International Journal of Pharmaceutics, 89 (1993) 177–181

IJP 02918

Effect of interpolymer complex formation of chitosan with pectin or acacia on the release behaviour of chlorpromazine HCl

M.M. Meshali and K.E. Gabr

Department of Pharmaceutics, Faculty of Pharmacy, Mansoura University, Mansoura (Egypt)

(Received 10 December 1991)
(Accepted 26 April 1992)

Key words: Interpolymer complex; Chitosan; Pectin; Acacia; Drug release; Polymer; Complex; Physical mixture

Summary

The interpolymer complexes of chitosan with pectin and acacia were investigated using viscosity measurements. The binding ratios of the complexes were found to be 1:10 and 1:20 for chitosan-pectin and chitosan-acacia, respectively. The solid complexes were separated and dried to be used as tablet matrices. The release of the water-soluble chlorpromazine HCl from tablets containing various concentrations of each of the polymers alone, the complexes or physical mixtures of chitosan and of pectin and acacia in the same ratio of their respective complexes, was evaluated. Increasing the concentrations of the polymers, complexes or the physical mixtures in the tablets retarded drug release. The effect of different polymers on drug release was dependent on the gel property of the polymers and the drug-polymer interaction. The physical mixture displayed the most efficient sustained release. The results were explained.

Introduction

Chitosan is a natural polysaccharide prepared from chitin of crabs and lobsters by *N*-deactylation with alkali. Chitosan has been reported to have some useful applications in the pharmaceutical field. Sawayanagi et al. (1982a,b) reported the usefulness of chitosan as a vehicle for directly compressed tablets and ground mixtures of drugs. Chitosan was examined as a vehicle for the sustained release of indomethacin and papaverine HCl (Miyazaki et al., 1981; Hou et al., 1985).

Correspondence to: M.M. Meshali, Department of Pharmaceutics, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

The applicability of other natural polysaccharides such as agar (Nakano et al., 1979) and pectin (Takahashi et al., 1978) in the design of dosage forms for sustained release was examined. Recently, tablets containing either hydroxypropylcellulose (HPC) and carboxyvinyl polymer (Satoh et al., 1989a,b) or chitosan and sodium hyaluronate (Takayama et al., 1990) were prepared. The bioadhesive properties as well as drug release from these tablets were assessed.

The aim of this work was to investigate and characterize the possible interaction between the natural cationic (chitosan) and anionic (pectin and acacia) polysaccharides. It was also intended to prepare sustained release tablets of chlorpromazine HCl that contain either each polymer alone, their complexes or their physical mixtures.

A comparison between the different matrices with regard to drug release was performed.

Experimental

Materials

Chitosan (Sigma Chemical Co.) was employed after grinding using a ball mill. Compactrol (water-soluble directly compressible vehicle) was obtained from Forum Chemical, U.K. Chlorpromazine HCl and pectin were generously supplied by the Nile Chemical Co. for Pharmaceutical and Chemical Ind., Cairo, Egypt. All powders were passed through a 100 mesh sieve. Other chemicals were of reagent grade.

Equipment

A Heraeus-Christ centrifuge (Osterode Germany GmbH), Haake RV3 Viscometer (Germany) and tablet press, hardness tester and USP dissolution apparatus (Erweka GmbH, Germany) were used.

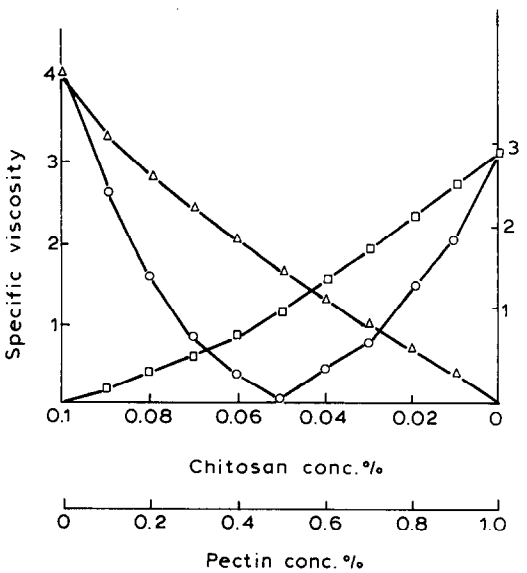

Fig. 1. Specific viscosity of the supernatant solutions of chitosan-pectin systems as a function of polymer ratios at 37 °C. (○——○) Chitosan-pectin solution; (△——△) chitosan solution alone; (□——□) pectin solution alone.

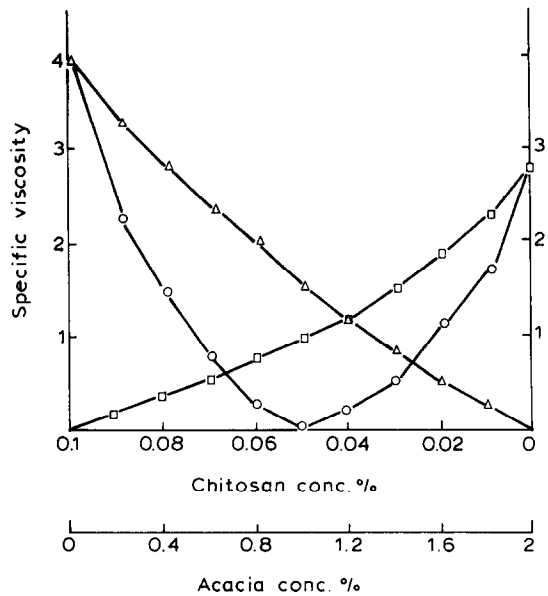

Fig. 2. Specific viscosity of the supernatant solutions of chitosan-acacia system as a function of polymer ratios at 37 °C. (○——○) Chitosan-acacia solution; (△——△) chitosan solution alone; (□——□) acacia solution alone.

Stoichiometry of the complex (viscosity measurements)

Chitosan solution in 5% acetic acid (40 ml; 0–0.1%) was mixed with pectin solution (40 ml; 0–1%) or with acacia solution (40 ml; 0–2%) at constant temperature (25 °C). The sample solution was then incubated at 37 °C for 24 h, centrifuged for 20 min at 7000 rpm and the viscosity of the supernatant was determined at 37 °C.

Preparation of the solid complexes

Mixtures of the polymer solutions which showed the lowest viscosity were used in the preparation of the solid complexes. Chitosan solution in 5% acetic acid (40 ml; 0.1) was mixed with either pectin (40 ml; 1%) or acacia (40 ml; 2%) solution in distilled water. The sample solution was then incubated at 37 °C for 24 h. The supernatant was decanted and the remaining gelatinous complex was dried at 40 °C for 24 h. The remaining solid complex was further dried under vacuum for 2 days at 37 °C. The dried complexes of chitosan-pectin and chitosan-acacia

were ground in a ball mill and passed through a 100 mesh sieve.

Preparation of the tablets

Tablets weighing 300 mg were directly and individually compressed using 50 mg of the drug and different combinations of compactrol and any of the following; chitosan, acacia, pectin, chitosan-acacia complex, chitosan-pectin complex or physical mixtures of chitosan with pectin and with acacia. The ratios of the polymers in the physical mixtures were similar to those found in the corresponding complexes, i.e., 1 : 10 and 1 : 20 for chitosan-pectin and chitosan-acacia, respectively. These ratios were chosen, since it has been reported that the best combination of polymers that results in proper sustained release is that of the complex ratio (Satoh et al., 1989a,b). The above polymers, complexes or physical mixtures were added to the formulations in four percentages, 10, 30, 60 and 80% of the tablet weight. Magnesium stearate (2%) was added as lubricant prior to compression. The tablet hardness was maintained constant within the range of 6–9 kp by changing the compression force.

Drug release studies

Drug release was performed on tablets using the USP dissolution apparatus at 50 rpm. The dissolution medium was 500 ml of 0.1 N HCl at 37 °C. Samples were collected at various time intervals and appropriately diluted using distilled water. The diluted samples were analyzed spectrophotometrically at 254 nm.

Results and Discussion

Confirmation of polyion complex

Polyion complex formation was confirmed by employing viscosity measurements (Takayama et al., 1990). Fig. 1 shows the viscosity of the supernatant in chitosan-pectin mixtures as a function of the percentages of chitosan and pectin in the medium. In the case of either chitosan or pectin alone, the viscosity of their solutions increased continuously with increasing polymer concentrations. On the other hand, the viscosity of the chitosan-pectin supernatant was observed to be the same as that of the medium, i.e., minimum at 0.05% and 0.5% w/v of the respective polymers. The observed decrease in viscosity indicated that the stoichiometry of the solid complex is 1 : 10 (w/w) chitosan-pectin. With chitosan-acacia complex, however, the weight ratio of the respective polymers was 1 : 20 (Fig. 2). Similar polyion interactions were reported by Takahashi et al. (1990) who investigated the interpolymer complexes of chitosan-sodium alginate (1 : 1) and chitosan-sodium polyacrylate (1 : 4).

Drug release studies

The release of chlorpromazine HCl from the different tablets was dependent on the type of

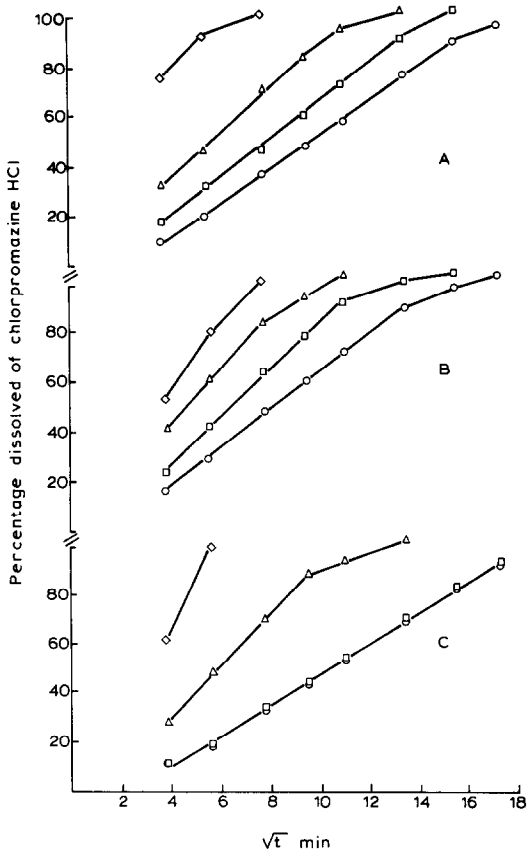

Fig. 3. Release of chlorpromazine HCl from tablets containing different concentrations of chitosan (A), acacia (B) or pectin (C) as a function of the square root of time. (◇——◇) 10%, (△——△) 30%, (□——□) 60%, (○——○) 80%.

polymer as well as on its concentration (Fig. 2). With increase in the percentage of polymer in the tablet, the rate of drug release was found to decrease. This is probably due to the accompanying decrease in the percentage of Compactrol. The effect of the type of polymer on drug release is rather variable. At 10% polymer concentration, the sequence of drug release was pectin > chitosan > acacia, while at 80% it was acacia > pectin = chitosan. This indicates that at low concentration acacia has greater retarding effect than either chitosan or pectin. At low concentrations chitosan acted as a disintegrant (Nigalaye et al., 1990) and at high concentrations the gel-forming properyl displayed a strong influence. Miyazaki et al. (1988) stated that increasing chitosan content in the granules decreased the release rate of the drug. In the case of pectin, it was reported (Takahashi et al., 1982) that chlorpromazine formed a complex with it that has a lower dissolution rate than that of the pure drug. Therefore, it might be concluded that at 10% concentration of pectin, drug was released mostly as the free form, whereas above 60% it was complexed with pectin. That is why both 60% and 80% concentrations of pectin showed the same drug release (Fig. 3C).

The dissolution data were analyzed using various kinetic equations and it was found that the $t^{1/2}$ equation of Higuchi (1963) fitted the data obtained from tablets containing 60% as well as 80% polymers (Fig. 3), complexes (Fig. 4) or physical mixtures (Fig. 5), up to 85% drug release. This indicated that the tested materials formed matrices at these concentrations. On the other hand, the square root of time equation did not fit the release data at 10 and 20% concentration levels. The rates of drug dissolution were calculated from the linear portions of the plots for the two aforementioned concentrations (60 and 80%), the results being listed in Table 1. On inspection of Figs 3 and 4 and Table 1, it is evident that the chitosan-acacia and chitosan-pectin complexes were not superior to any of the individual polymers in retarding drug release.

The physical mixtures of chitosan with either pectin or acacia (Fig. 5) resulted in tablets with efficient sustained release as compared with each polymer alone or the complexed polymers. This

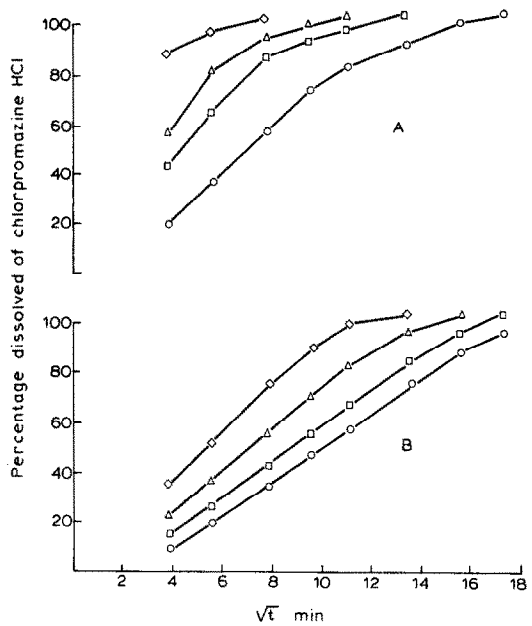

Fig. 4. Release of chlorpromazine HCl from tablets containing different concentrations of chitosan-acacia complex (A) or chitosan-pectin complex (B) as a function of the square root of time. Symbols as in Fig. 3.

retardation effect increased with increasing concentrations of physical mixture in the tablets. The differences among the complexes and physical mixtures with respect to drug release could be explained on the basis of laboratory observations during preparation of the complexes and the dis-

TABLE 1

Dissolution rate constant of chlorpromazine HCl from tablets containing different concentrations of polymers, interpolymer complexes and physical mixtures of polymers

Polymer complex or physical mixture	Dissolution rate (mg/min) at different polymer concentrations	
	60%	80%
Chitosan	8.0	7.2
Acacia	11.0	8.0
Pectin	6.5	6.5
Chitosan acacia complex	11.0	8.5
Chitosan pectin complex	7.2	6.6
Chitosan acacia physical mixture	6.2	4.1
Chitosan pectin physical mixture	4.6	3.7

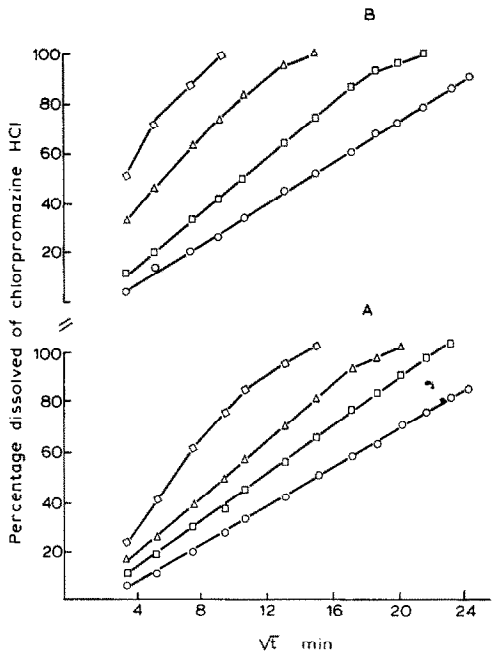

Fig. 5. Release of chlorpromazine HCl from tablets containing different concentrations of chitosan-acacia (A) or chitosan-pectin (B) physical mixtures in the same ratio of the complex as a function of the square root of time. Symbols as in Fig. 3.

solution runs. The preformed and dried complexes when used as tablet matrices demonstrated poor swelling capacity during the dissolution runs. Meanwhile, during the preparation of the complex it was noticed that the freshly formed voluminous complex was viscous and highly gelatinous, particularly when chitosan-pectin rather than chitosan-acacia was used. This most probably acted as an efficient matrix for retarding drug release when used as a physical mixture in tablets compared with the corresponding complex.

In conclusion, both the type and the concentration of the polymers played a major role in sustaining the drug release. The release of drug from tablets containing the dried complexes was approximately the same as that containing the polymers alone. On the other hand, the physical mixtures of chitosan-pectin and chitosan-acacia produced tablets with proper sustained release, suggesting that interpolymer complexes were formed during the dissolution process.

References

Higuchi, T., Mechanism of sustained-action medication: Theoretical rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.*, 52 (1963) 1145–1149.

Hou, W.M., Miyazaki, S., Takada, M. and Nadai, T., Sustained release of indomethacin from granules. *Chem. Pharm. Bull.*, 33 (1985) 3986–3992.

Miyazaki, S., Ishii, K. and Nadai, T., The use of chitin and chitosan as drug carriers. *Chem. Pharm. Bull.*, 29 (1981) 3067–3069.

Miyazaki, H., Yamaguch, H., Yokouch, C., Takara, M. and Hou, W.M., Sustained release of indomethacin from granules in beagle dogs. *J. Pharm. Pharmacol.*, 40 (1988) 642–643.

Nakano, M., Nakamura, Y., Takikawa, K., Kouketsu, M. and Arita, T., Sustained release of sulpham Sulphamethizole from agar beads. *J. Pharm. Pharmacol.*, 31 (1979) 869–872.

Nigalaye, A.G., Adusmilli, P. and Boltons, S. Investigation of prolonged drug release from matrix formulations of chitosan. *Drug. Dev. Ind. Pharm.*, 16 (1990) 449–467.

Satoh, K., Takayama, K., Machida, Y., Suzuki, Y. and Nagai, T., Disintegration and dissolution characteristics of compressed tablets consisting of hydroxypropyl cellulose and carboxyvinyl polymer. *Chem. Pharm. Bull.*, 37 (1989a) 1642–1644.

Satoh, K., Takayama, K., Machida, Y., Suzuki, Y., Nakagaki, M. and Nagai, T. Factors affecting the bioadhesive property of tablets consisting of hydroxypropyl cellulose and carboxyvinyl polymer. *Chem. Pharm. Bull.*, 37 (1989b) 1366–1368.

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

Sawayanagi, Y., Nambu, N. and Nagai, T., Enhancement of dissolution properties of griseofulvin from ground mixtures with chitin or chitosan. *Chem. Pharm. Bull.*, 30 (1982b) 4464–4467.

Takahashi, T., Takayama, K., Machida, Y. and Nagai, T. Characteristics of polyion complexes of chitosan with sodium alginate and sodium polyacrylate. *Int. J. Pharm.*, 61 (1990) 35–41.

Takahashi, Y., Nambu, N. and Nagai, T., Interaction of several nonsteroidal antiinflammatory drugs with pectin in aqueous solution and in solid state. *Chem. Pharm. Bull.*, 26 (1978) 3836–3842.

Takahashi, Y., Numbu, N. and Nagai, T. Interaction of phenothiazines with pectin in the solid state. *Chem. Pharm. Bull.*, 30 (1982) 2919–2925.

Takayama, K., Hirata, M., Machida, Y., Masada, T., Sannan, T. and Nagai, T. Effect of interpolymer complex formation on bioadhesive property and drug release phenomenon of compressed tablets consisting of chitosan and sodium Hyaluronate. *Chem. Pharm. Bull.*, 38 (1990) 1993–1997.