WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 14, 1192-1201. Research Article ISSN 2277– 7105

COMPARISON STUDIES SHOWING SWELLING EFFECT AND DRUG RELEASE PATTERN FROM MATRICES CONTAINING DIFFERENT DRUGS AND SAME POLYMER COMBINATIONS

Masheer Ahmed Khan*

School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshshila Campus, Khandwa Road, Indore, 452001, India.

Article Received on
20 September 2017,

Revised on 11 October 2017,
Accepted on 01 Nov. 2017

DOI: 10.20959/wjpr201714-10064

***Corresponding Author**
Masheer Ahmed Khan
School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshshila Campus, Khandwa Road, Indore, 452001, India.

ABSTRACT

Polymers are excellent drug carriers and widely used in the formulation of matrices to prolong the release of drug from the devices. The present comparison studies shows swelling effect and drug release pattern from matrices of Atenolol and Diltiazem hydrochloride drugs containing same polymer combinations. Matrices of both the drugs are prepared using same grades of hydroxypropyl methylcellulose (HPMC), viz, HPMCK4M, HPMCK15M and HPMCK100M. The study examines the degree of swelling and percent water uptake for matrices containing same polymer concentrations and combinations. The results indicate that swelling and release profiles were affected by concentration and viscosity grades of the polymer. 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 longer and 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 effect and drug release pattern from both the drugs matrices using the same polymer combinations. Comparison studies shows almost similar swelling effect and drug release pattern from matrices containing different drugs and same polymer combinations.

KEYWORDS: Polymer, Swelling, Matrices, Drug release.

INTRODUCTION

The aim of the present study was to compare swelling effect and drug release pattern from the matrices of atenolol and diltiazem hydrochloride prepared using same grades of

hydroxypropyl methylcellulose (HPMC), viz, HPMCK4M, HPMCK15M and HPMCK100M. Sustained release drug delivery system is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. Hydrophilic matrices devices are one of the least complicated approaches in the formulation of sustained release dosage forms and are finding increasing application in the pharmaceutical field.[1-6]

Drug release data from HPMC matrices for both the drugs 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. The degree of swelling and percent water uptake is determined to find the relationship between the drug release and swelling. The release mechanism is obtained from the dissolution data and the value of release rate exponent is determined. The value of release rate exponent (n) is a function of geometric shape of the drug delivery device. The release is mainly determined by the Fickian diffusion which is also confirmed from the n values.[7-12]

EXPERIMENTAL

MATERIALS AND METHODS

Atenolol and Diltiazem hydrochloride were 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 of Diltiazem hydrochloride 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. Similarly nine formulations of Atenolol containing the same grades of HPMC were prepared and coded F1, F2, F3, G1, G2, G3, H1, H2, and H3. 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.

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 –

% 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 –

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.

The weight of the polymer in the matrix (Wp) and final dry weight of the matrix (Wd) are shown in Table.[2]

Dissolution Studies

Dissolution studies were carried out for all the eighteen formulations in triplicate, employing dissolution apparatus, using distilled water pH 6.3 as the dissolution medium at 50 rpm and 37 ± 0.5^0C. An aliquot of sample was periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of plain dissolution medium. The diltiazem hydrochloride drug samples were analyzed at 237 nm. and the Atenolol drug samples were analyzed at 224 nm. (UV 1601 Shimadzu, Japan).

Table 1: Different ratios employed in formulations containing combinations of same HPMC grades.

Formulation Code	HPMCK4M	HPMCK100M	DILTIAZEM HCL
C1	1	1	1
C2	2	2	1
C3	3	3	1
Formulation Code	**HPMCK4M**	**HPMCK15M**	**DILTIAZEM HCL**
D1	1	1	1
D2	2	2	1
D3	3	3	1
Formulation Code	**HPMCK15M**	**HPMCK100M**	**DILTIAZEM HCL**
E1	1	1	1
E2	2	2	1
E3	3	3	1
Formulation Code	**HPMCK15M**	**HPMCK100M**	**ATENOLOL**
F1	1	1	1
F2	2	2	1
F3	3	3	1
Formulation Code	**HPMCK15M**	**HPMCK100M**	**ATENOLOL**
G1	1	1	1
G2	2	2	1
G3	3	3	1
Formulation Code	**HPMCK15M**	**HPMCK100M**	**ATENOLOL**
H1	1	1	1
H2	2	2	1
H3	3	3	1

Table 2: Final dry weight and weight of polymer in matrix tablets of different Formulations.

Formulation Code	Final Dry weight (Wd) (mg)	Weight of polymer in matrix (Wp) (mg)
C1	120	24
C2	127	48
C3	126	72
D1	124	24
D2	120	48
D3	125	72
E1	122	24
E2	125	48
E3	120	72
F1	120	24
F2	127	48
F3	126	72
G1	124	24
G2	122	48
G3	125	72
H1	122	24
H2	125	48
H3	125	72

RESULTS AND DISCUSSION

The percent water uptake as a function of time for formulations containing diltiazemh hydrochloride is reported in Table [3] Similarly Table [4] shows the result of formulations containing atenolol drug matrices of different codes. The degree of swelling as a function of time for formulations containing diltiazemh hydrochloride is reported in Table [5]. Similarly Table [6] shows the degree of swelling result of formulations containing atenolol drug matrices of different codes. The results of swelling studies are shown graphically for different formulations. Fig1a shows the plot for water uptake as a function of time for formulation codes C1, C2, C3, F1, F2 and F3 containing HPMC K4M and K100M combinations with different ratios and Fig1b shows plot for degree of swelling as a function of time for formulation codes C1, C2, C3, F1, F2, and F3. Similar plots are shown in Fig 2a and Fig 2b for formulation codes D1, D2, D3, G1, G2, and G3 containing HPMC K4M and K15M combinations with different ratios and Fig 3a and Fig 3b for formulation codes E1, E2, E3, H1, H2, and H3 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 [7].

Table 3: Percent Water Uptake as a Function of Time for Formulations Containing Diltiazem Hcl Drug.

Time Hrs.	C1	C2	C3	D1	D2	D3	E1	E2	E3
0.5	91.67	41.67	50	66.67	43.75	45.83	137.50	79.17	73.61
1	187.50	100.00	86.11	100.00	83.33	59.72	191.67	114.58	101.39
2	445.83	225.00	172.22	391.67	225.00	180.56	337.50	235.42	211.11
3	570.83	291.67	220.83	462.50	297.92	205.56	500.00	333.33	261.11
4	695.83	350.00	262.50	608.33	341.67	254.17	712.50	375.00	316.67
5	812.50	450.00	325.00	675.00	414.58	291.67	775.00	452.08	338.89
6	908.33	495.83	352.78	858.33	458.33	313.89	916.67	500.00	368.06
8	1020.83	547.92	429.17	920.83	497.92	379.17	1037.50	568.75	451.39
10	1191.67	652.08	516.67	1045.83	610.42	444.44	1137.50	666.67	562.50
12	1312.50	772.92	602.78	1237.50	735.42	527.78	1333.33	833.33	590.28

Table 4: Percent Water Uptake As A Function Of Time For Formulations Containing Atenolol Drug.

Time Hrs.	F1	F2	F3	G1	G2	G3	H1	H2	H3
0.5	83.33	33.33	45.83	58.33	37.50	41.67	125.00	72.92	69.44
1	175.00	95.83	81.94	87.50	77.08	55.56	170.83	112.50	97.22
2	433.33	220.83	168.06	379.17	218.75	176.39	325.00	229.17	206.94
3	558.33	285.42	215.28	441.67	291.67	201.39	487.50	322.92	256.94
4	683.33	343.75	256.94	587.50	335.42	250.00	708.33	366.67	312.50
5	800.00	443.75	315.28	658.33	410.42	284.72	762.50	445.83	333.33
6	895.83	485.42	347.22	837.50	452.08	309.72	904.17	493.75	361.11
8	1004.17	541.67	419.44	900.00	487.50	370.83	1025.00	556.25	444.44
10	1175.00	641.67	505.56	1025.00	602.08	437.50	1125.00	656.25	555.56
12	1291.67	756.25	588.89	1212.50	725.00	513.89	1320.83	822.92	595.83

Table 5: Degree of Swelling as a Function of Time for Formulations Containing Diltiazem Hcl Drug.

Time Hrs.	C1	C2	C3	D1	D2	D3	E1	E2	E3
0.5	18.33	15.75	28.57	22.50	15.75	28.57	27.05	30.4	44.17
1	37.50	37.80	49.21	45.83	37.80	49.21	37.70	44	60.83
2	89.17	85.04	98.41	95.83	85.04	98.41	66.39	90.4	126.67
3	114.17	110.24	126.19	122.50	110.24	126.19	98.36	128	156.67
4	139.17	132.28	150.00	145.83	132.28	150.00	140.16	144	190.00
5	162.50	170.08	185.71	185.83	170.08	185.71	152.46	173.6	203.33
6	181.67	187.40	201.59	204.17	187.40	201.59	180.33	192	220.83
8	204.17	207.09	245.24	225.00	207.09	245.24	204.10	218.4	270.83
10	238.33	246.46	295.24	266.67	246.46	295.24	223.77	256	337.50
12	262.50	292.13	344.44	315.00	292.13	344.44	262.30	320	354.17

Table 6: Degree of Swelling as a Function of Time for Formulations Containing Atenolol Drug.

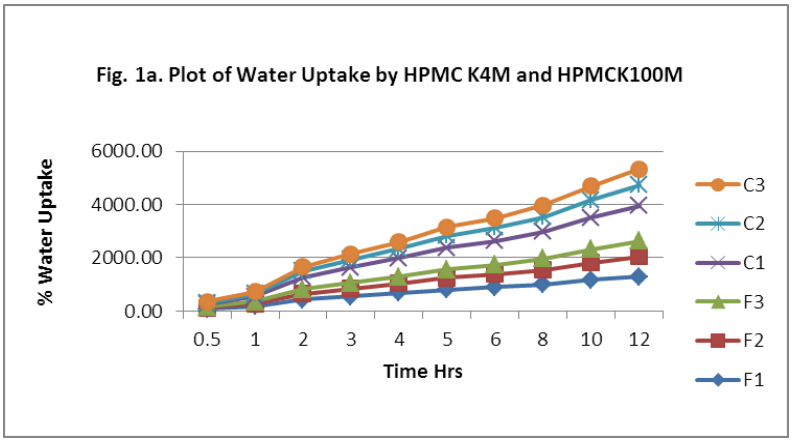
Time Hrs.	F1	F2	F3	G1	G2	G3	H1	H2	H3
0.5	16.67	12.60	26.19	15.00	10.24	23.02	24.59	28	41.67
1	35.00	36.22	46.83	20.83	25.20	30.95	33.61	43.2	58.33
2	86.67	83.46	96.03	79.17	78.74	100.00	63.93	88	124.17
3	111.67	107.87	123.02	91.67	106.30	114.29	95.90	124	154.17
4	136.67	129.92	146.83	120.83	122.83	142.06	139.34	140.8	187.50
5	160.00	167.72	180.16	135.00	151.18	161.90	150.00	171.2	200.00
6	179.17	183.46	198.41	170.83	166.93	176.19	177.87	189.6	216.67
8	200.83	204.72	239.68	183.33	180.31	211.11	201.64	213.6	266.67
10	235.00	242.52	288.89	208.33	223.62	249.21	221.31	252	333.33
12	258.33	285.83	336.51	245.83	270.08	292.86	259.84	316	357.50

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

irrespective of different grades 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 and thus enables faster drug release. It is also demonstrated that HPMC of higher viscosity grades swells to greater extent and has greater intrinsic water uptake property than that of the lower viscosity grades. Also it is investigated that in both the drugs the same polymer combinations shows the similar pattern of drug release.

Table 7: Dissolution Parameters of Different Formulations.

Formulation Code	Release at 12 hr.	N	Degree of Swelling (%)	Percent of water uptake
C1	97.14	0.512	262.5	1312.5
C2	84.87	0.461	292.13	772.50
C3	75.6	0.452	344.44	602.78
D1	104.6	0.559	315.00	1237.5
D2	103.33	0.555	292.13	735.42
D3	86.6	0.467	344.44	527.78
E1	93.65	0.516	262.30	1333.33
E2	75.59	0.452	320.00	833.33
E3	64.1	0.439	354.17	590.28
F1	96.14	0.502	258.33	1291.67
F2	83.86	0.451	285.83	756.25
F3	74.5	0.442	336.51	588.89
G1	103.5	0.548	245.83	1212.50
G2	102.2	0.545	270.08	725.00
G3	85.5	0.456	292.86	513.89
H1	93.6	0.506	259.84	1320.83
H2	74.6	0.442	316	822.92
H3	64.1	0.439	357.50	595.83



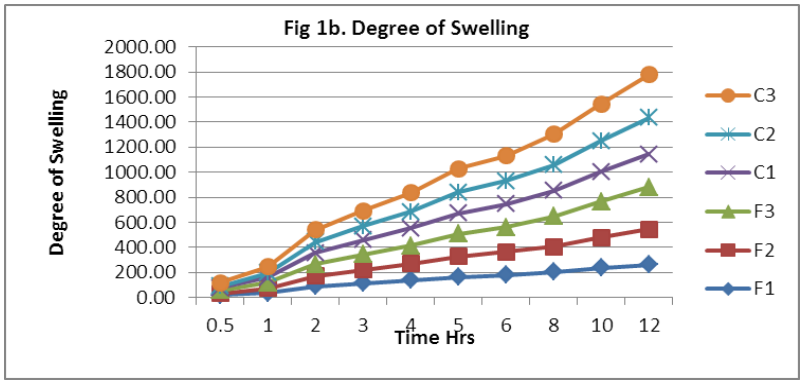


Fig 1b. Degree of Swelling
Degree of Swelling
2000.00
1800.00
1600.00
1400.00
1200.00
1000.00
800.00
600.00
400.00
200.00
0.00
0.5 1 2 3 4 5 6 8 10 12
Time Hrs
C3
C2
C1
F3
F2
F1

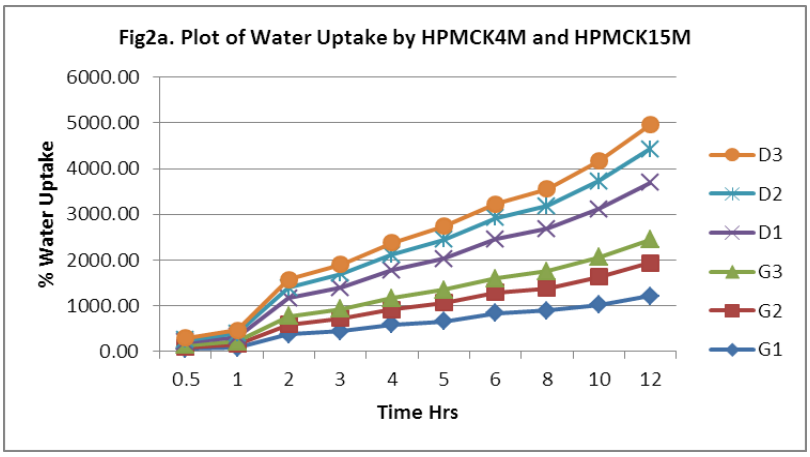


Fig2a. Plot of Water Uptake by HPMCK4M and HPMCK15M
% Water Uptake
6000.00
5000.00
4000.00
3000.00
2000.00
1000.00
0.00
0.5 1 2 3 4 5 6 8 10 12
Time Hrs
D3
D2
D1
G3
G2
G1

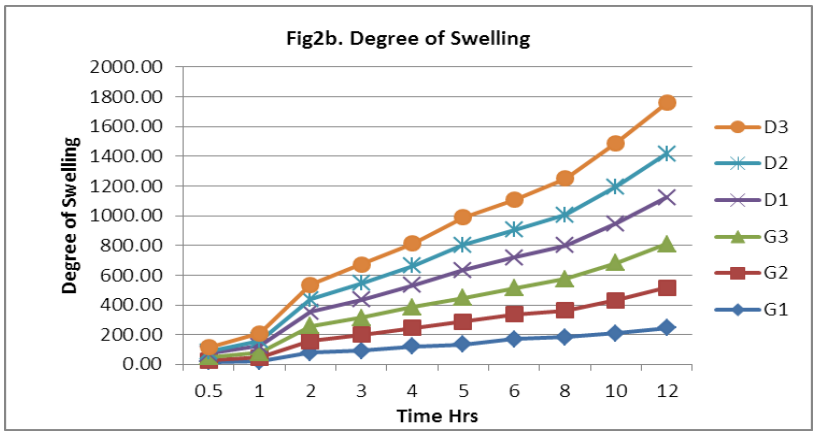


Fig2b. Degree of Swelling
Degree of Swelling
2000.00
1800.00
1600.00
1400.00
1200.00
1000.00
800.00
600.00
400.00
200.00
0.00
0.5 1 2 3 4 5 6 8 10 12
Time Hrs
D3
D2
D1
G3
G2
G1

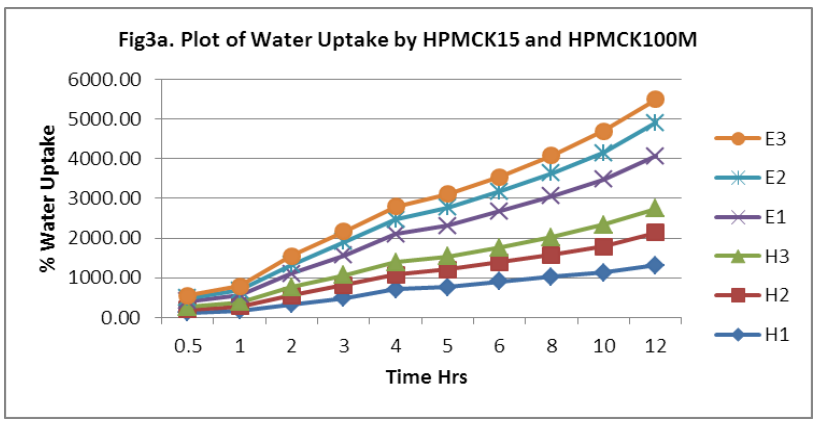
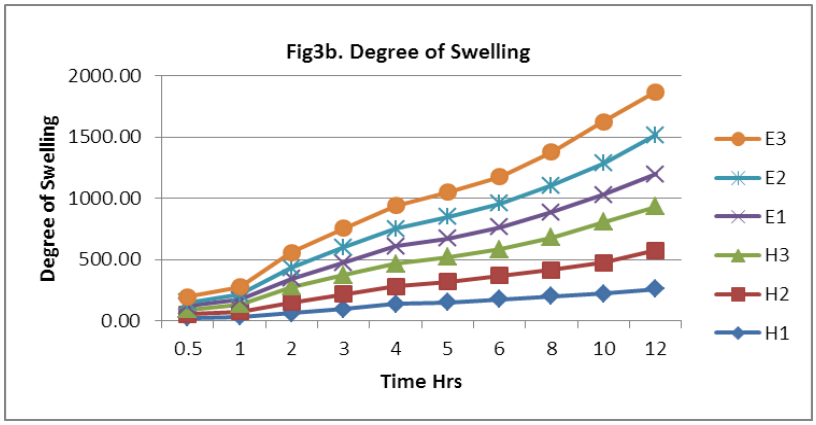


Fig3a. Plot of Water Uptake by HPMCK15 and HPMCK100M
% Water Uptake
6000.00
5000.00
4000.00
3000.00
2000.00
1000.00
0.00
0.5 1 2 3 4 5 6 8 10 12
Time Hrs
E3
E2
E1
H3
H2
H1



CONCLUSION

Swelling studies reveals an inverse relationship between swelling effect and drug release pattern from both the drugs matrices using the same polymer combinations. Comparison studies shows almost similar swelling effect and drug release pattern from matrices containing different drugs and same polymer combinations. Further, the rational combination of different grades of polymer can be used satisfactorily to regulate the release of different drugs in such matrices.

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