Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 250 (2003) 259–272
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Chitinosan-drug complexes: effect of electrolyte on naproxen release in vitro

Pankaj R. Rege [a,b,*], Dhruti J. Shukla [a], Lawrence H. Block [a]

[a] *Department of Medicinal Chemistry and Pharmaceutics, Duquesne University, Pittsburgh, PA 15282, USA*
[b] *Global Pharmaceutical Technologies, Bristol-Myers Squibb Company, New Brunswick, NJ 08903, USA*

Received 30 August 2002; received in revised form 2 October 2002; accepted 2 October 2002

Abstract

The purpose of this study was to examine the potential use of electrolytes to control naproxen sodium (**I**) release from chitinosan (**II**) tablets. An ANOVA was employed to evaluate the effects of molecular weight (MW) of **II**, electrolyte valence (EV), and pH of the dissolution medium on **I**'s release. The intrinsic dissolution rates and saturation solubilities of **I** were determined at each of the pHs used. Directly compressed tablets were prepared from admixtures containing: **I**, NaCl, $CaCl_2$, or $AlCl_3$, Mg stearate, and **II**. The tablets were characterized for their dimensions, crushing strengths, friability, disintegration times, and in vitro dissolution profiles. The slopes of the log–log cumulative percent released-time curves ($t = 0–5$ h) were compared using ANOVA. Based on the ANOVA, each of the variables—chitinosans, EVs, and pHs—significantly affected drug release ($P < 0.05$). Besides the poor aqueous solubility of **I**, the factors possibly affecting drug release included: (a) the formation of a rate-limiting **II** gel barrier; (b) the interaction of **I** with ionized amino groups of **II**; (c) the effect of electrolyte on the **II**'s gel barrier formation; and/or (d) decreased aqueous solubility of **I** in the presence of electrolyte.

Keywords: Chitinosan; Chitosan; Excipient; Naproxen sodium; Electrolyte; Tablets

1. Introduction

Naproxen sodium, a phenylacetic acid derivative, is a nonsteroidal anti-inflammatory drug that is available commercially for peroral administration. The gastric effects of perorally administered naproxen sodium may be alleviated, to some extent, by inhibiting its release in the gastric region (Insel, 1996). Chitinosan (Block, 1997) is a cationic biopolymer that is bioadhesive, biocompatible, and biodegradable (Muzzarelli, 1993). When used in a matrix-type tablet formulation, chitinosan forms a gel-barrier in an acid environment that can modulate or constrain drug release (Sawayanagi et al., 1982; Acartürk, 1989). In this way, naproxen sodium release in the gastric region may be minimized. 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

* Corresponding author. Tel.: +1-732-519-1270; fax: +1-732-519-1687
E-mail address: pankaj.rege@bms.com (P.R. Rege).

0378-5173/02/$ - see front matter
PII: S0378-5173(02)00551-3

drug delivery systems. 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, 1995). However, previous research from our laboratories has provided evidence to support the use of this biopolymer as a directly compressible tablet excipient (Sabnis et al., 1997; Rege et al., 1999).

Furthermore, chitinosan's chemical reactivity appears to depend inversely on its molecular weight (Sabnis, 1996). However, its swelling and gel-barrier formation tendencies have not been so characterized. Literature data do attest to the inverse effect of electrolytes on chitinosan solution viscosity (Al-Angary, 1994). Presumably, then, the presence of additional electrolyte in a tablet matrix could generate a localized, highly charged environment which could affect the polymer's viscosity and further modify drug release from the tablet matrix.

In this study, we attempted: (a) to directly compress both commercially available chitinosans and their depolymerized counterparts; (b) to elucidate the effect of electrolyte on chitinosans intrinsic viscosity; and (c) to evaluate the suitability of chitinosans as excipients for modifying/controlling the release of naproxen sodium from dosage forms.

Thus, the potential inhibition of naproxen sodium release from tablets, by commercial or depolymerized chitinosan, with or without additional electrolyte, was evaluated as a function of dissolution medium pH.

2. Materials and methods

Three different commercially available chitinosans F-LMW, F-MMW, and F-HMW (i.e. low, medium, and high molecular weight chitinosans) (from Fluka Chemie AG, Buchs, Switzerland) were selected in this study. The materials were milled (Wiley Mill, Model # 3, A.H. Thomas, Philadelphia, PA) and passed through a 60 mesh (250-μm) sieve prior to use. Furthermore, two chitinosans (F-LMW and F-HMW)—from among the three selected—were subsequently depolymerized (to yield batches DF-LMW and DF-HMW) and sieved before use in the study. Other chemicals and reagents were used as supplied: naproxen sodium (Sigma Chemical Co., St. Louis, MO), calcium chloride, USP grade (Fisher Scientific Co., Fair Lawn, NJ), aluminum chloride (Amend Drug and Chemical Co., Irwington, NJ) and reagent grades of glacial acetic acid, hydrochloric acid, methanol, potassium chloride, sodium acetate, sodium chloride, and sodium hydroxide were supplied by Fisher Scientific Co., Fair Lawn, NJ.

The chitinosans selected for use in this study had similar degrees of deacetylation ($P > 0.10$), but differed markedly in their degree of polymerization (i.e. molecular weight) ($P < 0.05$). The 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 (see below).

2.1. Depolymerization of chitinosans

Commercially available chitinosans (50 g each) were refluxed with 750 ml of 2.5 N hydrochloric acid in a three-necked flask under a nitrogen blanket at 80 °C for 1 h. The resultant mixture was cooled to room temperature and its pH adjusted to neutrality by the addition of 5 N sodium hydroxide. The precipitated polymer was then filtered and the precipitate washed several times with distilled water. Neutrality was confirmed by pH measurements of the filtrate. The resultant polymer was then dried in a hot-air oven at 60 °C for 48 h. The dried product was milled using a Waring blender (Model FCI 15, Waring Products Corp., NY), subsequently sieved and characterized.

Table 1
Degrees of deacetylation, molecular weights, and moisture contents of chitinosans selected in this study

Chitinosan	Degree of deacetylation (%)		Molecular weight (kD)		Moisture content (%)	
	Labeled	Determined*,a	Labeled	Determined*,a	Labeled	Determined*,b
F-LMW	84.8	80.2±0.7	150	183.4±16.2	n/a	11.1
F-MMW	84.5	79.1±0.6	400	263.6±6.4	n/a	9.8
F-HMW	83.0	79.3±0.7	600	499.4±9.8	n/a	10.1
DF-LMW[c]	n/a	79.1±1.4	n/a	6.1±0.1	n/a	14.1
DF-HMW[c]	n/a	79.1±0.6	n/a	4.7±0.7	n/a	9.9

n/a, no information available.
* Our data.
[a] Mean±S.D., $n=3$.
[b] Mean, $n=2$.
[c] Depolymerized batches.

2.2. Characterization of selected chitinosans

2.2.1. 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 Corp., 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.

2.2.2. Degree of polymerization determinations

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

$$[\eta] = K_m(\mathrm{MW})^a, \quad (1)$$

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.

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 Inc., Westboro, MA) prior to the viscosity measurements. The viscosity measurements were based on the efflux times of the filtered solutions in Ubbelohde viscometer (Model I136, Cannon Instrument Co., State College, PA) maintained in a constant-temperature bath at 25±0.1 °C.

2.2.3. 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.

2.2.4. Effect of electrolyte type and electrolyte concentration on the intrinsic viscosity of chitinosan

The effects of electrolyte valence (sodium chloride, calcium chloride, or aluminum chloride) and electrolyte concentration (0, 0.25, and 0.5 M) on the intrinsic viscosity of chitinosan were evaluated as follows: aqueous acetic acid solutions (0.5 M) of the respective chitinosans were prepared with varying concentrations (either 0, 0.25, or 0.5 M) of each electrolyte. The polymer solutions were filtered through a 5-μm nylon membrane filter (Magna-R, lot number 67498, Micron Separations

Inc., Westboro, MA) prior to the viscosity measurements.

Viscosity measurements were based on the efflux times of the filtered solutions in an Ubbelohde viscometer (Model I136, Cannon Instrument Co., State College, PA) maintained in a constant-temperature bath at 25 ± 0.1 °C. The intrinsic viscosities were determined by extrapolating the reduced viscosities to infinite dilution (Scott, 1991).

2.3. Development of an analytical method for naproxen sodium

Methanol was incorporated into the various dissolution media to compensate for the low solubility of naproxen sodium in water. The pH '1.2' buffer employed a hydrochloric acid–potassium chloride system whereas the pH '3.8' and '6.8' buffers were acetic acid–sodium acetate systems.[1] The ionic strength of these buffers was kept constant at 0.5. Standard solutions of naproxen sodium were prepared using a 30% v/v methanol–70% v/v buffer system. Calibration plots for subsequent UV analysis of naproxen were generated at each of the pHs employed. The analyses were conducted at wavelengths (λ_{max}) of 326.6, 326.8, and 328.0 nm which correspond, respectively, to the wavelengths of maximum absorbance for naproxen in the pH '1.2', '3.8', and '6.8' buffer solutions, using a Perkin–Elmer UV–Vis spectophotometer (Model λ-4A, UV–Vis Spectrophotometer, Perkin–Elmer, Norwalk, CT).

[1] Buffer solution compositions were based on calculations for buffer components in aqueous solutions at pHs 1.2, 3.8, and 6.8, respectively. Nonetheless, the authors are aware of the pH shift induced by the inclusion of methanol in the dissolution media. In fact, the measured pH values for these buffer solutions were 1.29, 4.23, and 6.97, respectively. Hence the use of quotation marks to denote the approximate pHs of the buffer solutions. These pH effects are in accordance with those reported by Wolff et al. (1987).

2.4. Evaluation of saturation solubility for naproxen sodium

Excess naproxen sodium (2 g) was suspended in 10 ml of each of the buffer solutions in 20 ml glass vials. The vials were sealed (polypropylene screw-caps), placed in a constant-temperature shaker bath (37 ± 0.5 °C), and periodically sampled (0.5 ml aliquots) until equilibrium was attained. The aliquots were filtered through a 5-μm filter (Precision Glide filter needle, lot number 7K076, Becton Dickinson & Co., Franklin Lakes, NJ) and analyzed spectrophotometrically for drug content.

2.5. Intrinsic dissolution rates for naproxen sodium

Intrinsic dissolution rates of naproxen sodium in the different dissolution media (pHs '1.2', '3.8', and '6.8') were determined as follows: naproxen sodium (200 mg) was compressed into disks using a Carver press at 5000 psig for 5–7 s. Each disk was secured in the die cavity, following the approach of Block and Patel (1973), so that only one surface of the disk was exposed to the dissolution medium (200 ml). The dissolutions were carried out using USP Type 2 dissolution apparatus equipped with 200 ml dissolution flask assembly (VanderKamp 6010, VanKel Industries Inc., Edison, NJ) at 37 ± 0.5 °C and a stirring speed of 50 rpm. Samples were withdrawn every 15 min over a 90 min period, filtered through a 5-μm nylon filter and analyzed for drug content spectrophotometrically.

2.6. Preparation of naproxen sodium–chitinosan tablets containing electrolyte

Directly compressed tablets were prepared from admixtures containing naproxen sodium, 25 mg; NaCl, $CaCl_2$, or $AlCl_3$, 0 or 1.5 mEq; Mg stearate, 1 mg; and chitinosan, q.s. ad 200 mg. The tablets were compressed using a Carver hydraulic press (Model C, Fred S. Carver, Menmonee 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. Table 2

Table 2
Naproxen sodium tablet formulations used in this study

Blend	Naproxen sodium (mg)	Electrolyte type	Electrolyte concentration (mEq)	Magnesium stearate (mg)	Chitinosan type[a]
1	25	–	–	1	F-LMW
2	25	NaCl	1.5	1	F-LMW
3	25	$CaCl_2$	1.5	1	F-LMW
4	25	$AlCl_3$	1.5	1	F-LMW
5	25	–	–	1	F-MMW
6	25	NaCl	1.5	1	F-MMW
7	25	$CaCl_2$	1.5	1	F-MMW
8	25	$AlCl_3$	1.5	1	F-MMW
9	25	–	–	1	F-HMW
10	25	NaCl	1.5	1	F-HMW
11	25	$CaCl_2$	1.5	1	F-HMW
12	25	$AlCl_3$	1.5	1	F-HMW
13	25	–	–	1	DF-LMW
14	25	NaCl	1.5	1	DF-LMW
15	25	$CaCl_2$	1.5	1	DF-LMW
16	25	$AlCl_3$	1.5	1	DF-LMW
17	25	–	–	1	DF-HMW
18	25	NaCl	1.5	1	DF-HMW
19	25	$CaCl_2$	1.5	1	DF-HMW
20	25	$AlCl_3$	1.5	1	DF-HMW

[a] q.s. with chitinosan to 200 mg.

describes the tablet formulations prepared for this study.

2.7. Tablet characterization

2.7.1. Determination of physical characteristics

Tablet diameter, thickness, and crushing strength of five 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 G.m.b.H., Heusenstamm, Germany).

2.7.2. Evaluation of disintegration times of the tablets

Disintegration times of the tablets in pH 1.2 buffer (USP XXIII method, without disks) were determined using a VanderKamp disintegration tester (VanKel Industries Inc., Edison, NJ). The buffer solution was maintained at 37 ± 0.5 °C in a constant-temperature bath (Precision water bath, Model 183, VanKel Industries Inc., Edison, NJ). Six tablets from each batch were evaluated for their disintegration times.

2.7.3. Study of in vitro drug release

In vitro drug dissolution studies were performed using a USP Type 2 dissolution apparatus (VanderKamp 600, VanKel Industries Inc., Edison, NJ). The dissolution medium was 900 ml of 30% methanol–70% aqueous buffer. Dissolution was evaluated at 37 ± 0.5 °C, at a stirring speed of 50 rpm, from 0 to 5 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 fillter and analyzed for drug content by UV spectrophotometry. As the sample volume was not replaced with fresh dissolution medium a correction factor was used to account for the lost volume. The loss of dissolution medium over the test period (i.e. $t_{0-5\ h}$) due to evaporation was determined to be insignificant ($< 1\%$).

2.8. Experimental design

2.8.1. To determine effect of electrolyte on the intrinsic viscosity of chitinosans

A $3 \times 3 \times 3$ full factorial experimental design was used to evaluate the effect of electrolyte on the intrinsic viscosity of chitinosans. The *independent* variables were electrolyte valence (NaCl, $CaCl_2$, and $AlCl_3$), electrolyte concentrations (0, 0.25, and 0.5 M), and the chitinosans used ($n = 3$). The *dependent* variable used was the resultant chitinosan intrinsic viscosity (cps).

2.8.2. Effect of electrolyte, pH of the dissolution medium, and chitinosans on naproxen sodium release

A $5 \times 4 \times 3$ full factorial experimental design was used to evaluate the effect of electrolyte, pH of the dissolution medium, and chitinosans on naproxen sodium release. The *independent* variables were the chitinosans used ($n = 5$), the electrolyte valence (no electrolytes, NaCl, $CaCl_2$, and $AlCl_3$), and the dissolution medium pHs ('1.2', '3.8', and '6.8'). The *dependent* variable used was the slopes of the percent drug released-square root of time profiles.

Data were analyzed using statistical analysis software (JMP, v. 3.1.5., SPSS, Inc., Chicago, IL).

3. Results and discussion

3.1. Effect of electrolyte type and concentration on chitinosan's intrinsic viscosity

The effect of electrolyte type and concentration on chitinosan's intrinsic viscosity was investigated by measuring the capillary efflux times of diluted solutions in solvents containing differing amounts of each electrolyte. The intrinsic viscosities are listed in Table 3 as a function of electrolyte valence and concentration. Specifically, intrinsic viscosities were measured using solvents containing 0.5 M acetic acid with either NaCl, $CaCl_2$, or $AlCl_3$ (0, 0.25, or 0.5 M). A $3 \times 3 \times 3$ full factorial experimental design [ANOVA] indicated that the electrolyte valence (NaCl, $CaCl_2$, or $AlCl_3$) did not significantly affect the intrinsic viscosity. However, the influence of electrolyte concentration and

Table 3
Effect of electrolyte type and concentration on intrinsic viscosity

Chitinosan	Intrinsic viscosity[a] (cps) of chitinosan as a function of NaCl concentration and ionic strength		
	0 M/0.002 μ	0.25 M/0.252 μ	0.5 M/0.502 μ
F-LMW	26.89 ± 0.14	6.14 ± 0.35	5.87 ± 0.12
F-MMW	36.92 ± 0.66	7.79 ± 0.14	5.25 ± 0.12
F-HMW	39.62 ± 1.39	11.8 ± 0.15	8.88 ± 0.09
	Intrinsic viscosity[a] (cps) of chitinosan as a function of $CaCl_2$ concentration		
	0 M/0.002 μ	0.25 M/0.752 μ	0.5 M/1.502 μ
F-LMW	26.89 ± 0.14	6.54 ± 0.16	5.80 ± 0.03
F-MMW	36.92 ± 0.66	8.33 ± 0.06	6.09 ± 0.05
F-HMW	39.62 ± 1.39	6.41 ± 0.09	5.73 ± 0.12
	Intrinsic viscosity[a] (cps) of chitinosan as a function of $AlCl_3$ concentration		
	0 M/0.002 μ	0.25 M/1.502 μ	0.5 M/3.002 μ
F-LMW	26.89 ± 0.14	7.23 ± 0.04	3.33 ± 0.04
F-MMW	36.92 ± 0.66	7.11 ± 0.11	5.66 ± 0.08
F-HMW	39.62 ± 1.39	6.39 ± 0.05	4.54 ± 0.07

[a] Mean ± S.D., $n = 3$.

Table 4
ANOVA outcome: effect of electrolyte on chitinosan intrinsic viscosity

Source	DF	SSQ	*F*-ratio	*P* value
Chitinosan type	2	133.3	49.9	< 0.0001
Electrolyte valence	2	7.4	2.8	0.12
Electrolyte concentration	2	12.6	2.3	< 0.0001
Chitinosan type × electrolyte valence	4	4676.3	1749.7	0.14
Chitinosan type × electrolyte concentration	4	143.3	26.8	0.0001
Electrolyte type × electrolyte concentration	4	4.8	0.9	0.51

chitinosan type (low, medium, or high molecular weight) on the intrinsic viscosity of chitinosans was highly significant ($P < 0.0001$) (Table 4). The increase in electrolyte concentration which resulted in increase in the ionic strength, decreased the intrinsic viscosity of chitinosans, presumably by increasing the polarity of the solvent environment thereby facilitating the extension of the ionized polymer and decreasing the resultant intrinsic viscosity.

3.2. Solubility characteristics of naproxen sodium

Fig. 1 shows the saturation solubility data (at 37 °C) for naproxen sodium in each of the aqueous buffers used in this study.

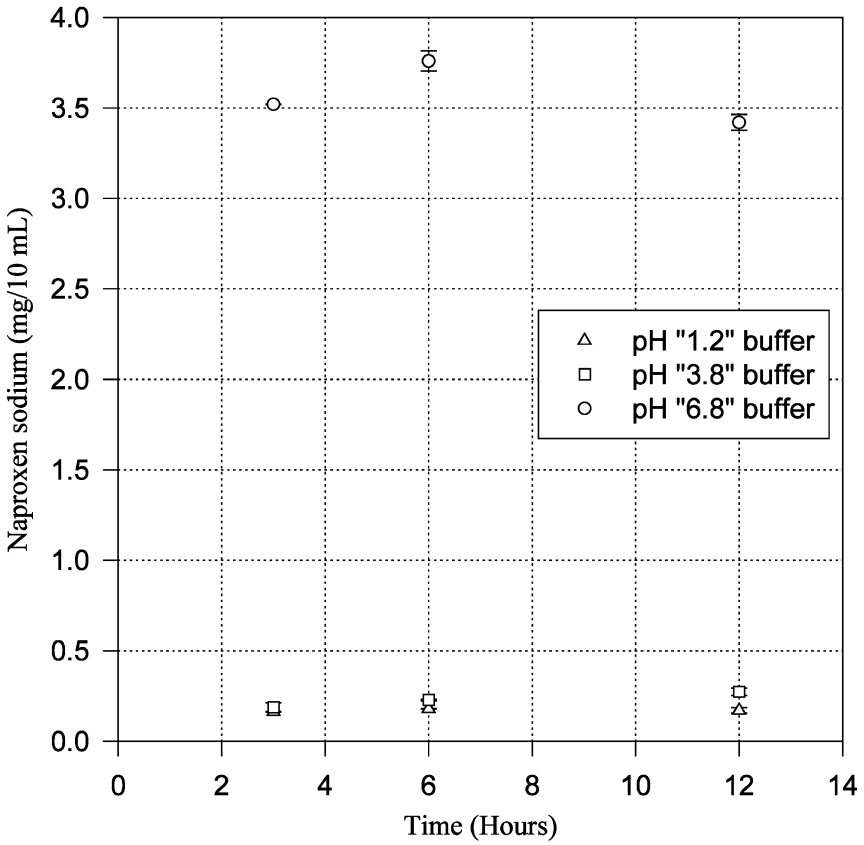


Fig. 1. Saturation solubility data for naproxen sodium in 10 ml of each of the dissolution media used in this study.

The solubility of naproxen sodium was dependent on the pH of the dissolution medium. Naproxen, with a $pK_a \sim 4.2$ (Newton and Kluza, 1978), exists mainly in the unionized form in an acid environment: it was sparingly soluble at lower pHs, whereas at higher pHs it mainly exists in the ionized form, and as a result is freely soluble. These observations are consistent with the extensive data reported by Fini et al. (1985).

The intrinsic dissolution profiles for naproxen sodium in each of the different aqueous buffers is shown in Fig. 2. Intrinsic dissolution rates increased with increasing pHs and may be explained by the substantial ionization of the drug molecule at higher pHs.

3.3. Physical characteristics of naproxen sodium–chitinosan tablets

The directly compressible naproxen sodium–chitinosan tablets were evaluated for their weights, dimensions, crushing strengths, friabilities, and disintegration times. These results are listed in Table 5.

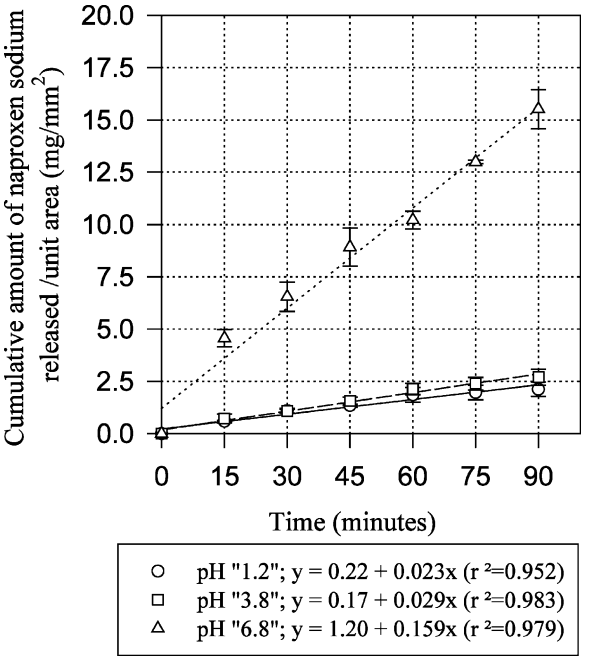
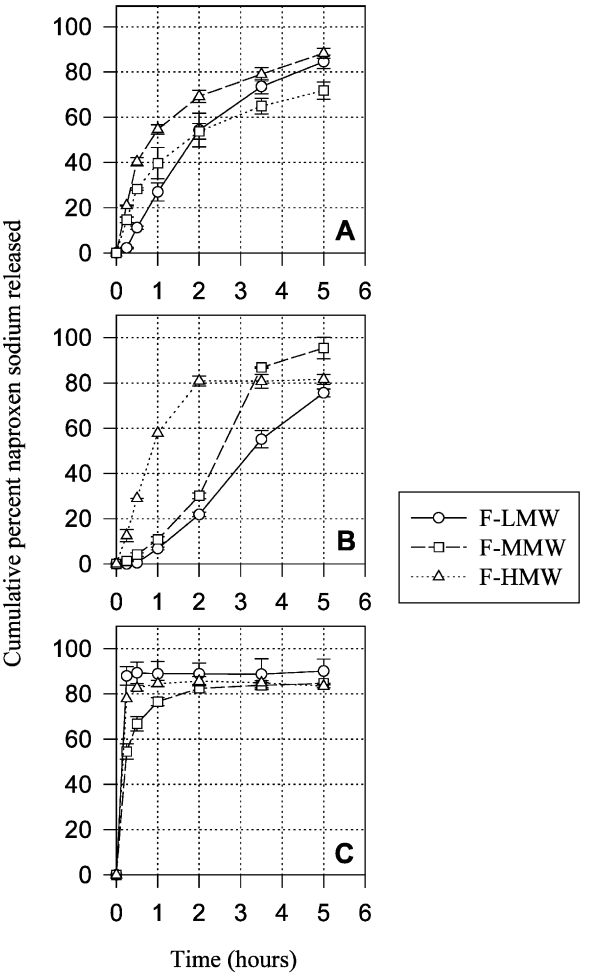


Fig. 2. Intrinsic dissolution rates for naproxen sodium.

Although friability of some tablet batches was marginally higher than generally accepted 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). Alternatively, it may be possible to improve tablet quality by optimization of the tableting process parameters. Our previous findings with chitinosan–salicylic acid complexes (Rege et al., 1999) have



A: pH ‘1.2”; B: pH “3.8”; C: pH “6.8”

Fig. 3. Naproxen sodium release as a function of chitinosan molecular weight.

Table 5
Tablet properties

Formulation	Weight[a] (mg)	Thickness[a] (mm)	Diameter[a] (mm)	Crushing strength[a] (kp)	Friability[b] (% loss)	Disintegration time[c] (min)
F-LMW	196.4±5.8	1.9±0.2	10.1±0.1	3.8±0.4	0.88	10.6±1.5
F-LMW+NaCl	201.6±2.7	1.7±0.2	10.2±0.2	1.8±0.1	1.12	0.9±0.2
F-LMW+$CaCl_2$	203.0±6.8	1.8±0.1	10.2±0.2	4.3±0.5	0.36	70.5±6.5
F-LMW+$AlCl_3$	204.0±2.8	2.7±0.1	10.5±0.1	1.5±0.4	–[d]	2.4±0.5
F-MMW	201.2±4.7	1.9±0.2	10.1±0.2	3.3±0.4	0.92	11.7±0.9
F-MMW+NaCl	199.4±2.1	1.7±0.1	10.1±0.1	1.4±0.2	–[d]	0.8±0.2
F-MMW+$CaCl_2$	203.4±8.1	1.8±0.2	10.1±0.2	6.2±1.0	0.35	80.3±3.6
F-MMW+$AlCl_3$	203.0±3.3	2.5±0.1	10.5±0.1	1.3±0.2	–[d]	11.3±1.5
F-HMW	205.8±2.4	2.1±0.2	10.1±0.1	2.6±0.3	0.69	4.7±0.5
F-HMW+NaCl	196.8±4.9	1.6±0.1	10.1±0.1	1.6±0.2	–[d]	1.3±0.2
F-HMW+$CaCl_2$	198.8±4.9	1.7±0.1	10.1±0.0	3.0±0.2	0.34	57.9±4.8
F-HMW+$AlCl_3$	206.2±2.9	2.2±0.1	10.4±0.0	3.2±0.3	0.73	18.8±1.3
DF-LMW	199.6±2.6	2.6±0.1	10.6±0.2	1.1±0.2	–[d]	3.6±0.5
DF-LMW+NaCl	199.5±2.3	2.4±0.2	10.5±0.1	1.1±0.1	–[d]	5.0±0.1
DF-LMW+$CaCl_2$	206.0±3.2	1.9±0.2	10.1±0.1	2.5±0.6	–[d]	21.8±0.4
DF-LMW+$AlCl_3$	197.0±3.7	2.2±0.2	10.3±0.1	3.1±0.4	0.70	22.3±6.4
DF-HMW	200.8±2.7	2.5±0.3	10.2±0.3	1.0±0.5	–[d]	1.0±0.2
DF-HMW+NaCl	203.1±1.5	2.3±0.2	10.3±0.2	0.9±0.5	–[d]	3.5±0.5
DF-HMW+$CaCl_2$	201.0±5.1	2.1±0.2	10.5±0.2	1.7±0.6	–[d]	19.3±1.3
DF-HMW+$AlCl_3$	198.0±1.5	2.1±0.1	10.4±0.1	2.9±0.1	0.14	20.2±0.4

[a] Mean±S.D., $n=5$.
[b] $n=10$.
[c] Mean±S.D., $n=6$.
[d] Tablets fractured.

demonstrated that chitinosan tablet properties were not significantly affected when compression pressure was varied from 5000 up to 15,000 psig.

Disintegration times of the chitinosan tablets were dependent on the electrolyte incorporated in the formulation: formulations containing sodium or aluminum chloride generally disintegrated more rapidly than those containing no electrolytes or calcium chloride. Tablets manufactured with commercial chitinosans and containing no electrolyte or calcium chloride exhibited larger crushing strengths and disintegration times than the corresponding tablets containing sodium or aluminum chloride. However, the crushing strengths and disintegration times of the tablets containing depolymerized chitinosans were directly proportional to the valence of the electrolyte incorporated. In general, irrespective of electrolyte valence, tablet crushing strengths were directly proportional to the corresponding disintegration times.

3.4. *In vitro naproxen sodium dissolution*

Naproxen sodium release profiles are shown as a function of chitinosan molecular weight in Fig. 3. In general, the extent of naproxen release increased with increasing chitinosan molecular weight. At acidic pHs, chitinosans ($pK_a \sim 6.1$) are ionized to a substantial extent, while naproxen—a

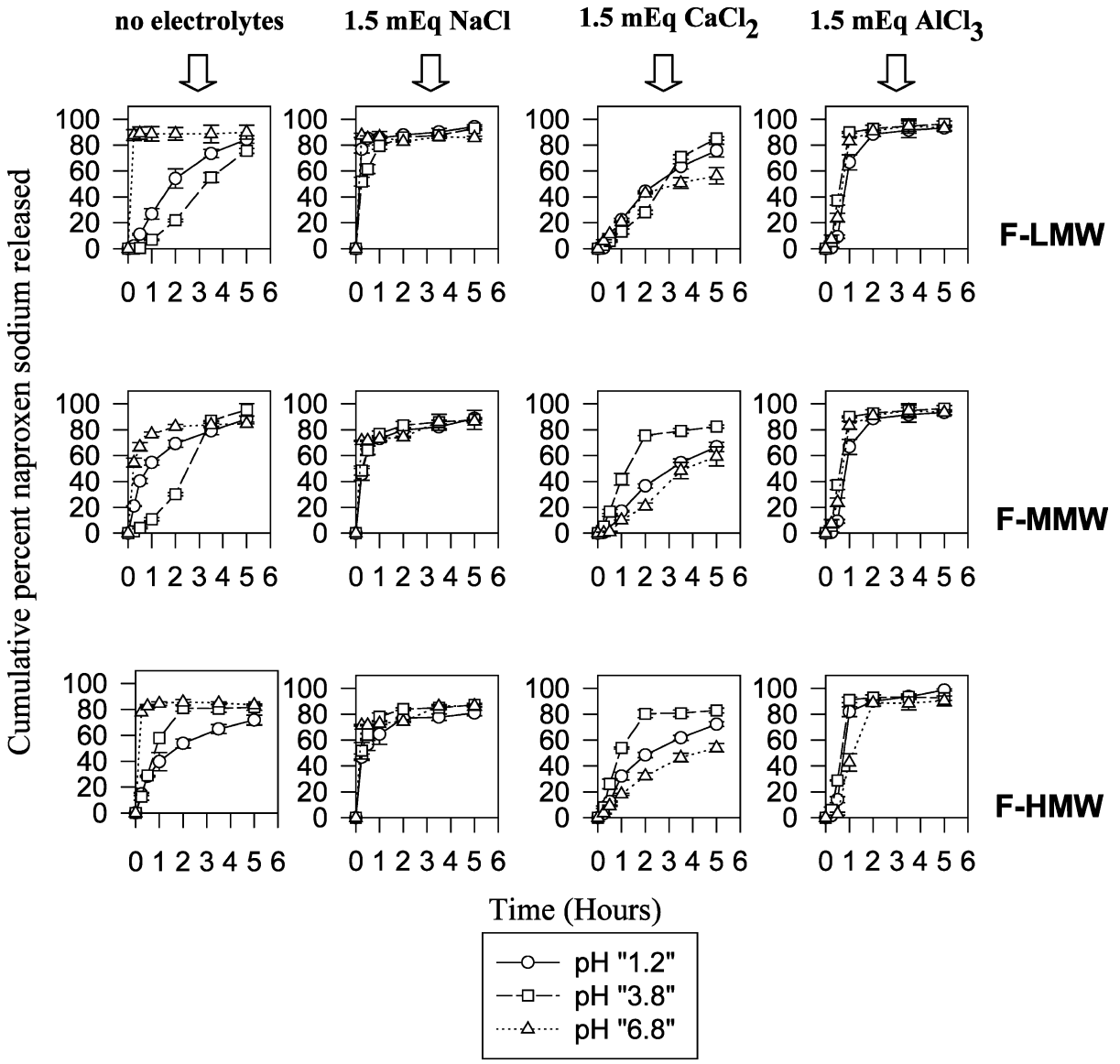


Fig. 4. Naproxen sodium release as a function of dissolution medium pH.

weak acid with a $pK_a \sim 4.2$—is only minimally ionized. Hence, the degree of ionic interaction—at acidic pHs—between the drug and polymer is minimal. Conversely, at intermediate pHs, both naproxen and chitinosan are ionized substantially resulting in a much more substantial degree of ionic interaction. In contrast to the data at an acidic pH, naproxen release at intermediate pH is *inversely* proportional to the molecular weight of the chitinosan. At higher pHs, although the drug is ionized to a substantial degree, chitinosan is not. Hence, the release profiles show little or no dependence on chitinosan molecular weight as was observed at an acidic pH.

The effect of pH of the dissolution medium on naproxen release from chitinosan matrices is shown in Fig. 4. The repeated measures ANOVA indicated the pH of the dissolution media had a

Table 6
ANOVA outcome: effect of electrolyte, pH of the dissolution medium, and chitinosans on naproxen release

Source	DF	SSQ	*F*-ratio	*P* value
Chitinosan type	4	287.57	2.36	0.08
Electrolyte	3	6225.73	68.47	<0.0001
Media pH	2	3023.77	49.64	<0.0001
Chitinosan type × electrolyte	12	2354.15	6.44	<0.0001
Chitinosan type × media pH	8	408.75	1.67	0.15
Electrolyte type × media pH	6	2931.75	16.05	<0.0001

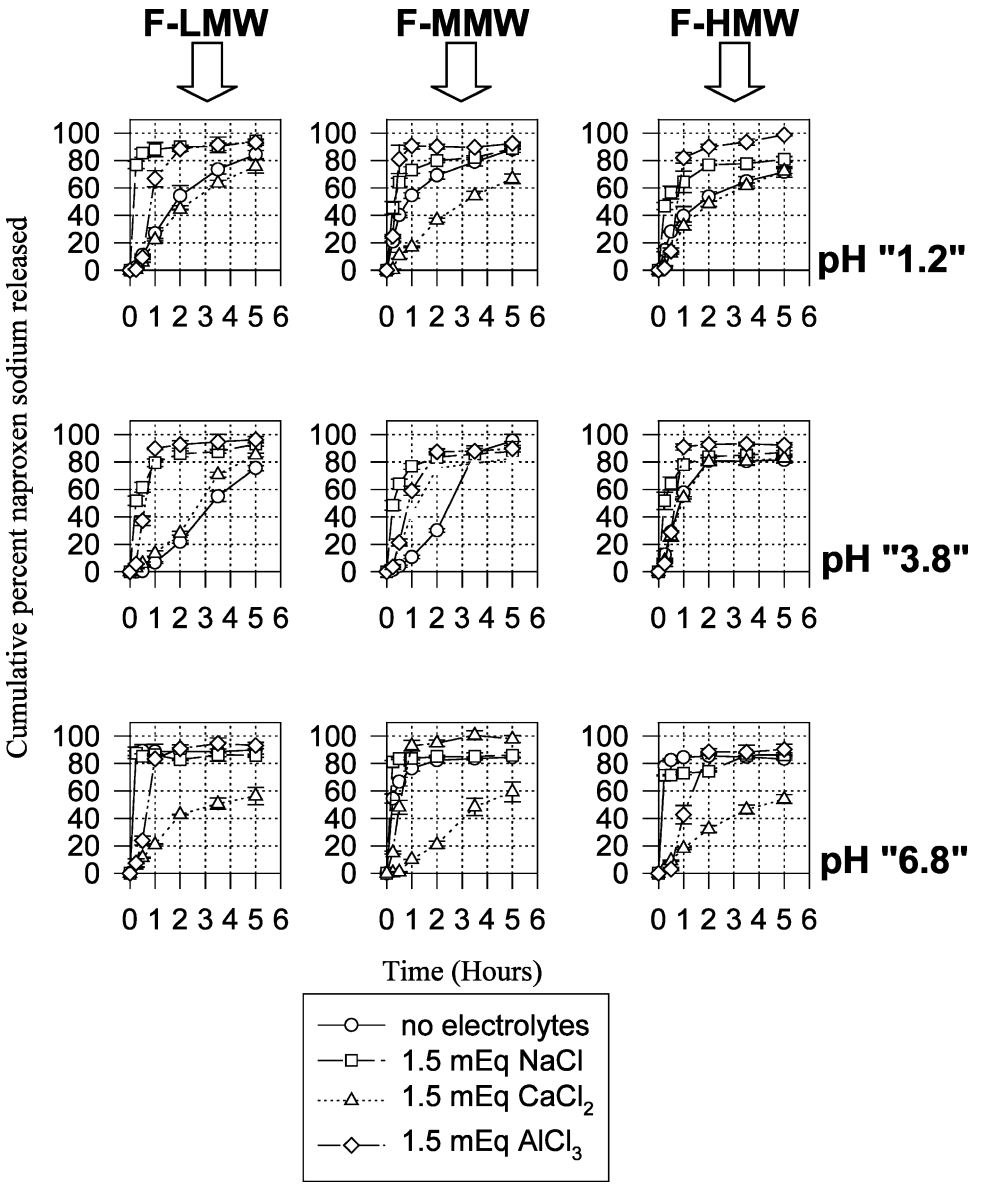


Fig. 5. Effect of electrolyte on the release profiles of naproxen sodium from chitinosan tablets.

significant impact on drug release ($P < 0.0001$) (Table 6). In general, with the absence of electrolyte in the tablet matrices, naproxen release was reduced at pHs '1.2' and '3.8' as compared to release at pH '6.8', as would be expected for a weak acid with a pK_a of ~4.2, i.e. strictly a function of the degree of ionization of the drug in the dissolution medium.

Incorporation of sodium or aluminum chloride in the tablet matrix did not sustain naproxen release from the matrix nor were the release profiles dependent on the pH of the dissolution medium. The effect of electrolyte incorporation in chitinosan tablets on naproxen sodium release is shown in Fig. 5. In general, electrolyte incorporation in the chitinosan matrix significantly affected drug release ($P < 0.0001$) (Table 6). Incorporation of calcium chloride in the tablet matrix reduced drug release substantially at pHs '1.2' and '6.8' when compared with the chitinosan formulation containing no added electrolyte. These differences in the naproxen release profiles are consistent with lower aqueous solubilities of calcium salts, in general, as compared to sodium or aluminum salts and the higher charge density of calcium ions as compared to that of sodium or aluminum ions (Israelachivili, 1992). Presumably, calcium ions' higher charge density in comparison to that for the other two ions, creates an environment which allows the chitinosan to have an extended con-

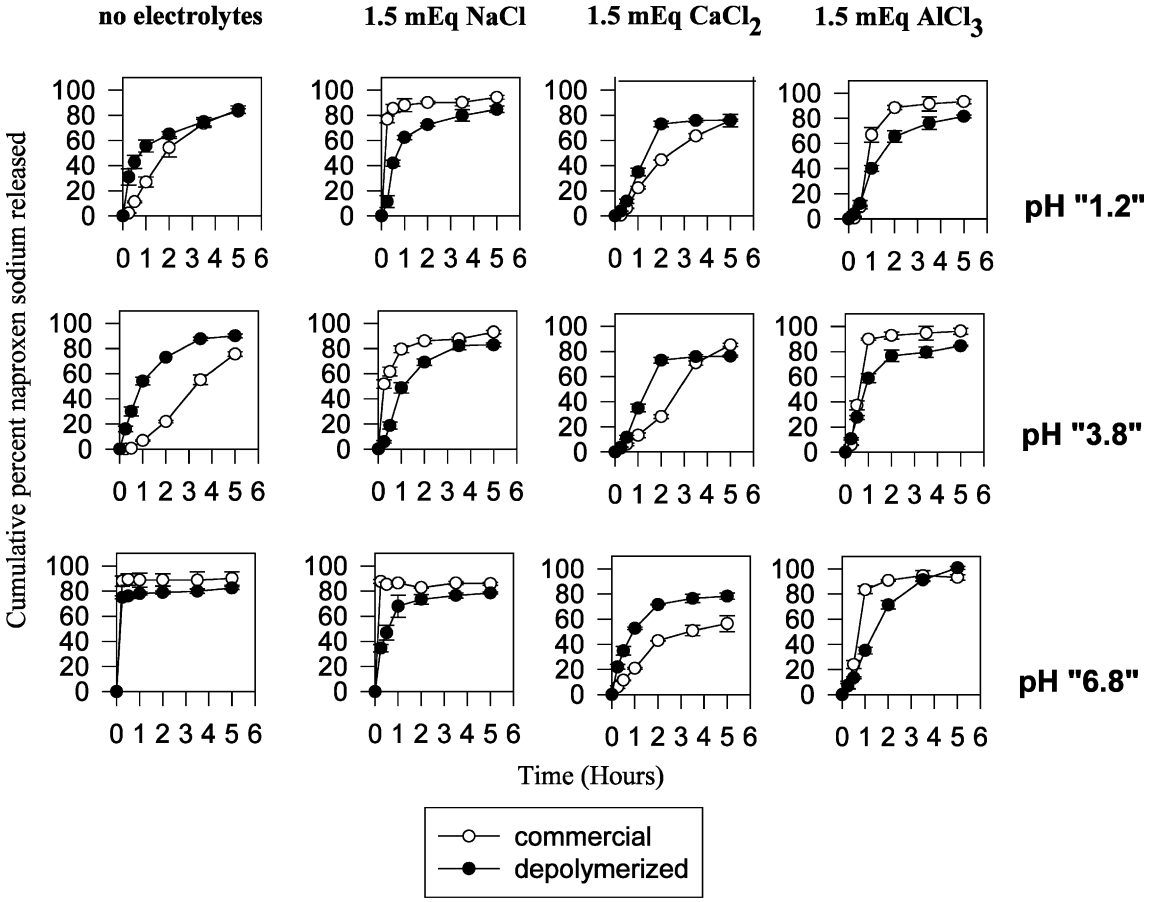


Fig. 6. Comparison of naproxen sodium release profiles from commercial chitinosans and their depolymerized counterparts.

formation, thereby increasing the accessibility of its amine groups and, as a consequence, facilitating its ionic interactions.

Naproxen release from tablet matrices prepared from commercial chitinosans and their corresponding depolymerized products are shown in Fig. 6. For matrices containing no added electrolyte, at acidic pHs, drug release is faster for depolymerized chitinosans than for commercial chitinosans. For matrices containing calcium chloride, irrespective of pH, drug release is faster for depolymerized chitinosans than for commercial chitinosans. However, for matrices containing sodium or aluminum chloride, drug release is slower for depolymerized chitinosans than for commercial chitinosans. The depolymerized materials used in this study possess molecular weights $\sim$4–6 kD. Our data agree with the observations made by Al-Angary (1994) where drug release was inversely proportional to chitinosan molecular weight. Al-Angary based his explanation on the fact that the higher molecular weight chitinosans possess lower aqueous solubility at acidic pHs, along with increased viscosity of the gel layer, thereby reducing drug release.

4. Summary and conclusions

The potential inhibition of naproxen sodium release by chitinosan, in the presence or absence of electrolyte in the tablet matrix, was evaluated as a function of electrolyte valence, dissolution medium pH, and chitinosan molecular weight. Although, these factors all affected naproxen release, the effects of sodium, calcium, and aluminum ions were significantly different from one another. While rapid release of naproxen was seen from matrices containing sodium and aluminum ions, naproxen release was relatively slow for calcium-containing matrices.

Thus, from a formulator's perspective, the inclusion of electrolyte in a chitinosan tablet matrix can have a significant effect on drug release. At the same time, as our studies have shown, the friability of these tablets remains problematic. Our current efforts, in part, are aimed at improving the compactibility and tablet characteristics of these matrices.

References

Acartürk, F., 1989. Preparation of a prolonged-release tablet formulation of diclofenac sodium, part I: using chitosan. Pharmazie 44, 547–547.

Akbuga, J., 1995. A biopolymer: chitosan. Int. J. Pharm. Adv. 1, 3–18.

Al-Angary, A.A., 1994. Effects of molecular weight and particle size of chitosan on chlorpheniramine maleate release from compressed tablets. Saudi Pharm. J. 2, 157–162.

Austin, P.R., Brine, C.J., 1981. Chitin powder and process for making it. U.S. Patent 4,286,087, 25 August.

Block, L.H., 1997. Chitinosans: enabling excipients for drug delivery systems. Internationales Symposium: Chitin/Chitosan Isolierung, Charakterisierung, Anwendung. Lübeck, Germany, 19–20 July.

Block, L.H., Patel, R.N., 1973. Solubility and dissolution of triamcinolone acetonide. J. Pharm. Sci. 62, 617–621.

Fini, A., Zecchi, V., Tartarini, A., 1985. Dissolution profiles of NSAID carboxylic acids and their salts with different counterions. Pharm. Acta Helv. 60, 58–62.

Gordon, R.E., Rosanske, T.W., Fonner, D.E., Anderson, N.R., Banker, G.S., 1990. Granulation technology and tablet characterization. In: Liebermann, H.A., Lachman, L., Schwartz, J.B. (Eds.), Pharmaceutical Dosage Forms: Tablets, vol. 2. Marcel Dekker, Inc, New York, pp. 245–348.

Israelachivili, J., 1992. Interactions involving polar molecules. In: Israelachivili, J. (Ed.), Intermolecular and Surface Forces. Academic Press, Inc, San Diego, CA, pp. 54–56.

Insel, P.A., 1996. Analgesic–antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman, J.G., Limbird, L.E., Molinoff, P.B., Ruddon, R.W., Gilman, A.G. (Eds.), The Pharmacological Basis of the Rapeutics, 9th ed. pp. 617–657.

Knapczyk, J., 1993. Excipient ability of chitosan for direct tableting. Int. J. Pharm. 89, 1–7.

Machida, Y., Nagai, T., 1989. Chitin/chitosan as pharmaceutical excipients. In: Breimer, D.D., Crommelin, D.J.A., Midha, K.K. (Eds.), Topics in Pharmaceutical Sciences. Federation Internationale Pharmaceutique (F.I.P), The Hague, pp. 211–220.

Muzzarelli, R.A.A., 1993. Biochemical significance of exogenous chitins and chitosans in animals and patients. Carbohydr. Res. 20, 7–16.

Newton, D.W., Kluza, R.B., 1978. pK_a values of medicinal compounds in pharmacy practice. Drug Intell. Clin. Pharm. 12, 546–554.

Rege, P.R., Shukla, D.J., Block, L.H., 1999. Chitinosans as tableting excipients for modified release delivery systems. Int. J. Pharm. 181, 49–60.

Sabnis, S.S., 1996. Development of modified chitosans as excipients for use in drug delivery systems. Ph.D. Thesis, Duquesne University, USA, pp. 127–132.

Sabnis, S.S., Block, L.H., 1997. Improved infrared spectroscopic method for the analysis of degree of *N*-deacetylation of chitosan. Polym. Bull. 39, 67–71.

Sabnis, S.S., Rege, P.R., Block, L.H., 1997. Use of chitosan in compressed tablets of diclofenac sodium: inhibition of drug release in an acidic environment. Pharm. Dev. Technol. 2, 243–255.

Sawayanagi, Y., Nambu, N., Nagai, T., 1982. Directly compressed tablets containing chitin or chitosan in addition to lactose or potato starch. Chem. Pharm. Bull. 30, 2935–2940.

Scott, H., 1991. Polymer science. In: Martin, A., Swarbrick, J., Cammarata, A. (Eds.), Physical Pharmacy, 3rd ed.. Lea and Febiger, Philadelphia, pp. 599–600.

Wolff, M., Kersten, D., Göber, B., 1987. Bestimmung und Berechnung von pH-Werten wäßrig-methanolischer Lösungen. Pharmazie 42, 820–823.