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International Journal of Pharmaceutics 121 (1995) 113–116

international journal of pharmaceutics

Notes

Controlled release of piroxicam from chitosan beads

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Received 26 July 1994; revised 1 November 1994; accepted 29 November 1994

Abstract

Piroxicam-loaded chitosan gel beads were prepared by dropping drug-containing solution of chitosan into tripolyphosphate solutions. The droplets instantaneously formed gelled spheres by ionotropic gelation. The mean diameter of beads was about 0.9 mm and drug-loading capacity was 90%. The drug was successfully encapsulated at pH 5. The release of piroxicam from chitosan beads was strongly affected by the method of drying and chitosan concentration. However, the release was not particularly affected by the other factors such as the drug and tripolyphosphate concentrations, volume of the external phase and the type of chitosan. The results were examined kinetically. 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.

Keywords: Controlled release; Piroxicam; Chitosan bead

Recently, the chitosan gel bead has received attention as an oral drug delivery vehicle for controlled-release preparations (Bodmeier and Paeratakul, 1989; Bodmeier et al., 1989a,b; Shiraishi et al., 1993).

In the present investigation, chitosan beads containing piroxicam were prepared by a polyelectrolyte complexation of sodium tripolyphosphate and chitosan. The interaction of positively charged, chitosan molecules with the anionic counterion caused the formation of gelled spheres. The effects of various factors on bead properties were also studied.

Chitosan beads containing piroxicam were prepared according to the method of Bodmeier et al. (1989b). Piroxicam (Deva, Turkey) was dispersed in a solution of chitosan (1.5% w/v) in acetic acid. This dispersion was dropped into a gently agitated tripolyphosphate (Sigma, USA) solution (1% w/v) adjusted to pH 5. For hardening, they were treated in 1% v/v formaldehyde solution, then washed with distilled water and air-dried ($n = 3$).

A number of variables such as drug concentration, type and concentration of chitosan, pH value of TPP solution, volume of the internal and external phases, gelation time and drying conditions were investigated for optimization of bead properties.

For release studies beads were suspended in phosphate buffer (pH 7.4) contained in a glass bottle. This medium was stirred at 100 rpm in a shaker bath at 37°C. Samples were periodically removed and analyzed spectrophotometrically at 253 nm ($n = 6$). Drug content was also spectrophotometrically determined.

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SSDI 0378-5173(94)00413-7

The polycationic polysaccharide, chitosan, forms gels with multivalent counterions through the formation of intermolecular or intramolecular linkages by ionic interaction (Kawashima et al., 1985a; Bodmeier et al., 1989b). The viscosity of a chitosan sample is of importance in the formation of beads. Chitosan beads could not be prepared from samples with viscosity below 500 cps. Extra-high viscosity chitosan samples also did not form beads due to the difficulty in dropping. This result is consistent with the work performed by Bodmeier et al. (1989b).

The particle size and drug-loading capacity of beads are given in Table 1. Larger beads were formed by the addition of drug in high concentration. Various factors such as drug concentration, chitosan concentration and volume of the external phase significantly affected the loading capacity of beads ($p < 0.05$). Moreover, the loss of piroxicam from beads was inhibited by changing the pH of the TPP solution. Therefore, the pH of the TPP phase was adjusted to 7 and 5, respectively, in order to minimize drug solubility. As the pH of the TPP solution decreased, the drug content of beads significantly increased ($p < 0.05$).

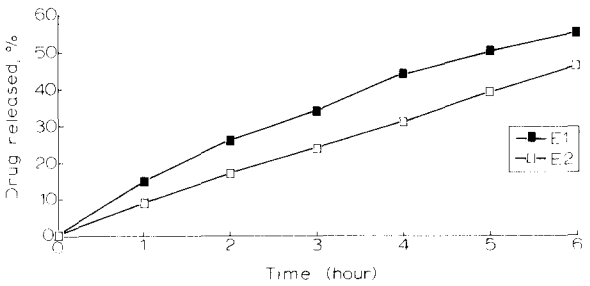

Fig. 1. Effect of chitosan concentration on drug release from beads.

Such behavior has also been observed by Shiraishi et al. (1993).

Gelation time is very important in the drug-incorporation efficiency of beads. This result suggested that 10 min was enough to achieve complete gelation.

In contrast to earlier reports (Bodmeier et al., 1989b; Shiraishi et al., 1993), piroxicam loading has no effect on drug release from beads ($p > 0.05$). On the other hand, the chitosan concentration in acetic acid solution markedly affected ($p < 0.05$) the drug release properties of beads

Table 1
Size and drug-loading capacity of chitosan beads

Variables			Mean particle size (mm) (±SD)	Incorporation efficiency (%) (±SD)
Drug concentration (%)	1.0	A_1	0.886 ± 0.030	90.4 ± 2.2
	2.5	A_2	1.027 ± 0.037	72.9 ± 1.7
	3.5	A_3	1.051 ± 0.056	74.7 ± 3.2
pH of external phase	5	B_1	0.886 ± 0.030	90.4 ± 2.2
	7	B_2	0.936 ± 0.036	86.5 ± 1.6
	9	B_3	0.924 ± 0.001	84.3 ± 1.0
Volume of external phase (ml)	100	C_1	0.886 ± 0.030	90.4 ± 2.2
	200	C_2	0.943 ± 0.016	87.1 ± 0.7
	400	C_3	0.903 ± 0.005	88.9 ± 1.4
	600	C_4	0.972 ± 0.013	73.9 ± 1.0
Volume of internal phase (ml)	10	D_1	0.886 ± 0.030	90.4 ± 2.2
	30	D_2	0.922 ± 0.057	87.5 ± 0.3
	50	D_3	0.911 ± 0.029	89.4 ± 0.1
Chitosan concentration (%)	1.25	E_2	0.926 ± 0.020	81.1 ± 4.0
Chitosan types	243	F_2	0.892 ± 0.082	90.8 ± 1.5
Drying methods	80°C/6 h	G_2	0.904 ± 0.029	94.3 ± 0.2
	80°C/12 h	G_3	0.957 ± 0.030	94.2 ± 0.9
TPP concentration (%)	1.5	H_2	0.875 ± 0.017	95.7 ± 0.5

A_1, E_1, F_1, G_1 and H_1 are the same formulation and are therefore not shown above.

(Fig. 1), however, similar release profiles were obtained with the different types of chitosan (Sea cure 243 and 340 with molecular mass of 150 and 250 kDa, respectively). Shiraishi et al. (1993) reported that release rate decreased with increasing molecular mass of chitosan types. According to our data, no difference was observed between the release profiles of beads prepared using different types of chitosan samples. This may depend on differences in the origin of the chitosan samples.

Furthermore, the volume of the internal phase and drying conditions also appeared to have a significant effect on the release properties of chitosan beads. The effect of the degree of dehydration on the release of piroxicam-loaded beads was investigated by drying the bead samples at 80°C for 6 and 12 h whilst others were left undried. As seen in Fig. 2, the release of piroxicam from beads was markedly affected by the drying conditions ($p < 0.005$). This may be due to surface cracks developing on the the beads after drying. Piroxicam release from beads was found to be independent of TPP concentration ($p > 0.05$). Furthermore, piroxicam beads did not disintegrate in 0.1 N HCl within 4 h but swelled in phosphate buffer (pH 7.4). This may be depend on the hardening of chitosan beads with formaldehyde during preparation. As previously noted by Kawashima et al. (1985b), on treatment with glutaraldehyde, chitosan in the coating film formed a Schiff base, which closely linked the chitosan chains. The aforementioned authors found that the surface of granules became seamless after hardening.

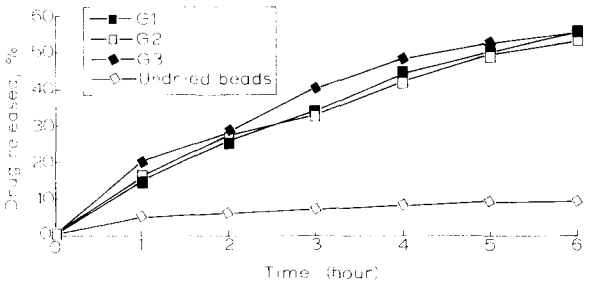

Fig. 2. Effect of drying methods on release characteristics of piroxicam from chitosan beads.

Table 2
Coefficients and exponents of drug release functions according to $M_t/M_\infty = Kt^n$ for chitosan beads

	r^2	n	k
A_1	0.998	0.760	−0.189
A_2	0.994	0.900	−0.550
A_3	0.992	0.852	−0.424
B_1	0.998	0.762	−0.189
B_2	0.992	0.688	0.026
B_3	0.996	1.100	−1.044
C_1	0.998	0.762	−0.189
C_2	0.988	0.840	−0.324
C_3	0.994	0.883	−0.576
C_4	0.992	0.913	−0.589
D_1	0.998	0.762	−0.189
D_2	0.984	0.875	−0.356
D_3	0.982	0.941	0.491
E_2	0.999	0.930	−0.713
F_2	0.997	0.707	−0.043
G_2	0.993	0.723	−0.102
G_3	0.992	0.642	0.131
H_2	0.994	0.612	0.162

r^2, coefficient of determination; n, release exponent in the above equation; K, coefficient in the above equation. A_1, E_1, F_1, G_1 and H_1 are the same formulation.

In order to understand the mode of release of drug from chitosan beads, the data ($\leq 60\%$) were fitted to the power law equation (Ritger and Peppas, 1987) ($M_t/M_\infty = Kt^n$). The values of n fell within the range of 0.61–1.10, indicating that drug release from chitosan beads is of the non-Fickian and super case II type (Table 2). 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 some formulations (A_2, B_3, D_3 and E_1) values of n were closer to 1, indicating that beads behave as a zero-order release system.

In conclusion, controlled-release chitosan beads containing piroxicam were successfully prepared by gelling the cationic polysaccharide with the anionic counterion, TPP. It is rapid and simple technique for bead preparation. The process factors are important for the beads' properties.

References

Bodmeier, R. and Paeratakul, O., Spherical agglomerates of water-insoluble drugs. *J. Pharm. Sci.*, 78 (1989) 964–967.

Bodmeier, R., Chen, H. and Paeratakul, O., A novel approach to the oral delivery of micro-and nanocapsules. *Pharm. Res.*, 6 (1989a) 413–417.

Bodmeier, R., Oh, K.H. and Pramar, Y., Preparation and evaluation of drug-containing chitosan beads. *Drug Dev. Ind. Pharm.*, 15 (1989b) 1475–1494.

Kawashima, Y., Handa, T., Kasai, A., Takenaka, H. and Lin, S.Y., The effects of thickness and hardness of the coating film on the drug release rate of theophylline granules coated with chitosan-sodium tripolyphosphate complex. *Chem. Pharm. Bull.*, 33 (1985b) 2469–2474.

Kawashima, Y., Handa, T., Kasai, A., Takenaka, H., Lin, S.Y. and Ando, Y., Novel method for the preparation of controlled-release theophylline granules coated with a polyelectrolyte complex of sodium polyphosphate-chitosan. *J. Pharm. Sci.*, 74 (1985a) 264–268.

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.

Shiraishi, S., Imai, T. and Otagìri, M., Controlled release of indomethacin by chitosan-polyelectrolyte complex: Optimization and in vivo/in vitro evaluation. *J. Controlled Release*, 25 (1993) 217–225.