International Journal of Pharmaceutics, 39 (1987) 39–45
Elsevier

IJP 01304

Zero-order release hydrophilic matrix tablets of β-adrenergic blockers

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(Received 18 February 1987)
(Accepted 31 March 1987)

Key words: Swellable matrix tablet; Zero-order release; HPMC and Na CMC; Rheological synergism; β-Blocker; Propranolol hydrochloride; Metoprolol tartrate; Alprenolol hydrochloride

Summary

A simple technique of obtaining nearly zero-order release from hydrophilic matrix tablets till entire drug is released is reported. In this technique, non-ionic hydroxypropylmethylcellulose (HPMC) and anionic sodium carboxymethylcellulose (Na CMC) were mixed in an optimum ratio with drug and compressed into tablets. To exemplify this fact, β-adrenergic blockers, namely propranolol hydrochloride, metoprolol tartrate and alprenolol hydrochloride, were chosen as model drugs. When the ratio of drug : HPMC : Na CMC was 1 : 0.25 : 2.25 for propranolol hydrochloride, 1 : 1.25 : 1.25 for metoprolol tartrate and 1 : 2.08 : 2.92 for alprenolol hydrochloride, total drug is released in about 12 h at a nearly zero-order rate. By optimising the ratio between the drug and total gum and also the ratio between these two gums, the rates of advancement of swelling front into the glassy polymer (core) and the attrition of the rubbery state polymer (gel at tablet periphery) were made equal so that the diffusional path length for the drug remains nearly constant. Extent of zero-order drug release from tablets was confirmed by fitting the dissolution data from 60% onwards to the equation of Korsmeyer and Peppas (1983).

Introduction

Hydrophilic matrix systems have attracted considerable attention in recent years as sustained release devices for the delivery of water soluble drugs. Various types of polymers used as hydrophilic matrices (Buri and Doelker, 1980) and their modelling aspects (Korsmeyer and Peppas, 1983; Gander et al., 1986a,b) were reviewed. Cellulose derivatives are the most commonly used hydrophilic polymers for oral sustained-release tablet formulations. A number of workers (Huber and Christenson, 1968; Lapidus and Lordi, 1968; Hardwood and Schwartz, 1982; Nakano et al., 1983; Daly et al., 1984) have reported that the release rate decreases as the viscosity of the polymer increases. Salomon et al., (1979) reported that viscosity of hydroxypropylmethylcellulose (HPMC) only affects the lag time before quasi-stationary diffusion but not the rate of release. Ford et al., (1985) reported that both lag time and release rate are unaffected by the viscosity grade of the polymer. Daly et al. (1984) increased the viscosity of HPMC by mixing it with anionic surfactant, sodium lauryl sulfate (SLS). Zero-order in vitro release of chlorpheniramine maleate was obtained for 6 h, by incorporating 15% SLS in the

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HPMC matrix (Daly et al., 1984). However, these workers have rightly admitted that such a high concentration of SLS is not suitable for oral administration. Walker and Wells (1982) found that a combination of the anionic sodium carboxymethylcellulose (Na CMC) with non-ionic cellulose gum produced a synergistic increase in viscosity. This was attributed to the stronger hydrogen bonding between the carboxyl groups on Na CMC and hydroxyl groups on the non-ionic gum, leading to stronger cross-linking between the two gums.

The major disadvantage of these hydrophilic swellable polymeric systems is that zero-order release has not generally been observed till the entire drug is released since the rates of penetration of solvent into the core of tablet and erosion of the gel are not equal. Hence, diffusional path length for the drug varies with time; as a result the plots of percent released vs time are non-linear.

We report here a simple technique of obtaining nearly zero-order release from hydrophilic matrix tablets till 100% of drug is released using a combination of HPMC and Na CMC. To illustrate this, β-adrenergic blockers, namely propranolol hydrochloride (PH), alprenolol hydrochloride (AH) and metoprolol tartrate (MT) were chosen as model drugs.

Materials and Methods

Propranolol hydrochloride, IP (PH), metoprolol tartrate, USP (MT), alprenolol hydrochloride (AH) and Methocel K4M Premium (HPMC) were received as gift samples from Indian Explosives Ltd., Madras; Cipla Laboratories Ltd., Bombay; Hassle, Mölndal, Sweden; Colorcon Ltd., Orpington, U.K. respectively. They were used as received. Na CMC of high viscosity grade supplied by Loba-Chemie Indoaustranat Co., Bombay, Batch No. 16531 (Na CMC-A) was used for PH and MT. Na CMC obtained from Amrut Industrial Products, Bombay (Na CMC-B) was used for AH.

Standardisation of Na CMC.

Na CMC was standardised by determining the pseudo-plastic properties (Metzner, 1961) of 2% w/v aqueous dispersion using MVI bob and cup assembly of Haake Rotovisko viscometer (1965 model). At 20 °C, flow and consistency indices of Na CMC-A were found to be 0.536 and 97.20 poise respectively. Flow and consistency indices of Na CMC-B at 25 °C were reported by Baveja and Ranga Rao (1986) as 0.655 and 18.66 poise respectively. Viscosity of 2% (w/v) Methocel K4M Premium was reported as about 40 poise at 20 °C by the manufacturers.

Preparation of tablets and in vitro dissolution study

Propranolol hydrochloride (80 mg), MT and AH (100 mg each) were mixed separately with HPMC or Na CMC (< 120 mesh, BS) in different ratios and compressed into tables (1.1 cm dia for AH and 9.5 mm dia for MT and PH) using single-punch hand-operated tablet machine fitted with flat-faced punches. They were subjected to dissolution in USP XVIII dissolution rate test apparatus at 37 ± 1 °C for 3 h in diluted HCl (pH 3.0) and later in 0.2 M phosphate buffer (pH 7.4) for another 9 h. The basket was rotated at 100 rpm. Results are shown in Figs. 1–6. Similar studies were carried out using a mixture of HPMC and Na CMC as matrix materials. By changing the ratio between drug and total gum and also by changing the ratio between the gums, different batches of tablets were prepared and subjected to dissolution as earlier, till 100% of drug was released in about 12 h at a nearly zero-order rate.

The optimised formulae contained drug : HPMC : Na CMC in the ratio 1 : 0.25 : 2.25 for PH (Fig. 7), 1 : 1.25 : 1.25 for MT (Fig. 8) and 1 : 2.08 : 2.92 for AH (Fig. 9). The reproducibility of results of these final formulations was confirmed by studying the release pattern of 1 tablet from each of the 10 different batches prepared in the same manner. The mean results are shown in Figs. 7–9.

Results and Discussion

To analyse the mechanism of release of drug from these tablets, the dissolution data obtained were fitted to the equation of Korsmeyer and

Peppas (1983) given below:

$$\frac{M_t}{M_\infty} = Kt^n$$

where M_t/M_∞ is the fractional release of drug, t is the release time, K is a constant incorporating structural and geometric characteristics of the controlled device, and n is the diffusional release exponent indicative of mechanism of release. They indicated that the value of n is 0.5 for Fickian transport and > 0.5 and < 1.0 for non-Fickian transport and 1 for zero-order (Case-II transport). When the value of n approaches 1.0, phenomenologically one may conclude that the release is approaching zero-order.

The values of K, n and coefficient of correlation, r^2 following linear regression of dissolution data corresponding to $M_t/M_\infty \geq 0.6$ and ≤ 1.0 when HPMC was used are given in Table 1. In all the formulations of AH, the values of n were closer to 0.5 indicating that the release mechanism was closer to Fikian transport. The values of n ranged from 0.556 to 0.793 for PH and from 0.570 to 0.760 for MT when $\simeq 60\%$ data was fitted to above equation. This indicates non-Fickian release. However, it is evident from Table 1, that the values of n decrease with time indicating that the mode of release approaches Fickian type. Figs. 1–3 reveal that the rate of release decreased with time and this may be due to an increase in diffusional path length for the drug which in turn may be due to slower erosion rate of the rubbery layer and faster advancement of swelling front into the glassy polymer.

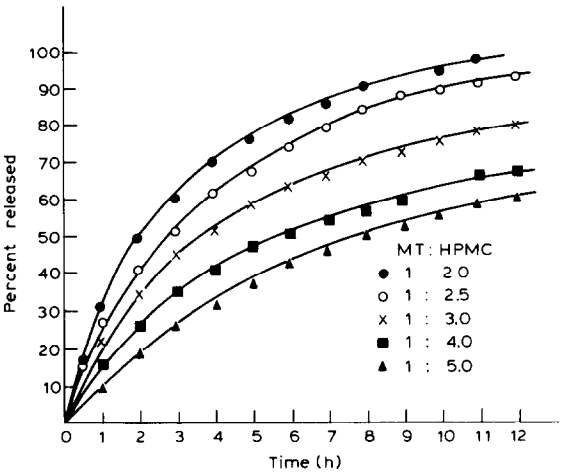

Fig. 2. Release of metoprolol tartrate (cumulative percent) as a function of time from tablets containing drug: HPMC in the ratios given.

When Na CMC alone was used (Figs. 4–6), the release was linear in diluted HCl (pH 3.0), but when changed to 0.2 M phosphate buffer (pH 7.4) the release rate increased which may be due to increase in erosion rate of the polymer.

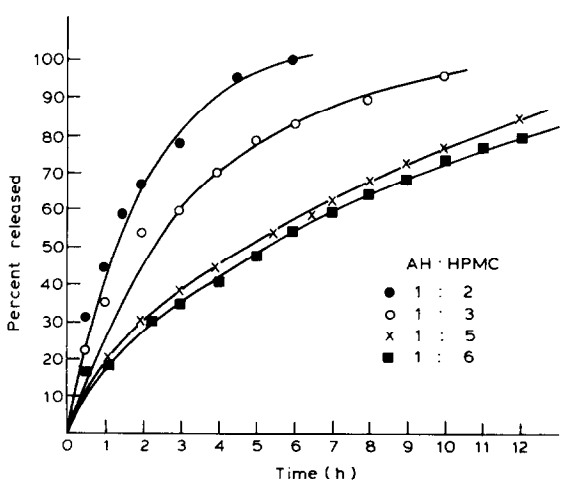

Fig. 1. Release of alprenolol hydrochloride (cumulative percent) as a function of time from tablets containing drug: HPMC in the ratios given.

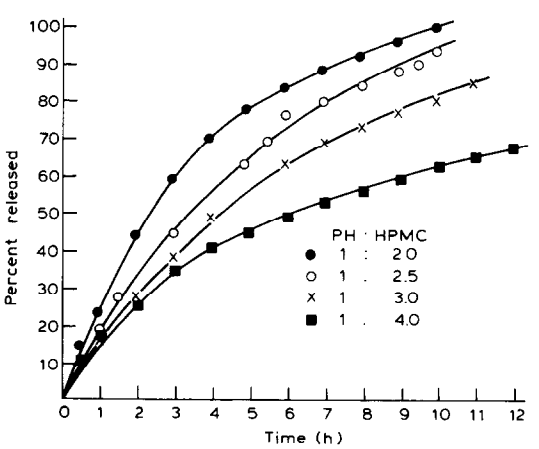

Fig. 3. Release of propranolol hydrochloride (cumulative percent) as a function of time from tablets containing drug: HPMC in the ratios given.

TABLE 1

Values of kinetic constant (k), release exponent (n) and coefficient of correlation (r^2) following linear regression of dissolution data for various values of $\frac{M_t}{M_\infty}$ when HPMC alone was used

Matrix composition	$\frac{M_t}{M_\infty}$	Time (h)	Kinetic constant k (h^{-n})	Release exponent (n)	Correlation coefficient (r^2)
PH : HPMC					
1 : 2	0.599	3.0	0.2554	0.7774	0.9968
	0.777	5.0	0.2546	0.7304	0.9944
	0.886	7.0	0.2563	0.6858	0.9880
	0.993	10.0	0.2615	0.6316	0.9773
1 : 2.5	0.764	6.0	0.1860	0.7932	0.9984
	0.844	8.0	0.1873	0.7651	0.9971
	0.939	10.0	0.1896	0.7363	0.9951
1 : 3.0	0.638	6.0	0.1721	0.7359	0.9965
	0.734	8.0	0.1749	0.7112	0.9958
	0.853	11.0	0.1806	0.6722	0.9918
1 : 4.0	0.592	9.0	0.1830	0.5562	0.9946
	0.651	11.0	0.1841	0.5449	0.9939
	0.656	12.0	0.1849	0.5376	0.9926
MT : HPMC					
1 : 2	0.603	3.0	0.2889	0.7598	0.9756
	0.757	5.0	0.2865	0.6675	0.9671
	0.851	7.0	0.2888	0.6137	0.9611
	0.966	11.0	0.2967	0.550	0.9481
MT : HPMC					
1 : 2.5	0.615	4.0	0.2580	0.6397	0.9971
	0.737	6.0	0.2583	0.6099	0.9931
	0.839	8.0	0.2596	0.5888	0.9960
	0.895	11.0	0.2638	0.5546	0.9849
1 : 3	0.622	6.0	0.2313	0.5703	0.9962
	0.716	9.0	0.2394	0.5239	0.9885
	0.791	12.0	0.2467	0.4925	0.9836
1 : 4	0.590	8.0	0.1699	0.6207	0.9885
	0.668	12.0	0.1783	0.5692	0.9794
1 : 5	0.606	12.0	0.1688	0.5134	0.9777
AH : HPMC					
1 : 2	0.662	2.0	0.455	0.5474	0.9934
	0.786	3.0	0.453	0.5240	0.9935
	1.00	6.0	0.4546	0.4793	0.9877
1 : 3	0.598	3.0	0.3452	0.5544	0.9838
	0.787	5.0	0.3443	0.5282	0.9891
	0.962	10.0	0.3491	0.4767	0.9809
1 : 5	0.582	6.5	0.2012	0.5699	0.9983
	0.678	8.0	0.2009	0.5758	0.9985
	0.854	12.0	0.2005	0.5809	0.9988
1 : 6	0.613	8.0	0.2062	0.5135	0.9861
	0.695	10.0	0.2057	0.5192	0.9946
	0.749	12.0	0.2055	0.5204	0.9912

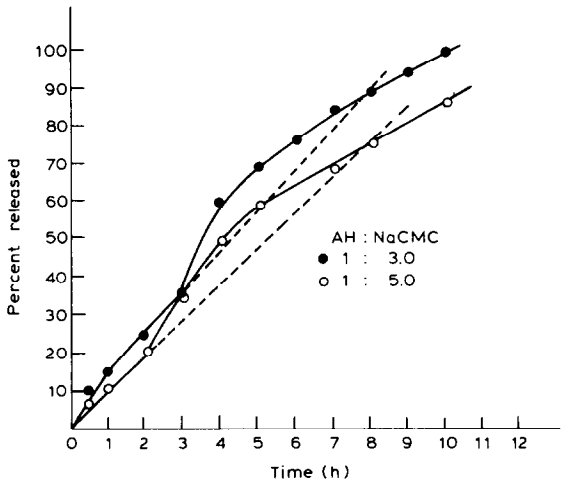

Fig. 4. Release of alprenolol hydrochloride (cumulative percent) as a function of time from tablets containing drug: Na CMC in the ratios given.

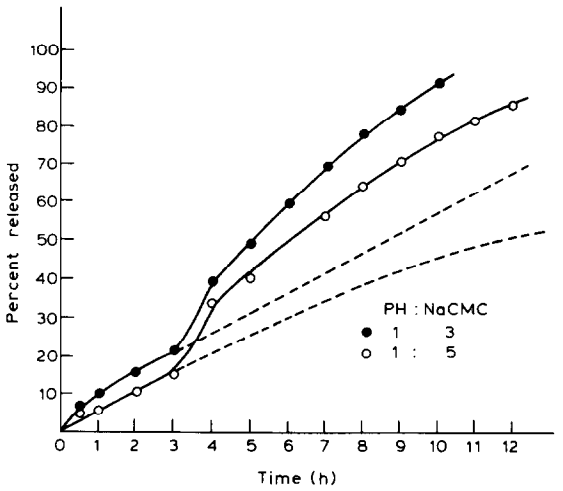

Fig. 6. Release of propranolol hydrochloride (cumulative percent) as a function of time from tablets containing drug: Na CMC in the ratios given.

When a mixture of HPMC and Na CMC was used, the values of n in all the formulations corresponding to $M_t/M_\infty \geqslant 0.6$ were closer to 1.0 (Table 2) indicating that the release mechanism is approaching zero-order. To elucidate the extent of zero-order release, the data corresponding to $M_t/M_\infty \geqslant 0.6$ and $\leqslant 1.0$ were also fitted to the above equation. For various values of M_t/M_∞, the values of n were closer to 1.0 indicating that phenomenologically the tablet on the whole behaves as a zero-order release system. As the value of M_t/M_∞ increased, the value of n changed to a negligible extent as shown in Table 2. Therefore, these practically constant values of n for $M_t/M_\infty \geqslant 0.6$ and $\leqslant 1.0$ confirm that deviation from zero-order release is practically negligible till 100%

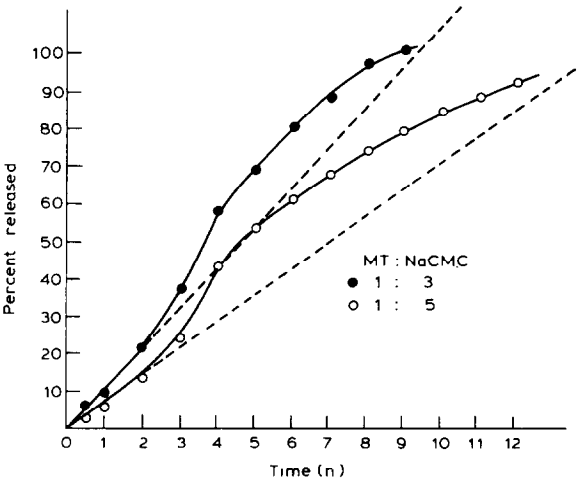

Fig. 5. Release of metoprolol tartrate (cumulative percent) as a function of time from tablets contain drug: Na CMC in the ratios given.

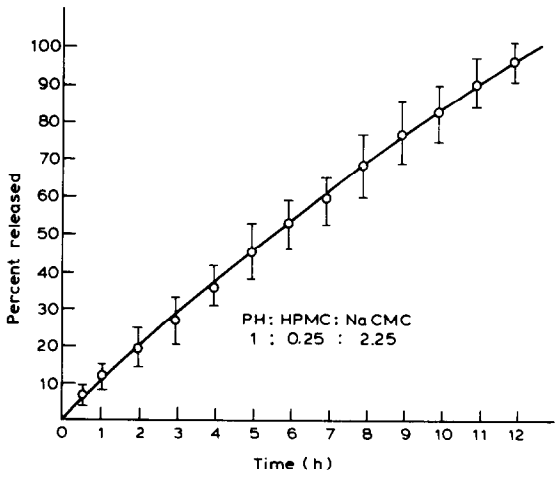

Fig. 7. Release of propranolol hydrochloride (cumulative percent) as a function of time from tablets of different batches ($n = 10$). Vertical bars indicate $\pm$S.D.

TABLE 2

Values of kinetic constant (k), release exponent (n) and coefficient of correlation (r^2) following linear regression of dissolution data for various values of $\frac{M_t}{M_\infty}$ when HPMC and Na CMC were used

Matrix composition	$\frac{M_t}{M_\infty}$	Time (h)	Kinetic constant k (h^{-n})	Release exponent (n)	Correlation coefficient (r^2)
PH : HPMC : Na CMC	0.594	7.0	0.1125	0.8430	0.9966
1 : 0.25 : 2.25	0.767	9.0	0.1120	0.8565	0.9969
	0.898	11.0	0.1118	0.8607	0.9975
	0.957	12.0	0.1117	0.8614	0.9984
MT : HPMC : Na CMC	0.622	7.0	0.1216	0.8222	0.9815
1 : 1.25 : 1.25	0.761	9.0	0.1213	0.8279	0.9864
	0.850	11.0	0.1216	0.8239	0.9945
	0.904	12.0	0.1247	0.8203	0.9897
AH : HPMC : Na CMC	0.618	7.0	0.1038	0.9006	0.9862
1 : 2.08 : 2.92	0.706	8.0	0.1036	0.9068	0.9882
	0.781	9.0	0.1034	0.9102	0.9897
	0.916	11.0	0.1035	0.9098	0.9918
	0.966	12.0	0.1036	0.9075	0.9925

of drug is released from the matrix tablets. (When only HPMC was used, in the case of PH and MT, the release pattern swiftly deviated from non-Fickian to Fickian type). This may also be attributed to the high degree of cross-linking between the non-ionic HPMC and anionic Na CMC leading to synergistic increase in gel viscosity at the tablet periphery. This will decrease the rate of advancement of swelling front into the glassy matrix resulting in a slow diffusion of the drug. As the swelling front advances into the glassy polymer, the rubbery state polymer (gel at the tablet periphery) which is devoid of the drug, undergoes attrition. When these two rates are equal, the

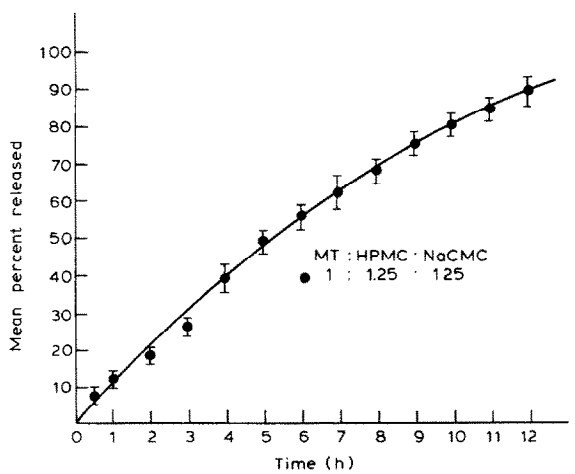

Fig. 8. Release of metoprolol tartrate (cumulative percent) as a function of time from tablets of different batches ($n = 10$). Vertical bars indicate ± S.D.

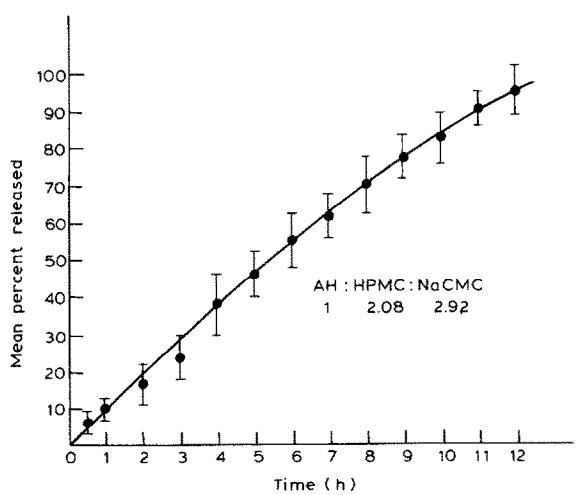

Fig. 9. Release of alprenolol hydrochloride (cumulative percent) as a function of time from tablets of different batches ($n = 10$). Vertical bars indicate ± S.D.

diffusional path length for the drug remains constant and zero-order release will be seen.

Therefore by optimising the ratio of total gum to drug and also the ratio between HPMC and Na CMC in the tablet, diffusional path length for the drug can be maintained constant so that zero-order release rate can be extended to the desired length of time.

Acknowledgements

We are grateful to Cipla Laboratories Ltd., Bombay; Hassle, Sweden; Indian Explosives Ltd., Madras and Colorcon Ltd., U.K. for their generous supply of metoprolol tartrate USP, alprenolol hydrochloride, propranolol hydrochloride IP and Methocel K4M Premium respectively. Financial assistance received from the University Grants Commission, New Delhi, is acknowledged.

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