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Relationship between gum content and half-life of soluble β blockers from hydrophilic matrix tablets

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Summary

The effect of the ratio of the amount of total gum to drug and also the ratio between the gums, i.e. hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaMC), on the release rate of drug was studied by taking 4 soluble β-adrenergic blockers, viz. propranolol hydrochloride, alprenolol hydrochloride, metoprolol tartrate and oxprenolol hydrochloride, as model drugs. A linear relationship existed in a particular range between the half-life of the tablet (time to release 50% of drug in vitro) and the ratio of total gum content to drug. This correlation holds good for these soluble β-blockers when HPMC alone or when a fixed ratio of HPMC and NaCMC was used as matrix materials. This relationship will be of immense help in optimising the composition of sustained release formulations.

Introduction

One of the diverse uses of hydrophilic polymers is to control the release of water-soluble drugs from solid dosage forms. The hydrophilic matrix consists of a mixture of one or more active ingredient(s) with one or more gel forming agent(s). Various types of polymers used as hydrophilic matrices (Buri and Doelker, 1980), cellulose ethers used as hydrophilic matrices (Alderman, 1984; Doelker, 1987) and their modeling aspects (Korsmeyer and Peppas, 1983; Gander et al., 1986a and b; Ritger and Peppas, 1987) were reviewed. Among these polymers, hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) are often used since they are directly compressible and can accommodate a relatively high percentage of drug.

Various factors influencing the release of drug from the hydrophilic matrices [viz. viscosity of the polymer (Salomon et al., 1979a; Nakano et al., 1983; Daly et al., 1984; Ford et al., 1985a and b); ratio of polymer-to-drug (Ford et al., 1985a and b); mixture of polymers (Baveja and Ranga Rao, 1986 and Baveja et al., 1987); compression pressure (Lapidus and Lordi, 1966 and 1968; Salomon et al., 1979b; Nakano et al., 1983); thickness of the tablet (Salomon et al., 1979b); particle size of the drug (Ford et al., 1985a and b); pH of the matrix (Ventouras et al., 1977; Ventouras and Buri, 1978); entrapped air in the tablets

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(Korsmeyer et al., 1983a); molecular size of drug (Korsmeyer et al., 1983b); molecular geometry of drug (Baveja et al., 1988); molecular size and solubility of drug (Ranga Rao et al., 1987)] were studied extensively by several workers.

To aid the formulator in optimising the content of HPMC needed to give a particular release rate from a tablet, and by carrying out a minimum number of trials in the laboratory, Ford et al. (1985a and b) have developed equations according to which linear relationship exists between: (i) Higuchian release rate and reciprocal of the content of HPMC in the tablet; and (ii) logarithm of the tablet HPMC content and logarithm of the Higuchian release rate. The objective of this work is to investigate the effect of the quantity of gum, i.e. HPMC or mixture of HPMC and NaCMC, on the in vitro half-life of drugs and to know whether any quantitative relationship exists between them. For this purpose, readily soluble β-blockers, namely propranolol hydrochloride (PH), metoprolol tartrate (MT), alprenolol hydrochloride (AH) and oxprenolol hydrochloride (OH), were chosen as model drugs.

Materials and Methods

Propranolol hydrochloride, IP (PH), metoprolol tartrate, USP (MT), alprenolol hydrochloride (AH), oxprenolol hydrochloride (OH) and Methocel K4M Premium (HPMC) received as gift samples from M/S Indian Explosives, Madras; M/S Cipla Laboratories, Bombay; M/S Hässle, Mölndal; M/S Hindustan Ciba-Geigy, Bombay and M/S Colorcon, Orpington, respectively, were used as such. NaCMC, high viscosity grade (two batches), supplied by Loba-Chemie Indoaustranat Co., Bombay was used (batch no. 16531 (NaCMC-A) for AH, PH and MT and batch no. 17731 (NaCMC-B) for OH).

Standardisation of NaCMC. Pseudoplastic properties (Metzner, 1961) of 2% w/v aqueous dispersion were determined using MVI bob-and-cup assembly of Haake Rotovisko viscometer (1965 model). At 20 °C, flow indices of NaCMC-A and -B were found to be 0.536 and 0.501, respectively, while their consistency indices were 97.20 and 166.61 poise, respectively. Viscosity of 2% w/v Methocel K4M Premium was reported to be about 40 poise at 20 °C by the manufacturers.

Preparation of tablets. Powders of HPMC and NaCMC (< 120 mesh) were stored under vacuum until used. Drug powder was mixed well with the required amount of NaCMC and/or HPMC, passed through a 120 mesh and compressed into tablets using a single-punch hand-operated tablet machine fitted with flat-faced punches (1.1 cm dia. for AH and 9.5 mm dia. for the rest). Three tablets of each formulation were subjected to dissolution in a USP XVIII dissolution rate test apparatus at 37 ± 1 °C in 900 ml of dil. HCl (pH 3.0) for 3 h and later in 0.2 M phosphate buffer (pH 7.4) for another 9 h. The basket was rotated at 100 rpm and drugs were assayed spectrophotometrically. The representative mean ($n = 3$) release profiles showing the effect of drug/gum ratio at a constant HPMC/NaCMC ratio and also the effect of HPMC/NaCMC ratio at constant drug/gum ratio are shown in Figs. 1 and 2, respectively. Release profiles of some formulations containing HPMC were given in our earlier communication (Baveja et al., 1987).

Results and Discussion

It is apparent from Fig. 1 that the percent of drug released at any time decreases as the ratio of total gum-to-drug in the tablet increased. Similarly, as shown in Fig. 2, percent drug released increases after 3 h, as the NaCMC content in the matrix increased. In order to fit this data to the linear relationships suggested by Ford et al. (1985a and b), Higuchian release rates of all the formulations were determined by regressing the release data up to $\leq 60\%$, as shown in Tables 1 and 2. As observed by Ford et al. (1985a and b), good correlation was seen between: (i) the Higuchian release rate and the reciprocal of gum content; and (ii) the logarithm of the Higuchian release rate and the logarithm of gum content for formulations containing only HPMC, as shown in Tables 3 and 4. For formulations containing a mixture of HPMC and NaCMC, the relationships of Ford et al. (1985a and b) did not hold true.

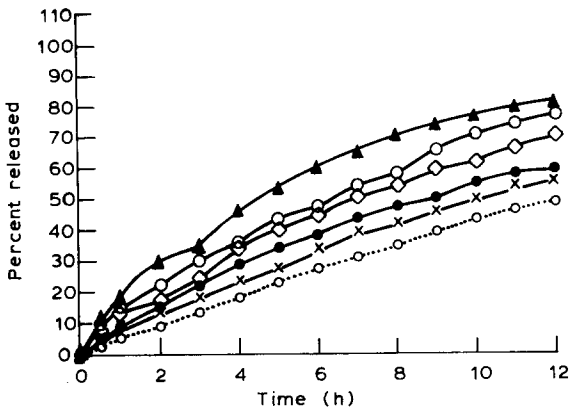

Fig. 1. Release of oxprenolol hydrochloride (cumulative percent) as a function of time from tablets containing drug: total gum in the ratio of: (▲) 1:2; (⊖) 1:2.5; (◈) 1:3; (●) 1:3.5; (*) 1:4 and (○) 1:5. The ratio between HPMC and NaCMC is 5:5.

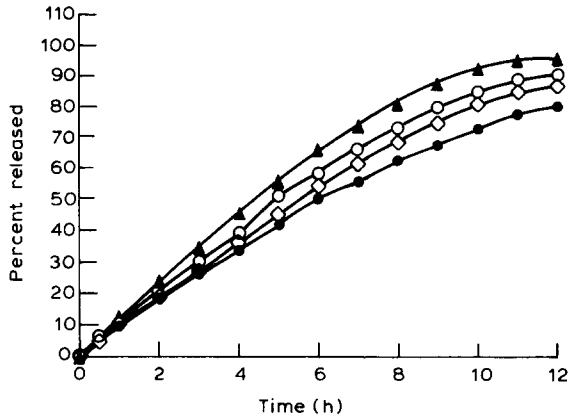

Fig. 2. Release of metoprolol tartrate (cumulative percent) as a function of time from tablets containing HPMC: NaCMC in the ratio of (▲) 1:9; (⊖) 2:8; (◈) 4:6 and (●) 5:5. The ratio between drug and total gum is 1:3.

TABLE 1

Formulation details and estimated values of slope (Higuchian release rate), intercept and coefficient of correlation (r^2) following linear regression of dissolution data up to ≤ 60% from tablets containing only HPMC

Matrix composition	Gum content, (mg)	$t_{50\%}$ (h)	Slope, ($\% \cdot h^{-1/2}$)	Intercept, (%)	r^2
AH : HPMC					
1:2	200	1.182	51.40	−5.624	0.9867
1:3	300	1.951	37.20	−2.109	0.9764
1:5	500	4.939	24.52	−4.395	0.9986
1:6	600	5.612	22.32	−2.118	0.9889
PH : HPMC					
1:2	160	2.372	44.333	−17.732	0.9927
1:2.5	200	3.468	35.315	−15.584	0.9992
1:3	240	4.260	32.963	−17.389	0.9934
1:4	320	6.092	20.772	−1.697	0.9948
MT : HPMC					
1:2	200	2.058	43.357	−13.451	0.9943
1:2.5	250	2.813	34.637	−8.085	0.9986
1:3	300	3.865	28.831	−6.019	0.9984
1:4	400	5.691	21.621	−3.277	0.9819
1:5	500	8.342	20.556	−9.372	0.9976
OH : HPMC					
1:2	160	3.157	34.800	−11.583	0.9925
1:3	240	4.410	29.109	−11.294	0.9949
1:4	320	5.221	25.385	−8.169	0.9915
1:5	400	6.075	23.653	−9.023	0.9962

TABLE 2

Formulation details and estimated values of slope (Higuchian release rate), intercept and coefficient of correlation (r^2) following linear regression of dissolution data up to ≤ 60% from tablets containing HPMC and NaCMC

Matrix composition	Gum content, (mg)	$t_{50\%}$ (h)	Slope, (% · $h^{-1/2}$)	Intercept (%)	r_2
AH : Total gum [a]					
1 : 2	200	4.425	24.605	−1.816	0.9908
1 : 3	300	5.166	23.475	−3.439	0.9872
1 : 4	400	8.914	19.614	−9.039	0.9947
1 : 5	500	10.546	20.773	−18.902	0.9863
PH : Total gum [a]					
1 : 2	160	4.383	24.599	−0.207	0.9742
1 : 2.5	200	6.083	24.455	−9.337	0.9708
1 : 3	240	7.725	22.252	−10.770	0.9797
1 : 4	320	10.718	19.005	−13.547	0.9822
1 : 6	480	14.905	16.268	−15.563	0.9616
MT : Total gum [a]					
1 : 2	200	4.915	30.725	−16.625	0.9709
1 : 2.5	250	5.723	30.078	−20.688	0.9571
1 : 3	300	6.152	29.022	−21.761	0.9899
1 : 4	400	6.561	24.292	−17.467	0.9781
OH : Total gum [a]					
1 : 2	160	4.541	30.125	−12.475	1.0000
1 : 2.5	200	6.405	23.419	−9.173	0.9935
1 : 3	240	7.170	23.195	−11.880	0.9857
1 : 3.5	280	8.736	21.553	−14.091	0.9979
1 : 4	320	10.207	20.570	−16.762	0.9916
1 : 5	400	11.712	18.977	−17.809	0.9864
PH : Total gum [b]					
1 : 1.75	140	3.558	34.310	−15.348	0.9937
1 : 2.0	160	4.047	33.096	−18.080	0.9956
1 : 2.5	200	4.837	34.279	−21.312	0.9447
1 : 3.0	240	5.712	28.800	−19.601	0.9815
1 : 3.5	280	7.061	27.392	−22.378	0.9481
MT : Total gum [b]					
1 : 2	200	3.692	34.371	−13.631	0.9816
1 : 2.5	250	3.504	38.365	−21.910	0.9819
1 : 3	300	4.398	35.853	−25.648	0.9905
1 : 4	400	5.711	29.476	−19.835	0.9754
1 : 5	500	6.510	29.695	−25.736	0.9796
OH : Total gum [b]					
1 : 2	160	5.322	31.922	−25.142	0.9855
1 : 2.5	200	6.038	26.256	−15.621	0.9768
1 : 3	240	6.704	24.900	−14.175	0.9790
1 : 4	320	8.024	23.165	−16.289	0.9826

[a] HPMC : NaCMC (5 : 5)
[b] HPMC : NaCMC (2 : 8).

Therefore attempts were made to find out the quantitative relationship (if any) between the half-life of the tablet (time to release 50% of the drug in vitro, $t_{50\%}$) and the ratio of total gum-to-drug content in the tablet. The exact time taken to release 50% of the drug from the tablet was calcu-

TABLE 3

Estimated values of slope, intercept and coefficient of correlation following linear regression of log of Higuchian release rate [a] versus log of HPMC content [b] in tablets of formulations given in Table 1 (according to Ford et al., 1985b)

Matrix composition	Slope ($\%\cdot h^{-1/2}\cdot mg^{-1}$)	Intercept, ($\%\cdot h^{-1/2}$)	r^2
AH : HPMC	−0.7736	3.4885	0.9974
PH : HPMC	−1.0579	3.9910	0.9509
MT : HPMC	−0.8506	3.5797	0.9704
OH : HPMC	−0.4292	2.4859	0.9961

[a and b] Values were taken from Table 1.

TABLE 4

Estimated values of slope, intercept and coefficient of correlation following linear regression of Higuchian release rate [a] versus reciprocal of HPMC content [b] in tablets of formulations given in Table 1 (according to Ford et al., 1985a)

Matrix composition	Slope ($\%\cdot h^{-1/2}\cdot mg^{-1}$)	Intercept ($\%\cdot h$)	r^2
AH : HPMC	8842.0	7.4195	0.9985
PH : HPMC	7171.7	0.1134	0.9768
MT : HPMC	7904.7	3.2406	0.9866
OH : HPMC	2995.9	16.2269	0.9966

[a and b] Values were taken from Table 1.

lated from the equation obtained by regressing the linear portion of the dissolution profile up to $\leq 60\%$. The values of $t_{50\%}$ for various formulations containing only HPMC and a mixture of HPMC and NaCMC are also given in Tables 1 and 2. Linear regression analysis of $t_{50\%}$ values versus total gum-to-drug ratios showed a very high correlation for all 4 drugs when either HPMC or when a fixed ratio of both HPMC and NaCMC were present as shown for the latter in Fig. 3. The general relationship observed can be given by the following equation:

$$t_{50\%} = M(G/D) + C$$

where M = slope of the derived line; C = intercept; G/D = ratio of the total gum-to-drug in the tablet.

The values M, C and the statistical parameters following linear regression of $t_{50\%}$ versus G/D

TABLE 5

*Estimated values of slope, intercept and statistical parameters following linear regression of $t_{50\%}$ * versus total gum-to-drug ratio of formulations given in Tables 1 and 2*

Matrix composition	Range of G/D	Slope (h)	Intercept (h)	r^2	F-ratio [+,d]	d.f. **	S [c]
AH : HPMC	2–6	1.1849	−1.3190	0.9831	116.359	1,2	0.9746
PH : HPMC	2–4	1.8321	−1.2188	0.9977	845.291	1,2	0.9965
MT : HPMC	2–4	1.8424	−1.6898	0.9979	960.079	1,2	0.9969
OH : HPMC	2–5	0.9564	1.3683	0.9888	177.125	1,2	0.9833
AH : Total gum [a]	2–5	2.2112	−0.4766	0.9420	32.3562	1,2	0.9127
PH : Total gum [a]	2–6	2.6103	−0.3731	0.9875	237.1227	1,3	0.9833
MT : Total gum [a]	2–4	1.2939	2.3709	0.9929	281.5234	1,2	0.9894
OH : Total gum [a]	2–5	2.3997	0.1294	0.9797	192.7021	1,4	0.9746
PH : Total gum [b]	1.75–3.5	1.9336	0.1126	0.9880	246.4370	1,3	0.9840
MT : Total gum [b]	2–5	1.0592	1.2679	0.9543	62.6851	1,3	0.9391
OH : Total gum [b]	2–4	1.3455	2.6539	1.0000	6497.0181	1,2	1.0000

* Values were taken from Tables 1 and 2.

** Degrees of freedom.

[a] HPMC : NaCMC (5 : 5).

[b] HPMC : NaCMC (2 : 8).

[c] Standard error of the estimate values.

[d] $P < 0.05$.

r^2: correlation coefficient.

[+] Significance of regression.

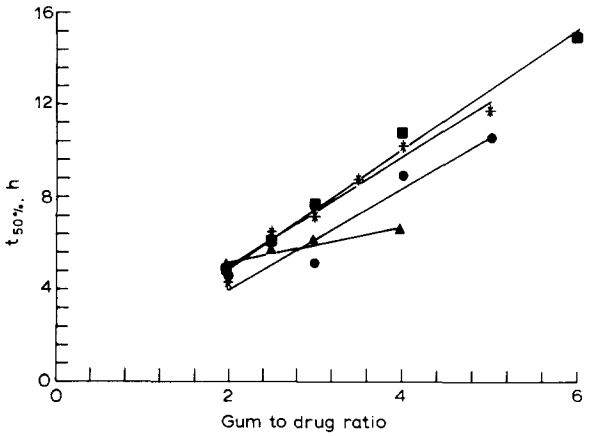

Fig. 3. Effect of gum-to-drug ratio on the in vitro half-life of β-blockers from tablets containing HPMC and NaCMC in the ratio of 1:1. (●) alprenolol hydrochloride; (■) propranolol hydrochloride; (▲) metoprolol tartrate and (*) oxprenolol hydrochloride.

values (for the range studied) of various formulations are given in Table 5.

This relationship has a greater utility to the formulator in the development of sustained release formulations using celluloses since it is true not only when HPMC alone but also when a mixture of HPMC and NaCMC were present in the matrix.

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