International Journal of Pharmaceutics, 98 (1993) 181–188

IJP 03262

Use of chitosan and chitosan malate as an excipient in wet granulation of three water soluble drugs

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(Received 10 February 1993)
(Accepted 30 March 1993)

Key words: Chitosan; Chitosan malate; Wet granulation; Drug release rate; Sustained release; Theophylline; Sodium salicylate; Chloroquine phosphate

Summary

The drug release from granules containing two different chitosan qualities was studied, using three model drugs. Granules were prepared by standard wet granulation, starting with a dry blend of drug and chitosan followed by spraying with a granulating fluid. The resulting granules have good flow properties, except from formulations with the cationic model drug (chloroquine), which gave electrical charged granules. Theophylline granules containing from 25 to 75% of chitosan malate showed an increasing sustained release effect when the chitosan malate content was increased. Zero-order kinetics for the dissolution rate was observed for all three drugs in formulations with a content of 75% chitosan malate. This was probably due to the swelling of the granules in acidic solution. In contrast to the formulations containing chitosan malate as an excipient, theophylline granules containing 25–90% chitosan (SeaCure 452) showed more rapid dissolution than the pure drug, due to fast disintegration and a wetting effect. In dissolution medium no. 2 (pH 6.8), the swelling was less marked, but an interaction between the phosphate buffer and chitosan malate appeared to influence the drug release rate.

Introduction

Chitosan [(1 → 4)-2-amino-2-deoxy-β-D-glucan] is prepared by alkaline *N*-deacetylation of chitin [(1 → 4)-2-acetamido-2-deoxy-β-D-glucan] which is a polysaccharide widely distributed in nature.

During the last decade, chitosan has been reported to have useful pharmaceutical applications in different drug delivery systems (Miyazaki et al., 1981; Nagai et al., 1984; Pangburn et al., 1984; Brine 1988). This interest in the use of the polysaccharide is mainly due to its good biocompatibility and biodegradable properties (Hirano et al., 1988), together with its polymer cationic character and accessible functional groups (see Fig. 1). The lack of satisfactory methods for characterizing the polymer has limited its usefulness in scientific research and in practical application. Work in this area, however, is in progress (Vårum et al., 1991a,b).

The use of chitosan in pharmaceutical preparations has also been shown to be able to compete economically with existing alternatives (Brine, 1988).

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Chitosan has been used as an excipient for direct tabletting of pharmaceuticals (Sawayanagi et al., 1982a,b; Nagai et al., 1984), to enhance the dissolution properties of some less soluble drugs (Sawayanagi et al., 1982c, Nagai et al., 1984), and to give sustained release of drugs (Kawashima et al., 1985a,b; Miyazaki et al., 1988; Acartürk, 1989; Inoye et al., 1989).

Kawashima et al. (1985a) described the preparation of a prolonged-release tablet of aspirin using wet granulation with a chitosan solution. The aim of the present study was to prepare granules of chitosan/drug, starting with a simple dry mixture of the two, followed by addition of a suitable granulating fluid. The influence of the chitosan/drug ratio on the drug release pattern was studied, using three model substances: theophylline (neutral), sodium salicylate (anionic) and chloroquine phosphate (cationic). Accordingly, one part of the study was to compare the release rates of theophylline from formulations containing increasing amounts of chitosan or chitosan malate. The other was to evaluate the release rates of the three model drugs using a chitosan malate/drug ratio of 3:1.

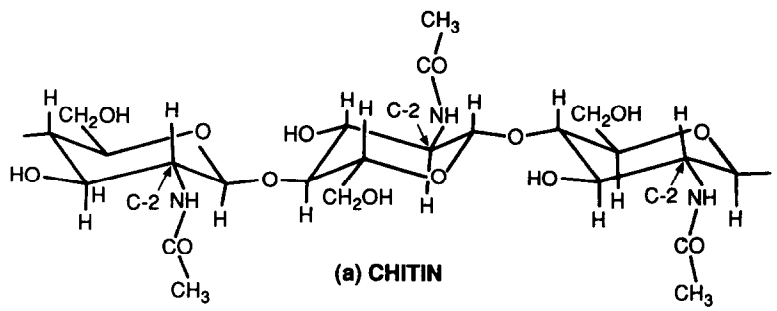
In this study, two different qualities of chitosan were used in the formulations; one is soluble in water, and the other in dilute acidic solution. A further aim of this study was to compare the dissolution rates of theophylline from granules containing chitosan with those containing chitosan malate as an excipient.

Materials and Methods

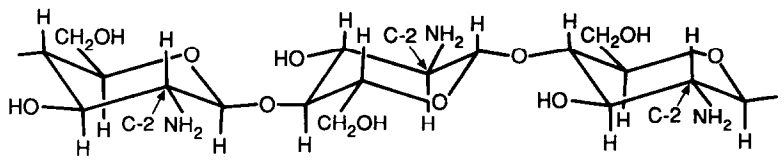
Qualities of chitosan

Chitosan (SeaCure 452), 60 mesh, with 77.3% degree of deacetylation, was used. This quality is soluble in acidic solution only.

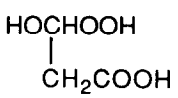
Chitosan malate (SeaCure +210) was prepared by dissolving chitosan in malic acid (Fig. 1c) and subsequent spray-drying of the blend. The quality used contained 50% of chitosan and



(a) CHITIN



(b) CHITOSAN



(c) Malic acid

Fig. 1. Structures of chitin, chitosan and malic acid.

50% of malic acid (w/w %), and was used after passing through a 100 mesh sieve. In the formulations, the mass ratio chitosan malate/drug includes the malate. Accordingly, the chitosan/drug ratio is actually lower.

The above-mentioned grades of chitosan were supplied by Pronova Biopolymer A/S, Drammen.

Model drugs

Monohydric theophylline and sodium salicylate were purchased from the Norwegian Medicinal Depot. Chloroquine diphosphate was obtained from Weifa, Oslo.

The model drugs were used after passing through a 100 mesh sieve.

Granulating fluids

De-ionized water was used in formulations with chitosan malate (SeaCure +210). A 5% solution of acetic acid was used in the formulations with chitosan (SeaCure 452).

Granulation

Dry blends of the two components (chitosan/drug or chitosan malate/drug) were sprayed with granulating fluid and granulated manually in a mortar. The mass was sieved through a 22 mesh sieve, and the resulting granules were dried overnight under a cold air flow.

The dry granules sized 22–50 mesh were filled in hard gelatine capsules no. 1.

Table 1 shows the composition of the different formulations.

Reference formulations

100 mg of drug/capsule were used as a reference formulation when measuring the drug release rate.

Dissolution test

Dissolution tests of the model drugs with the formulations termed 1–9 in Table 1 were conducted by the basket method (USP XXI, 1985) with stirring at 50 rpm. The dissolution medium was 1000 ml of 0.1 N HCl (medium 1, pH 1) or phosphate buffer of pH 6.8, according to JP X (JP X, 1981), second fluid (medium 2), at 37 ± 0.5°C.

A 4 ml aliquot was sampled and filtered with a GF/C glass microfibre filter (Millipore). The amount of drug in the filtrate was determined by spectrophotometric analysis using a Shimadzu UV-160A UV-visible recording spectrophotometer. Absorption was recorded at the following wavelengths: theophylline, 270 nm (both media); chloroquine, 220.6 nm (both media) and salicylate, 237 nm (medium 1) and 296.2 nm (medium 2).

Curve fitting

The data from the dissolution test were fitted to the Weibull function, as described by Sande et al.(1989).

Angle of repose

The angle of repose was measured for some formulations, using Granulatum simplex (Ph.

TABLE 1

Composition of formulations

No.	Model drug (1)	mg	Chitosan quality (2)	mg	(1) + (2)
1	theophylline	100	chitosan	33.3	3 + 1
2	theophylline	100	chitosan	100	1 + 1
3	theophylline	15	chitosan	135	1 + 9
4	theophylline	100	chitosan malate	33.3	3 + 1
5	theophylline	100	chitosan malate	100	1 + 1
6	theophylline	50	chitosan malate	150	1 + 3
7	sodium salicylate	50	chitosan malate	150	1 + 3
8	chloroquine phosphate	50	chitosan malate	150	1 + 3

TABLE 2

Flow properties of selected formulations

Formulation no.	Flow time (s)	Angle of repose (°)
Granulatum simplex +5% lubricant	4.2	22.7
1	7.4	24.2
1 + 5% lubricant	7.7	26.1
4	7.7	23.7
4 + 5% lubricant	7.9	25.5
6	8.3	28.8
6 + 5% lubricant	8.0	27.4
7	8.3	28.2
7 + 5% lubricant	8.1	27.7
8	no flow through	
8 + 5% lubricant	measuring device	

Nord., 1971) 0.7 mm as a reference, and 5% magnesium stearate/talc 1:9 as lubricant. Flow time and angle of repose were measured with a Pharma Test equipment type PTG, program 1 (Hainberg).

Results

Mechanical properties of the granules

After drying under a cold air flow overnight, the granulates still contained from 7.0 to 9.5 % of water, measured as the weight loss at 140°C. This weight loss increases with an increase in temperature above 140°C, and is probably due to loss of water bound more or less tightly to chitosan.

The dried granules had different flow properties, as shown in Table 2. Flow time and angle of repose appear to be best with the granules having the lowest chitosan/drug ratio (i.e., 1:4). The addition of 5% lubricant had no apparent effect on the flow properties of the chitosan formulations, but was necessary to provide adequate flow of Granulatum simplex. Formulation no. 8 ap-

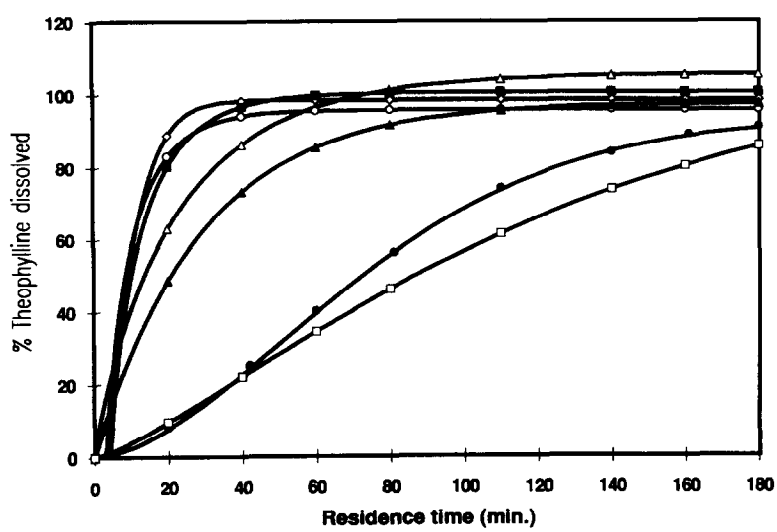


Fig. 2. Dissolution rate profile of theophylline in medium 1 (pH 1) from formulations: (△) theophylline reference, (○) no. 1, (◇) no. 2, (■) no. 3, (▲) no. 4, (●) no. 5, (□) no. 6.

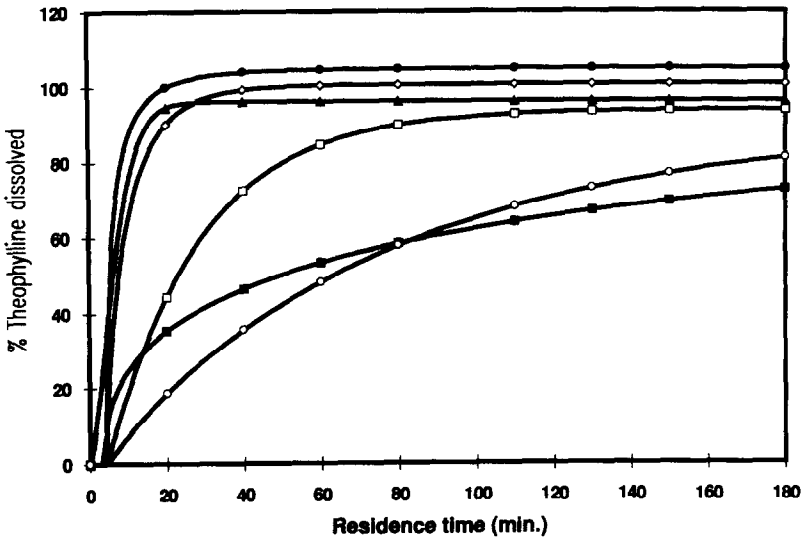


Fig. 3. Dissolution rate profile of theophylline in medium 2 (pH 6.8) from formulations: (▲) theophylline reference, (◇) no. 1, (●) no. 2, (■) no. 4, (□) no. 5, (○) no. 6.

peared different from the others; it was quite electrostatic, and when left in its container for some time aggregates were clearly formed. Accordingly, the flow was not measurable. Preparation of a similar formulation with another cationic model drug (dexchlorpheniramine) gave the same results.

Dissolution study

The absorption spectra of chitosan and chitosan malate show only negligible absorbance at the wavelengths used in the UV measurements of the drugs.

The dissolution profiles of theophylline formulations (formulation nos 1–6) and reference theo-

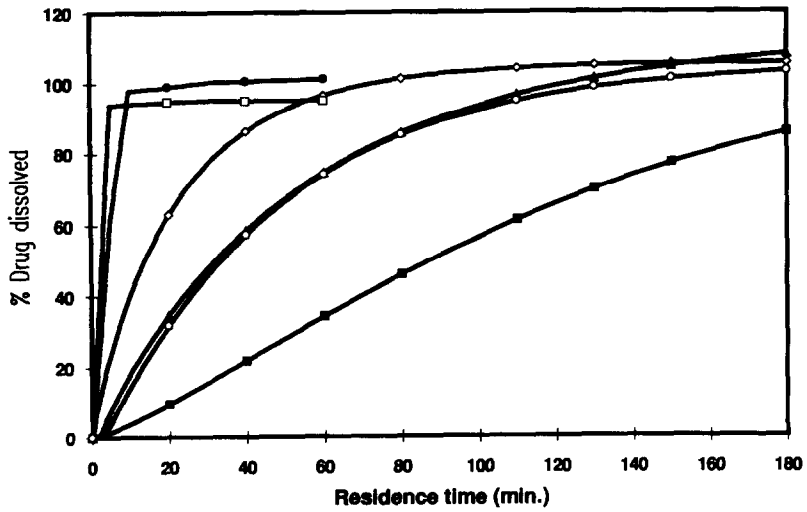


Fig. 4. Dissolution rate profile of three model drugs in medium 1 (pH 1) from formulations: (◇) theophylline reference, (■) no. 6, (□) sodium salicylate reference, (▲) no. 7, (●) chloroquine phosphate reference, (○) no. 8.

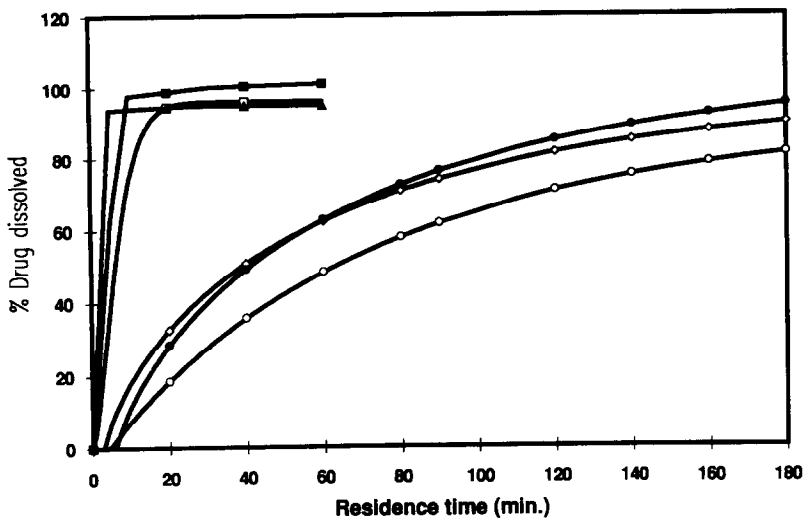


Fig. 5. Dissolution rate profile of three model drugs in medium 2 (pH 6.8) from formulations: (□) theophylline reference, (○) no. 6, (▲) sodium salicylate reference, (◇) no. 7, (■) chloroquine phosphate reference, (●) no. 8.

phylline at pH 1 are shown in Fig. 2. High levels of chitosan malate led to the retardation of drug dissolution, but chitosan alone did not show this effect. At pH 6.8 (Fig. 3), retarded drug release can be seen with chitosan malate, but the data sets show no obvious tendency in the retardation effect towards increasing retardation with increasing chitosan malate/drug ratio.

Fig. 4 compares the dissolution rates of three formulations, nos 6–8 at pH 1. These formulations, which contain 75% chitosan malate and 25% model drug, all display sustained release when compared to their reference formulations in acidic solution. Theophylline appears to undergo the greatest retardation, with zero-order controlled release of the drug from the granules.

In Fig. 5, the dissolution rates of the formulations are shown in phosphate buffer at pH 6.8. Sustained release is also apparent with formulation nos 6–8 in this medium.

Discussion

The dissolution profiles in Figs 2 and 3 demonstrate that raising the chitosan (SeaCure 452) content from 25 to 90% had no significant influence on the dissolution rate of theophylline. However, as compared with the theophylline reference formulation, formulation nos 1–3 all show more rapid dissolution. This may be due to the greater extent of wetting of the drug in formulations with chitosan, as the pure drug powder in the reference capsules tends to float on the solvent surface or remain in the baskets as particle aggregates. Earlier studies on the enhancement of dissolution rates of drugs in mixtures with chitosan appear to be consistent with this conclusion. (Sawayanagi, 1982c).

The content of chitosan malate in formulation nos 4–6 was 25, 50 and 75%, respectively. Fig. 2 shows that raising the chitosan malate content results in the sustained release of theophylline in dissolution medium at pH 1. In Fig. 4, the three model drugs are compared in formulation nos 6–8.

Theophylline in formulation no. 6 appears to be most retarded. However, this drug also has the lowest dissolution rate at pH 1, compared to the sodium salicylate and chloroquine phosphate references. This indicates that the rate-determining step is the dissolution of the pure drug particles

in the granules as the solvent penetrates the matrix, rather than the dissolution of the chitosan malate matrix itself.

Chitosan has the property of undergoing a certain degree of thickening at low pH, and this could be observed in the dissolution study; after 3 h, some of the granules remained in the baskets as a gel. With chitosan malate, most of the granules had dissolved after 3 h, whereas chitosan appeared to dissolve more slowly under the given conditions. A possible explanation of the different dissolution profiles from formulations with chitosan and those with chitosan malate may be as follows: with chitosan malate, a swollen structure is formed quite rapidly and retards the dissolution of drug from the granules. However, with chitosan, gelling is too slow to retard the dissolution of the drug, and drug release is controlled by the dissolution of the drug compound.

In one study (not described here), a flow-through cell was used to construct a dissolution rate profile as a function of a change of dissolution medium. The dissolution rate did not change significantly on exposing formulation no. 6 to medium 1 for 1 h, followed by medium 2 for 2 h. Similarly, Sawayanagi (1982d) described how a chitosan tablet retained its gelled structure after being transferred from a medium of pH 1 to pH 6.8. Reduction of the chitosan/drug ratio results in a non-disintegrating tablet at pH 1 due to the formation of a viscous surface layer. The reduced surface area and hard structure of the tablet compared to the granules in the capsule produces a more pronounced sustained release effect.

Fig. 3 does not show any obvious connection between the increase in chitosan malate content and the dissolution rate at pH 6.8. Chitosan malate and chitosan do not dissolve in the buffer at this pH, but it is possible that a high local concentration of chitosan malate may lead to some dissolution. Dissolved chitosan may then undergo interaction with the phosphate buffer (crosslinking of chitosan chains by phosphate).

Flow properties of the granules

Table 2 shows the angle of repose and flow time of some formulations. For practical purposes, the angle of repose should be in the range 20–45°. Usually, values between 20 and 30° are necessary for large-scale production of oral medical formulations. All formulations, except no. 8, had acceptable flow behaviour without the addition of 5% lubricant.

The electrostatic properties of the formulation with a cationic model drug indicate that some kind of interaction exists between the drug and chitosan malate. However, this interaction does not appear to influence the dissolution rate of the drug, as formulation nos 7 and 8 exhibit quite similar dissolution profiles (see Figs 4 and 5).

In summary, it appears that chitosan can be used to achieve controlled release of drugs using a simple wet-granulation technique. The two different qualities of chitosan used had opposite effects on the drug release rate, chitosan (SeaCure 452) enhancing and chitosan malate (SeaCure +210) retarding the dissolution of the three model drugs. An interaction between chitosan malate and chloroquine phosphate may exist, as judged from the physical appearance of the granules, however, this does not seem to influence the dissolution rate of the drug from the formulation. Formulation nos 1–7 have good flow properties. These formulations should be suitable for large-scale production of capsules and tablets. Compression of the granules into tablets would probably give a more pronounced sustained release effect when chitosan malate is used as excipient.

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