	<0.0001
Replicate	4	1.3	0.03	0.9986

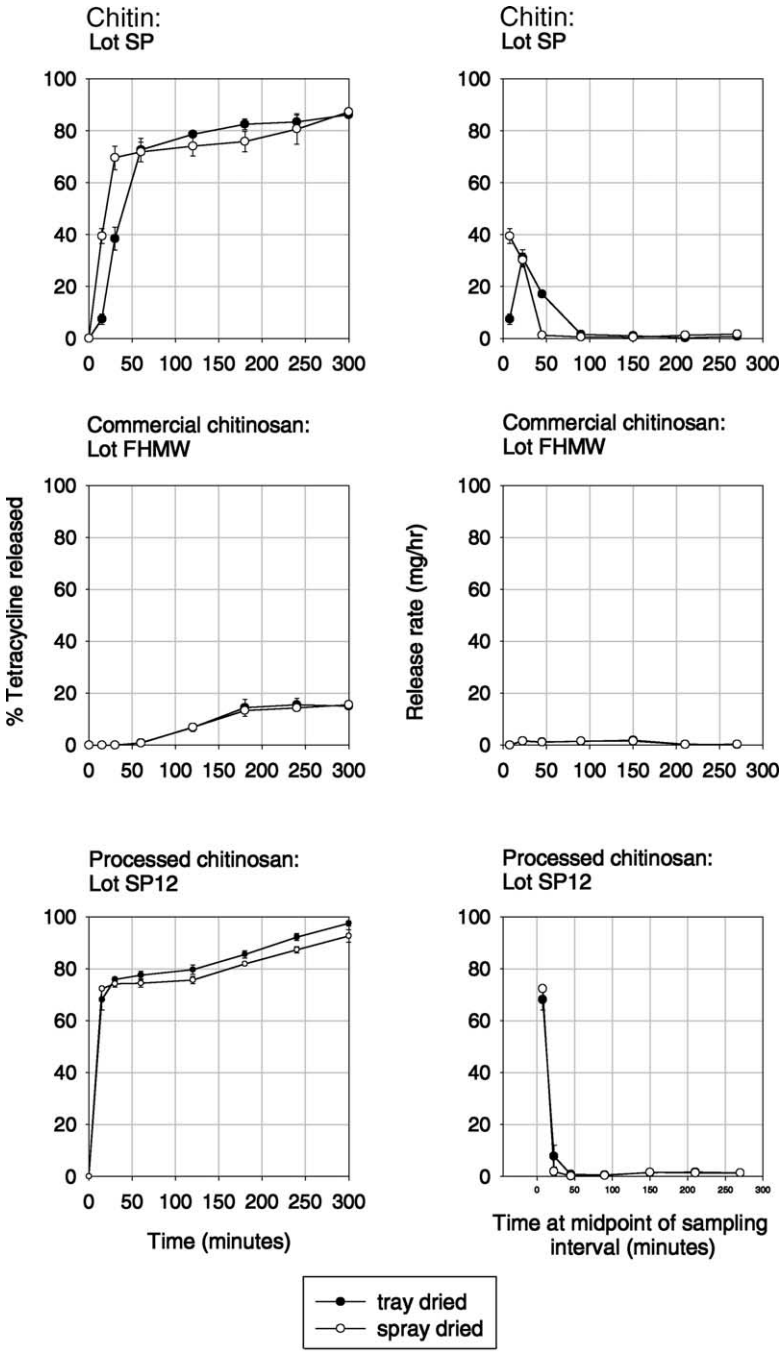

Fig. 1. Dissolution profiles and release rates of tetracycline from chitinosan tablets.

Table 4
ANOVA outcome, dependent variable: tablet disintegration time

Source	d.f.	SSQ	*F*-ratio	*P*-alue
Chitinosan	6	298527.1	240.5	<0.0001
Drying method	1	3.0	0.01	0.9048
Replicate	2	60.5	0.1	0.8645

3.2. In vitro tetracycline dissolution profiles

In vitro tetracycline dissolution studies were performed using an USP Type 2 dissolution apparatus. The release data were transformed to yield the rate (milligrams per hour) at which tetracycline was released from the tablet matrix. The release rates were plotted as a function of time (Fig. 1). Fig. 1 compares the release rate of tetracycline from tablets containing spray-dried chitinosan or corresponding tray-dried chitinosan. The release rates were used as the dependent variable in a full factorial ANOVA to examine the effect of chitinosans as well as the drying method used in chitinosan manufacture on drug release. Drug release from the tablets was significantly affected by the type of chitinosan used as the excipient ($P < 0.025$), but was not affected by the drying method used ($P > 0.5$). The ANOVA outcome is reported in Table 5. Multiple comparisons between the drug release rates for spray- and tray-dried chitinosans using post hoc tests (i.e. Fisher's PLSD test, Scheffe test, Bonferroni/Dunn test, Tukey/Kramer test, and Student–Newman–Keuls test) confirmed that the drying method used during chitinosan manufacture did not significantly affect drug release (data not shown).

Table 5
ANOVA outcome, dependent variable: drug release rate

	d.f.	SSQ	*F*-ratio	*P*-value
Source				
Chitinosan	6	5122.23	3.56	0.0200
Drying method	1	99.85	0.42	0.5188
Replicate	6	293.29	0.20	0.9753
Effect of drying method on drug release				
Chitinosan				
FHMW	1	0.020	0.39	0.8438
FLMW	1	33.66	9.36	0.0039[a]
SP	1	52.41	0.28	0.6007
SP12	1	1.700	0.003	0.9582
SP21	1	140.8	0.365	0.5493
SF11	1	3.515	0.100	0.9217
SF22	1	160.9	1.264	0.2676

[a] Significant at $P = 0.05$.

4. Conclusions

Although chitinosans have been evaluated as directly compressible tablet excipients, virtually all formulations developed necessitated the addition of other ingredients to facilitate compression (Sawayanagi et al., 1982; Knapczyk, 1993). Previous reports from our laboratories have demonstrated the potential use of chitinosans as excipients for directly compressible tablet formulations (Sabnis et al., 1997; Shukla et al., 1998; Rege et al., 1999). Although chitinosans can be directly compressed, the resultant tablets, generally, are friable and soft. Previous reports from our laboratories have dealt with the processing issues (Rege and Block, 1999) as well as the physicochemical and micromeritic characterization of these biopolymers (Part I of this series). In this study, we have explored the use of spray-dried chitinosans as excipients for directly compressible tablet formulations.

Not surprisingly, tablet physical properties were dependent on the specific chitinosan selected as well as by the drying method used in chitinosan manufacture. In general, tablets containing spray-dried chitinosans were less friable and exhibited higher crushing strength values than those resulting from tablets containing tray-dried materials. However, tetracycline release was not dependent on the drying method used in chitinosan manufacture: tablets containing spray-dried chitinosans or their corresponding tray-dried products exhibited similar release profiles. Thus, while the selection of drying method alters the micromeritic and tablet physical properties, the drug release rates from these chitinosan matrices are not significantly affected. Using the spray drying procedures developed previously in our laboratory, we achieved compressibility and, at the same time, improved the crushing strengths of the resultant tablets. These drug release–time data coupled with other data in the literature (Sabnis et al., 1997; Shukla et al., 1998; Rege et al., 1999) further support the use of chitinosans as excipients in drug delivery systems.

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