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Chitinosans as tableting excipients for modified release delivery systems

Pankaj R. Rege, Dhruti J. Shukla, Lawrence H. Block *

Department of Medicinal Chemistry and Pharmaceutics, 437 Mellon Hall of Science, School of Pharmacy, Duquesne University, Pittsburgh, PA 15282, USA

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Abstract

The term 'chitinosans' embraces the spectrum of acetylated poly(*N*-glucosamines) ranging from chitin to chitosan. Chitinosans (**I**), at acidic pH, have protonated amines which can interact with oppositely charged drug ions and, thereby, modify drug release from drug delivery systems. Tablets were compressed from a physical mixture containing salicylic acid (**II**) as the model drug, **I**, and magnesium stearate. Five commercial **I** compounds, varying in degree of deacetylation and molecular weight, were selected. Tablets were compressed at 5000, 10 000, and 15 000 psig using a Carver and a single punch tablet press. The differential scanning calorimetry thermograms provided evidence of **I**–**II** interaction in the powder blend. Analysis of variance (ANOVA) indicated that the compression pressure did not significantly affect the crushing strength (CS) or the release profile of **II** from the **I**-matrix tablets ($P > 0.05$). Furthermore, the ANOVA also indicated that the tablet press used during manufacture did not affect the above properties ($P > 0.05$); however, the chitinosans significantly affected the CS as well as the release profile of **II** from **I**-matrix tablets ($P < 0.05$). This study provides further evidence for the use of commercial **I** compounds as excipients for use in modified release drug delivery systems.

Keywords: Chitinosan; Chitosan; Excipient; Polyelectrolyte complex

1. Introduction

The term 'chitinosans' (Fig. 1) embraces the spectrum of acetylated poly(*N*-glucosamines), ranging from chitin (0% deacetylated) to chitosan (100% deacetylated) (Block, 1997). If the term 'chitin' is reserved for poly(*N*-acetyl-glucosamine), where the degree of deacetylation is 0%, and the term 'chitosan' is employed for poly(glucosamine), with a 100% degree of deacetylation, then in general, commercially available 'chitosans' are heterogeneous, poorly charac-

* Corresponding author. Tel.: +1-412-396-6362; fax: +1-412-396-5130.

E-mail address: block@duq.edu (L.H. Block)

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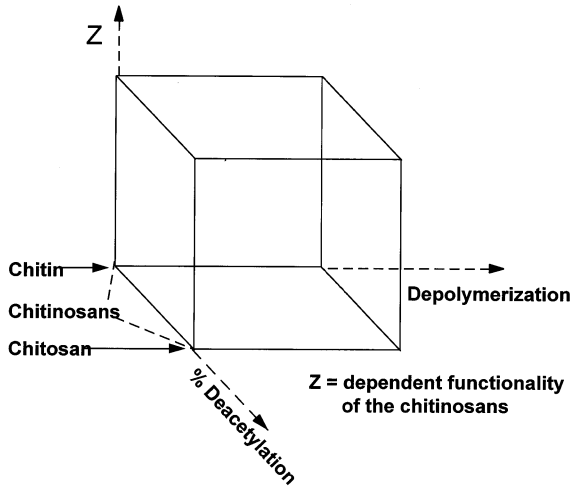

Fig. 1. The chitinosan spectrum.

terized materials for which the degree of deacetylation ranges from 60 to 90%. Hence, commercially available 'chitosans' have both *N*-acetyl-glucosamine, as well as glucosamine, moieties. In addition, the molecular weights (MW) of these commercial materials typically range from 50 to 2000 kDa. The heterogeneity of these chitinosans is the result of the relatively uncontrolled commercial processing of native chitin involving both *N*-deacetylation and depolymerization.

An extensive review and evaluation of the published literature and our own laboratory data reveal the dependence of chitinosan properties (e.g. solubility, ionizability, reactivity) and functionality (Akbuga, 1995) (e.g. as a bioadhesive (Lehr et al., 1992), as a wound healing agent (Akbuga, 1995), as a paracellular transport enhancer (Schipper et al., 1996), and as a complexing agent for drugs (Al-Angary, 1994) on two fundamental parameters: degree of deacetylation and degree of polymerization (i.e. MW).

The main driving force in the development of new applications for chitinosans lies in the fact that this cationic polymer is not only readily and economically processed from naturally abundant chitin, but also is non-toxic, biodegradable, and multifunctional (Akbuga, 1994). Nonetheless, chitinosans have not been widely adopted as pharmaceutical excipients or formulation components. One area of concern involves their utilization in directly compressible tablet formulations. Although chitinosans have been evaluated as directly compressible tablet excipients, virtually all formulations developed to date necessitate the addition of other ingredients to facilitate compression (Machida and Nagai, 1989; Knapczyk, 1993; Akbuga, 1994). This reflects the fact that these commercially available polymers, as supplied, lack good flow properties and compressibility (Sabnis et al., 1997).

In this study, we attempted to directly compress commercially available chitinosans and evaluate their suitability as tableting excipients.

Table 1
Degrees of deacetylation, molecular weights, and moisture contents of commercial chitinosans

Chitinosan	Degree of deacetylation (%)		Molecular weight (kDa)		Moisture content (%)	
	Labeled*	Experiment[a]	Labeled	Experiment[a]	Labeled	Experiment[b]
S-P[c]	n/a	65.9 ± 0.3	n/a	n/a	n/a	7.1 ± 0.1
S-F[c]	n/a	71.5 ± 0.4	n/a	n/a	n/a	8.4 ± 0.1
F-LMW[d]	89.3	89.4 ± 2.0	70	52.4 ± 6.8	n/a	10.5 ± 0.2
F-MMW[d]	84.5	81.6 ± 0.8	400	284.8 ± 9.7	n/a	9.3 ± 0.7
F-HMW[d]	83.0	91.5 ± 0.4	600	418.9 ± 14.4	n/a	10.2 ± 0.3

* n/a, no information available.
[a] Our data; mean ± S.D., $n = 3$.
[b] Our data; mean ± S.D., $n = 2$.
[c] Sigma, St. Louis, MO.
[d] Fluka Chemie, Buchs, Switzerland.

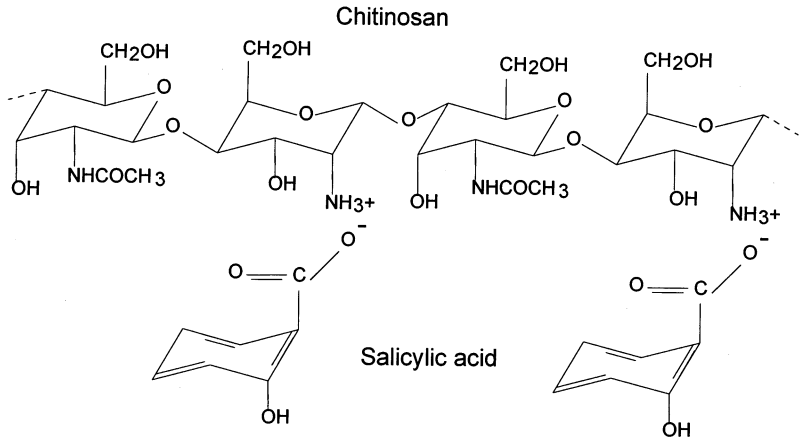

Fig. 2. Depiction of salicylic acid–chitinosan ionic interaction.

2. Materials and methods

2.1. Characterization of selected chitinosans

Five different commercially available chitinosans differing in their molecular weights and degrees of deacetylation were selected. The suppliers/ manufacturers are listed in Table 1. The chitinosans were used as supplied, except that the materials were milled (Wiley Mill, Model # 3; A.H. Thomas, Philadelphia, PA) and passed through a 100 mesh (150 μm) sieve prior to use.

2.1.1. Degree of deacetylation determinations

The degree of deacetylation was determined by an IR spectroscopic method (Sabnis and Block, 1997) using a Perkin-Elmer FT–IR spectrometer (Model 1605; Perkin Elmer, Norwalk, CT). Approximately 25 mg of dried chitinosan was triturated with 100 mg of potassium bromide (IR grade) and the mixture passed through a 100 mesh (150 μm) sieve; about 40 mg of the sieved mixture was then used to prepare a pellet.

2.1.2. Degree of polymerization determinations

Chitinosan MW (viscosity average) was calculated from the classical Mark–Houwink relationship,

$$[\eta] = K_m(MW)^a \quad (1)$$

where $[\eta]$ is the intrinsic viscosity, $K_m = 2.14 \times 10^{-3}$, and $a = 0.657$. The values of K_m and a were previously determined by laser light-scattering techniques (Sabnis, 1996).

Polymer solutions, of known concentrations, were prepared in a solvent system consisting of 0.5 M acetic acid and 0.25 M sodium chloride in deionized water. The solutions were then filtered through a 5 μm nylon filter (Magna-R, Lot number 67498; Micron Separations, Westboro, MA) prior to the viscosity measurements. The viscosity measurements were made, in triplicate, by recording the efflux times of the filtered solutions in Ubbelohde viscometers maintained in a constant-temperature bath at 25 ± 0.1°C.

2.1.3. Moisture content determinations

The moisture content of the chitinosans employed in this study was determined using a Computrac moisture analyzer (Model Max 2000; Arizona Instruments, Phoenix, AZ). Accurately weighed chitinosan samples (0.5 g) were placed on aluminum pans, heated from 50 to 200°C, and the corresponding percentage moisture content computed.

The degrees of deacetylation, the molecular weights, and the moisture contents of the various chitinosans employed in this study are listed in Table 1.

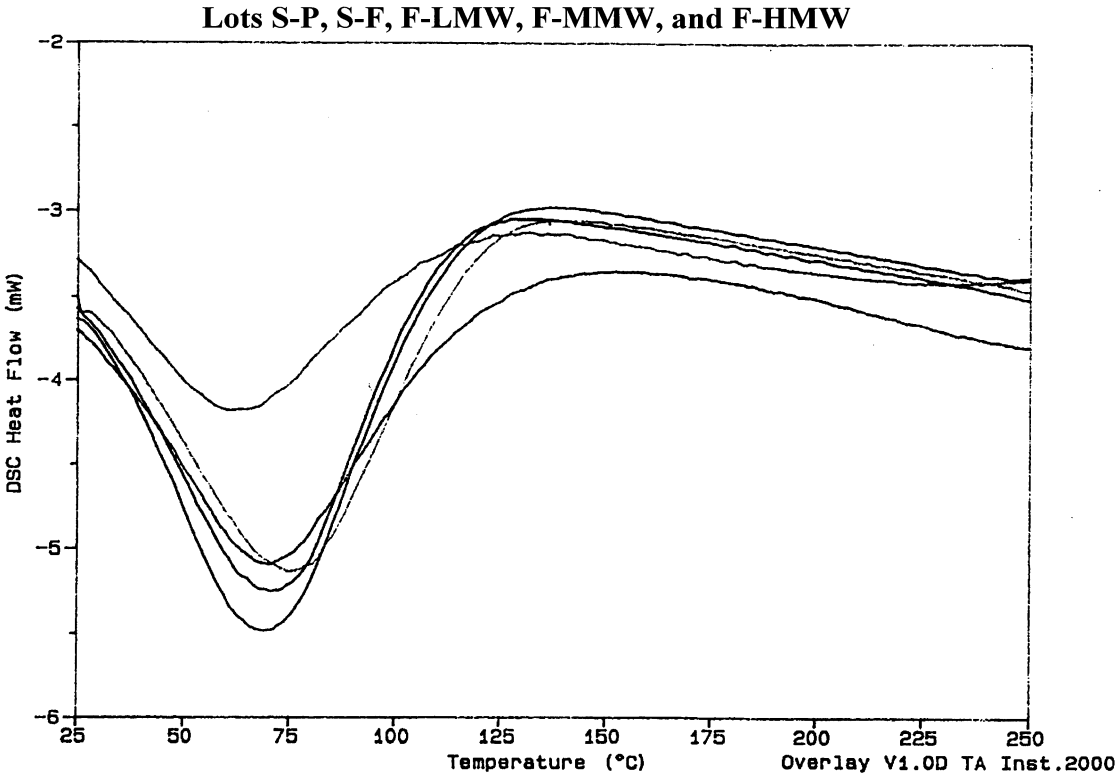

Fig. 3. DSC thermograms of chitinosans used in this study.

2.1.4. Differential scanning calorimetry determinations

Differential scanning calorimetry (DSC) thermograms of chitinosan samples (approximately 5 mg) were generated using a DuPont 2910 TA/DSC instrument (TA Instruments, New Castle, DE) equipped with Thermal Analyst 2000 software. The DSC heating rate employed was 5°C/min over a temperature range of 25–250°C.

2.2. Model drug selection and tablet formulation

Chitinosans, at acidic pH, have protonated amines (depending on the extent of their degrees of deacetylation) which can interact with oppositely charged drug ions and, thereby, modify drug release from drug delivery systems. Salicylic acid was chosen as the model drug in this study. The salicylic acid–chitinosan ionic interaction is depicted in Fig. 2.

The tablet formulations contained salicylic acid, chitinosan, and magnesium stearate. Tablets weighing approximately 200 mg were compressed from a physical mixture containing 13.6% w/w salicylic acid, 85.9% w/w chitinosan, and 0.5% w/w magnesium stearate.

2.3. Tablet compression

2.3.1. Carver press (Model C)

In order to determine the effect of compression pressure on the tablet properties, tablet formulations (containing chitinosans S-F and S-P) were compressed using the Carver press (Model C; Fred S. Carver, Menmonee Falls, WI) at 5000, 10 000, and 15 000 psig. The Fluka products were only compressed at 5000 psig on the Carver press. The Carver press was 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 the desired pressure for the rest of the duration.

2.3.2. Single punch press (Model 511-1)

All chitinosans were compressed using the Stokes single punch tablet press (Model 511-1; F.J. Stokes, Philadelphia, PA) equipped with 7/16-in standard concave punches and corresponding dies.

2.4. Tablet characterization

2.4.1. 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, NJ). The friability of 10 tablets from each batch was determined using an Erweka friability tester (Model TA3; Erweka Apparatebau, Heusenstamm, Germany).

2.4.2. Evaluation of disintegration times of the tablets

Disintegration times of the tablets in pH 7.4 phosphate buffer (USP XXIII method, without disks) were determined using a VanderKamp disintegration tester (VanKel Industries, Edison, NJ). The buffer solution was maintained at 37 ± 0.5°C in a constant-temperature bath (Precision water bath, Model 183; VanKel Industries, Edison, NJ). Six tablets from each batch were evaluated for their disintegration times.

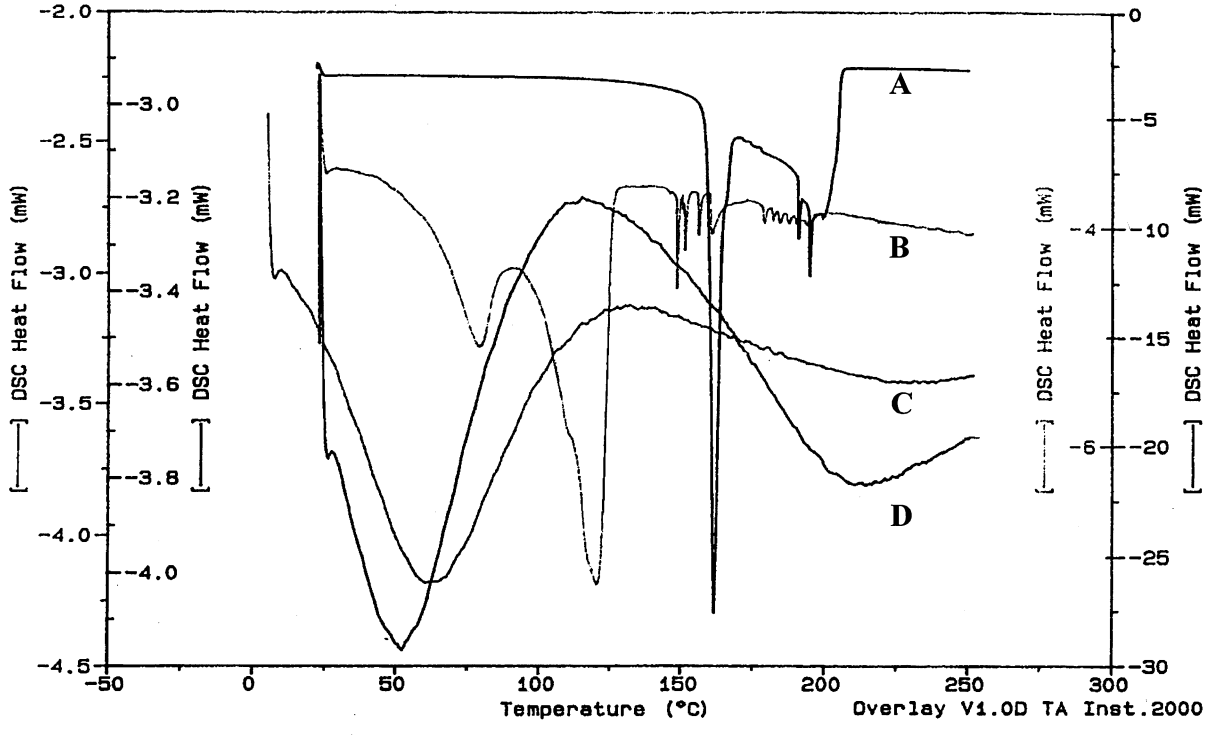

Fig. 4. Representative thermogram for salicylic acid–chitinosan formulation blend.

Table 2
Characteristics of salicylic acid–chitinosan tablets

Chitinosan	Tablet press[a]	Weight[b] (mg)	Thickness[b] (mm)	Diameter[b] (mm)	Crushing strength[b] (Kp)	Friability[c] (% loss)	Disintegration time[d] (min)
S-P	CP 5000 psig	198.20 ± 1.81	1.96 ± 0.06	10.03 ± 0.02	3.71 ± 0.22	0.63	<1
	CP 10 000 psig	197.90 ± 3.45	1.91 ± 0.06	10.00 ± 0.01	4.41 ± 0.38	0.60	<1
	CP 15 000 psig	196.20 ± 1.32	1.91 ± 0.05	10.01 ± 0.01	4.43 ± 0.29	0.73	<1
	SP	198.40 ± 3.86	3.33 ± 0.04	9.31 ± 0.25	1.24 ± 0.22	1.94	<1
S-F	CP 5000 psig	201.20 ± 1.99	2.09 ± 0.13	10.09 ± 0.11	2.93 ± 0.34	2.31	<1
	CP 10 000 psig	200.90 ± 1.37	1.95 ± 0.11	10.05 ± 0.11	3.73 ± 0.38	0.88	<1
	CP 15 000 psig	200.30 ± 1.77	1.91 ± 0.04	10.03 ± 0.01	4.09 ± 0.93	0.49	<1
	SP	201.30 ± 3.62	3.29 ± 0.05	9.24 ± 0.01	1.41 ± 0.22	2.27	<1
F-LMW	CP	198.60 ± 1.90	1.87 ± 0.02	9.97 ± 0.01	14.96 ± 0.92	0.12	>120
	SP	200.90 ± 1.23	3.03 ± 0.13	9.21 ± 0.01	9.53 ± 1.36	0.04	>120
F-MMW	CP	201.30 ± 1.16	1.99 ± 0.11	10.05 ± 0.11	4.43 ± 1.01	0.76	>120
	SP	201.10 ± 6.81	3.21 ± 0.06	9.24 ± 0.01	2.81 ± 0.43	0.49	>120
F-HMW	CP	199.30 ± 1.49	1.87 ± 0.12	10.02 ± 0.11	4.00 ± 0.97	0.96	>120
	SP	205.10 ± 3.93	3.16 ± 0.06	9.21 ± 0.01	2.02 ± 0.47	0.93	>120

[a] CP, Carver press; SP, Stokes single punch press.
[b] Mean ± S.D., $n = 10$ tablets.
[c] $n = 10$ tablets.
[d] $n = 6$ tablets.

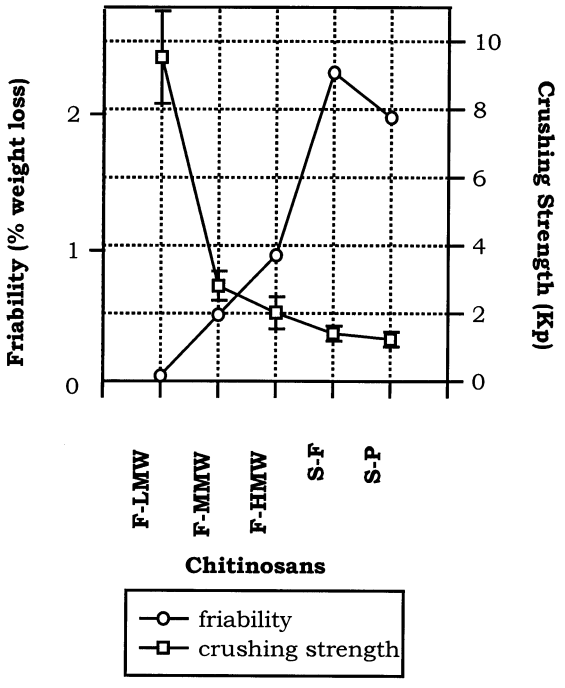

Fig. 5. Effect of chitinosans on the physical properties of salicylic acid–chitinosan tablets.

2.4.3. Study of in vitro drug release

2.4.3.1. USP apparatus 2. In vitro drug dissolution studies were performed using a USP Type 2 dissolution apparatus (VanderKamp 600; VanKel Industries, Edison, NJ). The dissolution medium was 900 ml of pH 7.4 phosphate buffer. Dissolution was evaluated at 37 ± 0.5°C, at a stirring speed of 50 rpm, from 0 to 24 h. Three replicates from each batch were tested. Samples of the dissolution medium were withdrawn at predetermined time intervals, filtered through a 5 μm nylon filter (B-D filter needle, Lot 7B015; Becton Dickinson, Franklin Lakes, NJ) and analyzed for drug content by UV spectrophotometry (Model λ-4A, UV–VIS Spectrophotometer; Perkin Elmer, Norwalk, CT). The sample volume was not replaced by an equal volume of fresh dissolution medium, but a correction factor was used in the calculations to account for the lost volume.

Table 3
Effect of compression pressures used on Carver press on the resultant tablet crushing strengths (ANOVA table)[a]

Source	DF	SSQ	*F* ratio	*P* value
Compression pressure	2	0.98	18.57	0.051
Chitinosans	1	0.54	20.30	0.045
	$r^2 = 0.966$			

[a] Dependent variable, tablet crushing strength (K_p).

2.4.3.2. USP apparatus 3. All tablet batches were subjected to in vitro drug release studies using a USP Type 3 apparatus (Bio Dis II; VanKel Industries, Edison, NJ). Release studies were performed at 37 ± 0.5°C, using dissolution media at different pH values: 200 ml of each pH buffer was placed in each of the glass vessels of the Bio Dis tester. The glass reciprocating cylinders were fitted with 40 mesh sieves (250 μm) at the top and bottom. Release tests were conducted at 15 strokes per minute (stroke = upward and downward cycle of the reciprocating cylinder) in pH 1.5 buffer for 2 h, followed by 1 h each in pH 4.0, 4.5, 5.5, and 6.8, and, finally, 2 h in pH 7.4 media. Samples of the dissolution medium were withdrawn, filtered through a 5 μm nylon filter (B-D filter needle, Lot 7B015; Becton Dickinson, Franklin Lakes, NJ), and analyzed by UV spectrophotometry for drug content. Calibration equations were generated to quantitate the amount of salicylic acid released in each of the release media.

2.5. Data analysis

2.5.1. To determine effect of compression pressure on salicylic acid–chitinosan tablets

A 2×3 factorial experimental design was used to evaluate the effect of compression pressure on tablet properties.

The *independent* variables were:

- compression pressures on the Carver press: 5000, 10 000, and 15 000 psig;
- chitinosans: S-F and S-P.

The *dependent* variables were:

- crushing strengths;

- area under the cumulative salicylic acid released–time plots from 0 to 6 h ($AUC_{0-6\ h}$).

2.5.2. Comparison of tablets compressed using different tablet presses

A 5×2 full factorial experimental design was used to evaluate the effect of compression pressure on tablet properties.

The *independent* variables were:

- chitinosans: S-F, S-P, F-LMW, F-MMW, and F-HMW;
- tablet presses: Carver and Stokes single punch press.

The *dependent* variable was:

- area under the cumulative salicylic acid released–time plots from 0 to 6 h ($AUC_{0-6\ h}$).

3. Results and discussion

3.1. Characterization of commercial chitinosans

Degrees of deacetylation, viscosity averaged molecular weights, and moisture contents of the commercial chitinosans used in the study are listed in Table 1. The degrees of deacetylation and molecular weights reported by the manufacturer/supplier are listed and compared with the degrees of deacetylation and molecular weights determined in our laboratory. The chitinosans S-F and S-P were labeled 'chitin', whereas F-LMW, F-MMW, and F-HMW were labeled 'chitosan' by the manufacturer. The molecular weights of chitinosans S-F and S-P could not be determined as the polymer supplied was insoluble (more chitin-like), which is not surprising given the relatively low degree of deacetylation ($< 75\%$). The moisture content of chitinosans ranged between 7 and 11%, and did not seem to be dependent on the degree of deacetylation or the molecular weight of the polymer. The DSC thermograms for chitinosans exhibited a characteristic endothermic peak between 60 and 75°C (Fig. 3), which may be due to the loss of physically adsorbed water. Fig. 4 shows a representative DSC thermogram for a salicylic acid–chitinosan formulation. The absence of characteristic peaks for salicylic acid indicates some degree of interaction between the polymer and the drug.

Table 4
Effect of compression pressures used on Carver press on the drug release profiles (ANOVA table)[a]

Source	DF	SSQ	*F* ratio	*P* value
Compression pressure	2	2.5×10^6	5.21	0.1609
Chitinosans	1 $r^2 = 0.991$	5.2×10^7	211.77	0.0047

[a] Dependent variable, $AUC_{0-6\ h}$

3.2. Physical characteristics of salicylic acid–chitinosan tablets

The physical characteristics of the salicylic acid–chitinosan tablets are listed in Table 2. Although friability of some tablet batches was marginally higher than generally acceptable limits (Gordon et al., 1990), it may be possible to improve this property by altering the drying conditions during chitinosan manufacture. Austin and Brine (1981) contend that the physical properties of chitinosans can be altered by accelerating the drying process (e.g. spray-drying). The results reported herein for tablets made with commercial chitinosans suggest the potential of chitinosan as a directly compressible tablet excipient.

The effects of chitinosan source on the friability and crushing strength of the salicylic acid–chitinosan tablets (compressed on Stokes single punch press) are shown in Fig. 5. Tablets containing chitinosans S-F and S-P disintegrated rapidly (complete disintegration under 1 min) irrespective of the compression pressure or tablet press used in their manufacture, whereas tablets containing F-LMW, F-MMW, and F-HMW remained intact 2 h into the test. Chitinosans S-F and S-P were labeled as 'chitin' by the supplier, and hence are assumed to possess relatively higher molecular weights and a relatively lower degree of deacetylation. However, the Fluka products are of a relatively lower degree of polymerization and a higher degree of deacetylation (Table 1). Furthermore,

the tablets containing the Fluka chitinosans swelled visibly after exposure to the dissolution medium. Presumably, swelling was inversely proportional to polymer molecular weight. These observations suggest that chitinosans with a lower degree of depolymerization and a higher degree of deacetylation may be more water soluble, thus promoting better interaction (swelling) with solvent and subsequently modifying drug release to a greater extent than for more highly polymerized, less deacetylated chitinosans.

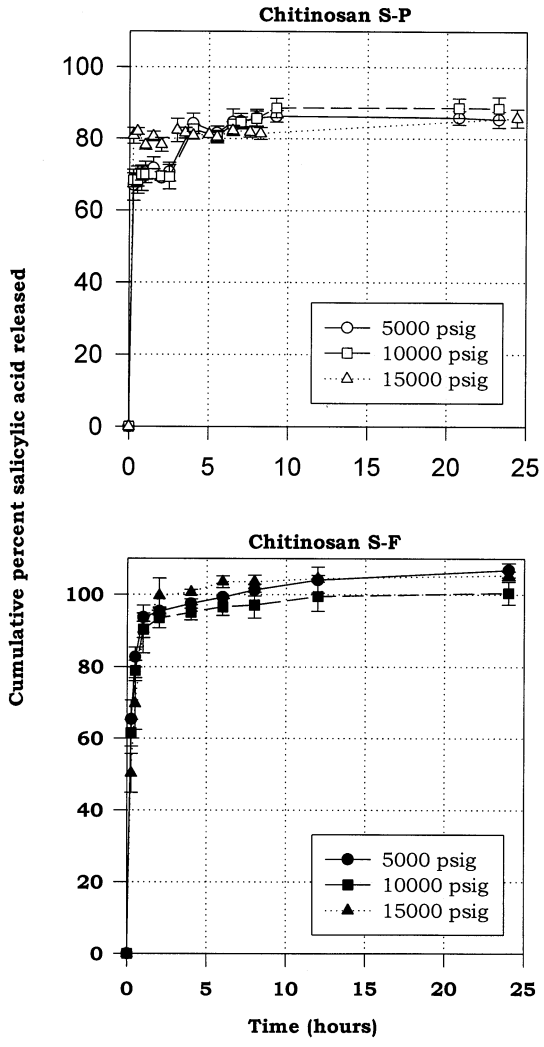

Fig. 6. Cumulative percent of salicylic acid released from chitinosan tablets compressed at different pressures using the Carver tablet press.

3.3. Effect of compression pressure on tablet properties

A 2×3 factorial experimental design was used to study the effect of compression pressure on tablet properties. The analysis of variance (ANOVA) results for the S-F and S-P formulations indicated that compression pressure did not significantly affect the crushing strength or the disintegration time of the tablets ($P > 0.05$) (Table 3).

The $AUC_{0-6\ h}$ was used to assess the effect of the compression pressure on the drug release profile. The ANOVA indicated that the release profiles were similar ($P > 0.05$) (Table 4). The release profiles are shown in Fig. 6.

3.4. Effect of tablet press model on tablet properties

A 5×2 factorial experimental design was used to study the tablet properties resulting from the use of different tablet presses (Carver and Stokes). The dissolution profiles of salicylic acid resulting from chitinosan tablets compressed on the Carver press (5000 psig for 5–7 s) and those compressed using Stokes single punch press are shown in Fig. 7. The $AUC_{0-6\ h}$ was used to assess the effects resulting from the use of the different tablet presses on the drug release profile. The ANOVA indicated that the release profiles for each batch were similar ($P > 0.05$) irrespective of the tablet press used for compression (Table 5). The chitinosans used in the tablet formulations significantly affected drug release ($P < 0.05$) (Fig. 8). Since the tablet press model did not significantly affect drug release, all drug release profiles shown are those resulting from dissolution of tablets compressed using a Stokes single punch press, unless noted otherwise.

3.5. In vitro salicylic acid dissolution

In order to design an in vitro dissolution test which would produce meaningful data—to assess batch-to-batch equivalence and provide in vitro–in vivo correlations—one should account for the physiological conditions found in the gastrointes-

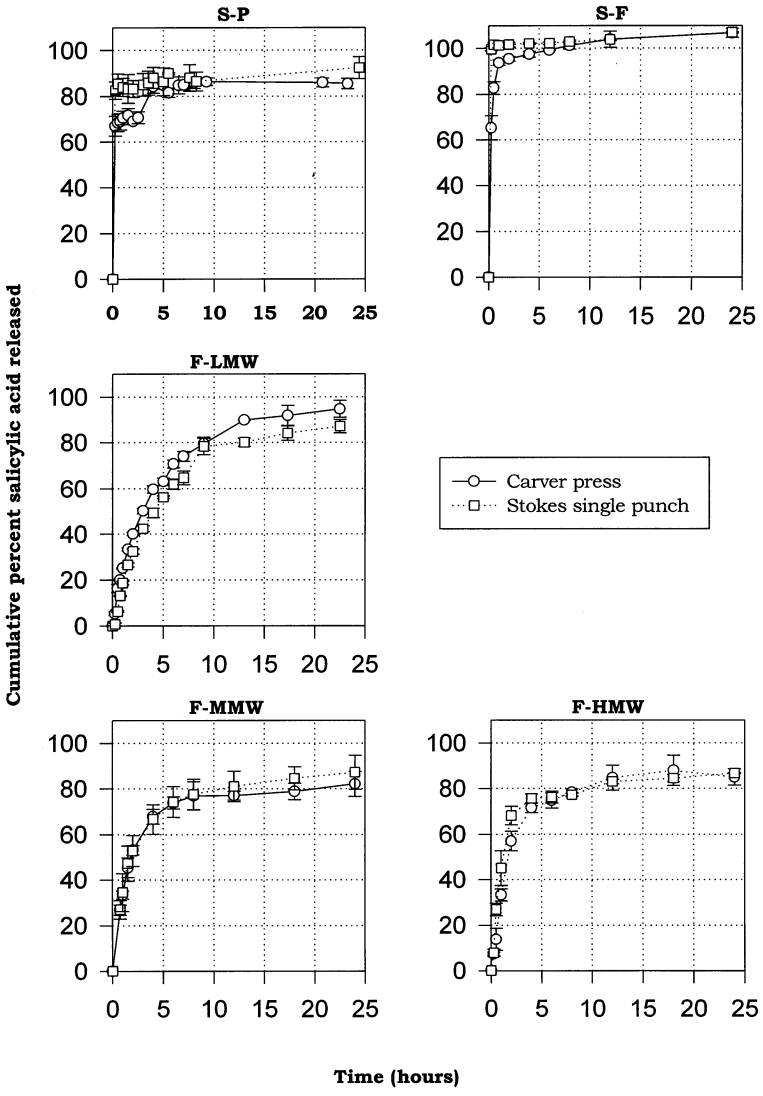

Fig. 7. Cumulative percent release profiles of salicylic acid from chitinosan tablets compressed using Carver and Stokes tablet presses.

tinal (GI) tract and incorporate those parameters in the in vitro set-up. The USP apparatus 3 allows for release testing to be conducted in dissolution media of varying pH. Tablet batches (compressed using and Stokes tablet presses) were subjected to release testing as already described. Representative release profiles are shown in Fig. 9.

Rapid tablet disintegration was observed when S-F and S-P chitinosans were used; however, the tablets containing Fluka products, in general, did not disintegrate in the dissolution media. ANOVA indicated that specific chitinosans significantly affected drug release ($P < 0.05$).

The release profiles of salicylic acid, irrespective of the method of testing, show direct dependence on polymer molecular weight. As the molecular weight decreases, more amino groups may become available for ionic interaction with the oppositely charged drug ions.

Table 5
Effect of tablet press used on the drug release profiles (ANOVA table)[a]

Source	DF	SSQ	*F* ratio	*P* value
Chitinosans	4	1.3×10^8	7.13	0.0416
Tablet press	1	2.4×10^6	0.54	0.5020
	$r^2 = 0.879$			

[a] Dependent variable, $AUC_{0-6\ h}$.

4. Summary and conclusions

Chitinosans have been evaluated as directly compressible tablet excipients. However, all formulations developed to date necessitate the addition of other ingredients to facilitate compression. In this study, we evaluated the use of chitinosans as directly compressible excipients without the addition of any other excipients to achieve compressibility. Not surprisingly, tablet physical properties and drug release profiles were significantly affected by the specific chitinosan selected. Thermograms (obtained via DSC) provide evidence for an interaction between the cationic polymer and the anionic drug. The drug release–time data suggest the possibility of achieving controlled drug release by the use of chitinosan matrices. The direct dependence of salicylic acid release on polymer molecular weight is consistent with the increased availability of amino groups for ionic interaction with the oppositely charged drug ions, i.e. greater possibility for ionic complex formation. This study provides further evidence to support the potential use of chitinosans as directly compressible excipients for use in modified release drug delivery systems without the need for additional adjuvants.

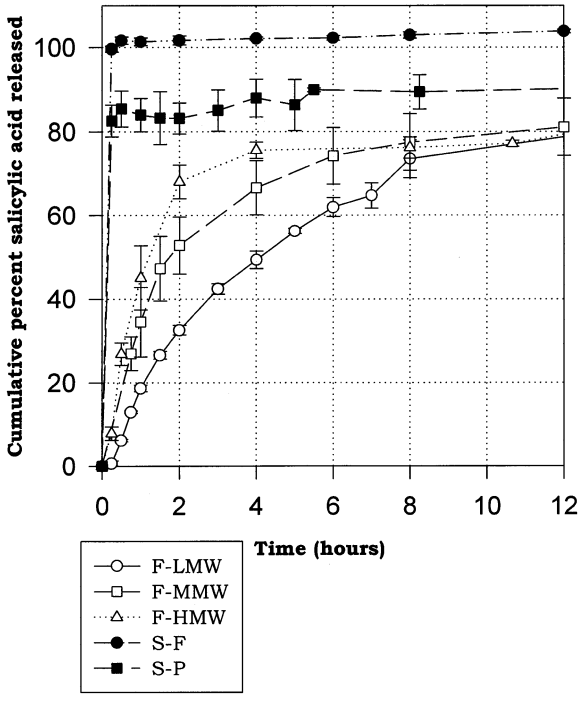

Fig. 8. Cumulative percent release profiles of salicylic acid from chitinosan tablets: effect of chitinosans.

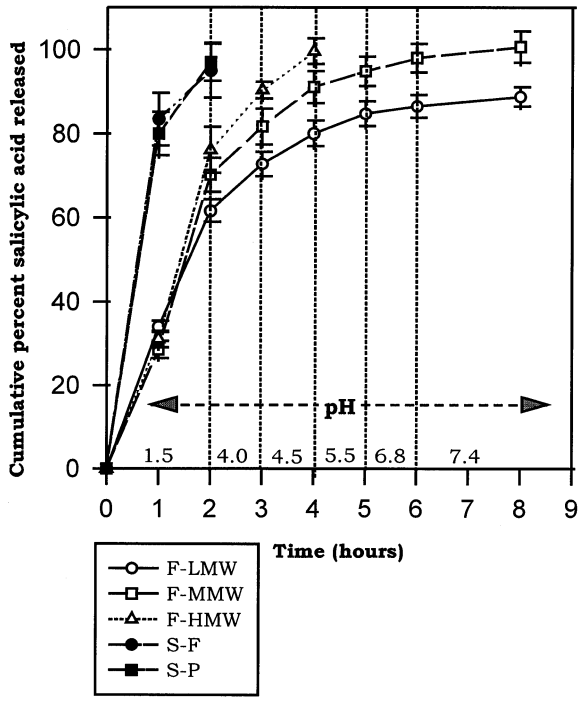

Fig. 9. Cumulative percent release profiles of salicylic acid from chitinosan tablets (using USP apparatus 3).

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