International Journal of Pharmaceutics, 89 (1993) 19–24
© 1993 Elsevier Science Publishers B.V. All rights reserved 0378-5173/93/$06.00

IJP 02859

Use of chitosonium malate as a matrix in sustained-release tablets

Jülide Akbuğa

University of Marmara, Faculty of Pharmacy, Haydarpaşa, Istanbul (Turkey)

(Received 9 January 1992)
(Modified version received 27 March 1992)
(Accepted 31 March 1992)

Key words: Chitosan; Chitosonium malate; Swelling control; Tablets; Furosemide; Directly compressible tablets; Release mechanism

Summary

A salt of chitosan (chitosonium malate) was examined as a matrix for sustained-release tablets. Furosemide was chosen as a model drug in this study. Sustained-release tablets were prepared by direct compression and wet-granulation techniques. Sustained-release properties of chitosan and chitosonium malate were compared. The effect of different concentrations of chitosonium malate (5, 10, 30 and 50%; formulations I–IV) on drug release profiles was studied. As the concentration of chitosonium malate increased, the rate of release of the drug decreased. Chitosonium malate shows sustained-release properties even at low concentrations. The results are examined kinetically and the mechanism is discussed. When the release data were fitted to the simple power law equation, the mode of drug release was of the non-Fickian and super case II types.

Introduction

Recently much attention has been devoted to the formulation of swelling controlled-release matrix formulations. Various types of polymers have been used as matrices (Buri and Doelker, 1980; Rango Rao, 1988). The usefulness of chitosan as a matrix for sustained-release preparations has been reported (Miyazaki et al., 1981; Sawayanagi et al., 1982; Inouye et al., 1987; Acartürk, 1989). However, chitosan when used alone in a tablet formulation, did not impart sustained release properties at low concentrations, but when employed at a concentration of more than 50% an insoluble non-erosion type matrix was formed (Sawayanagi et al., 1982; Nigalaye et al., 1990). Citric acid slowed down the release of drug from chitosan matrix tablets (Nigalaye et al., 1990). Chitosan readily forms a gel at low pH but shows poor gel-forming ability at high pH.

Therefore, a gel-forming carrier system containing chitosan malate was investigated for

Correspondence to: J. Akbuğa, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Marmara, Nişantaşı, Istanbul, Turkey.

preparation of sustained-release tablets. Furosemide was used as a model drug and the release mechanism was also examined.

Experimental

Materials

Furosemide (Hoechst AG, Frankfurt, Germany), chitosan (in which the degree of deacetylation was 80%, 20–200 mPa s viscosity grade, Protan A/S, Drammen, Norway), chitosonium malate (chitosonium salt of malic acid) (20 mPa s viscosity grade, Protan A/S, Drammen, Norway) and lactose monohydrate (E. Merck, Darmstadt, Germany) were used. Chitosan and chitosan malate were used after passage through a 200-mesh sieve.

Methods

Preparation of tablets Drug was mixed with chitosan or chitosan malate and lactose in various ratios (Table 1) and compressed into flat-faced tablets (400 mg; 13.06 mm diameter) using a hydraulic press (Specac, U.K.) at 5000 kg/cm^2 for 30 s.

Tablets were also prepared by the wet-granulation method. Water was added to a dry blend of drug and excipients and massed. After drying, the wetted mass was passed through a 100-mesh screen.

Effect of formulation factors Various chitosan malate concentrations (5, 10, 30 and 50%; formulations I–IV) were used in order to investigate the effect of matrix concentration on drug release. Furthermore, drug concentrations (10, 30 and 40%; formulations V–VII) were varied by keeping the amount of chitosan malate constant (120 mg) and the effect of drug amount on drug release was also studied.

Release studies Release experiments were performed using the USP XXII paddle method. pH 7.4 phosphate buffer was used as a medium and maintained at 37 ± 0.2°C. The rate of rotation was 100 rpm. The samples were periodically removed and analyzed spectrophotometrically (Shimadzu UV-2100, Japan) at 276.5 nm. The means of six determinations are given. Corrections were made for any absorption due to excipients.

Results and Discussion

Release profiles of drug from the matrices containing chitosan or chitosan malate are shown in Fig. 1. Matrices containing chitosan as seen in Fig. 1 did not show sustained release of the drug for a long time. Hence chitosan alone is not an ideal polymer to prepare a sustained-release matrix. This may be due to chitosan readily forming a gel at low pH, but showing a poor gel-forming ability at high pH. Furthermore, Sawayanagi et al. (1982) also noted that at least 80% of chitosan was needed to achieve sufficient sustained release from tablets.

On the other hand, when chitosan malate was used at different concentrations in tablet formulations, the release rate decreased as the amount of chitosan malate increased (Fig. 1), i.e., high levels of chitosan malate retarded drug release remarkably. This was attributed to the extent of

TABLE 1

Composition of tablets

Materials (mg)	Tablet										
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
Furosemide	80	80	80	80	40	120	160	40	80	80	80
Lactose monohydrate	300	280	200	120	240	160	120	–	280	200	120
Chitosan malate	20	40	120	200	120	120	120	360	–	–	–
Chitosan	–	–	–	–	–	–	–	–	40	120	200

TABLE 2

Kinetic data of tablets prepared with chitosonium malate

Kinetic model		Formulations										
		I	II	III	IV	V	VI	VII	VIII	II [a]	III [a]	IV [a]
Zero-order	k	0.203	0.116	0.170	0.160	0.213	0.109	0.055	0.244	0.114	0.190	0.149
	r^2	0.944	0.966	0.956	0.970	0.958	0.908	0.984	0.968	0.685	0.954	0.990
First-order	k	7.3×10^{-3}	9.1×10^{-3}	0.010	0.012	0.011	0.010	0.010	0.013	0.057	0.057	0.058
	r^2	0.462	0.667	0.779	0.874	0.585	0.602	0.580	0.832	0.469	0.474	0.478
Higuchi	k	4.93	2.72	3.32	3.01	4.12	2.24	1.08	4.30	4.02	3.82	2.74
	r^2	0.992	0.998	0.925	0.876	0.923	0.938	0.958	0.819	0.817	0.950	0.881
Bamba et al.	k	8.3×10^{-3}	1.8×10^{-3}	2.4×10^{-3}	2.1×10^{-3}	3.4×10^{-3}	1.3×10^{-3}	6.3×10^{-4}	4.1×10^{-3}	4.2×10^{-3}	3.0×10^{-3}	1.9×10^{-3}
	r^2	0.835	0.972	0.982	0.966	0.986	0.938	0.988	0.929	0.808	0.995	0.990

k, release rate constant; r^2, coefficient of determination.

[a] Tablets were prepared by wet granulation.

gel formation, as previously reported for chitosan tablets (Sawayanagi et al., 1982; Nigalaye et al., 1990). As shown in Fig. 1, as the chitosan malate concentration increased to 30 and 50%, a noticeable lag time was observed for the release profiles.

During the test, none of the tablets disintegrated and in each case tablets swelled and gelation occurred.

As observed in Fig. 2, as the drug concentration increased in the constant amount of matrix, the release rate gradually decreased.

On the other hand, tablets prepared by both methods (direct compression and wet-granulation techniques) did not show any significant difference in their drug release characteristics.

Release mechanism

In order to investigate the mechanism, the release data were fitted to models representing zero-order, first-order, Higuchi's (1963) square-root of time and Bamba's (1979) equation, indicative of release mechanisms related solely to time, drug diffusion or its dissolution rate, respectively.

It is known that the rate of release from a planar matrix is usually proportional to the square root of time (Higuchi, 1963), while the release

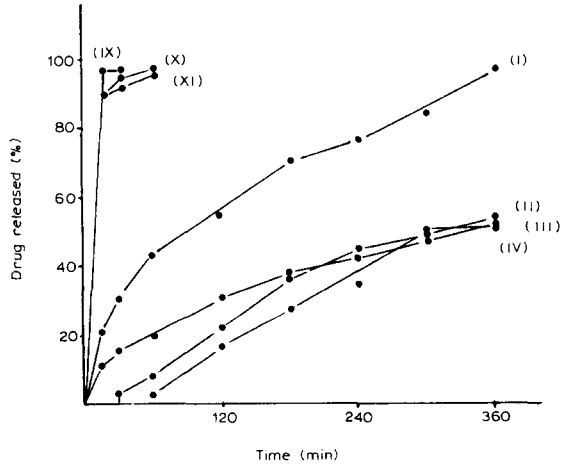

Fig. 1. Release profiles of tablets prepared with chitosan and chitosonium malate at different concentrations. Tablets containing 5% (I), 10% (II), 30% (III), 50% (IV) chitosonium malate and 10% (IX), 30% (X), 50% (XI) chitosan.

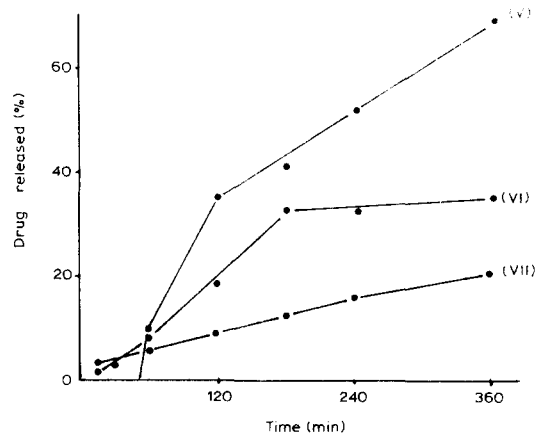

Fig. 2. Effect of drug concentrations on drug release from chitosonium malate matrix tablets. Tablets containing 10% (V), 30% (VI) and 40% (VII) drug and a constant amount (120 mg; 30%) of chitosonium malate.

from gel-formed matrices has been discussed by Bamba et al. (1979).

An equation derived by Bamba et al. (1979) was used:

$$\ln(100 - m) = bt + a \qquad (1)$$

where m is the percentage of drug remaining undissolved, a (time^{-1}) and b respectively denote the slopes and intercepts of curves, and t is time.

The equation of Bamba et al. assumes that the drug molecules diffuse out through a dissolving gel-like layer formed around the drug during the dissolution process.

The linear regression analysis for each trial is summarized in Table 2.

Among all the formulae examined, the zero-order and Bamba equations appeared to provide the best fits to the data for the tablets.

For characterizing the mode of drug release or penetration of the solvent through the swelling controlled release system, certain dimensionless numbers such as the Deborah number (Vrentas et al., 1975), α of Hopfenberg et al. (1991), the swelling interface number S_w (Peppas and Franson, 1983) and the release exponent n (Ritger and Peppas, 1987) were proposed.

In order to understand the mode of release of drug from swellable matrices, the data ($\leqslant 60\%$)

TABLE 3

Coefficients and exponents of drug release functions according to $M_t/M_\infty = Kt^n$ *for tablets containing chitosonium malate or chitosan*

Formulation	r^2	n	K
I	0.922	0.469	0.783
II	0.995	0.999	0.435
III	0.972	1.286	1.422
IV	0.922	1.575	2.229
V	0.925	1.080	0.861
VI	0.933	1.208	1.252
VII	0.829	1.118	1.183
VIII	0.955	1.622	2.190
II [a]	0.342	0.187	1.327
III [a]	0.661	0.684	0.134
IV [a]	0.620	0.699	0.015
IX	0.448	0.202	1.422
X	0.272	0.118	1.625
XI	0.184	0.078	1.725

r^2, coefficient of determination; n, release exponent in Eqn 2; K, coefficient in Eqn 2.

[a] Tablets were prepared by wet granulation.

were fitted to the following power law equation (Ritger and Peppas, 1987).

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

where M_t/M_∞ is the fraction of drug released up to time t, K denotes a constant incorporating the structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of release.

The value of n for a cylinder is $\leqslant 0.45$ for Fickian release, > 0.45 and < 0.89 for non-Fickian release, 0.89 for case II release and $>$ 0.89 for super case II type release. The values of K, n and the coefficient of determination (r^2) obtained are listed in Table 3. The values of n fell within the range of 0.99–1.62, indicating that drug release from the chitosan malate matrix is of the non-Fickian and super case II type. This kind of diffusion corresponds to a more predictable type of swelling-controlled system and describes diffusion in which the diffusion coefficient depends on both the concentration and time and in which the rate of solvent uptake into a polymer is largely determined by the rate of swelling and relaxation of the polymer chains. For tablets containing chitosan malate at 5 and 10% concentrations (formulations I and II), values of n were closer to 1.0, indicating that the tablets behave as a zero-order release system.

On the other hand, as seen in Table 3, for tablets prepared by using chitosan and the wet-granulation method, r^2 values were in the range of 0.2–0.6 and linearity was very poor.

In conclusion, chitosan malate can be used for the preparation of sustained-release tablets. It has many more advantages than chitosan. The release rate can be changed by varying the concentration of chitosan malate and tablets can also be prepared by direct compression.

Acknowledgements

The author wishes to thank Protan A/S and A. Kadioğlu for generous gifts of chitosan samples and also Z. Aydin for her assistance in the experimental work.

References

Acartürk, F., Preparation of a prolonged-release tablet formulation of diclofenac sodium. *Pharmazie,* 44 (1989) 547–549.

Bamba, M., Puisieux, F., Marty, J.P. and Carstensen, J.T., Release mechanisms in gel-forming sustained release preparations. *Int. J. Pharm.,* 2 (1979) 307–315.

Buri, P. and Doelker, E., Formulation des comprimés à liberation prolongée II. Matrices hydrophiles. *Pharm. Acta Helv.,* 55 (1980) 189–197.

Higuchi, T., Mechanism of sustained action medication, *J. Pharm. Sci.,* 52 (1963) 1145–1149.

Hopfenberg, H.B., Apicella, A. and Saleeby, D.E., Factors affecting water sorption and solute release from glassy ethylene-vinyl alcohol copolymers, *J. Membrane Sci.,* 8 (1981) 273–282.

Inouye, K., Machida, Y. and Nagai, T., Sustained release tablets based on chitosan and carboxy methyl cellulose sodium, *Drug Design Del.,* 1 (1987) 297–305.

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

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

Peppas, N.A. and Franson, N.M., The swelling interface number as a criterion for prediction of diffusional solute release mechanisms in swellable polymers. *J. Polym. Sci. Polym. Phys. Ed.,* 21 (1983) 983–997.

Rango Rao, K.V. and Devi, K.P., Swelling controlled-released systems: recent developments and applications. *Int. J. Pharm.*, 48 (1988) 1–13.

Ritger, P.L. and Peppas, N.A., A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. *J. Controlled Release*, 5 (1987) 37–42.

Sawayanagi, Y., Nambu, N. and Nagai, T., Use of Chitosan for sustained release preparations of water-soluble drugs. *Chem. Pharm. Bull.*, 30 (1982) 4213–4215.

Vrentas, J.S., Jarzebski, C.M. and Duda, J.L., A Deborah number for diffusion in polymer solvent systems. *AIChE J.*, 21 (1975) 894–905.