

Investigation of the Swelling, Erosion and Release Mechanism from Hydroxy Propyl Methyl Cellulose Based Matrix Tablets

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Abstract: The aim of this study was concerned with analysis of swelling, erosion and release behaviour of hydrophilic matrix tablets containing different grades of hydroxy propyl methyl cellulose (HPMC); i.e. HPMC K100 LV Premium, HPMC K4M & HPMC K100M in the preparation of controlled release tablets. Prazosin Hydrochloride (PHCl) was used as a model drug. Tablets were prepared by direct compression method. After evaluation of all physical parameters, swelling, erosion and release behaviour of hydrophilic matrix tablets were carried out in phosphate buffer pH 7.4. Viscosity of HPMC played a major role in controlling swelling and erosion profile. Swelling data revealed that the matrices of F1 swelled for 6 - 12 hrs and then retained a near constant volume. F1 showed increased swelling with an increase in the concentration of HPMC in the matrix, but the change was found insignificant ($P < 0.05$) above 60% w/w. The matrices eroded within 16 hrs in the dissolution medium. Formulation of batch F4 exhibited a much slower rate in swelling and erosion which extended up to 24 hrs. Due to high viscosity of HPMC K100M with DCP and suitable as controlled release system.

Keywords: Prazosin, HPMC, swelling, erosion, drug release.

INTRODUCTION

Hydrophilic matrices are become more popular and widely used as novel drug delivery system because of their good compatibility, easy to make on a commercial scale and faster production. Matrix tablet by using direct compression method is also a great choice and least complicated approach amongst other controlled drug delivery system [1].

In hydrophilic polymer matrix system drug is homogeneously distributed within polymer matrix [2]. The dynamic system in controlled drug delivery system is dependent on polymer swelling, hydration and dissolution of drug [3]. At the same time, the polymer matrix gets absorb and swell, resulting in changes in dimension of the matrix and diffuse out of the matrix. Finally polymer, excipients or drug complex gets erodes or dissolves away [4].

Hydroxypropylmethyl cellulose (HPMC) has been found to be a versatile material and widely accepted novel retardant polymer for the preparation of CR matrix tablet, is mixed alkyl hydroxyalkyl cellulose either containing methoxyl and hydroxypropyl groups. Rate of hydration of HPMC depends on the nature of these substituents, such as the molecular structure and the degree of substitution [5].

Prazosin hydrochloride (PRH) is the hydrochloride salt of 1-(4-amino-6, 7-dimethoxy-2-quinazolinyl)-4-(2-furoylcarbonyl) piperazine, a selective α_1 adrenergic receptor antagonist approved for

clinical use is widely used for the treatment of moderate to severe hypertension either alone or adjunct to diuretics and beta blockers. Due to shorter biological half-life (2.5-4 hours) and poor bioavailability, it is required frequent administration to maintain the desired therapeutic concentration of drug in the blood [6].

Hence, the study was aimed to investigate the effect of different viscosity grades of hydroxy propyl methyl cellulose (HPMC) on swelling, erosion and release mechanism from HPMC based matrix tablets.

MATERIALS AND METHODS

Materials

Prazosin HCl was received as a gift sample from Sun Pharma Laboratories Ltd., Jammu. Different viscosity grades of HPMC (i.e. HPMC K100 LV Premium, HPMC K4M, HPMC K100M), MCC PH102, Dibasic Calcium Phosphate (DCP), Colloidal Silicon Dioxide and Magnesium Stearate were also gifted from Sun Pharma Laboratories Ltd., Jammu. All other chemicals and reagents were of analytical grade.

Preparation of HPMC based matrix tablets

Matrix based CR tablets were prepared by direct compression method using different viscosity grades HPMC shown in Table 1. Prior to mixing, individually all the materials (except different viscosity grades of HPMC) were passed through sieve no. 60 and HPMCs were passed through sieve no.40 to avoid aggregations. In formulations MCC PH102 or Di calcium phosphate was used as filler-binder for

increasing the compressibility and flow of the ingredients. Different viscosity grades HPMC were used as retardant polymers. Colloidal silicon dioxide and magnesium stearate was used as glidant and lubricant respectively. The tablets were compressed at 150 mg weight on a 10 station Mini press-1 rotary tablet compression machine using 8 mm flat faced punches at a constant compression force [7].

Table 1: Preparation of HPMC based matrix tablets

Ingredients	Amount per tablet in formulation (mg)			
	Formulation-1	Formulation-2	Formulation-3	Formulation-4
Prazosin HCl	5	5	5	5
MCC PH102	0	7.5	7.5	0
Dibasic Calcium Phosphate	7.5	0	0	7.5
HPMC K100 LV Premium	135	0	0	0
HPMC K4M	0	135	0	0
HPMC K100M	0	0	135	135
Colloidal Silicon Dioxide	1	1	1	1
Magnesium Stearate	1.5	1.5	1.5	1.5
Total weight	150	150	150	150

Swelling index study

The extent of swelling was measured in terms of percentage weight gain by the tablet. The swelling behaviour of all formulation was studied. One tablet from each formulation was kept in a petridis containing pH 7.4 phosphate buffers. The tablet was removed at 0, 3, 6, 9, 12, 16, 20 and 24 hour interval and excess water blotted carefully using filter paper. The swollen tablets were re-weighed (W₂). The swelling index (SI) of each tablet was calculated according to the following equation-1 [8]:

$$S.I. = \{(W_t - W_0) / W_0\} \times 100 \quad [1]$$

Where, W₀ = initial weight, W_t = final weight

Matrix erosion studies

After the swelling studies, matrix erosion studies were performed as already reported by Roy & Rohera [9]. After swelling studies at same time interval, the wet samples were then dried in a hot air oven at 80°C until achieve constant weight and then final dry weight (W₃) was taken. The experiment was carried out in triplicate. The percent of matrix erosion at time, t was calculated by using following equation -2 [10]:

$$\% \text{ Matrix erosion} = (W_1 - W_3) / W_1 \times 100 \quad [2]$$

In vitro drug release studies

The United States Pharmacopoeia (USP) basket method was used for all the *in vitro* dissolution studies in triplicate. In this method, phosphate buffer pH 7.4 without enzyme was used as dissolution media [11]. The rate of stirring was 100 rpm. The amount of prazosin hydrochloride was 5 mg in all formulations. The matrices were placed in 900 mL of phosphate

buffer pH 7.4 and maintained temperature at 37 ± 0.1 °C for 2 h in Electrolab TDT 08 dissolution testing apparatus. At appropriate intervals, 5 mL of the samples were taken and filtered through a 0.45 mm Millipore filter. The dissolution media was replaced by 5 mL of fresh dissolution fluid to maintain sink condition. The samples were then analyzed at 248 nm by JASCO V-550 Double Beam UV spectrophotometer. The mean of three determinations was used to calculate the drug release from each of the formulations [12].

Analysis of release data

In order to understand the release mechanism and kinetics of the release data from polymeric system, first 60% release data were fitted to Korsmeyer-Peppas model (Equation-3). This model is generally used when more than one release mechanism are involved [13]:

$$M_t / M_\infty = k \cdot t^n \quad [3]$$

Where M_t / M_∞ is the fraction of drug released at time t, k is a kinetic constant introducing structural and geometric release system; n is the release exponent indicative release mechanism of drug. To find out the appropriate release exponent for different matrix tablet, data obtained from in-vitro drug release studies were plotted as log percentage drug released vs log time and equation-4 can be written as [14]:

$$\log [M_t / M_\infty] = \log k + n \log t \quad [4]$$

Drug release from cylindrical tablets, if the exponent $n \leq 0.45$ corresponds to a Fickian diffusion, if $0.45 < n < 0.89$ then it is non-Fickian diffusion or anomalous transport (diffusion/polymer relaxation). Exponent value, n equals to 0.89 or greater than 0.89

corresponds to case II and super case II transport respectively [15].

STATISTICAL ANALYSIS OF DATA

For optimization of formulations, statistical analysis of drug release profiles, swelling data and matrix erosion of different formulations were carried out by one-way analysis of variance (ANOVA) using software Origin 8.0 professional. Differences between formulations were considered statistically significant at $P < 0.05$ [16].

RESULTS AND DISCUSSION

The physical characteristics of all formulations were evaluated for physical appearance, weight variation, hardness, thickness and friability. All formulations resulted in acceptable limits including hardness between 4.68-5.11kp, thickness between 3.38-3.46 mm, friability less than 1%, diameter 8mm and weight variation of 150mg \pm 1%.

Swelling and erosion data of all the formulations of batches F1-F4 were shown in table 1 and table 2 respectively. Swelling data revealed that the matrices of F1 swelled for 6-12 h and then retained a near constant volume. Minimum swelling and fastest erosion of tablet F1 might be due to the improper gelling of HPMC at any concentration below 25% w/w

(minimum percolation threshold) and change was found insignificant ($P < 0.05$) above 60% w/w. These matrices eroded within 16 h in the dissolution medium. Formulation of batches F2-F4 exhibited a much slower rate in swelling and erosion which extended upto 24 h. It was observed that the viscosity of HPMC played a major role in controlling swelling and erosion profile. Water uptake of these formulation matrices took place very slow for longer period of time due to the presence of high viscosity grade HPMC K100M. Surface polymer of the matrices formed stronger gel immediately in contact with dissolution media which delayed further liquid permeation to the inner cores and subsequently slowed down swelling process. Tablets of batch F4 showed most sustained swelling over a period of 24 h due to the presence of larger amount of highest viscosity grade HPMC K100M. Results also revealed that the difference in swelling profile of MCC PH 102 and DCP containing matrices were insignificant ($P < 0.05$). But a faster erosion profile was observed in MCC PH 102 containing matrices. The reason may be due to the capillary action and compact disintegration of MCC matrix without swelling. Optimized formulations F4 showed higher swelling rate and lower erosion behaviour which extended upto 24 h due to formulations containing higher percent of HPMC K100M with diluents DCP [Fig.1(A)&(B)].

Table-2: Swelling weight gain by different matrix tablets as a function of time in p^H 7.4 phosphate buffer

Formulation code	Time							
	0 h	3 h	6 h	9 h	12 h	16 h	20 h	24 h
F1 (mg)	149.2 \pm 1.25	279.19 \pm 0.78	322.56 \pm 1.22	351.37 \pm 2.23	337.28 \pm 0.55	318.23 \pm 1.10	298.74 \pm 1.37	277.16 \pm 0.79
F2 (mg)	150.9 \pm 0.65	378.52 \pm 1.54	511.23 \pm 1.91	675.89 \pm 1.44	804.16 \pm 0.85	901.96 \pm 1.20	970.57 \pm 1.66	1008.30 \pm 2.39
F3 (mg)	148.2 \pm 1.48	430.22 \pm 1.27	516.59 \pm 0.89	621.32 \pm 2.32	714.48 \pm 1.28	767.32 \pm 1.07	805.22 \pm 1.59	913.52 \pm 1.32
F4 (mg)	148.7 \pm 2.05	356.54 \pm 0.43	528.34 \pm 2.24	702.17 \pm 1.43	816.41 \pm 1.65	913.19 \pm 1.21	989.85 \pm 0.45	1023.70 \pm 2.88

Table-3: Erosion data by different matrix tablets as a function of time in p^H 7.4 phosphate buffer

Formulation code	Time							
	0 h	3 h	6 h	9 h	12 h	16 h	20 h	24 h
F1 (mg)	149.82 \pm 1.80	142.40 \pm 1.68	100.89 \pm 3.75	85.68 \pm 0.87	70.72 \pm 1.34	54.95 \pm 1.67	43.94 \pm 0.88	38.14 \pm 2.32
F2 (mg)	148.60 \pm 1.32	139.64 \pm 1.93	117.34 \pm 1.87	105.59 \pm 1.44	68.73 \pm 0.80	58.38 \pm 2.38	42.60 \pm 3.40	35.03 \pm 1.10
F3 (mg)	149.84 \pm 1.09	139.67 \pm 2.33	117.27 \pm 3.11	102.65 \pm 1.50	65.51 \pm 2.56	50.88 \pm 1.90	36.68 \pm 2.30	27.75 \pm 1.93
F4 (mg)	149.82 \pm 2.20	142.40 \pm 0.99	119.19 \pm 1.30	100.89 \pm 1.25	70.72 \pm 0.98	54.95 \pm 2.77	43.94 \pm 0.80	38.14 \pm 1.76

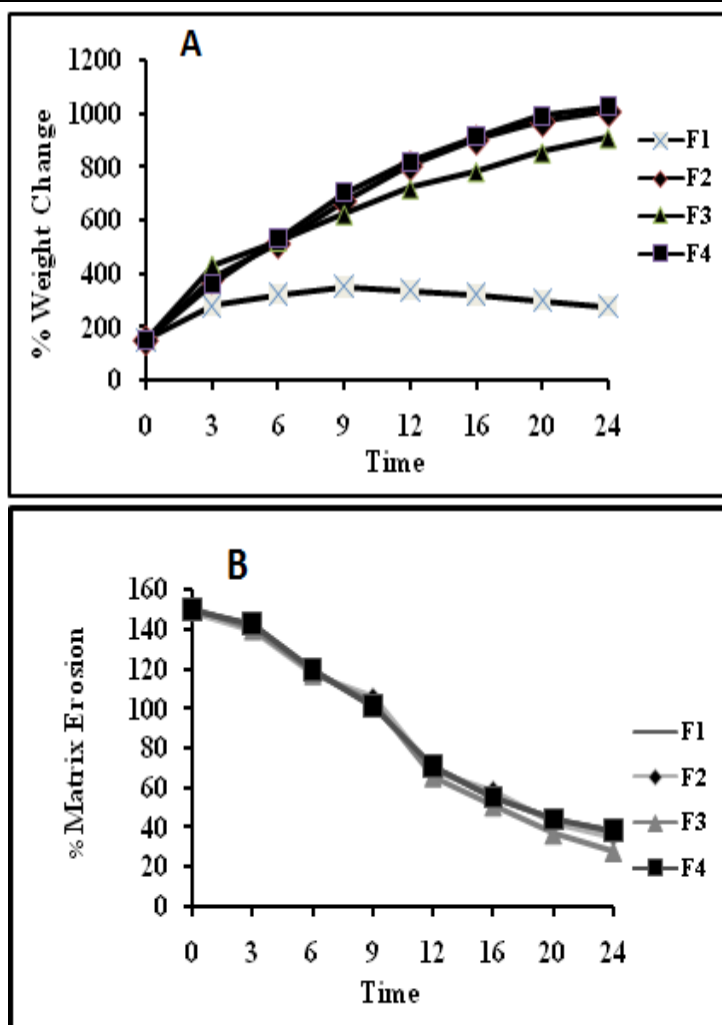


Fig-1: (A) Swelling or water uptake and (B) Percent erosion by different matrix tablets as a function of time in pH 7.4 phosphate buffer (mean ± SD, n = 3)

In vitro release

The dissolution profiles of prazosin hydrochloride (PHCl) released from different batches (F1-F4) of HPMC matrix tablets were shown in Fig. 2. The rate of release of PHCl with lower viscosity grade of HPMC (HPMC K100 LV) released over 80% drug

within 9 h. highly viscous HPMC matrices (F7-F12) containing HPMC K4M and K100M exhibited much slower drug release extending upto 22 h. The HPMC particles with high viscosity require a longer time for dissolution to form a gel layer, resulting in a decreased release rate.

Table-4: Release kinetics parameters of controlled release matrix tablet of PHCl (Mean ± SD, n = 6). K, kinetic constant; R, coefficient of correlation; n, release exponent; t80%, time (h) when 80% of PHCl is dissolved to the dissolution medium.

Code	Zero order		First order		Higuchi model		KP model		Drug release t80% (h)
	R	K	R	K	R	K	n	R	
F1	0.947	6.08	0.988	-0.121	0.990	26.6	0.45	0.999	8.68 ± 0.56
F2	0.916	3.02	0.991	-0.031	0.986	18.83	0.71	0.995	20.5 ± 0.24
F3	0.959	3.47	0.997	-0.052	0.988	15.42	0.59	0.997	20.24 ± 0.68
F4	0.948	2.34	0.997	-0.028	0.983	18.85	0.74	0.992	22.08 ± 0.74

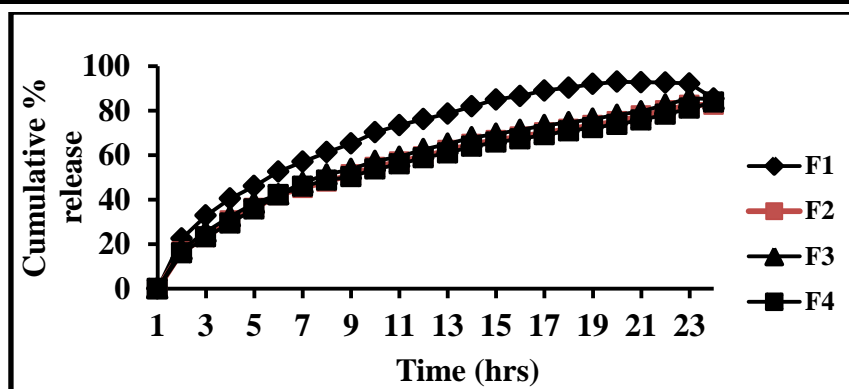


Fig-2: *In vitro* drug release profile of different matrix tablets in p^H 7.4 phosphate buffer (mean \pm SD, n = 3)

A directly compressible excipient MCC PH102 showed higher dissolution velocity than Dibasic Calcium Phosphate. MCC worked as a disintegrant in the matrix due to its strong capillary action and promoted compact disintegration. Dibasic Calcium Phosphate in the matrix caused the formation of stronger and larger compacts resulting in the slowing down of drug release. *In vitro* release data of formulation F1-F4 were fitted to different release kinetic models and regression parameters were calculated (Table 4). It was observed that the rank order of goodness of fit of various models for formulation F1 was KP model > Higuchi > first order > zero order. The release data of F3-F4 followed all the kinetic models except zero order. The value of “n” in Korsmeyer Peppas model indicated the mechanism of drug release from block shaped matrices. The formulation of batches F1 exhibited n value 0.45, which indicated Fickian diffusion of the drug from the matrices. In these formulations matrix volume increased upto 8-10 h and then decreased slowly for rest of the period. So the path length for drug diffusion increased with time and that resulted square root pattern in drug release (Higuchi model). F2-F4 matrices exhibited an anomalous behaviour (non-Fickian mechanism) in drug release where both drug diffusion through the gel layer and macromolecular relaxation were involved ($n = 0.74$). In these cases dissolution pattern became more linear due to the constant gel layer thickness.

CONCLUSION

HPMC based matrix tablets of PHCl was successfully developed by direct compression method. The matrix tablets swelled or eroded while in contact with medium phosphate buffer p^H 7.4 and formed a continuous gel layer or underwent combination of swelling and erosion. Drug release from matrix tablets was apparently influenced by the viscosity of the HPMC and presence of diluents in the formulation. The extent of matrix swelling, erosion and release of drug determined the kinetics as well as mechanism of drug release from HPMC based matrix tablets. The release data showed a good fit into the Korsmeyer-Peppas

equation indicating diffusion/polymer relaxation and showed Fickian diffusion (F1) and anomalous transport (F2-F4).

These findings were attributed to the effect of swelling and erosion on the drug release from HPMC based matrix tablets, which is an interesting way to formulating oral controlled release matrix tablets using a process that is easy to make on a commercial scale, inexpensive, good compatibility and faster production.

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