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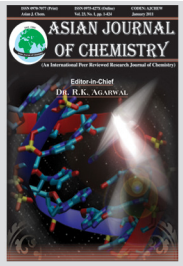

Swelling and Drug Release Studies from Hydrophilic Matrices Containing Combination of Different Grades of Hydroxyl Propyl Methylcellulose

MASHEER AHMED KHAN* and S.C. CHATURVEDI

School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshshila Campus, Khandwa Road, Indore-452 001, India

*Corresponding author: E-mail: masheerak@yahoo.com

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Polymers are very popular and widely used in formulating sustained release tablets because they are excellent drug carriers. The current study examines the drug release from the hydrophilic matrices prepared using combination of different grades of hydroxylpropyl 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. This swelling action of hydroxyl propyl methylcellulose of different grades in turn is controlled by the rate of water uptake into the matrices. An inverse relationship exists between the drug release rate and matrix-swelling rate. This implies that rational combination of the different grades tends to provide quite regulated release of drug. The swelling behaviour is therefore useful in predicting drug release.

Key Words: Hydroxy propyl methylcellulose, Hydrophilic matrices.

INTRODUCTION

Hydrophillic matrices are the least complicated devices in the formulation of sustained release dosage form. Hydroxypropyl methyl cellulose (HPMC) of different grades are used as the gel forming agent in matrices[1,2]. Swellable systems consisting of hydrophilic polymers, in the presence of water, absorb a significant amount of water dissolution medium to form gel. As the dissolution medium penetrates the matrix, polymer material swelling starts and drug molecules begin to move out of the system by diffusion[3-8].

The aim of the present study is to investigate the role of combination of different grades of polymer on swelling, the effect of swelling on drug release and also to describe the release kinetics. Drug release data from hydroxypropyl methyl cellulose matrices follows the classical Higuchi dissolution equation relating drug release with square root of time[9-12].

EXPERIMENTAL

Zolpidem tartrate was obtained as a gift sample from Ranbaxy Labs. Ltd., Dewas, (M.P.), Methocel (K4M, K15M, K100M) were provided by Colorcon India Ltd., Goa, dicalcium phosphate, microcrystalline cellulose (Avicel pH_{101}), 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 hydroxypropyl methyl cellulose 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

TABLE-1
DIFFERENT RATIOS EMPLOYED IN FORMULATIONS CONTAINING HPMC OF DIFFERENT GRADES

Formulation code	HPMCK4M	HPMCK100M	ZPM
C1	1	1	1
C2	2	2	1
C3	3	3	1
Formulation code	HPMCK4M	HPMCK15M	ZPM
D1	1	1	1
D2	2	2	1
D3	3	3	1
Formulation code	HPMCK15M	HPMCK100M	ZPM
E1	1	1	1
E2	2	2	1
E3	3	3	1

dissolution medium pH 6.3, at 37 ºC. At different time intervals, the previously weighed tablets were removed, gently wiped with a tissue to remove surface water and reweighed. The per cent water uptake *i.e.*, degree of swelling due to absorbed test liquid, can be estimated at regular time intervals using the following equation:

$$\text{Water uptake } (\%) = \frac{(Ws - Wi)}{Wp} \times 100$$

where, Ws = weight of the swollen matrix at time t, Wi = initial weight of the matrix, Wp = weight 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:

$$\text{Degree of swelling} = \frac{(Ws - Wd)}{Wd} \times 100$$

where, Wd = final dry weight of the matrix, Ws = swollen weight of the same matrix at immersion time (t), The swelling degree is the mean of at least three determinations.

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 ± 0.5 ºC. 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 245 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 per cent water uptake data was observed.

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)
C1	120	24
C2	127	48
C3	125	72
D1	121	24
D2	120	48
D3	124	72
E1	124	24
E2	125	48
E3	122	72

The results of swelling studies are shown graphically in Double-Y plots showing dissolution profiles of zolpidem (ZP) release and swelling from matrices containing HPMC K4M and K100M grades combinations, (formulation codes C1, C2, C3) (Fig. 1a). The per cent uptake swelling or water uptake plots are shown in Fig. 1b. Similar plots are shown in Fig. 2a and 2b for formulation codes D1, D2, D3, containing HPMC K4M and K15M combinations with different ratios and Fig. 3a and 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. 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. Formulation C1 has n = 0.504, C2 has n = 0.453 and C3 has n = 0.444 indicating that the release mechanism is very close to Fickian transport *i.e.* belong to the Higuchi model.

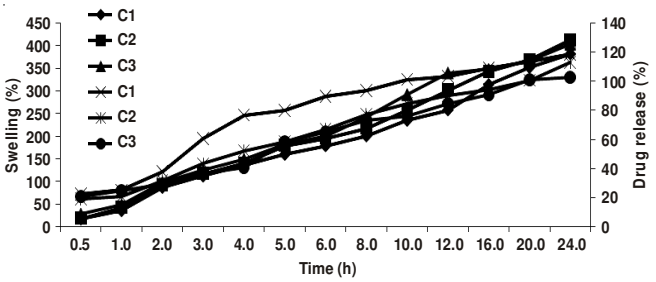

Fig. 1a. Double-Y plots showing dissolution profiles of drug release and swelling for matrices containing HPMCK4M and HPMCK100M (C1-C3) batches

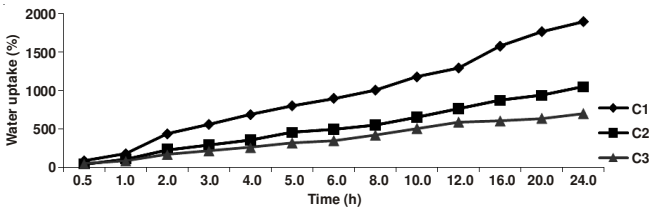

Fig. 1b. Plot of water uptake by HPMCK4M and HPMCK100M matrices as a function of time

TABLE-3
DISSOLUTION PARAMETERS OF VARIED FORMULATIONS WITH DIFFERENT POLYMER RATIO COMBINATIONS

Formulation code	n	k	MDT	Rel 12 h	Rel 24 h	r^2	da/dt
C1	0.504	0.295	3.761	96.54	N.C.	0.986	1.247
C2	0.453	0.254	6.393	84.27	101.35	0.979	0.927
C3	0.444	0.235	8.009	75.00	84.82	0.977	0.817
D1	0.551	0.312	2.921	104.00	N.C.	0.974	1.449
D2	0.547	0.305	3.093	102.73	N.C.	0.975	1.382
D3	0.459	0.257	6.050	86.00	102.08	0.971	0.955
E1	0.508	0.288	3.885	93.05	N.C.	0.968	1.130
E2	0.444	0.235	8.008	74.99	84.82	0.977	0.817
E3	0.431	0.218	10.220	63.50	91.58	0.980	0.790

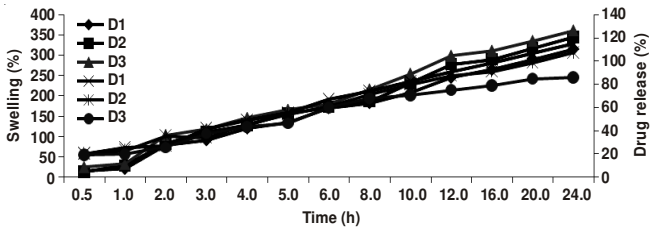

Fig. 2a. Double-Y plots showing dissolution profiles of drug release and swelling for matrices containing HPMCK4M and HPMCK15M (D1-D3) batches

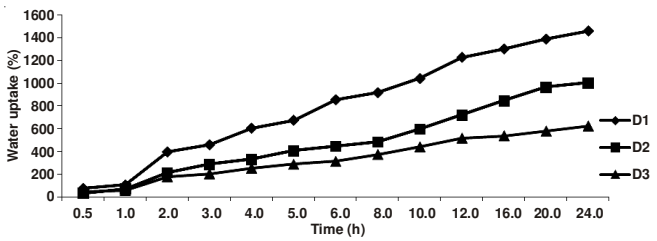

Fig. 2b. Plot of water uptake by HPMCK4M and HPMCK15M matrices as a function of time

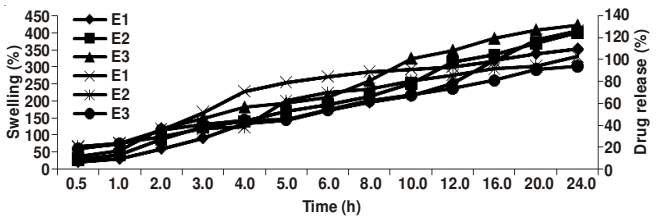

Fig. 3a. Double-Y plots showing dissolution profiles of drug release and swelling for matrices containing HPMCK15M and HPMCK100M (E1-D3) batches

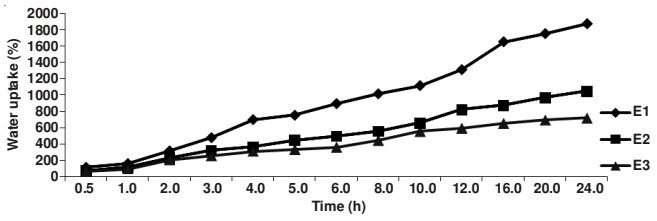

Fig. 3b. Plot of water uptake by HPMCK15M and HPMCK100M matrices as a function of time

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. Hydroxypropyl methyl cellulose of higher viscosity grades swells to greater extent and has greater intrinsic water uptake property than that of the lower viscosity grades.

Conclusion

Swelling studies reveals an inverse relationship between swelling and drug release. The rational combination of different grades of hydroxypropyl methyl cellulose tends to provide quite regulated release of zolpidem tartrate over an extended period of time. The diffusional exponent n generally agreed with the release kinetic employed and decreased with polymer concentration.

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