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CELLULOSE MATRICES FOR ZERO-ORDER RELEASE OF SOLUBLE DRUGS

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ABSTRACT

Release of two very soluble beta adrenergic blockers namely: metoprolol tartrate and alprenolol HCl from cellulose matrices containing hydroxypropylcellulose (HPC) or sodium carboxymethylcellulose (Na CMC) or methylcellulose (MC), or MC + Na CMC or HPC + Na CMC in different ratios was studied in distilled water using USP dissolution apparatus 2 . Increase in the ratio of total polymer to drug has decreased the release rate in a nonlinear manner. When only one polymer (HPC or Na CMC) was used, the release profiles were of first-order or sigmoidal in nature respectively. MC matrices disintegrated in < 1 h. By mixing the drug with an optimum amount of the nonionic (HPC or MC) and anionic (Na CMC) polymers, zero-order release profiles with excellent reproducibility were obtained. Rate of erosion of the matrix was 2.5 times higher when drug, Na CMC and HPC were present compared to the matrix containing only drug and HPC. This indicates that the diffusional pathlength for the drug increases with time when HPC alone was present and the former might be constant when an optimum percent of nonionic (HPC or MC) and anionic (Na CMC) polymers were present in the matrix.

INTRODUCTION

Over the past two decades, hydrophilic matrices are becoming extremely popular in controlling the release of soluble drugs from solid dosage forms. Hydrophilic matrix consists of a mixture of one or more active Ingredient(s) with one or more gel forming agent(s). The mixture is usually compressed into tablets. Various types of polymers used as hydrophilic matrices were reviewed[1]. Among the various hydrophilic polymers, water-swellable cellulose ethers namely: methylcellulose(MC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose(HPC) and sodium carboxymethylcellulose(Na CMC) listed in various pharmacopoeiae are frequently encountered in pharmaceutical literature as matrices for drug delivery systems. MC, HPC and Na CMC have been considered as safe materials by the Food and Drug Administration. Ease of compression, their ability to accomodate large percentage of drug and negligible influence of the processing variables on release rates are some of the other reasons for their popularity. Various cellulose ethers which are available commercially and can be used to controle the release of active agent have been thoroughly reviewed[2,3].

The first report on the use of compressed cellulose matrices for oral controlled release dosage form has appeared in 1962[4]. Later, from time to time various formulation factors influencing the release of drugs from compressed hydrophilic matrices viz: viscosity of the polymer[5-9], ratio of the polymer to the drug[8,9], mixture of the polymers[10-12] compression pressure[6, 13-15], thickness of the tablet[15], tablet shape and added diluents[16], particle size of the drug[8,9] micro pH of the matrix[17-19], entrapped air in the tablets[20], surface area of the tablet[21], influence of the surfactants[22], molecular size of the drug[23,24], molecular geometry of the drug[25], solubility of the drug[24] were studied by several workers and have been reviewed recently[3,12]. In an attempt to understand the mechanism of release of drug from the hydrophilic matrices, several mathematical models have been proposed [26-33] and were reviewed[33-35].

Most of the researchers working in the area of controlled drug delivery believe that, ideally the drug must be released from the dosage form at a zero-order rate. The major draw-back of the hydrophilic swellable matrices is that, drug release rate declines continuously in a manner that essentially follows the classical square root of time relationship[8,9]. Baveja and Ranga Rao[10] were the first to suggest the use of both anionic and nonionic cellulose ethers as a solution to this formulation problem. Later, by using a mixture of anionic Na CMC and nonionic HPMC in an optimum ratio, nearly zero-order release tablets were prepared for very soluble beta blockers namely propranolol hydrochloride, metoprolol tartrate (MT) and alprenolol hydrochloride (AH)[11]. These workers have indicated that besides the ratio of drug to total polymer, the ratio between the anionic and non ionic gums is important to obtain zero-order release till the entire drug is released from the tablets.

In this investigation the utility of the other FDA approved nonionic cellulose polymers (HPC and MC) in formulating zero-order release dosage forms of soluble drugs was studied.Two very soluble beta blockers namely MT and AH were chosen as the model drugs. To understand the mechanism of release of the drug, erosion of the matrix with time was also studied.

MATERIALS

Metoprolol tartrate, USP (MT) and alprenolol hydrochloride (AH) were obtained as gift samples from Astra-IDL Ltd., Bangalore (India) and Hässle, Mölndal (Sweden) respectively. Blanose 7H4FD (Na CMC) and Klucel MF (HPC) of Aqualon Company, Delaware (U.S.A.), and Methocel A4M Premium (MC) of Colorcon Ltd., Orpington (U.K.) were generously supplied by Scheller, Zürich (Switzerland). The nominal viscosity of 2% w/v aqueous dispersions of all the polymers was reported as about 4,000 cP at 20 °C by

the manufacturers. All the materials were fractionated and particles of 63-125 μm size range were stored in vacuum and used in the entire study.

METHODS

Matrix Preparation and Dissolution Studies :

Drug (MT or AH) was mixed manually with MC or HPC and / or Na CMC in various ratios and compressed into tablets of 1cm diameter using flat faced punches and Specac hydraulic press (Kontron AG, Zürich, Switzerland) at 20 kN. The amount of drug present in the tablet was 100 ± 1mg. Three tablets of each formulation were subjected to dissolution using USP dissolution apparatus 2 (Sotax AT6, Sotax AG, Basel, Switzerland) in 1,000 ml distilled water maintained at 37 ± 0.2 °C and rotated the paddle at 100 rpm. A flow through apparatus connected to a UV-Vis spectrophotometer (Beckman, model 35; Beckman Instruments, Inc., Fullerton, CA, USA) through a piston pump (Dissotest CY, Sotax AG, Basel, Switzerland) was used in the entire study. The pump was operated at a delivery rate of 15 ml / min. Absorbance of the dissolution medium at 274 nm for MT and 271 nm for AH was recorded automatically at regular intervals. From this, percent of the drug released at various times was calculated and the mean data are given in the release profiles (Fig 1-6).

Erosion Studies:

Erosion studies were conducted with tablets of AH containing HPC, and HPC along with Na CMC . For this, the tablets were subjected to dissolution in distilled water as earlier and at regular intervals, the tablet remaining in the beaker was taken out and dried

to constant weight in a hot air oven at 70 °C. Plots of mean (n = 2) percent remaining (w / w) versus time of these formulations are shown in Fig 7 .

RESULTS AND DISCUSSION

Release profiles of MT and AH from the matrices containing HPC or Na CMC are shown in Fig 1 and 2 respectively. Matrices containing MC alone did not sustain the drug for long time and they disintegrated in <1 h. Hence their release profiles are not given. It is clear from Fig 1 that drug release from the HPC matrices was faster in the beginning and the release rate decreased with time. A nonlinear inverse relationship is seen between the release rate and the ratio of gum to drug.

When only Na CMC was used, the release profiles (Fig 2) are far from zero-order. Initially the release was slower and later it became faster due to high erosion rate of the swollen outer layer. Similar results were reported by Baveja et al.,[11] when they studied the release of AH and MT from Na CMC matrices in dil HCl (pH 3.0) for 3 h and in 0.2 M phosphate buffer for another 9h. Hence Na CMC alone is not an ideal polymer to prepare sustained release matrix formulations. When HPC or MC was used along with Na CMC in different ratios, the release profiles obtained are shown in Figs 3 and 4.

When HPC and Na CMC were used in different ratios, the release rate decreased as the percent of HPC in the matrix was increased (Fig 3). But when MC and Na CMC were used in a similar manner, the release rate increased as the percent of MC in the matrix was increased (Fig 4). This shows that the erosion rate of the matrix is significantly influencing the shape of the release profile. It is obvious from Figs 3 and 4, that when both nonionic and anionic polymers were used as the matrix materials, the release profiles were no longer convex to the percent released axis.

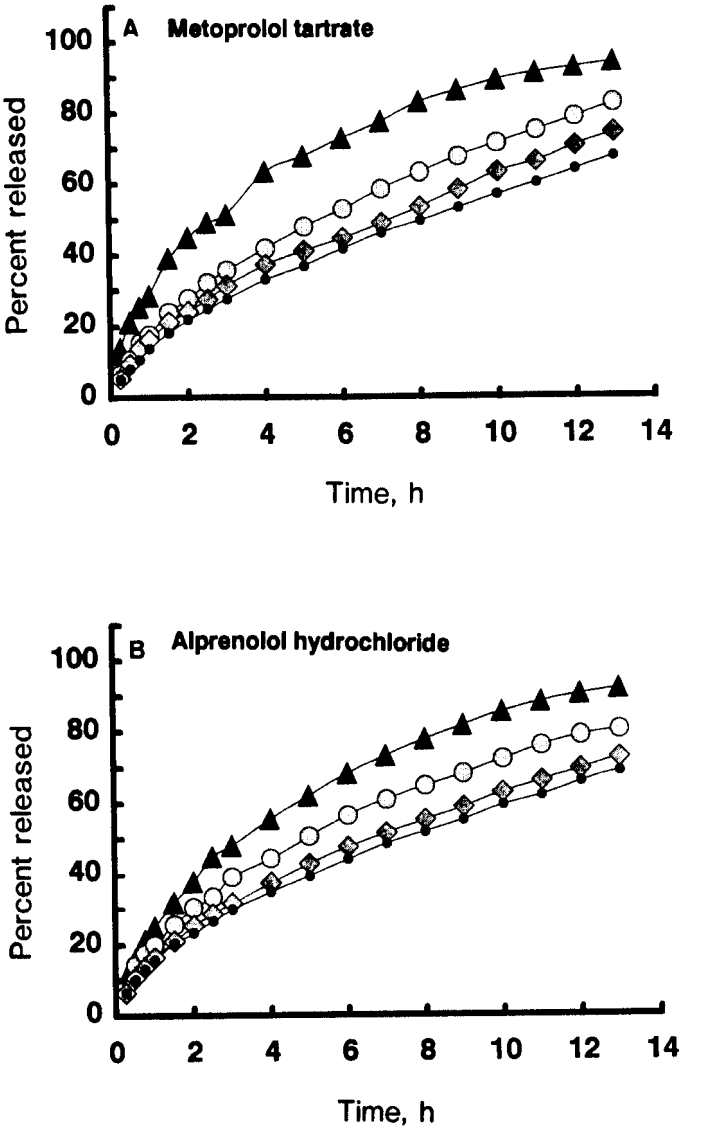

FIGURE 1

Release Profiles of Drugs from Tablets Containing: (A) MT : HPC in the Ratio of: (▲) 1 : 1; (◎)1 : 2 ; (◈) 1 : 3 and (●) 1 : 4. (B) AH : HPC in the Ratio of : (▲) 1 : 1; (◎) 1 : 2 ; (◈) 1 : 3 and (●) 1 : 4.

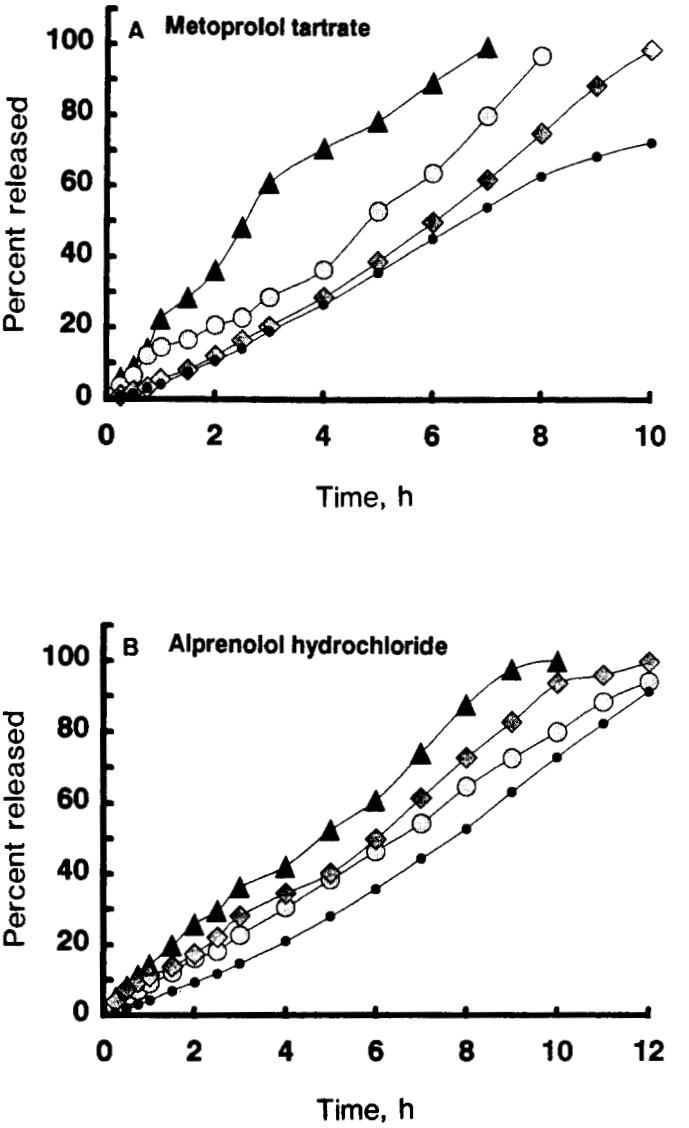

FIGURE 2

Release Profiles of Drugs from Tablets Containing: (**A**) MT : Na CMC in the Ratio of: (▲) 1 : 1 ; (⊗) 1 : 3 ; (◈) 1: 4 and (●) 1: 5. (**B**) AH : Na CMC in the Ratio of : (▲) 1 : 1; (◈) 1 : 2 ; (⊗) 1 : 3 and (●) 1 : 4.

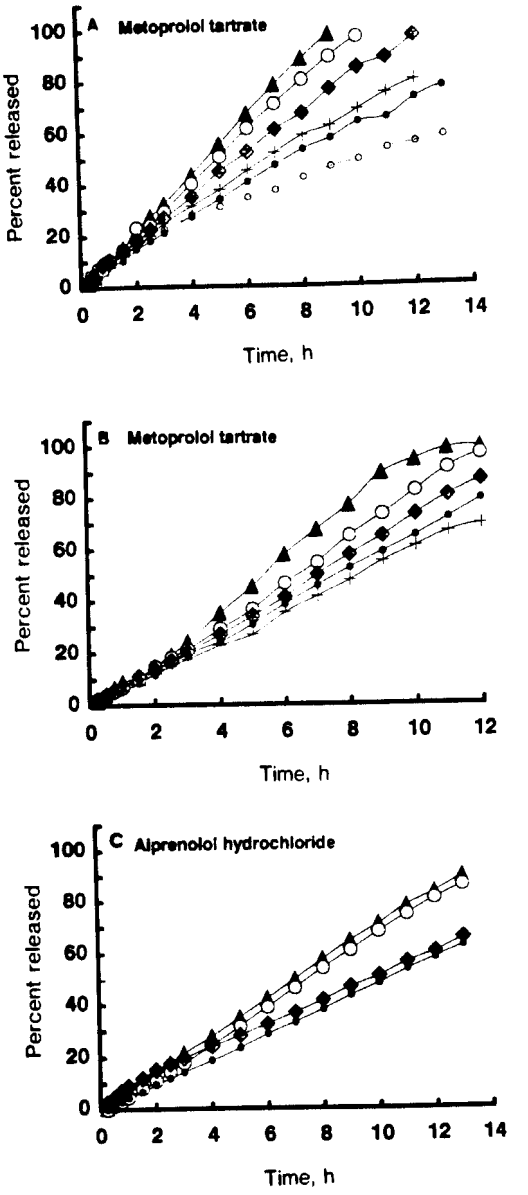

FIGURE 3

Release Profiles of Drugs from Tablets Containing : (A) MT : HPC : Na CMC in the Ratio of : (▲) 1.0 : 0.2 : 1.8 ; (◎) 1.0 : 0.4 : 1.6 ; (◈) 1.0 : 0.8 : 1.2 ; (×) 1 : 1 : 1; (●) 1.0 : 1.2 : 0.8 and (○) 1.0 : 1.4 : 0.6. (B) MT : HPC : Na CMC in the Ratio of : (▲) 1.0 : 0.3 : 2.7 ; (◎) 1.0 : 0.6 : 2.4; (◈) 1.0 : 1.2 : 1.8 ; (●) 1.0 : 1.5 : 1.5 and (×) 1.0 : 1.8 : 1.2. (C) AH : HPC : Na CMC in the Ratio of : (▲) 1.0 : 0.2 : 1.8 ; (◎) 1.0 : 0.4 : 1.6; (◈) 1.0 : 0.8 : 1.2 and (●) 1.0 : 1.2 : 0.8.

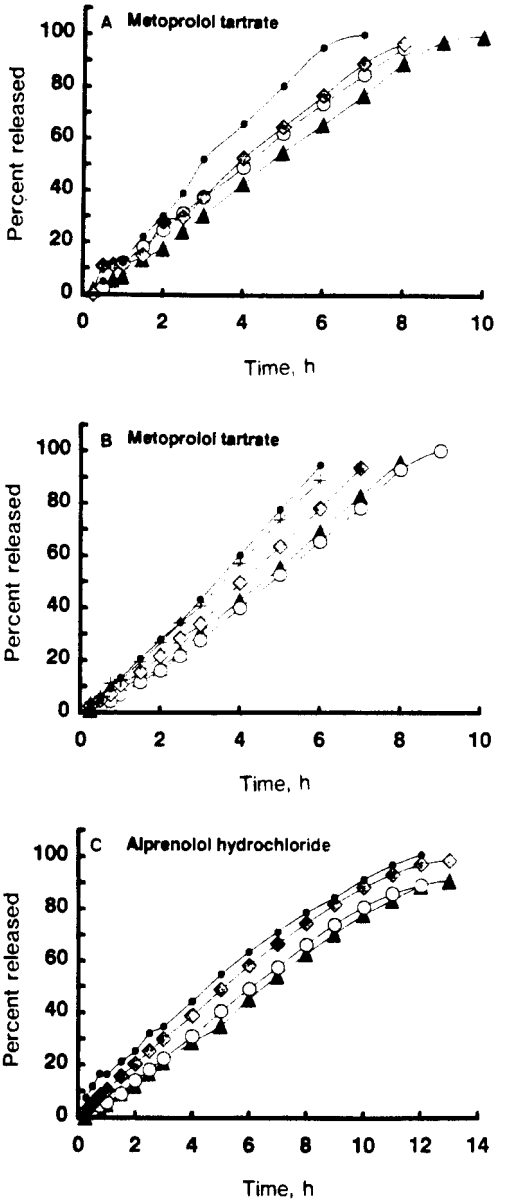

FIGURE 4

Release Profiles of Drugs from Tablets Containing : (**A**) MT : MC : Na CMC in the Ratio of : (●) 1.0 : 1.2 : 0.8 ; (◈) 1.0 : 0.6 : 1.4 ; (⊛) 1.0 : 0.4 : 1.6 and (▲) 1.0 : 0.2 : 1.8. (**B**) MT : MC : Na CMC in the Ratio of : (●) 1.0 : 1.8 : 1.2 ; (×) 1.0 : 1.5 : 1.5 ; (◈) 1.0 : 1.2 : 1.8 ; (▲)1.0 : 0.6 : 2.4 ; (⊛) 1 : 0.3 : 2.7. (**C**) AH : MC : Na CMC in the Ratio of : (▲) 1.0 : 0.2 : 1.8 ; (⊛) 1.0 : 0.4 : 1.6 ; (◈) 1.0 : 0.8 : 1.2 and (●) 1 : 1 : 1.

In order to analyse the mode of release of the drug from these matrices, the release data of formulations containing HPC as well as HPC or MC with Na CMC of both the drugs was analysed by the following empirical equation[33].

$$M_t / M_\infty = K. t^n$$

where M_t / M_∞ is the fraction of drug released up to time t,

K is a constant incorporating structural and geometric characteristics of the tablet,

n is the diffusional exponent indicative of the mechanism of release.

When the equilibrium swelling ratio of the matrix is $\geq$ 1.33, the values of n are 0.45 and 0.89 for Fickian and Case-II transport respectively. When the value of n is >0.45 and <0.89, the release is said to be non-Fickian[32]. When the value of n is greater than that of the Case-II transport, the release is said to be Super Case-II transport[33]. The values of K, n and correlation coefficient (r^2) obtained for various formulations and for different values of M_t / M_∞ ($\geq$ 0.6 and $\leq$1.0) are given in Tables 1 - 3.

A close look at the values of the release exponent, n given in Table 1 for various formulations reveal that when only HPC was present, the values of n were in the range of 0.488 - 0.645 indicating that the drug is released by non-Fickian behaviour. But when HPC or MC was present along with Na CMC, the values of n are relatively high and were in the range of 0.883 - 1.406 (Tables 2 and 3) indicating non-Fickian or Super Case-II transport. This significant increase in the values of n may be because of the stronger hydrogen bonding between the carboxyl groups on Na CMC and hydroxyl groups on the nonionic gum leading to stronger cross-linking between the two gums.

In order to evaluate the reproducibility of this release pattern, six different batches of one formulation each for MT and AH containing both the anionic and nonionic polymers

Table 1

Values of Kinetic Constant (k), Release Exponent (n) and Correlation Coefficient (r^2) Following Linear Regression of Dissolution Data for Various Values of M_t / M_∞ of Formulations Containing Only HPC.

Matrix Composition	Time (h)	M_t / M_∞	Kinetic Constant, k	Release Exponent, n	Coefficient of Correlation, r^2
MT : HPC					
1 : 1	4.0	0.6364	0.2999	0.5381	0.9950
	8.0	0.8300	0.2985	0.5111	0.9948
	12.0	0.9251	0.2992	0.4882	0.9922
1 : 2	7.0	0.5853	0.1734	0.6448	0.9960
	9.0	0.6756	0.1734	0.6361	0.9964
	12.0	0.7854	0.1738	0.6252	0.9964
1 : 3	9.0	0.5829	0.1514	0.6304	0.9904
	12.0	0.7049	0.1514	0.6254	0.9926
1 : 4	11.0	0.6024	0.2262	0.6454	0.9997
AH : HPC					
1 : 1	5.0	0.6219	0.2495	0.5947	0.9978
	8.0	0.7780	0.2489	0.5739	0.9936
	10.0	0.8546	0.2489	0.5623	0.9958
	12.0	0.9030	0.2489	0.5507	0.9952
1 : 2	7.0	0.6094	0.2018	0.5782	0.9958
	10.0	0.7219	0.2018	0.5677	0.9964
	12.0	0.7876	0.2023	0.5624	0.9966
1 : 3	9.0	0.5891	0.1622	0.6020	0.9982
	12.0	0.6937	0.1622	0.5956	0.9984
1 : 4	10.0	0.5937	0.1549	0.5865	0.9990
	12.0	0.6593	0.1552	0.5852	0.9992

Table 2

Values of Kinetic Constant (k), Release Exponent (n) and Correlation Coefficient (r^2) Following Linear Regression of Dissolution Data for Various Values of M_t / M_∞ of Formulations Containing HPC and Na CMC.

Matrix Composition	Time (h)	M_t / M_∞	Kinetic Constant, k	Release Exponent, n	Coefficient of Correlation, r^2
MT : HPC : Na CMC					
1 : 0.2 : 1.8	5.0	0.5549	0.0991	1.1003	0.9964
	7.0	0.7854	0.0989	1.0875	0.9972
	9.0	0.9792	0.0989	1.0739	0.9974
1 : 0.4 : 1.6	6.0	0.6170	0.1004	1.0164	0.9966
	8.0	0.8037	0.1004	1.0116	0.9976
	10.0	0.9683	0.1004	1.0042	0.9978
1 : 0.8 : 1.2	7.0	0.6135	0.0955	0.9529	0.9898
	10.0	0.8488	0.0955	0.9500	0.9930
	12.0	0.9683	0.0955	0.9443	0.9940
1 : 1.0 : 1.0	8.0	0.5902	0.0918	0.8924	0.9982
	10.0	0.6890	0.0918	0.8866	0.9984
	12.0	0.7976	0.0918	0.8825	0.9986
AH : HPC : Na CMC					
1 : 0.2 :1.8	9.0	0.6468	0.0606	1.1160	0.9882
	12.0	0.8344	0.0608	1.0936	0.9900
1 : 0.4 : 1.6	9.0	0.6093	0.0404	1.2262	0.9954
	12.0	0.8093	0.0448	1.2004	0.9956
1 : 1.2 : 0.8	12.0	0.5797	0.0302	1.2761	0.9882

Table 3

Values of Kinetic Constant (k), Release Exponent (n) and Correlation Coefficient (r^2) Following Linear Regression of Dissolution Data for Various Values of M_t / M_∞ of Formulations Containing MC and Na CMC.

Matrix Composition	Time (h)	M_t / M_∞	Kinetic Constant, k	Release Exponent, n	Coefficient of Correlation, r^2
MT : MC : Na CMC					
1 : 0.2 : 1.8	6.0	0.6402	0.1259	0.9625	0.9811
	8.0	0.8952	0.1265	0.9808	0.9866
	9.0	0.9829	0.1265	0.9819	0.9884
1 : 0.4 : 1.6	5.0	0.6427	0.1102	1.1012	0.9988
	7.0	0.8902	0.1099	1.0943	0.9990
	8.0	0.9879	0.1099	1.0866	0.9988
1 : 0.6 : 1.4	5.0	0.6707	0.1371	0.9681	0.9835
	6.0	0.7940	0.1371	0.9710	0.9864
	7.0	0.9183	0.1371	0.9723	0.9886
1 : 1.2 : 0.8	4.0	0.7000	0.1837	0.9146	0.9908
	5.0	0.8476	0.1841	0.9233	0.9924
	6.0	0.9428	0.1837	0.9207	0.9936
AH : MC : Na CMC					
1 : 0.2 : 1.8	8.0	0.6281	0.0417	1.4062	0.9502
	10.0	0.7797	0.0418	1.3643	0.9555
	12.0	0.8898	0.0420	1.3276	0.9580
1 : 0.4 : 1.6	7.0	0.5758	0.0634	1.1371	0.9986
	10.0	0.8085	0.0634	1.1280	0.9968
	12.0	0.8906	0.0635	1.1124	0.9982
1 : 0.8 : 1.2	6.0	0.5828	0.1033	0.9763	0.9982
	8.0	0.7461	0.1033	0.9681	0.9984
	10.0	0.8851	0.1033	0.9580	0.9984
	12.0	0.9727	0.1035	0.9437	0.9976

were made. One tablet from each batch was subjected to dissolution in the similar manner and the mean results are given in Figs 5 and 6. When the mean release data of percent released versus time was regressed, the values of correlation coefficient (r^2) were > 0.9944 indicating that the drug is released by zero-order from these matrices. The mean ± SD values of slopes of the six regressed lines of individual tablets' data were 6.635 ± 0.344, 7.749 ± 0.329, 7.594 ± 0.299 and 10.413 ± 0.609 respectively for formulations containing AH : HPC : Na CMC (1 : 0.4 : 1.6), AH : MC : Na CMC (1 : 0.4 : 1.6), MT : HPC : Na CMC (1 : 0.8 : 1.2) and MT : MC : Na CMC (1 : 0.4 : 1.6). This indicates that the variations in the results from batch to batch are not significant. The values of k, n and r^2 for various values of M_t / M_∞ for these four formulations are given in Table 4. The values of n were in the range of 1.012 - 1.117. The small deviation in the n values compared to the theoretical value (0.89) may be because of the high swelling nature of these formulations. As postulated earlier [11], the rate of advancement of the swelling front into the glassy polymer and the attrition of the rubbery state polymer might have been nearly equal in these formulations resulting in constant diffusional path length for the drug till the entire drug was released from the tablet. To confirm this, erosion studies were conducted with the tablets of AH containing only HPC, and HPC + Na CMC. The results obtained are given in Fig 7.

It is clear from Fig 7 that the erosion rate of HPC + Na CMC containing formulation is 2.50 times higher compared to the formulation containing equal amount of the total gum but only HPC. When the tablet is put in dissolution medium, the outer layers swell and form a gel. These rubbery layers offer minimum resistance for the penetration of the dissolution medium towards the glassy core. Hence the rate of advancement of the swelling front into the glassy core might be constant throughout. But when the erosion rate of the swollen gel is slow compared to this, the diffusional pathlength for the drug increases with time. Hence the drug release rate decreases with time as observed in

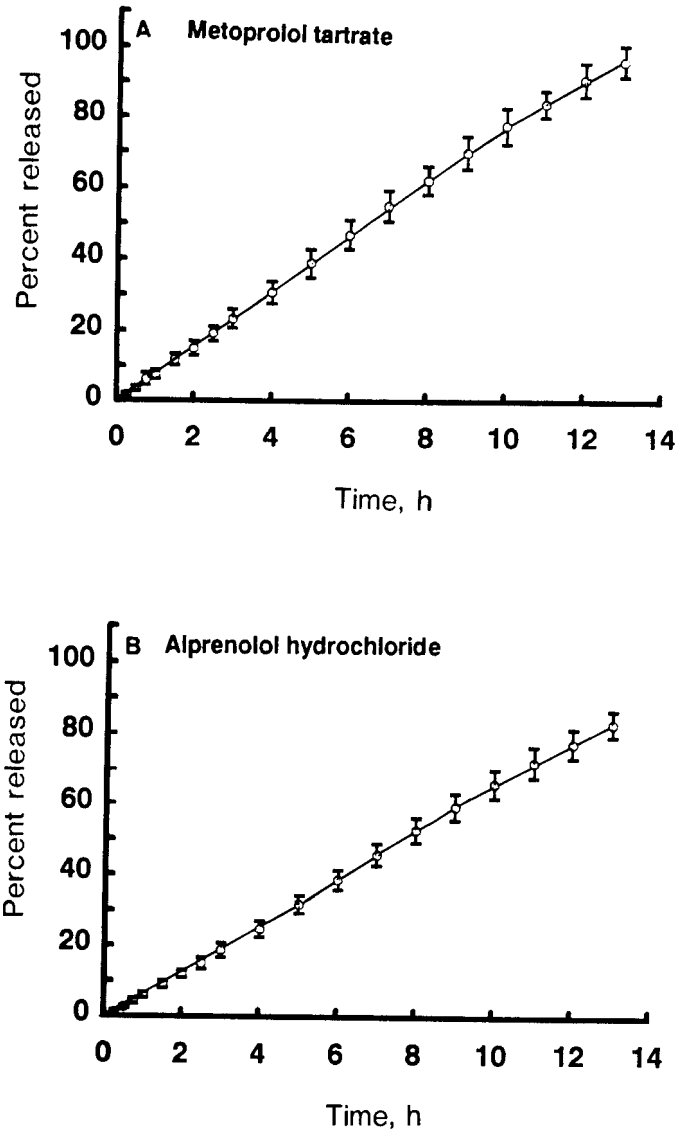

FIGURE 5

Mean Release Profiles of Drugs from Tablets Containing : (**A**) MT : HPC : Na CMC in the Ratio of 1.0 : 0.8 : 1.2 (n = 6). (**B**) AH : HPC : Na CMC in the Ratio of 1.0 : 0.4 : 1.6 (n = 6) Vertical Bars Indicate ± SD.

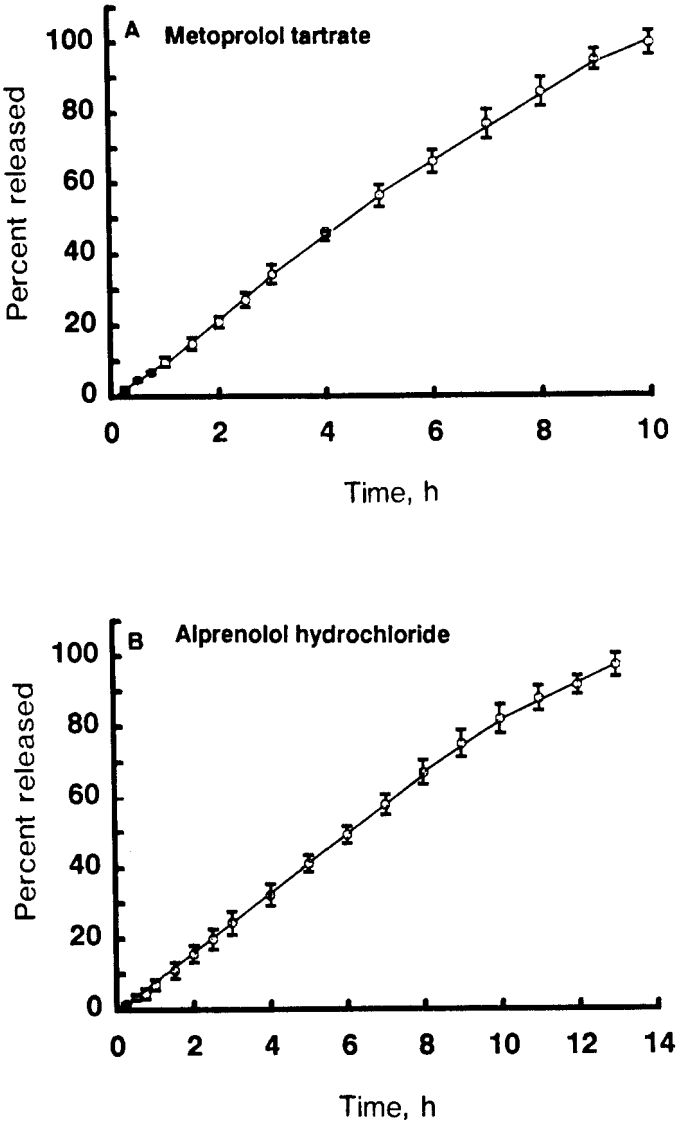

FIGURE 6

Mean Release Profiles of Drugs from Tablets Containing : (**A**) MT : MC : Na CMC in the Ratio of 1.0 : 0.4 : 1.6 (n = 6). (**B**) AH : MC : Na CMC in the Ratio of 1.0 : 0.4 : 1.6 (n = 6) . Vertical Bars Indicate ± SD.

Table 4

Values of Kinetic Constant (k), Release Exponent (n) and Correlation Coefficient (r^2) Following Linear Regression of Mean (n = 6) Dissolution Data for Various Values of M_t / M_∞ of Formulations Releasing the Drug at a Zero-order Rate.

Matrix Composition	Time (h)	M_t / M_∞	Kinetic Constant, k	Release Exponent, n	Coefficient of Correlation, r^2
MT : HPC : Na CMC					
1 : 0.8 : 1.2	8.0	0.6237	0.0753	1.0248	0.9986
	10.0	0.7771	0.0753	1.0214	0.9990
	12.0	0.9090	0.0753	1.0163	0.9990
AH : HPC : Na CMC					
1 : 0.4 : 1.6	9.0	0.5955	0.0578	1.0661	0.9992
	11.0	0.7217	0.0578	1.0626	0.9994
	13.0	0.8330	0.0579	1.0568	0.9994
MT : MC : Na CMC					
1 : 0.4 : 1.6	5.0	0.5638	0.0968	1.1174	0.9994
	7.0	0.7654	0.0964	1.0976	0.9988
	9.0	0.9457	0.0964	1.0790	0.9982
	10.0	0.9917	0.0964	1.0673	0.9974
AH : MC : Na CMC					
1 : 0.4 : 1.6	7.0	0.5781	0.0713	1.0901	0.9982
	9.0	0.7494	0.0711	1.0845	0.9986
	11.0	0.8762	0.0713	1.0674	0.9984
	13.0	0.9694	0.0714	1.0600	0.9976

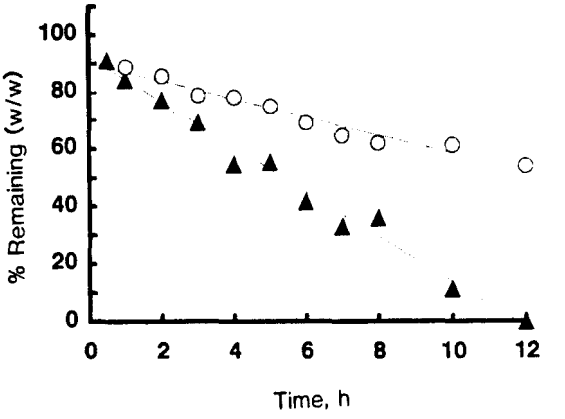

FIGURE 7

Plot of Percent Remaining (w/w) in the Matrix vs Time When the Tablets Containing (●) AH : HPC (1 : 2) and (▲) AH : HPC : Na CMC (1.0 : 0.4 : 1.6) were Subjected to Dissolution in Distilled Water at 37 °C. Paddle was Rotated at 100 rpm. The Linear Curve Fits the Equation : $Y = 90.09 - 3.16X$ ($r^2 = 0.9624$) for (●) and $Y = 92.21 - 7.85X$ ($r^2 = 0.9845$) for (▲).

matrices containing only drug and HPC. These studies support the hypothesis of Baveja et al.,[11] although the rate of advancement of the swelling front into the glassy matrix has to be measured for confirmation. Studies in this direction are in progress in our laboratory.

CONCLUSIONS

Two very soluble beta adrenergic blockers namely: metoprolol tartrate (MT) and alprenolol hydrochloride (AH) were mixed separately with cellulose ethers of nonionic (HPC and MC) and anionic (Na CMC) type in different ratios and compressed into tablets. Release of the drug from these matrix tablets was studied in distilled water using USP dissolution apparatus 2 and paddle was rotated at 100 rpm. Release rate decreased with time when only HPC was used and was not uniform when Na CMC alone was used. A

nonlinear inverse relationship was seen between the release rate and the ratio of HPC or Na CMC to drug. MC matrices disintegrated quickly.

When HPC or MC was mixed in different ratios with Na CMC, it was observed that increase in the percent of HPC or decrease in the percent of MC in the matrix decreased the release rate. When nonionic as well as anionic polymers were present in the tablet, the release profiles were not convex to the percent released axis unlike those of the matrices containing only HPC. By optimising the ratio between the drug, HPC or MC, and Na CMC, zero-order release could be obtained from the tablets. Reproducibility of this zero-order release pattern was confirmed by making six different batches of one formulation for each drug and by subjecting one tablet from each batch to dissolution. When the release data of percent released versus time was regressed, the variations in the values of release rates (slopes) from batch to batch were not significant. When the release data ($\geq$60% and $\leq$100%) were analysed by the empirical equation $M_t / M_\infty = K t^n$, the values of n (indicative of the mechanism of release) were in the range of 0.488 - 0.645 when HPC alone was used and 0.883 - 1.406 when HPC or MC was mixed along with Na CMC. For formulations exhibiting zero-order release, the values of n were in the range of 1.012 - 1.117.

Erosion studies with tablets containing AH, HPC as well as AH, HPC and Na CMC revealed that the erosion rate of the latter is 2.50 times higher than that of the former although the ratio of the total gum to drug is constant in both the cases. Due to slow erosion rate, the diffusional pathlength for the drug might be increasing with time when only HPC was present and may be the reason why the release rate decreased with time in these matrices. Due to faster erosion rate in formulations containing optimum ratio of HPC and Na CMC, the diffusional pathlength for the drug might be constant and perhaps due to this the release rate is nearly zero-order.

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