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Research paper

In vitro evaluation of microcrystalline chitosan (MCCh) as gel-forming excipient in matrix granules

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Abstract

Although much research has been carried out into the effects of chitosan and its chemical properties on drug release, less attention has been paid to the effects of its physical properties. The aim of this study was to characterize microcrystalline chitosan (MCCh) as a gel-forming excipient. Matrix granules containing chitosans of differing physicochemical properties (crystallinity, molecular weight, degree of deacetylation) and ibuprofen or paracetamol as model drugs were prepared. Gel formation by the chitosans in the granules and subsequent effects on drug release were studied at pH 1.2 and pH 5.8. The chitosan granules acted as slow-release formulations in the case of ibuprofen (a class-II drug in the Biopharmaceutics Classification System) but with paracetamol (class-I) no controlled-release formulation could be developed. Microcrystalline grades of chitosan had the most marked retardant effects on drug release, with the efficacy of gel formation by MCCh explaining the results. The kinetic constant for ibuprofen release (at pH 5.8) ranged from 22%·h^{-1} (MCCh) to 31%·h^{-1} (unmodified chitosan). The release rate was easily controlled by varying the amount or molecular weight of MCCh, and to a lesser extent by the degree of deacetylation. The effects were most pronounced when pH was markedly acidic, suggesting that MCCh granules might be particularly useful in preparing stomach-specific slow-release dosage forms.

Keywords: Chitosan; Crystallinity; Gel formation; Slow-release; Controlled-release

1. Introduction

In recent years, there has been increasing interest in the pharmaceutical field in the use of renewable materials of natural origins, such as chitosan. Chitosan is a polysaccharide derived from the chitin of crustaceans, with crab- and shrimp-shell wastes as its principal sources [1]. Its properties as a cationic polysaccharide, and its low toxicity and good biocompatibility [2,3], make it interesting for study as an excipient.

Chitosan, which contains a number of amino groups in the polymer backbone, is polycationic in acidic environments [4]. It possesses an ability to form gels at acidic pH values, because it is hydrophilic and can retain water in its structure. Important chemical properties of chitosan include the extent of deacetylation, defined in terms of the percentage of primary amino groups in the polymer backbone, and the average molecular weight of the polymer. Because of its gel-forming ability, chitosan has received attention as a possible release-rate modifying excipient in hydrogel-based controlled-release systems. Drug release from viscous chitosan gels has been found to be slow [5]. As amounts of chitosan increase release rates decline. Findings relating to solid dosage forms such as tablets and granules have been similar. Drug release is retarded after formation of chitosan gels in acidic aqueous environments [6–9]. Release rates decrease as the molecular weight of chitosan increases or the extent of deacetylation reaches the optimum [10,11]. The retardant effects of chitosans that differ in chemical properties can be explained by slow diffusion of drug through gels of high viscosities. Rates at which a drug is released from hydrogel-based chitosan formulations also depend on the character of the drug. Substances with low solubilities in water and/or high molecular weights are the most slowly released [12].

Although much research has been carried out into the effects of the chemical properties of chitosan on drug release, less attention has been paid to the effects of the physical properties of chitosan, such as its crystallinity and crystal structure. Detailed knowledge of the structure of chitosan has, however, increased in recent years, revealing the importance of the physical characteristics of chitosan for its functional properties. Chitosans derived from different marine sources have been shown to depend, as

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regards reactivity, on the crystalline type of chitin extracted [13]. The physical characteristics of the chitosan obtained are closely related to the source of the chitin from which it is derived, chitosan derived from crystalline chitin being highly oriented [14]. Characteristics of chitosan can also be modified by changing reaction conditions during its manufacture. By using an appropriate method, the crystallinity of chitosan can be significantly increased, allowing microcrystalline chitosan (MCCh) to be obtained [15]. So far, most pharmaceutical-formulation studies have been carried out using chitosans produced commercially by conventional methods. Such chitosans, unlike MCCh, are fairly amorphous, as powder X-ray diffraction patterns show [15–18]. MCCh also has favourable functional properties, e.g. a high water-retention value, which reflects the substantial surface area of MCCh. MCCh can retain three to four times as much water as the parent chitosan, potentially increasing its capacity to form gels. Such a functional property could be of particular value in hydrogel-based slow-release formulations. The effects of chitosan crystallinity on drug release therefore required evaluation.

The aim of this study was to characterize MCCh as a gel-forming excipient in hydrogel-based multiparticulate matrix-type formulations in vitro. If gel formation by MCCh in acidic environments like the stomach were good, it could be valuable as an excipient for modifying drug-release rates in oral dosage forms. The bioadhesive properties of chitosan [19,20] could make hydrogel-based MCCh formulations valuable as carriers for drugs that have sites of action in the stomach. Stomach-specific slow-release dosage forms could also be useful for drugs absorption of which is site-specific in the upper parts of the gastrointestinal tract. Use of MCCh could offer advantages over other hydrophilic excipients, because gel formation by other excipients is in general less efficient in markedly acidic environments like the stomach, e.g. a stable hydroxypropyl methylcellulose (HPMC) gel is formed over the pH range 3–11 [21]. In the study reported here, gel formation by MCCh in matrix granules and effects of MCCh on drug release were studied in vitro at markedly and slightly acidic pH values. Formulations containing different amounts of MCCh were prepared, using MCCh grades of differing molecular weights and extents of deacetylation. Two model drugs of differing aqueous solubilities were incorporated in the granules. Characteristics of MCCh as a gel-forming excipient in granules were evaluated in comparison with those of unmodified chitosan. Gels were also prepared to evaluate the effects of the amount of chitosan and its grade on gel viscosity and pH.

2. Materials and methods

2.1. Materials

MCCh (Novasso Ltd., Finland) differing in extents of deacetylation (DD%) and molecular weights (Mw), and unmodified chitosan (Ch) (Primex Ingredients ASA, Norway) were studied as gel-forming excipients. The unmodified chitosan originated from shrimp shells, and MCCh was manufactured from it in accordance with specifications [15], using a continuous manufacture method [22]. Chitosan physicochemical properties are shown in Table 1. The information was provided by the supplier (Novasso Ltd., Finland). Mw values are approximate mean values, and the variation range is ±20–30 kDa. Grades A, C and D are representatives for high Mw chitosans, and grade B for a low Mw chitosan. Grade A is a representative for chitosan with a low DD%, and grade C for a high DD%. Ibuprofen (Ph.Eur.) and paracetamol (Ph.Eur.) were chosen as model drugs. The solubility of ibuprofen (pK_a 5.3, Mw 206.3 g/mol) is low at acid pH levels. Paracetamol (pK_a 9.5, Mw 151.2 g/mol) is readily soluble within the physiological pH range, irrespective of pH. In the Biopharmaceutics Classification System (BCS) [23], ibuprofen and paracetamol belong to classes II and I, respectively.

2.2. Preparation of chitosan gels

Gels containing 1, 2 and 4% of chitosan were prepared by mixing chitosan with 0.5, 1 and 2.5% aqueous solutions of acetic acid manually in a mortar. The gels were hydrated for 1 h at room temperature, after which viscosity and pH were studied. Hydrochloric acid buffer pH 1.2 (USP 24) and phosphate buffer pH 5.8 (USP 24) were similarly used to prepare gels. The reproducibility of the manufacturing method was checked by preparing two batches of each formulation in parallel. Variability in results between the batches was minimal. Presented data are for batch one.

2.3. Preparation of chitosan matrix granules

Mixtures with different ratios of chitosan to drug were granulated using a 2.5% aqueous solution of acetic acid (q.s.). Percentages of chitosan in the formulations were 5, 10, 15, 20, 30, 40, 50 and 60% for granules containing ibuprofen, and 15, 30 and 60% for granules containing paracetamol. Powder masses were moistened with granulating fluid manually in a mortar. Masses were granulated through a 2.0 mm sieve and dried overnight at room temperature. The size fraction 1.18–1.68 mm was separated by sieving and used in the study. The reproducibility of the manufac-

Table 1
Physicochemical properties of chitosans[a]

Chitosan grade	Quality	DD (%)	Mw (kDa)
A	MCCh	75	150
B	MCCh	75	25
C	MCCh	90	120
D	Ch	90	160

[a] MCCh, microcrystalline chitosan; Ch, unmodified chitosan; DD, approximate degree of deacetylation; Mw, approximate molecular weight.

turing method was checked by preparing two batches of each formulation in parallel. Variability in results between the batches was minimal. Presented data are for batch one.

2.4. Characterization of chitosan gels

Viscosities and pH values of gels were measured 1 h after preparation. Viscosity measurements were performed using a Brookfield digital viscometer (DV-II, Brookfield Engineering Laboratories, USA) at room temperature after 1 min of rotation of the spindle (LV4). The speed of rotation was 100 min^{-1}. A Mettler Toledo InLab412 combination electrode (Mettler-Toledo, Switzerland) was used for pH measurement.

2.5. Characterization of chitosan matrix granules

2.5.1. Gel formation

Gel formation by chitosan in granules ($n = 3$) containing ibuprofen was studied at different pH levels by means of light microscopy (Leica DMLB 020-519.511, Leica Mikroskopie und Systeme, Germany). Hydrochloric acid buffers of pH 1.2 and pH 2.2 (USP 24) and phosphate buffer of pH 5.8 (USP 24) were used as hydration media. The granules were attached to a Petri dish with double-sided adhesive tape and hydration medium (10 ml) was added. Hydration and gel formation by chitosan were observed at intervals, and expressed in terms of granule relative equivalent diameter (REL d_{ekv}). Granule areas were measured using imaging software (Leica Qwin Imaging Systems, Germany) and converted to equivalent diameters (d_{ekv}). Relative equivalent granule diameters (REL d_{ekv}) were calculated using the equation:

$$\text{REL } d_{ekv} = d_{ekv\ t}/d_{ekv\ 0} \quad (1)$$

where $d_{ekv\ 0}$ is the equivalent diameter of a granule before addition of hydration medium and $d_{ekv\ t}$ is the equivalent diameter at time t during hydration.

2.5.2. Drug release

Drug release from granules ($n = 6$) was studied by means of dissolution tests using the basket method described in USP 24 (Distek Premiere 5100 Apparatus, Distek, USA). The dissolution media used were phosphate buffer pH 5.8 (USP 24) (1000 ml, 37 ± 0.5 °C) for granules containing ibuprofen, and hydrochloric acid buffer pH 1.2 (USP 24) and phosphate buffer pH 5.8 (USP 24) (500 ml, 37 ± 0.5 °C) for granules containing paracetamol. Speeds of rotation were 100 min^{-1} (ibuprofen) and 50 min^{-1} (paracetamol). Amounts of drug released were determined spectrophotometrically. The dissolution apparatus was connected to a flow-through spectrophotometer (Ultrospec 4000, Pharmacia Biotech, UK) via a peristaltic pump (Icalis PCP490, Icalis Data System, UK). Absorbances at 221 nm (ibuprofen) and 244 nm (paracetamol) were recorded automatically using dissolution software (Icalis Data Systems, UK), and converted to percentage of drug released as a function of time.

Drug-release kinetics were evaluated using the equation proposed by Ritger and Peppas for description of fractional release [24]. The equation used, in general form, is:

$$M_t/M_\infty = kt^n \quad (2)$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released at infinity, k is the kinetic constant, and n is the diffusional exponent, indicative of the mechanism of release. Percentages of drug released (≤60%) of individual curves were fitted to the equation, and drug-release kinetics and mechanisms of release were evaluated. In cases of diffusion-controlled Fickian release from swellable devices, n has limit values of 0.50, 0.45 and 0.43 for release from slabs, cylinders and spheres, respectively [25]. Greater values of n indicate non-Fickian release. In such cases diffusional drug release depends on the ratio between the polymer relaxation rate and the rate of diffusion of drug in gel. If $n = 1$, drug release is independent of time, i.e. release kinetics are zero-order.

3. Results and discussion

3.1. Characterization of dilute chitosan gels

The viscosities of chitosan gels depended on amounts and molecular weights of polymer. This is shown in Fig. 1 for gels prepared with 2.5% acetic acid. Results for gels prepared with 1 or 0.5% acetic acid were in accordance with those in Fig. 1. In general, as the amount or molecular weight of chitosan increased, so did the viscosity of the gel. Gels made with MCCh grade with a low degree of deacetylation (grade A) were more viscous than gels made with MCCh grade with a high degree of deacetylation (grade C). However, no confident conclusion could be reached about the effect of the degree of deacetylation on gel viscosity because the chitosans that differed in respect of extent of deacetylation (A and C) had slightly different molecular weights. Undoubtedly, chitosan crystallinity had no marked effect on viscosities of dilute chitosan gels, macromolecular solutions of polymer. The viscosities of gels made with unmodified chitosan (grade D) were higher than the viscosities of gels made with MCCh (grade A) but the molecular weight of the grade D chitosan was slightly higher than that of the grade A. Fig. 2 shows that the amount of chitosan used also had a marked effect on pH values of gels prepared in dilute acetic acid. Levels of pH rose as amounts of cationic chitosan increased. The effect of chitosan grade on pH was less marked. Levels of pH were slightly higher in gels containing chitosan with high degrees of deacetylation (grades C and D).

Chitosan gel viscosity was affected by pH, as shown for grade A chitosan in Table 2. Results with other chitosan grades were similar. Gels prepared in hydrochloric acid

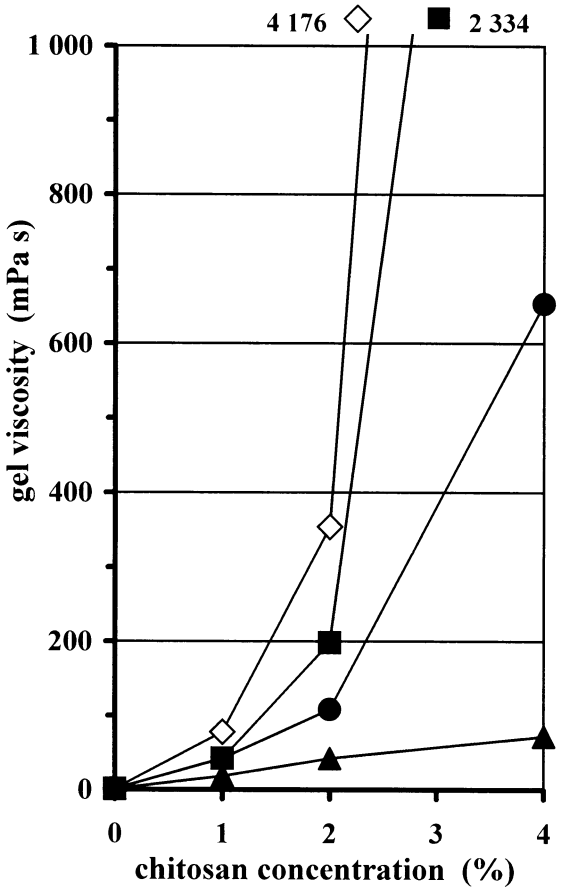

Fig. 1. Effects of the amount and grade of chitosan on the viscosity of chitosan gels prepared in 2.5% aqueous acetic acid (rotation speed 100 min^{-1}): ■, MCCh (grade A); ▲, MCCh (grade B); ●, MCCh (grade C); ◇, Ch (grade D).

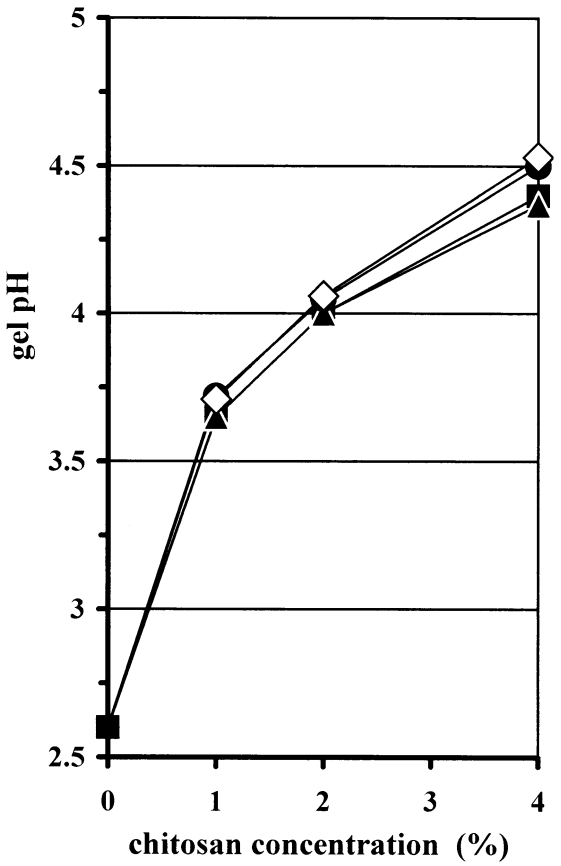

Fig. 2. Effects of the amount and grade of chitosan on pH of chitosan gels prepared in 2.5% aqueous acetic acid: ■, MCCh (grade A); ▲, MCCh (grade B); ●, MCCh (grade C); ◇, Ch (grade D).

buffer of pH 1.2 were markedly more viscous than gels prepared with phosphate buffer of pH 5.8. At pH 5.8, the viscosities of all gels were low, below 100 mPa s. Gels prepared with 0.5% acetic acid were consistently less viscous than gels prepared with 1% acetic acid.

3.2. Characterization of chitosan matrix granules

3.2.1. Gel formation

All of the chitosans in granules formed translucent gels at pH 1.2 and pH 2.2. Hydration and gel formation involved swelling of granules, the extent of swelling being dependent on the chitosan grade (Fig. 3a,b). Granules of MCCh of high molecular weights (grades A and C) increased more in diameter than corresponding granules prepared from unmodified chitosan (grade D). In the latter case an initial increase in granule diameter was followed by a steep decline. Such differences suggest that hydration of and gel formation by granules made from MCCh were more efficient than was the case with granules made from unmodified chitosan. Less efficient gel formation could result in faster granule degradation. Granules containing MCCh of low molecular weight (grade B) also degraded rapidly.

At pH 5.8 only MCCh grades with low degrees of deacetylation (grades A and B) formed proper gels. Swelling and gel formation of chitosan granules at pH 5.8 was less marked than at pH 1.2 or pH 2.2. All gels were fairly opaque, indicating that gel formation occurred primarily at granule surfaces. Some granule degradation can also be assumed from the fact that diameters of granules declined slightly (Fig. 3c).

In a previous study [15] it was shown, using chitosan in powder form, that the capacity of MCCh to retain water

Table 2
Effect of solvent on viscosities of chitosan (grade A) gels with different polymer concentrations (rotation speed 100 min^{-1})

Solvent	Initial pH	Gel viscosity (mPa s)		
		1%	2%	4%
2.5% acetic acid	2.6	42	198	2334
1.0% acetic acid	2.9	66	204	5676
0.5% acetic acid	3.0	27	192	5004
HCl buffer	1.2	3	96	5052
Phosphate buffer	5.8	72	66	66

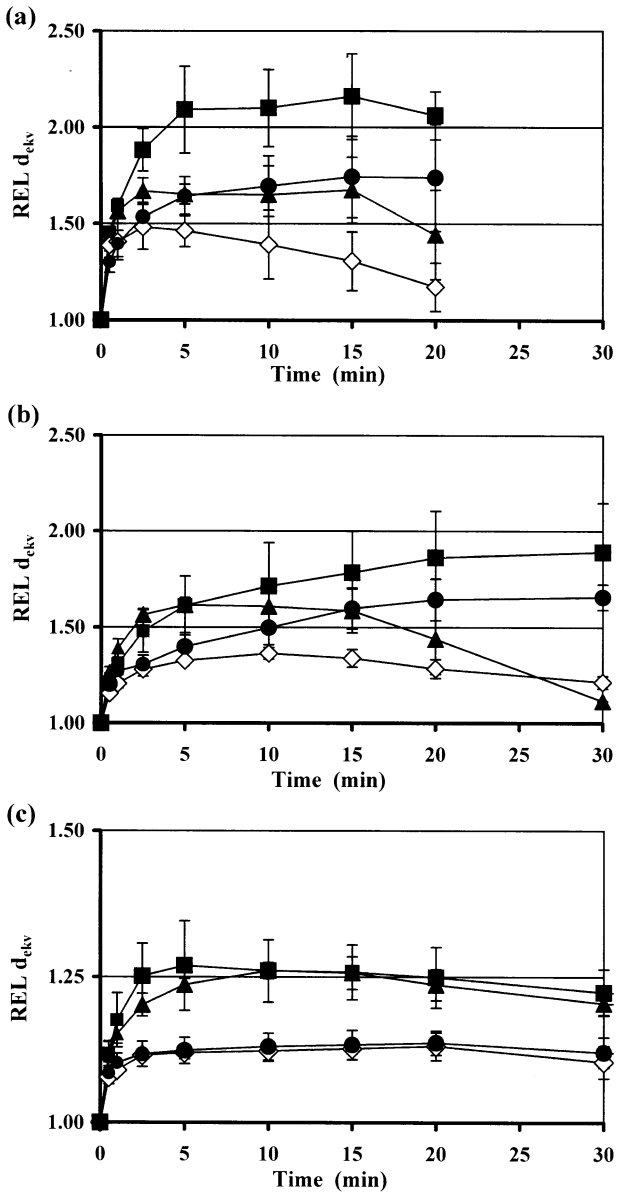

Fig. 3. Effects of the grade of chitosan at different pH levels on diameters of swollen granules (REL d_{ekv}) containing 40% of chitosan and 60% of ibuprofen as a function of time at pH 1.2 (a), pH 2.2 (b), and pH 5.8 (c) (mean ± SD; $n = 3$): ■, MCCh (grade A); ▲, MCCh (grade B); ●, MCCh (grade C); ◇, Ch (grade D).

when hydrated is markedly greater than that of unmodified chitosan. The results of the study reported here indicate that this property means that MCCh could have advantages over unmodified chitosan when the substances are used as gel-forming excipients in hydrogel-based matrix-type dosage forms. The efficacy of gel formation by MCCh in formulations at acidic pH values could be beneficial if slow-release dosage forms are being developed, particularly in the case of formulations intended to release drugs in the stomach.

3.2.2. Drug release

All of the chitosans studied retarded the release of the model drugs at pH 1.2 (paracetamol) and at pH 5.8 (ibuprofen and paracetamol). Ibuprofen was released particularly slowly from the granules whereas retardation of paracetamol release was minimal (Figs. 4–8). Data relating to release kinetics are shown in Tables 3 and 4. The release mechanism for both model drugs was non-Fickian diffusion, on the basis of diffusional exponent (n) values. Progressive hydration and gel formation by chitosan in granules and gradual erosion of gels as a result of dissolution of chitosan could explain non-Fickian release. The solubility of the drug was of importance, and a drug with a slow dissolution rate was more slowly released (ibuprofen).

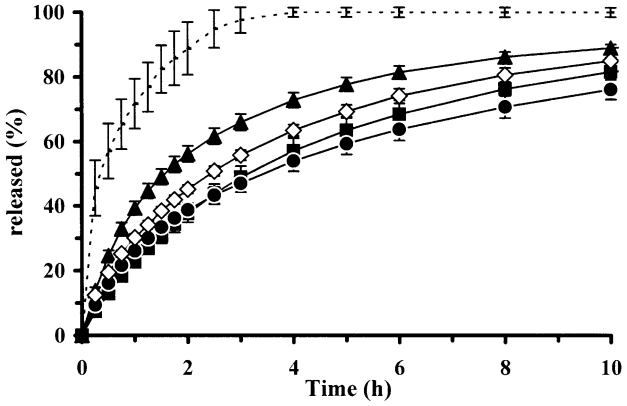

Fig. 4. Effects of the grade of chitosan on drug release from granules containing 40% of chitosan and 60% ibuprofen at pH 5.8 (mean ± SD; $n = 6$): ■, MCCh (grade A); ▲, MCCh (grade B); ●, MCCh (grade C); ◇, Ch (grade D); —, drug alone.

Fig. 4 shows the effects of the grade of chitosan on release of ibuprofen at pH 5.8 from granules containing 40% of chitosan. MCCh grades of high molecular weights (grades A and C) retarded drug release more than unmodified chitosan (grade D). The kinetic constant (k) was $31\%{\cdot}h^{-1}$ for granules containing grade D (Table 3). With corresponding formulations containing grades A and C

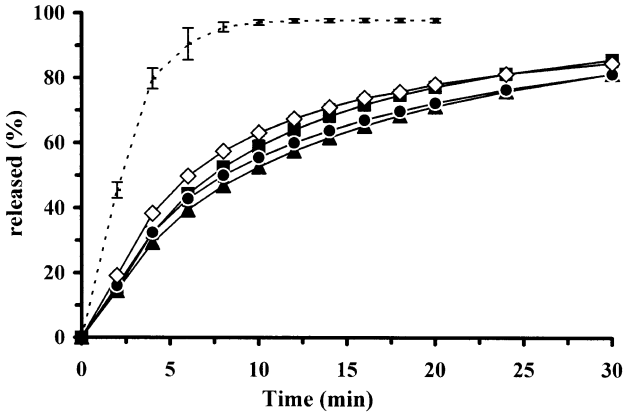

Fig. 5. Effects of the grade of chitosan on drug release from granules containing 60% of chitosan and 40% paracetamol at pH 5.8 (mean ± SD; $n = 6$): ■, MCCh (grade A); ▲, MCCh (grade B); ●, MCCh (grade C); ◇, Ch (grade D); —, drug alone.

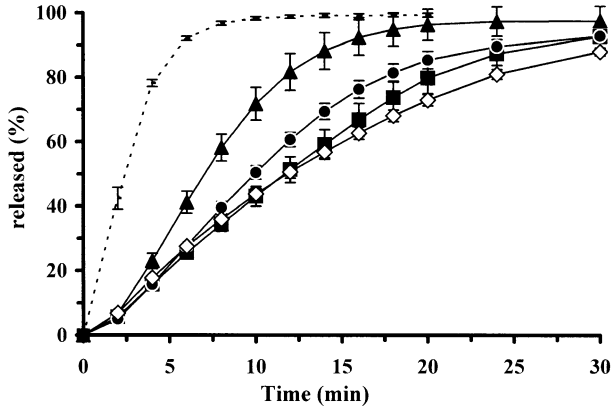

Fig. 6. Effects of the grade of chitosan on drug release from granules containing 60% of chitosan and 40% paracetamol at pH 1.2 (mean ± SD; $n = 6$): ■, MCCh (grade A); ▲, MCCh (grade B); ●, MCCh (grade C); ◇, Ch (grade D); —, drug alone.

values of k were 22%·h^{-1} and 25%·h^{-1}, respectively. The differences in release rates indicate that the various grades of MCCh could offer advantages over unmodified chitosan when slow-release formulations are being developed. Quite an important property of MCCh is molecular weight. When the degree of deacetylation was constant, drug release was retarded as molecular weight increased (grade A versus B) (Fig. 4, Table 3). The degree of deacetylation had little effect on drug release (grade A versus C). However, the highest value of the diffusional exponent (n) was achieved with MCCh grade A ($n = 0.72$). The drug-release profile in this case was closest to zero-order kinetics. In many cases it is desirable for drug release from a slow-release dosage form to be approximately constant over a long period. Our findings suggest that this might be achievable through use of MCCh grades with low degrees of deacetylation and high molecular weights.

Figs. 5 and 6 show the release of paracetamol at pH 5.8 and pH 1.2 from granules containing 60% of chitosan. Data relating to release kinetics are shown in Table 4. The overall effects of chitosan grade on drug release were fairly similar

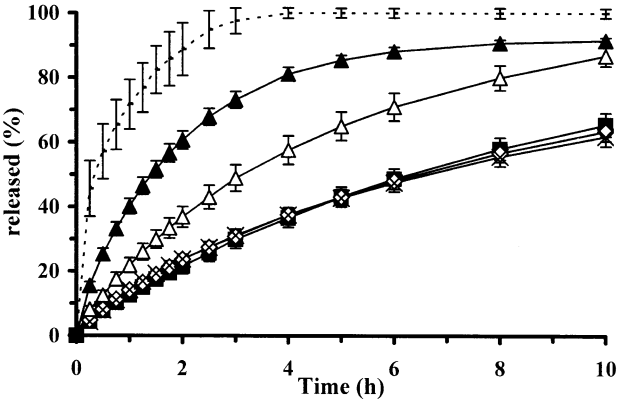

Fig. 7. Effects of the amount of MCCh (grade A) on the release of ibuprofen from granules at pH 5.8 (mean ± SD; $n = 6$). Amount of MCCh in granules: ×, 5%; ◇, 10%; ■, 20%; △, 40%; ▲, 60%; —, drug alone.

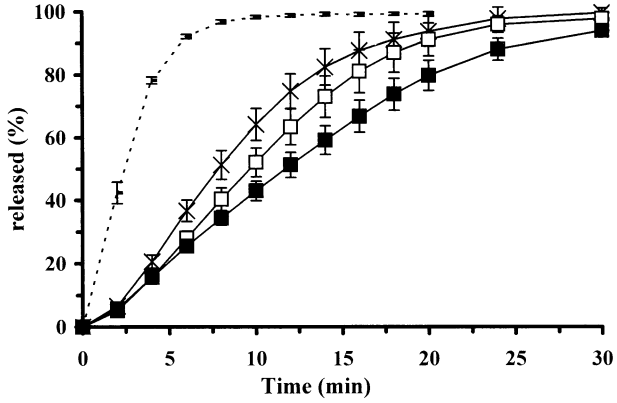

Fig. 8. Effect of the amount of MCCh (grade A) on the release of paracetamol from granules at pH 1.2 (mean ± SD; $n = 6$). Amount of MCCh in granules: ×, 15%; □, 30%; ■, 60%; —, drug alone.

for both paracetamol and ibuprofen but with paracetamol the differences in effects of the various grades of chitosan were fairly small. The most important finding in relation to paracetamol formulations was that the kinetic profile of drug release depended on pH. The release of paracetamol was slower at pH 1.2 than at pH 5.8, as the values for k in Table 4 show. The value of the diffusional exponent (n) at pH 1.2 always exceeded 1, meaning that the dissolution rate of paracetamol slowly increased during the dissolution test period, at least until 60% had been released. With chitosans of the highest molecular weights (grades A and D), n was close to 1. It was concluded from the results with paracetamol that the gel-forming ability of chitosan and consequent retardant effects on drug release are most pronounced at markedly acidic pH values, and that near-zero-order drug release can be achieved in acid environments. The use of chitosan granules might therefore be desirable if zero-order drug release in the stomach were wanted, like in stomach-specific dosage forms. Slow-release formulations are likely to be achievable only with drugs of low solubility.

In previous studies, less attention has been paid to the effects of crystallinity of chitosan on drug release. Only Sabnis et al. [10], who studied chitosans as directly compressible excipients in tablets of diclofenac sodium, also evaluated chitosans of high crystallinity. In their study, chitosan

Table 3
Values of k (%·h^{-1}) and n for ibuprofen release at pH 5.8 from matrix granules containing 40% of chitosan, calculated using the equation $M_t/M_\infty = kt^n$ (mean ± SD; $n = 6$)[a]

Chitosan grade	pH 5.8		
	k	n	r
A	22.15 ± 1.40	0.72 ± 0.02	0.996
B	37.54 ± 1.48	0.59 ± 0.02	0.993
C	25.32 ± 1.03	0.56 ± 0.03	0.993
D	30.84 ± 1.89	0.55 ± 0.02	0.997

[a] k, kinetic constant; n, diffusional exponent, indicative of mechanism of release; r, correlation coefficient.

Table 4
Values of k (%·min^{-1}) and n for paracetamol release at different pH levels from matrix granules containing 60% of chitosan, calculated using the equation $M_t/M_\infty = kt^n$ (mean ± SD; n =6)[a]

Chitosan grade	pH 1.2			pH 5.8		
	k	n	r	k	n	r
A	2.75 ± 0.29	1.20 ± 0.07	0.992	8.41 ± 0.54	0.90 ± 0.04	0.986
B	2.27 ± 0.36	1.62 ± 0.10	0.995	9.41 ± 0.62	0.76 ± 0.02	0.985
C	2.00 ± 0.20	1.43 ± 0.05	0.995	10.42 ± 0.77	0.75 ± 0.04	0.981
D	3.70 ± 0.47	1.07 ± 0.06	0.988	11.44 ± 0.31	0.81 ± 0.02	0.987

[a] k, kinetic constant; n, diffusional exponent, indicative of mechanism of release; r, correlation coefficient.

was subjected to depolymerization to improve crystallinity and, accordingly, compressibility. The resulting chitosan tablets behaved as extended-release formulations at acidic pH values, efficient formation of a chitosan gel barrier being one theoretical explanation for the markedly slow drug-release rates. However, only tablets made from depolymerized chitosan were studied because the compressibility of unmodified chitosans was poor. In the study reported here, we showed that microcrystalline grades of chitosan as excipient in matrix granules retarded drug release more efficiently than unmodified chitosan. The retardant effects of MCCh can be explained by findings that indicate efficient gel formation by MCCh in granules (Section 3.2.1). The greatest equivalent diameter of swollen granules was achieved with MCCh grade A, which also had the greatest retardant effect on drug release. Findings of high viscosities of chitosan gels (Section 3.1) and high efficacies of gel formation by chitosan in granules (Section 3.2.1) at acidic pH values explain why the retardant effects of chitosan on drug release were most marked at low pH values. It was unfortunate that dissolution studies to evaluate the effects of pH on the characteristics of chitosan granules could not be undertaken with ibuprofen at both pH 1.2 and pH 5.8, because of the low solubility of ibuprofen at acidic pH levels. Undoubtedly, results of dissolution tests at pH values of 1–2 best allow the in vivo behaviour of chitosan granules in the stomach to be predicted. Paracetamol, which is readily soluble throughout the physiological pH range, irrespective of pH, was therefore used as an alternative model drug.

In the last part of the study reported here the effect of the amount of polymer on drug release was studied. Fig. 7 shows the effect of the amount of chitosan on the release of ibuprofen at pH 5.8 with MCCh grade A. Results with other grades (B to D) were in accordance with those in Fig. 7. In general, ibuprofen release was fastest from formulations containing the highest amounts of chitosan. The maximal retardant effect on drug release was achieved with 5–20% of MCCh grade A in matrix granules. With paracetamol, the effect of the amount of chitosan on drug release was the opposite to that seen with ibuprofen. The highest amounts of chitosan were associated with the lowest release rates (Fig. 8). The effect was more pronounced at pH 1.2 than at pH 5.8. It was, however, not possible to prepare slow-release formulations of paracetamol by increasing amounts of chitosan. With every formulation practically all of the paracetamol was released within 30 min, at both pH 1.2 and pH 5.8.

In a previous study [18] it was noted that chitosan could increase dissolution rates of drugs of low solubility. One explanation suggested was that the hydrophilic chitosan could be acting as a wetting agent, hastening drug release. In the study reported here, the hydrophilic nature of chitosan could also explain the results seen with ibuprofen, the solubility of which is low at acid pH levels. Another mechanism of action could have been that large amounts of MCCh in granules increased the pH values of the gels formed, and that the dissolution rate of ibuprofen therefore increased. The finding that pH in gels increased as amounts of chitosan increased (Section 3.1) corresponds well with this mechanism of action. However, the mechanism suggested could operate only in slightly acidic environments, with drugs that are weak acids, e.g. at pH 5.8 with ibuprofen. In such cases, slight increases in pH near the pK_a value of the weak acid could markedly increase dissolution rates. With paracetamol, the solubility of which is independent of pH, the effect of the amount of chitosan on release rates was opposite to that with ibuprofen. The release rate decreased as the amount of chitosan increased. This finding is understandable because gel viscosity increases with the amount of chitosan (Section 3.1).

4. Conclusions

The results of the study reported indicate that chitosan matrix granules may be a valuable means of preparing slow-release oral dosage forms with ease. Drug release is controlled by gel formation by chitosan in acidic environments, e.g. in the stomach, and thereafter by both drug diffusion through the gel and erosion of the gel matrix. The effects of chitosan are pronounced at markedly acidic pH values.

Microcrystalline grades of chitosan in granules could offer advantages over unmodified chitosan, because gels form more easily and drug release is more retarded. Drug-release rates can easily be controlled by varying the amount

or molecular weight of the polymer, and to a lesser extent by the degree of deacetylation. However, slow-release formulations are likely to be achievable only with drugs of low solubility (BCS class-II and class-IV drugs). This might restrict the use of chitosan granules.

Further studies, including bioavailability tests and bioadhesion studies, will be performed to evaluate whether MCCh granules might be useful in preparing stomach-specific slow-release dosage forms.

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