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CHITOSAN MATRIX TABLETS: THE INFLUENCE OF EXCIPIENTS ON DRUG RELEASE

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ABSTRACT

The influence of excipients on drug release from chitosan matrix tablets was investigated, using diltiazem hydrochloride as model drug. Tablets were prepared by direct compression and the effect of different concentrations of the excipients lactose, sodium lauryl sulphate, sodium alginate, carbopol 934, citric acid and hydroxypropylmethyl-cellulose on drug release profiles was studied. Sustained release of the drug was obtained in all cases but the results indicate that both type and amount of excipient used influences drug release rate. The results support the idea that chitosan can be suitable as a basis for sustained release matrix tablets, and that drug release rate can be influenced by the addition of excipients. It is possible to make use of the interaction between chitosan and excipients in the formulation to provide further prolongation of release.

INTRODUCTION

Chitin is one of the main constituents in the shell of crustaceans and the second most plentiful polymer found in nature. In chemical structure chitin is a polysaccharide composed of (1-->4) 2-acetamido-2-deoxy-ß-D-glucane. It is a highly hydrophobic material insoluble in water as well as most organic solvents but by deacetylation it is possible to increase its aqueous solubility. Chitosan is a partially N-deacetylated product of the natural polymer, chitin, its aqueous solubility being dependent upon the degree of deacetylation which can be varied

according to the intended use. Chitin and chitosan are biocompatible and biodegradable compounds and these properties have lead to an interest in their use for the formulation of dosage forms (1, 2, 3).

Matrix tablets are frequently used for oral sustained delivery of drugs. Matrix tablets have the advantage of being relatively uncomplicated to manufacture since they can often be produced by direct compression of a blend of drug, matrix carrier and excipients. The most commonly used matrix substances are cellulose ether derivatives, but studies have shown that chitosan appears to be a promising matrix carrier for sustained drug release (4, 5, 6). It has been reported that in order to obtain sustained release from chitosan matrix tablets it is necessary to have at least 50 % of the substance in the formulation (7, 8). Chitosan is a cationic polymer and has been found to interact with anionic compounds. It is therefore possible that the cationic chitosan will interact with either drug or excipients in a matrix formulation thereby affecting the release rate of the drug.

The objective of this work was to investigate the influence of excipients on drug release from chitosan matrix tablets. The excipients chosen were lactose, sodium lauryl sulphate, sodium alginate, hydroxypropylmethylcellulose, carbopol 934 and citric acid. Diltiazem hydrochloride, which is easily water-soluble, was chosen as model drug for the release studies.

MATERIALS AND METHODS

Materials

Chitosan with more than 85% degree of deacetylation (Protan, Sea Cure 443) was comminuted with a cutting type mill and sieved through a 125 µm sieve. Diltiazem hydrochloride was obtained from Profarmaco, carbopol® 934 from Nomeco, citric acid anhydrous e.p. from Merck, hydroxypropylmethylcellulose from Mecobenzon, sodium lauryl sulphate and lactose from NMD and sodium alginate (medium viscosity 3500 cps) from Sigma. All other materials were analytical grade.

Preparation of tablets

Tablets were prepared using direct compression in a Carver laboratory press. The tablets which were 13 mm in diameter were compressed applying a pressure of 565 kg/ cm^2 for 30 seconds.

The drug loading of the chitosan tablets was kept constant at 120 mg and the total weight of the tablets was 300 mg. The type and amount of excipient was varied. The excipients used were lactose, sodium lauryl sulphate, sodium alginate, hydroxypropylmethylcellulose, carbopol 934 and citric acid.

Friability and hardness

The friability of the tablets was estimated using the Roche Friabilitor, which was operated for 4 min. at a rate of 25 rpm. The hardness of the tablets was estimated using a Pharmatest hardness tester.

Dissolution

Dissolution profiles were obtained in simulated gastric and intestinal fluids without enzymes, using the USPXXII dissolution apparatus 2 (basket method). Stirring rate was maintained at 100 r.p.m. and the temperature at 37°C. The tablets were initially placed in simulated gastric fluid (pH 1.2) for two hours and then transferred to simulated intestinal fluid (pH 7.5). Dissolution of the active ingredient was monitored by UV-spectrophotometry at 240 nm. Each experiment was carried out in triplicate.

RESULTS AND DISCUSSION

Tablets prepared without excipients had a low friability index (1.2 %) and mean hardenss of 7.8 kp. Both hardness and friability were affected by the inclusion of excipients. An increase in concentration of carbomer 934 and citric acid caused an increase in the hardness values and a decrease in friability. The presence of sodium lauryl sulphate or lactose in the formulation had the opposite effect. Maximum friability was obtained with lactose and minimum with carbomer 934. The tablets did not disintegrate during dissolution testing and maintained their shape throughout 24 hours.

The type of chitosan used in this work is soluble in acid media. Due to the solubility of chitosan at low pH there was gel formation on the tablet surface in simulated gastric fluid but on transfer to the simulated intestinal fluid chitosan solubility decreased, causing diminished gel formation. This is reflected in the dissolution results which show that drug release rate decreases when the dissolution medium is changed. Release profiles of drug from chitosan matrices are shown in Figure 1. Diltiazem release rate was influenced by the ratio of drug to chitosan in the tablets, the release rate decreased as the proportion of chitosan increased. It was found that drug release was independent of compression pressure used to prepare the matrix (within the range of 565-942 kg/cm^2). The release of diltiazem is linear with respect to the square root of time, indicating that drug release obeys the Higuchi diffusion controlled model (9) and diltiazem is thus released primarily by diffusion through the hydrated matrix. The Higuchi equation predicts a zero intercept but a small negative intercept is obtained presumably due to the time it takes for the matrix to hydrate.

The effect of sodium alginate on the release of diltiazem from chitosan matrices appears in Figure 2. The release rate of diltiazem increased with

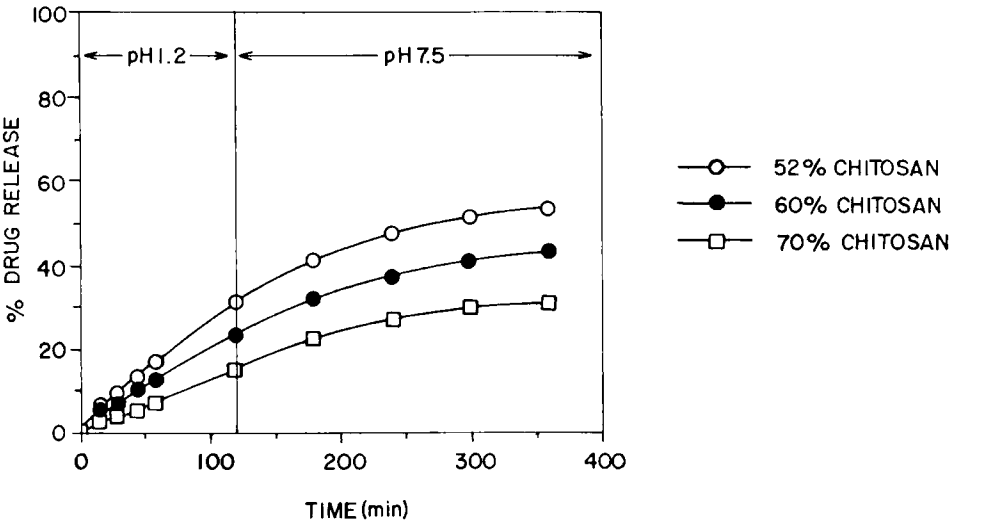

FIGURE 1

Release of diltiazem from chitosan matrices prepared with different ratios of chitosan to drug.

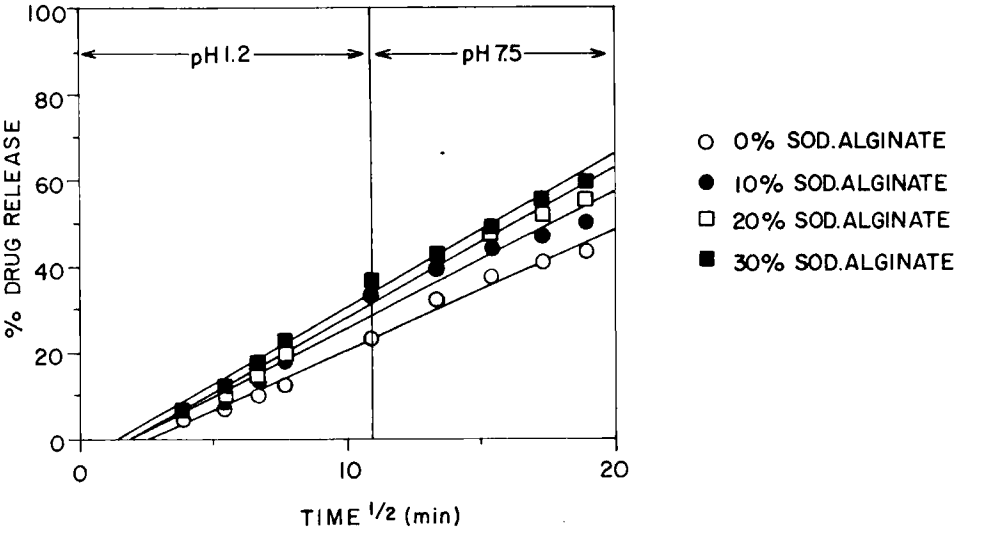

FIGURE 2

Effect of sodium alginate on release of diltiazem from chitosan matrices.

increased sodium alginate concentration. Takahashi et al. have reported the formation of polyion complexes between chitosan and sodium alginate (10). It is doubtful whether there is complex formation at the conditions used in this work, as sodium alginate is not soluble in simulated gastric fluid (pH 1.2) and is at that point as an inert, insoluble excipient. In simulated intestinal fluid (pH 7.5) when sodium alginate dissolves, chitosan is not soluble. Increase in the ratio of sodium alginate to chitosan could cause less gel-layer formation at low pH and hence decrease the diffusion path length for diltiazem through the gel-layer, resulting in increased release rate.

The release of diltiazem from chitosan matrices was retarded by the presence of the anionic surfactant sodium lauryl sulphate (NaLS), with drug release rate decreasing with increasing surfactant concentration (Figure 3). Solubility experiments showed that diltiazem can form a complex of low aqueous solubility with NaLS. If such a complex forms in situ within the matrix the release would rely upon erosion of the matrix. Feely and Davis found that a surfactant can be an important parameter affecting release of drugs from hydoxypropylmethylcellulose (HPMC) matrices. They showed that NaLS can retarded the release rate of cationic drugs in HPMC matrix tablets (11). This also compares with the results reported by Ford et al. that the presence of NaLS in HPMC tablets did decrease the release rate of propranolol hydrochlorid by the in situ formation of propranolol lauryl sulphas (12). Another factor affecting the release rate of diltiazem could be complex formation between chitosan and NaLS which could change the consistence of the gel-layer and cause a decline in diltiazem release rate. NaLS has previously been shown to bind to polymers, thereby causing an increase in gel viscosity (13).

In Figure 4 the t_{40} % (time required to release 40 % of the diltiazem content) is plotted as a function of citric acid content in the chitosan matrices. It can be seen that the release rate of diltiazem increases with increasing citric acid concentration. It has been shown previously that citric acid forms a water soluble complex with chitosan, hence it is possible that diltiazem diffuses faster through chitosan-citric acid gel that through chitosan gel (7).

The presence of up to 5 % carbomer 934 in the chitosan matrices was not found to influence the release rate of diltiazem. Others have reported that carbomer 934 forms a complex with chitosan producing a hydrated erosion type of matrix which results in a retardation of drug release (7). In this work the ratio of chitosan to carbomer 934 is high and the effect of carbomer on the chitosan gel could therefore be negligible.

Figure 5 shows the effect of HPMC on the release rate of diltiazem. The presence of HPMC in the chitosan matrices caused an increase in the release rate of the drug. Both chitosan and HPMC are hydrophilic polymers who form gels when they come into contact with water. In the tablets HPMC replaces chitosan in part as a gel forming matrix substance and diltiazem hydrochloride appears to

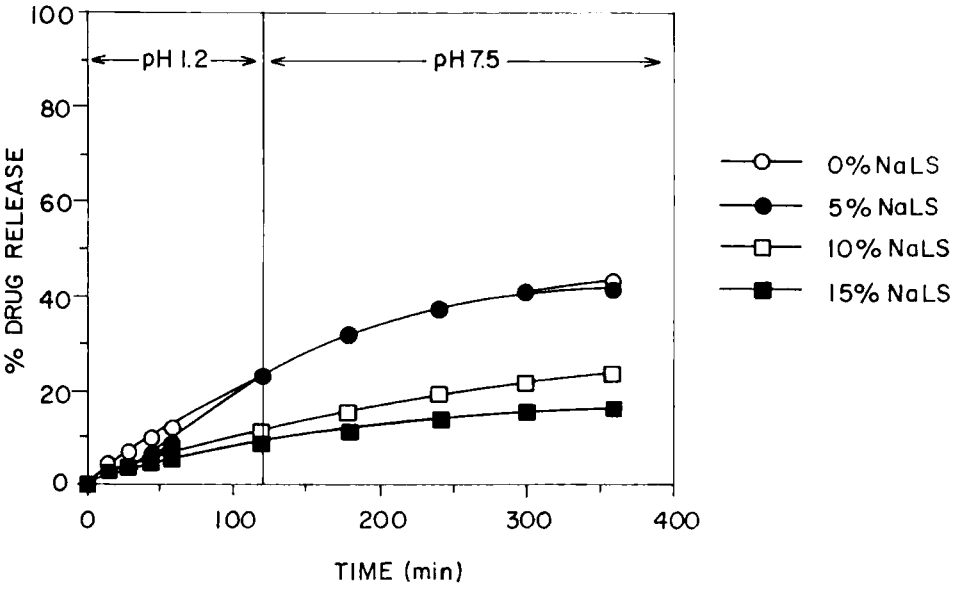

FIGURE 3
Effect of sodium lauryl sulphate on release of diltiazem from chitosan matrices.

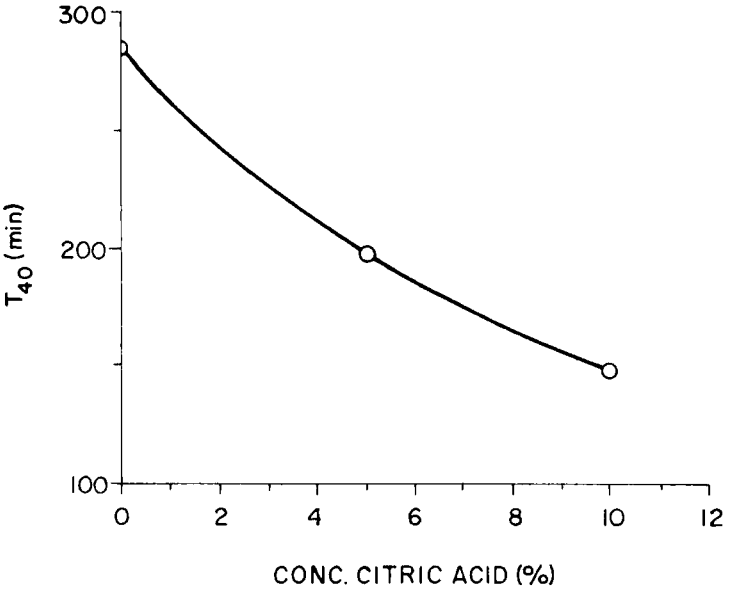

FIGURE 4
Effect of citric acid on the time required to release 40 % of diltiazem content in chitosan matrices.

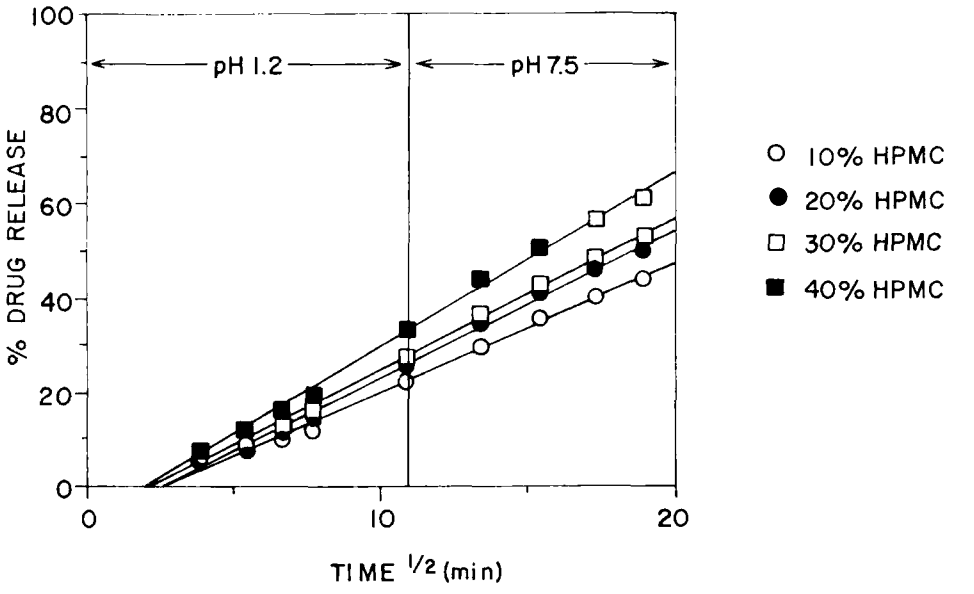

FIGURE 5
Release of diltiazem from chitosan matrices containing different concentrations of HPMC.

diffuse faster through the HPMC-chitosan gel than through chitosan gel alone. This may be explained by HPMC being more hydrophilic than chitosan and more water being contained in the HPMC-chitosan gel layer than in the chitosan gel. This would lead to increased diffusion of the hydrophilic drug through the HPMC-chitosan gel layer.

Lactose, being easily soluble in water increased the porosity of the matrix resulting in considerable increase in diltiazem release rate. That is in concurrence with results obtained by Sawayanagi et al. in their work on the release of propranolol hydrochloride from chitosan tablets (8).

CONCLUSIONS

The parameters controlling drug release rate from chitosan matrix tablets were the ratio of drug to chitosan and type and amount of excipient used. The results support the idea that chitosan can be suitable as a basis for sustained release matrix tablets, and that drug release rate can be influenced by the addition of

excipients. It is possible to make use of the interaction between chitosan and excipients in the formulation to provide further prolongation of release.

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REFERENCES

1. S. Hirano, H. Seino, Y. Akiyama, I. Nonaka, Polym. Mat. Sci. Eng. 59, 897, (1998).
2. Y. Machida, and T. Nagai, in "Topics in Pharmaceutical Sciences" D.D. Breimer, D.J.A.Crommelin, K.K. Midha, eds., Hague, 1989.
3. J. Knapczyk, Int. J. Pharm., 89, 1 (1993).
4. Y. Machida, T. Nagai, M. Abe, T. Sannan, Drug Design Del., 1, 119 (1986).
5. K. Inouye, Y. Machida, T. Nagai, Drug Design Del., 1, 297 (1987).
6. T. Cahndry, C.P. Sharma, C.P. Biomat., Art. Cells & Immob.Biotech., 19, 745 (1991).
7. A.G. Nigalaye, P. Adusumilli and S. Bolton, Drug Dev. Ind.Pharm., 16(3), 449 (1990).
8. Y. Sawayanagi, N. Nambu and T. Nagai, Chem. Pharm. Bull. 30 (11) 4213 (1982).
9. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).
10. T. Takahashi, T. Takayama, Y. Machida, T. Nagai, Int. J. Pharm., 61, 35 (1990).
11. L.C. Feely and S.S. Davis, Int. J. Pharm., 41, 83 (1988).
12. J. L. Ford, K. Mitchell, D. Sawh, S. Ramdour, D.J. Armstrong, P.N.C. Elliott, C. Rostron, J.E. Hogan, Int. J. Pharm., 71, 213 (1991).
13. Saito, S., J. Colloid Sci. 15, 283 (1960).