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Studies of Swelling Effect and Drug Release in Hydrophilic Matrices Containing Different Grades of Polymers.

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ABSTRACT

Polymers are very popular and widely used in formulating sustained release tablets because they are excellent drug carriers. The current study examines the relationship between swelling and drug release from the hydrophilic matrices of diltiazem hydrochloride prepared using different grades of hydroxypropyl methylcellulose (HPMC), viz, HPMCK4M, HPMCK15M and HPMCK100M. The results indicate that swelling and release profiles were affected by concentration and viscosity grade of the polymer. When the amount of polymer in the matrix is high, wetting improves and water uptake into matrices is enhanced. The higher amount of polymer causes a greater degree of swelling this in turn reduces the drug release, as the diffusional path length of drug is now longer. Conversely, reduction in the amount of polymer reduces the degree of swelling and the thickness of gel layer, this enables faster drug release. Swelling studies reveals an inverse relationship between swelling and drug release in the sustained release hydrophilic matrices containing different grades of polymer.

Keywords: Polymer, HPMC,Swelling

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INTRODUCTION

The aim of the present study was to investigate relationship between swelling and drug release from the sustained release hydrophilic matrices of diltiazem hydrochloride prepared using different grades of hydroxypropyl methylcellulose (HPMC), viz, HPMCK4M, HPMCK15M and HPMCK100M [1,6]. Drug release data from HPMC matrices follows the classical Higuchi dissolution equation, relating drug release with square root of time. Swellable systems consisting of hydrophilic polymers, in the presence of water, absorb a significant amount of water to form a gel. As the dissolution medium penetrates the matrix, polymer material swelling starts and drug molecules begin to move out of the system by diffusion [7-12].

In order to elucidate the release mechanism, the data were fitted to equation described by Peppas and Korsmeyer ($Mt/M \alpha Kt^{n.}$). The value of release rate exponent (n) is a function of geometric shape of the drug delivery device. The results indicate that the mechanism of release is influenced greatly by the polymer concentration of the formulations as can be seen from the r^2 values and n was generally in accordance with these indications. The release is mainly determined by the Fickian diffusion which is also confirmed from the n values [13-17].

EXPERIMENTAL

Materials and Methods

Diltiazem hydrochloride was obtained as a gift sample from Pure Pharma. Labs Ltd, Indore, (M.P.), HPMC (K4M, K15M, K100M) were provided by Colorcon India Ltd., Goa, dicalcium phosphate, microcrystalline cellulose (Avicel), talc , magnesium stearate and all other reagent used were of analytical grade.

Preparation of Matrices

Nine formulations employed for investigations containing different ratios of HPMC of different grades were prepared by direct compression and coded C1, C2, C3, D1, D2, D3, E1, E2 and E3. The ratios of different grades of HPMC employed are shown in Table [1]. The amount of drug, magnesium stearate, MCC and talc were kept constant while dicalcium phosphate was taken in sufficient quantity to maintain a constant tablet weight of 120 mg. All the products and process variables (other than the concentrations of two polymers) like mixing time, compaction force, etc, were kept constant. Ten tablets from each batch were weighed individually and subjected to physical evaluation.

Matrix Swelling and Water Uptake Studies

Swelling was evaluated by weight. The matrices were placed in 900 ml dissolution medium pH 6.3, at 37^0C. At different time intervals, the previously weighed tablets were removed, gently wiped with a tissue to remove surface water, and reweighed. The percent

water uptake i.e., degree of swelling due to absorbed test liquid, can be estimated at regular time intervals using the following equation –

$$\% \text{ water Uptake} = (Ws-Wi)/Wp *100$$

Where, Ws = Wt. of the swollen matrix at time t, Wi = Initial wt. of the matrix, Wp = wt. of the polymer in the matrix. The polymer swelling or water uptake are mean of three determinations.

The degree of swelling can be calculated by the following formula –

$$\text{Degree of swelling} = Ws-Wd/Wd*100$$

Where, Wd = Final dry wt. of the matrix, Ws = Swollen wt. of the same matrix at immersion time (t). The swelling degree is the mean of at least three determinations.

Dissolution Studies

Dissolution studies were carried out for all the nine formulations in triplicate, employing dissolution apparatus, using distilled water pH 6.3 as the dissolution medium at 50 rpm and 37 $\pm$ 0.5^{0}C. An aliquot of sample was periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of plain dissolution medium. The samples were analyzed at 237 nm.

RESULTS AND DISCUSSION

The weight of the polymer in the matrix (Wp) and final dry weight of the matrix (Wd) are shown in Table [2]. The weight of the swollen matrix at different time intervals, degree of swelling and percent water uptake data was observed.

The results of swelling studies are shown graphically in Double –Y plots showing dissolution profiles of diltiazem hydrochloride release and swelling from matrices containing HPMC K4M and K100M grades combinations, (formulation codes C1,C2,C3, Fig .[1a]. The percent uptake swelling or water uptake plots are shown in Fig. [1b]. Similar plots are shown in Fig [2a] and Fig [2b] for formulation codes D1, D2, D3, containing HPMC K4M and K15M combinations with different ratios and Fig [3a] and Fig [3b] for formulation codes E1, E2, E3, containing HPMC K15M and K100M combinations with different ratios.The dissolution parameters of varied formulation with different ratios of polymer combinations obtained during studies are shown in Table [3]. Formulation C1 has n= 0.50, C2 has n=0.45 and C3 has

n=0.44 indicating that the release mechanism is very close to Fickian transport i.e. belong to the Higuchi model.

In this investigation it has been demonstrated that an inverse relationship exists between the drug release rate and matrix-swelling rate. When the amount of HPMC in the matrix is high, wetting improves and water uptake into matrices is enhanced. The higher amount of HPMC causes a greater degree of swelling. This in turn reduces the drug release, as the diffusional path length of drug is now longer. Conversely, reduction in the amount of HPMC reduces the degree of swelling and the thickness of gel layer. This enables faster drug release. Similar results are observed with the different viscosity grades of HPMC formulations, viz D1, D2, D3 and E1, E2, E3. HPMC of higher viscosity grades swells to greater extent and has greater intrinsic water uptake property than that of the lower viscosity grades.

Table [1]. Different ratios employed in formulations containing HPMC of different grades.

Formulation Code	HPMCK4M	HPMCK100M	ZPM	Formulation Code	HPMC K4M	HPMC K15M	ZPM	Formulation Code	HPMCK15M	HPMCK100M	ZPM
C1	1	1	1	D1	1	1	1	E1	1	1	1
C2	2	2	1	D2	2	2	1	E2	2	2	1
C3	3	3	1	D3	3	3	1	E3	3	3	1

Table [2] Final dry weight and weight of polymer in matrix tablets of different batches.

Formulation Code	Final Dry weight (Wd) (mg)	Weight of polymer in matrix (Wp) (mg)	Formulation Code	Final Dry weight (Wd) (mg)	Weight of polymer in matrix (Wp) (mg)	Formulation Code	Final Dry weight (Wd) (mg)	Weight of polymer in matrix (Wp) (mg)
C1	120	24	D1	121	24	E1	125	24
C2	125	48	D2	120	48	E2	127	48
C3	122	72	D3	124	72	E3	122	72

Table [3] Dissolution parameters of varied formulations with different polymer ratio combinations.

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Formulation Code	n	k	MDT	Rel 12 hr	Rel 24 hr	r^2	da/dt
C1	0.50	0.30	3.77	96.60	N.C.	0.998	1.25
C2	0.45	0.25	6.34	84.30	102.00	0.975	0.93
C3	0.44	0.24	8.00	75.00	85.00	0.977	0.82
D1	0.55	0.31	2.93	103.00	N.C.	0.974	1.45
D2	0.55	0.30	3.10	103.80	N.C.	0.975	1.40
D3	0.46	0.26	6.05	86.00	103.00	0.971	0.96
E1	0.51	0.29	3.89	93.00	N.C.	0.968	1.13
E2	0.44	0.24	8.00	75.00	85.50	0.977	0.82
E3	0.43	0.22	10.22	64.00	92.00	0.980	0.80

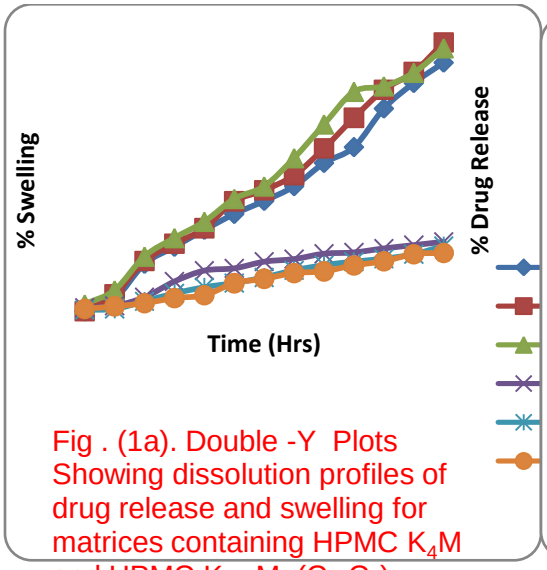

Fig . (1a). Double -Y Plots Showing dissolution profiles of drug release and swelling for matrices containing HPMC K_4M and HPMC $K_{100}M$ (C_1-C_3)

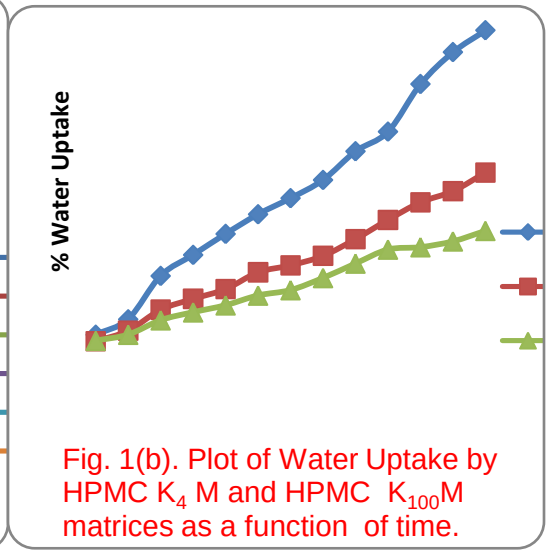

Fig. 1(b). Plot of Water Uptake by HPMC K_4 M and HPMC $K_{100}M$ matrices as a function of time.

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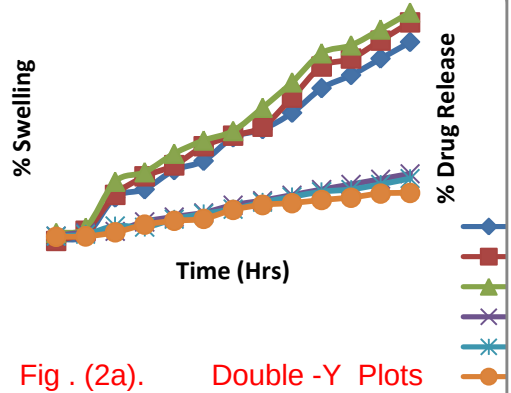

Fig . (2a). Double -Y Plots Showing dissolution profiles of drug release and swelling for matrices containing HPMC K_4M and HPMC $K_{15}M$ (D_1-D_3)

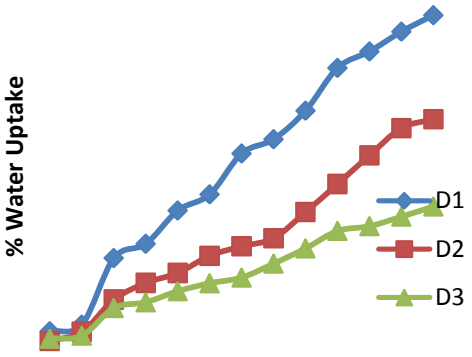

Fig. (2b). Plot of Water Uptake by HPMC K4 M and HPMC $K_{15}M$ matrices as a function of time.

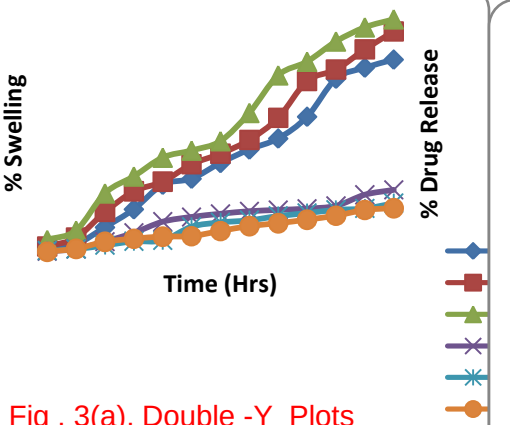

Fig . 3(a). Double -Y Plots Showing dissolution profiles of drug release and swelling for matrices containing HPMC $K_{15}M$ and HPMC $K_{100}M$ (E_1-E_3)

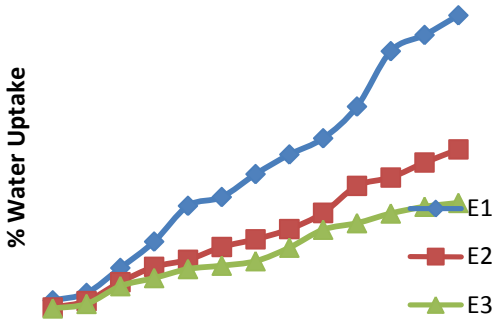

Fig. 3(b). Plot of Water Uptake by HPMC K_{15} M and HPMC K_{100} M matrices as a function of time.

CONCLUSION

Swelling studies reveals an inverse relationship between swelling and drug release. The rational combination of different grades of HPMC tends to provide quite regulated release of diltiazem hydrochloride over an extended period of time.

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