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Synthesis, Characterization and Evaluation of Effect of Chemical Modification of Hydroxypropyl Methylcellulose on Drug Release

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ABSTRACT

A novel polymer, hydroxypropyl methylcellulose (HPMC) chemically modified by reacting with maleic anhydride was synthesized. FTIR and NMR spectroscopy, DSC analysis and determination of physicochemical property like viscosity were used to confirm the formation of novel polymer. Ibuprofen, paracetamol and diclofenac sodium matrix tablets were prepared employing HPMC and novel modified HPMC to evaluate the effect of chemical modification on drug release properties of HPMC. Drug release was found to be increased from modified HPMC matrices and unlike HPMC, release mechanism was found to be due to polymer erosion. Thus, it can be concluded that biocompatible chemical modifications of polymers could make better options accessible for specific formulation objectives.

Keywords: HPMC, chemically modified HPMC, drug release, matrix tablets, polymer erosion.

INTRODUCTION

Hydrophilic matrix systems are widely used for modified drug release because of its simplicity in manufacture. In such systems, the drug release is controlled by a combination of several physical processes which include diffusion, polymer swelling, erosion and dissolution [1-3]. The penetration of water through the tablet and the resultant drug dissolution and diffusion primarily depends on the swellability of the polymer [4]. Polymer swellability, erosion control, and the drug release rate, all depend on the polymer molecular weight, degree of substitution, and the polymer concentration [5-7].

Swelling controlled release systems consist of a drug molecularly dispersed or dissolved in a polymer matrix at low or high concentrations. As water penetrates the polymer, swelling occurs and a thin layer of polymer in the rubbery state is formed. Drug diffusion through this gel layer is

relatively fast. Drug delivery from such systems is governed by the gel layer thickness. During drug delivery as swelling and dissolution compete, the gel layer thickness first increases due to swelling, then remains constant due to synchronization of swelling, drug diffusion, and dissolution, and finally decreases as dissolution takes over [8-14].

The polymer dissolution in a solvent is an important phenomenon in a variety of applications. In controlled release applications of polymers, a solute is dispersed or molecularly dissolved in a polymer phase. The release process can be controlled either by solvent diffusion or by polymer dissolution [15, 16]. Characterization of polymer dissolution has been carried out by various scientists and different mechanisms and mathematical models have been proposed [17-21].

For the formulation of an efficient hydrophilic system, one must select a polymer that will wet, hydrate, and swell to form a gelatinous layer fast enough to prevent the disintegration of the tablet and to protect the interior of the tablet content from dissolving during the initial wetting and hydration phases. For this purpose, various types of cellulosic derivatives and their combinations have been extensively used in the preparation of matrix tablets. Hydroxypropyl methylcellulose is the dominant hydrophilic carrier material used for the preparation of oral controlled drug delivery systems. One of its most important characteristics is the high swellability, which has a significant effect on the release kinetics of a drug. Upon contact with a dissolution medium, water or biological fluid diffuses into the tablet, resulting in polymer chain relaxation with volume expansion. The drug then diffuses out of the device [22, 23].

Modulation of polymer swelling in controlling the drug release is a novel concept [24, 25]. A lot of work has been carried out by various scientists on the modification of cellulosic derivatives and the effect of modification on polymer swelling and drug release has been observed [26-30].
In the present investigation, an attempt has been made to chemically modify hydroxypropyl methylcellulose by substituting some of the hydroxyl groups of it with a biocompatible acid derivative, maleic anhydride for modifying the swelling characteristics. The prime objective for the work was to obtain chemically modified HPMC wherein the mechanism of release is more due to erosion than swelling and diffusion.

MATERIALS AND METHODS

Materials

HPMC K4M was supplied by Lupin Pharmaceuticals, (Goa, India) as the gift sample. Maleic anhydride was procured from Rajesh chemicals, (Mumbai, India). Polyvinyl pyrrolidone K30 (PVP K30) and mannitol were procured from Loba Chemie, (Mumbai, India). Ibuprofen and paracetamol were supplied by Mediorals Pvt. Ltd., (Satara, India) as the gift sample, whereas diclofenac sodium was supplied by Sun and Kingly Pharma Pvt. Ltd., (Satara, India) as the gift sample. All the other ingredients used were of analytical grade.

Methods

Modification of hydroxypropyl methylcellulose with maleic anhydride

Three different ratios of HPMC to maleic anhydride were computed on the basis of the molecular weight and the number of free hydroxyl groups present in each monomer unit of HPMC. Initially required quantity of maleic anhydride was dissolved in water followed by addition of required quantity of HPMC slowly with constant stirring to avoid aggregation. The entire system was heated at 40 ^{0}C for 24 h (fig.1). After the completion of reaction; the novel modified polymer was spray dried (Labultima, 2220, Mumbai, India) and passed through a #30

mesh screen. Physicochemical characterization of the modified polymers led to the selection of one modified polymer (1:1 substituted) for evaluation.

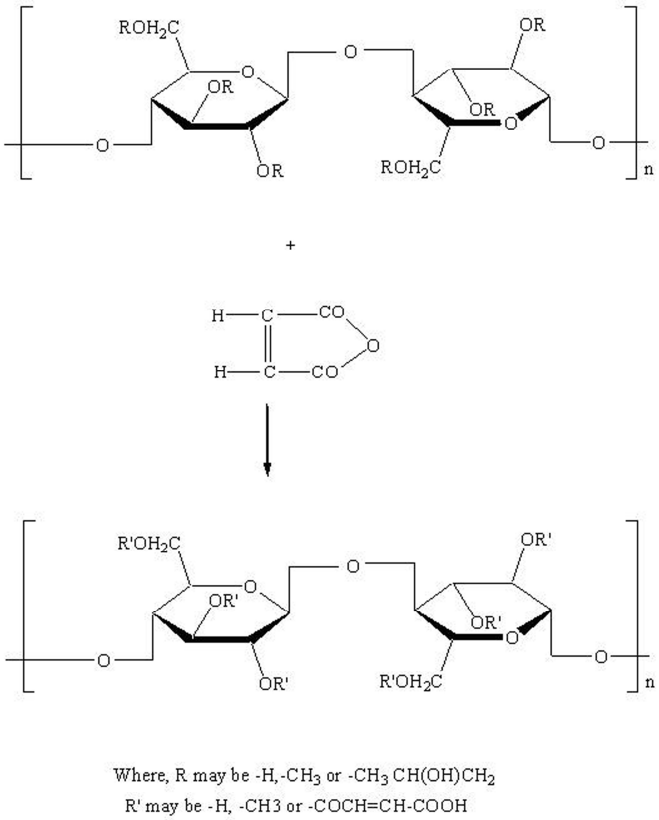

Figure 1: Scheme of chemical modification of HPMC K4M with maleic anhydride

FTIR spectroscopy

FTIR spectra of HPMC and modified HPMC were recorded using FTIR spectrophotometer (Jasco 4100, Japan) between wavelengths of 400-4000 cm^{-1}.

NMR spectroscopy

Nuclear magnetic resonance (NMR) analysis was done to characterize the modified hydroxypropyl methylcellulose using a 300 MHz NMR and ^{1}H NMR spectrum was recorded on a Varian Mercury 300 MHz spectrometer using deutorated chloroform as the solvent.

Differential Scanning Calorimetric (DSC) Studies

Thermal analysis of unmodified and chemically modified HPMC was carried out using Mettler Toledo 821^{e} DSC (Switzerland) thermal analyzer. The samples (1-2 mg) were hermetically sealed in an aluminum pan and heated at a constant rate of 10 ^{0}C per minute, over a temperature range of 50 ^{0}C- 500 ^{0}C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 20 ml/min.

Viscosity study

The viscosity of varying concentrations (0.1-0.5%) of HPMC and HPMC modified with maleic anhydride solutions was determined at 25 ^{0}C using LVDV 2+ Pro viscometer (Brookfield, USA) at a shear rate of 100.

Physical properties of granules and matrix tablet preparation

Granules of paracetamol, ibuprofen and diclofenac sodium were prepared using the wet granulation method. Each formulation contained 100 mg of active drug and 50 mg of HPMC and modified HPMC. Thus the drug to polymer ratio was kept at 2:1 (w/w). The formulae for all the formulations are as given in table 1. Active drug, mannitol, and polymer were passed through a # 12 mesh separately. All the ingredients were weighed accurately and added in a blender in ascending order of their weight and blended for 30 min. The blend was transferred to a glass mortar and granulated with 6% PVP K30 in isopropyl alcohol by trituration with a pestle. The granules were dried in hot air oven (Labhosp, India) at 40 ^{0}C for 30 min and passed through a # 30 mesh screen. Magnesium stearate and talc were individually passed through a # 60 mesh screen and added to the granules and blended for 5 min in a blender.

Table 1: Matrix tablets of ibuprofen, diclofenac sodium and paracetamol using HPMC K4M and novel chemically modified HPMC K4M

Sr. No.	Name of Ingredient	Formulation					
		HPM1	HPM2	HPM3	HPM4	HPM5	HPM6
1	Ibuprofen	100	100	--	--	--	--
2	Diclofenac Sodium	--	--	100	100	--	--
3	Paracetamol	--	--	--	--	100	100
4	Chemically modified HPMC	50		50		50	
5	HPMC K4M		50		50		50
6	Polyvinyl Pyrrolidone (PVP K30)	15	15	15	15	15	15
7	Mannitol	80	80	80	80	80	80
8	Talc	2.5	2.5	2.5	2.5	2.5	2.5
9	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Total weight		250	250	250	250	250	250

Formula for one tablet is shown in table. All ingredients are in mg.

Physical properties of granules such as bulk density, tapped density, percent compressibility, Hausner's ratio, and angle of repose were determined using bulk density test apparatus (Electrolab, India). Percent compressibility and Hausner's ratio were calculated using the formula

$$\% \text{ Compressibility} = \{(D_t - D_b)/D_t\} * 100 \quad \text{---------- Eq. 1}$$

$$\text{Hausner's ratio} = D_t/D_b \quad \text{---------- Eq.2}$$

Where D_t and D_b are tapped density and bulk density respectively.

The tablets were compacted using 10 mm concave punches on a single punch tablet machine (Cadmach, India) to get the tablets of 250 mg weight. A batch of 100 tablets was prepared for all the formulations.

Characterization of the tablets

Physical parameters

Tablets from all the formulations were evaluated for various parameters such as diameter (Vernier caliper), thickness (Micrometer screw guage), hardness (Pfizer hardness tester), weight variation test and friability (Roche friabilator).

Swelling study

The swelling study was performed as a function of water uptake by tablets prepared using HPMC and modified HPMC. The tablets were placed in separate baskets of dissolution apparatus containing purified water. Tablets were removed and weighed on a digital balance (Adventure, Ohaus Corp., USA) at the regular interval of 1 h. The amount of water uptake was compared from the weight difference.

In vitro dissolution study

In vitro dissolution studies were conducted using USP XXIII type II dissolution apparatus (TDT 08 L, Electrolab, India) in 900 ml of purified water at 37 ± 0.5 ^{0}C and at a paddle speed of 100 rpm. For ibuprofen the dissolution medium used was phosphate buffer pH 7.2. The study was carried out in triplicate. Aliquots of dissolution medium were withdrawn at specified time intervals, filtered through 0.45 µm filter and were analyzed spectrophotometrically for ibuprofen, diclofenac sodium, and paracetamol at their respective λ_{max} of 221, 276, and 243 nm.

RESULTS AND DISCUSSION

Characterization of the novel modified HPMC

FTIR spectroscopy

A relatively characteristic and sharp peak close to 1450 indicates the introduction of ethylene moiety in the chemically modified HPMC and thus confirms the acylation of some free hydroxyl groups in HPMC by maleic anhydride (fig.2)

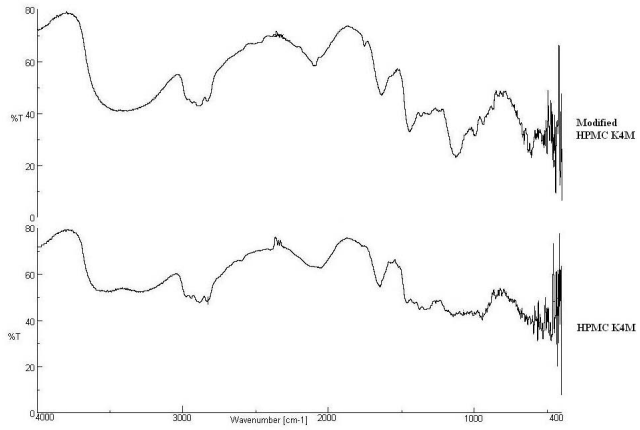

Figure 2: FTIR spectra of hydroxypropyl methylcellulose k 4M and novel chemically modified hydroxypropyl methylcellulose K 4M with maleic anhydride.

NMR spectroscopy

The relative increase in the number of protons in the region between δ = 3.4-4.8 and especially in the region close to δ = 4.6 indicates that the 2-butendioic acyl moiety has been substituted in the HPMC (fig. 3a and 3b).

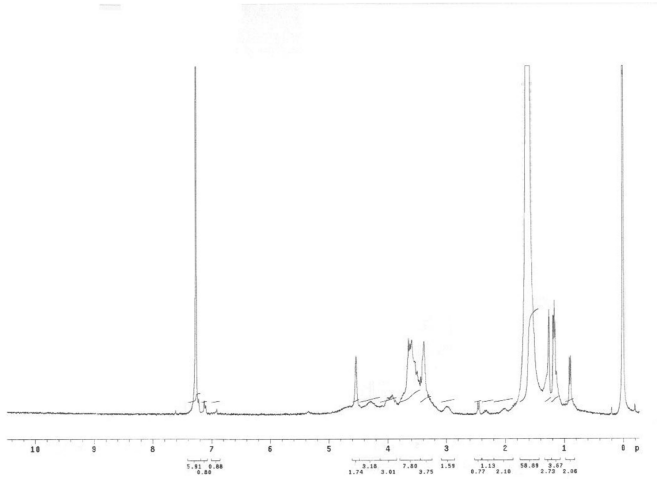

Figure 3a: ^{1}H NMR spectrum of HPMC

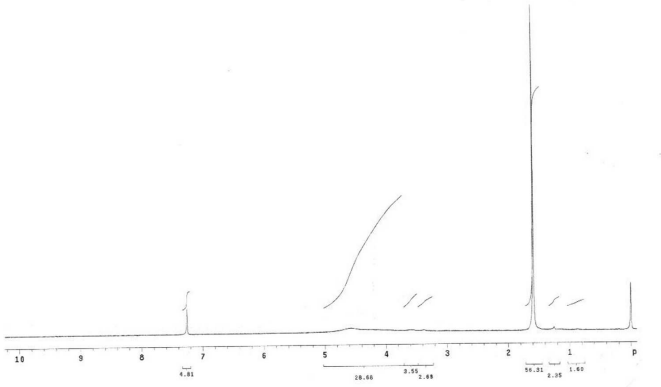

Figure 3b: ^{1}H NMR spectrum of chemically modified HPMC

Differential Scanning Calorimetric analysis:

As both hydroxypropyl methylcellulose and modified hydroxypropyl methylcellulose do not have exact melting points and char when heated, no sharp endothermic peaks were observed for both of them indicting no exact melting points. A broad endothermic bend in thermogram 4a from 40-110 ^{0}C for hydroxypropyl methylcellulose and from 40-110 ^{0}C in thermogram 4b for modified hydroxypropyl methylcellulose can plausibly be attributable to the vaporization of the moisture present in the samples. A shallow endothermic peak from 130-150 ^{0}C in the thermogram of modified hydroxypropyl methylcellulose may plausibly be attributable to the glass transition temperature of the polymer.

Viscosity

Viscosity of both the polymers was found to be increased as the function of concentration (w/w). Viscosity of HPMC was found to be decreased after its chemical modification (esterification) with maleic anhydride. The reduction in the viscosity of modified HPMC was might be due to its increased solubility and decreased swellability. The data for the viscosity is given in table 2, and fig.5.

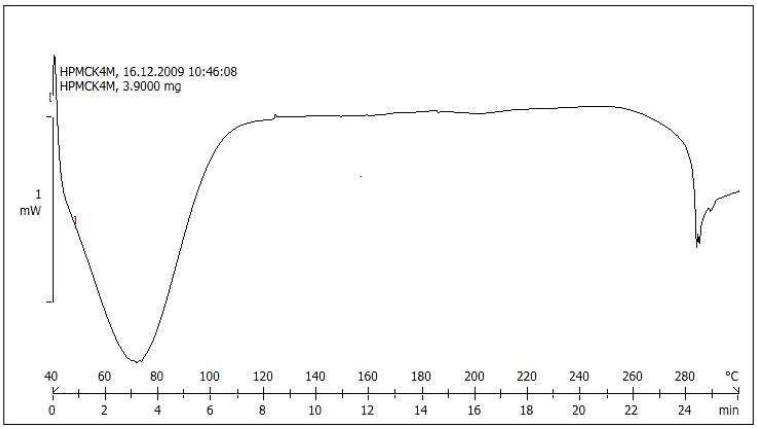

Figure 4a: DSC thermogram of HPMC K4M

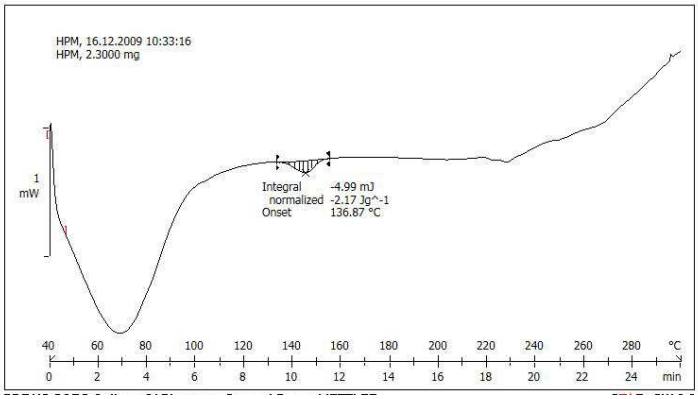

Figure 4b: DSC thermogram of modified HPMC K4M

Table 2: Viscosity study of HPMC and modified HPMC

Concentration (%)	HPMC K4M	Modified HPMC
0.1	126.3	94
0.2	160	104
0.3	202	112
0.4	289	126
0.5	456	164

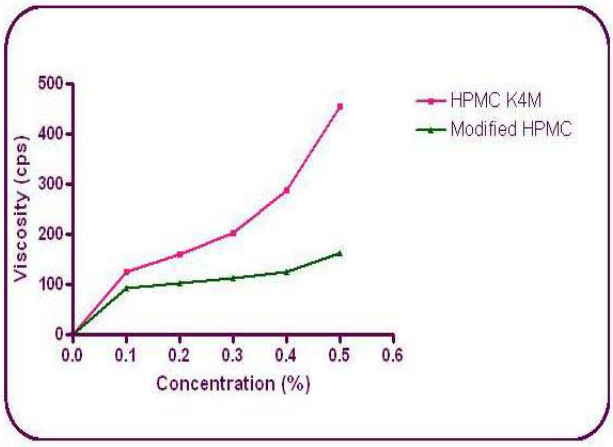

Figure 5: Viscosity of HPMC and modified HPMC

Physical properties of the granules

The granules of all the batches exhibited good flow property (angle of repose $<30^0$). Bulk density was found to be between 0.303-0.385 g/cc while the tapped density was found to be in the range of 0.324-0.442 g/cc. From density data percent compressibility (Carr's index) and Hausner ratio were calculated and were found to be between 8.31- 14.28 and 1.10-1.17 respectively. All these properties indicate good flow property of granules, uniform die fill and good compression characteristics. The data for physical properties of the granules is given in table 3.

Table 3: Physical Properties of granules

Formulation	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index	Hausner's Ratio	Angle of Repose (^{0})
HPM1	0.307 ± 0.009	0.332 ± 0.020	9.99 ± 1.45	1.11 ± 0.02	28.17 ± 1.21
HPM2	0.311 ± .0156	0.360 ± 0.031	8.31 ± 1.07	1.16 ± 0.04	25.24 ± 0.52
HPM3	0.318 ± 0.022	0.388 ± 0.017	14.28 ± 2.40	1.17 ± 0.04	25.48 ± 1.84
HPM4	0.385 ± 0.015	0.442 ± 0.019	12.79 ± 0.47	1.14 ± 0.01	22.8 ± 0.45
HPM5	0.330 ± 0.017	0.363 ± 0.021	9.19 ± 1.54	1.10 ± 0.02	27.06 ± 1.19
HPM6	0.303 ± 0.008	0.324 ± 0.010	10.52 ± 1.24	1.12 ± 0.02	24.26 ± 0.63

All Values are expressed as mean± S.D. n =3

Physical parameters of the tablets

Tablets prepared by wet granulation method were evaluated for various official and non official tests. As the granules were free flowing, there was uniform die fill and the tablets of uniform weight with acceptable variation as per I.P. specification (<5%) were obtained. Thickness of the tablets was found to be in the range of 3.33-3.83 mm. diameter was observed in the range of 10.03- 10.16 mm. Hardness was observed in the range of 5.83-6.5 kg/cm^2. Percent friability for all the formulations was found to be less than 1%., which is an indication of good mechanical strength of tablets that can withstand the shocks during transportation or shipping. The values obtained for tablet dimensions, hardness and percent friability are as given in table 4. Thus the chemical modification of HPMC has added some advantage with respect to the mechanism of drug release and at the same time the other desirable properties of the HPMC have been retained.

Table 4: Physical parameters of the tablets

Formulation	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation Test †
HPM1	3.33 ± 0.29	10.1 ± 0.1	6.17 ± 0.29	0.42 ± 0.17	Passes
HPM2	3.67 ± 0.29	10.16 ± 0.06	6 ± 0.5	0.3 ± 0.22	Passes
HPM3	3.33 ± 0.58	10.07 ± 0.06	5.83 ± 0.29	0.52 ± 0.09	Passes
HPM4	3.83 ± 0.29	10.03 ± 0.06	6.5 ± 0.5	0.37 ± 0.10	Passes
HPM5	3.67 ± 0.58	10.13 ± 0.12	6.33 ± 0.58	0.36 ± 0.07	Passes
HPM6	3.33 ± 0.29	10.03 ± 0.06	6.33 ± 0.76	.43 ± 0.31	Passes

Values shown in the figure are the mean of 3 determinations ± SD. † indicates n = 20

Swelling study

It was found that there was swelling initially for 1h, but there onwards erosion dominated in the tablets prepared with modified HPMC (HPM1, HPM3 and HPM5). In formulations containing HPMC, higher swelling was found and the tablets were found to be swelling for 5 h (formulation HPM4, and HPM6) and for 6 h (formulation HPM2) and later erosion of the

polymer matrices started. The earlier but slow erosion of the matrix tablets prepared with modified HPMC as compared to HPMC matrix tablets may be due decrease in the uniformity of the repetitive monomer units of modified polymer due to limited acylation of maleic anhydride. This irregularity in the structure could be responsible for loss of film forming ability and hence swellability while the substitution of hydroxyl group by a relatively non-polar and sterically larger 2-butendioyl moiety may be responsible for slow rate of erosion observed. The data for swelling and erosion of tablets is given in table 5, and fig. 6.

Table 5: Swelling study of tablets

Time (h)	Formulation					
	HPM1	HPM2	HPM3	HPM4	HPM5	HPM6
0	248.13±1.14	247.33±1.40	247.47±2.21	247.53±1.68	247.77±1.65	247.87±1.29
1	456.37±3.98	474.73±3.98	419.37±2.60	435.33±2.91	455.1±2.49	446.17±2.70
2	409.53±3.43	513.83±3.04	388.40±3.54	475.23±2.47	401.23±2.01	484.77±2.50
3	337.4±2.68	527.13±3.52	299.85±2.05	504.9±2.36	316.33±1.55	505.07±2.61
4	271.4± 3.25	558.13±3.68	248.53±2.85	524.3±2.36	254.3±2.07	524.87±3.05
5	202.9±3.86	569.80±2.75	178.17±3.65	587.83±3.46	187.07±2.36	592.03±5.57
6	148.5±3.15	603.7±2.07	135.8±3.07	502.17±2.32	136.83±2.29	505.87±3.14
7	58.03 ± 3.20	500.73±2.99	23.93±2.93	473.7±2.85	46.4±2.43	486.83±3.12
8	14.23 ± 1.78	307.67±3.16	15.37±2.92	294.1±2.40	9.53±2.80	304.87±2.30

Values shown in the figure are the mean of 3 determinations ± SD.

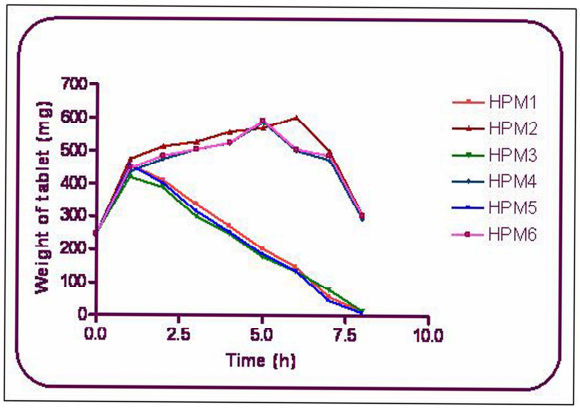

Figure 6: Swelling study of tablets

In vitro dissolution study

For all the designed formulations, the drug release at the end of 8 h was found to be varied. The drug release was found to be increased from the formulations prepared with modified HPMC (formulations HPM1, HPM3 and HPM5). An increase of 13-20% in drug release was found from modified HPMC matrix tablets as compared to HPMC matrix tablets. The data for drug release is given in table 6, and fig.7.

This increase in the drug release can be attributed to a marked reduction in viscosity of modified HPMC as well as to the change in the polarity and steric properties of HPMC. The relatively hydrophobic and bulkier group replacing H- of the hydroxyl group of HPMC could be responsible for decrease in the duration of swelling observed. The decrease in the number of free hydroxyl groups as well as physical masking of some adjacent hydroxyl groups due to the hydrophobic bulkier substituent could be responsible for decreased swelling. The disruption of the systematic arrangement of the monomers in HPMC due to a dissimilar substituent could also be a contributing factor. The hydrophobic linear carbon chain along with the terminal carbohydroxyl group may be responsible for retarding erosion rate due to limited access to water molecules. Release of drugs at a consistent rate attributed to erosion could be responsible for a net increase in release at the end of 8 h.

Table 6: In Vitro dissolution profile of tablets

Time (h)	Formulation					
	HPM1	**HPM2**	**HPM3**	**HPM4**	**HPM5**	**HPM6**
0	0 ± 0	0± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	32.45±1.14	24.19±1.21	33.39±2.47	26.78 ± 0.60	38.26 ± 2.12	33.11 ± 1.22
2	44.64±1.20	31.47±1.19	45.48±0.51	30.40 ± 0.23	48.94 ± 1.82	44.36 ± 0.98
3	60.85±1.22	39.52±1.25	54.41±3.47	37.11 ± 1.77	61.05 ± 1.10	52.03 ± 1.35
4	68.93±1.07	45.89±1.47	64.80±3.62	50.52 ± 2.67	73.55 ± 1.31	57.76 ± 0.70
5	75.34±0.63	52.25±0.35	83.40±2.30	60.48 ± 2.99	82.74 ± 1.78	62.12 ± 1.70
6	81.13±1.06	59.34±0.93	87.35±2.19	69.77 ± 1.45	90.03 ± 1.14	68.62 ± 1.78
7	93.28±1.22	63.48±1.19	87.51±2.58	76.83 ± 2.71	95.68 ± 1.01	72.04 ± 1.33
8	99.06±1.18	71.20±1.0	98.77±1.92	85.36 ± 2.25	100.15±1.66	80.65 ± 2.08

Values shown in the figure are the mean of 3 determinations ± SD.

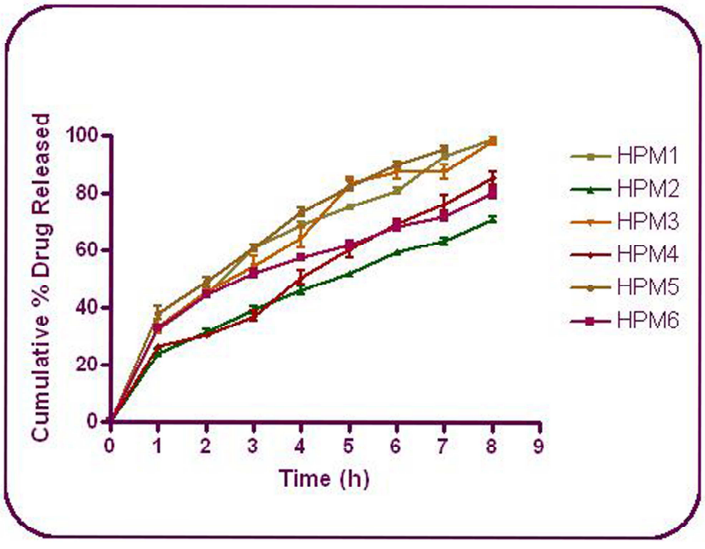

Figure 7: In Vitro dissolution profile of tablets

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REFERENCES

[1] T. Nagai, F. Sekigawa , N. Hoshi, *Drug Dev. Pharm. Sci*., **1989**; 36, 81.
[2] V. Mahaguna, R. Talbert, J. Peters, S. Adams, T. Reynolds, F. Lam, III R Williams, *Eur. J. Pharm. Biopharm.*, **2003**, 56,461.
[3] J. Siepmann, H. Kranz, R. Bodmeier, N.A. Peppas, *Pharm. Res*., **1999**, 146,1748.
[4] L.C. Wan, K.P. Prasad, *Int. J. Pharm*.,**1989**, 50,147.
[5] C. Kim, *Drug Dev.Ind. Pharm*., **1998**,24, 645.
[6] K. Mitchell, J.L. Ford, D.J. Armstrong, P.N.C. Elliot, J.E. Hogan, C. Rostron, *Int. J. Pharm.*,**1993**, 100,143.
[7] N. Shah, G. Zhang, V. Apelian, F. Zeng, M. H. Infield, W.A. Malick, *Pharm. Res.*,**1993**,10,1693.
[8] P. Colombo, *Adv. Drug. Del. Rev*.,**1993**,11, 37.
[9] [9] J. Siepmann, K. Poudal, M. Sriwongjanya, N.A. Peppas, R. Bodmeier, *J. Pharm. Sci.*, **1999**, 88(1), 65.
[10] B. Narsimhan, N.A. Peppas, *J.Pharm. Sci.*, **1997**,86 (3), 297.
[11] P. Colombo, P.L. Cattelani, N.A. Peppas, L. Maggi, U. Conte, *Int. J. Pharm*.,**1992**, 88, 99.
[12] P. Colombo, R. Bettini, G. Massimo, P.L. Cattelani, P. Santi, N.A. Peppas, *J. Pharm. Sci*.,**1997,** 86(3), 297.
[13] E.E.Personage, N.A. Peppas, P.I. Lee,. *J. Vac. Sci. Technol*., **1987**,135,538.
[14] R.K. Drummond, G.L.Boydston, N.A. Peppas, *J. Appl. Polym. Sci*.**1990**, 39, 2267
[15] P. Colombo, A. Gazzaniga, C. Caramella, U. Conte, A.L. Manna, *Acta. Pharm. Technol*., **1987**,33(1),15.
[16] U. Conte, P. Colombo, A.Gazzaniga, M.E. Sangalli, A.L. Manna, *Biomat.*, **1988**; 9, 489.
[17] A.C. Ouano, J.A. Carothers, *Polym. Eng. Sci*., **1980**,20, 160.
[18] E.E. Personage, N.A. Peppas, *Br. Polym. J*., **1987**,19, 469.
[19] W.J. Cooper, P.D. Krasicky, F. Rodriguez, *Polym*., **1985**, 26,1069.
[20] A.C. Ouano, *Polym. Eng. Sci*.,**1978**,18, 306..
[21] H.S. Harland, A. Gazzaniga, M.E. Sangalli, P. Colombo, N.A. Peppas, *Pharm. Res.*, **1988**; 5, 466.
[22] B. Narsimhan, N.A. Peppas, *J. Polym. Sci. Polym. Phys*.,**1996**, 34,947.
[23] S.K. Mallapragada, N.A. Peppas, *J. Polym. Sci.Polym. Phys.*,**1996**, 34, 1339.
[24] N.A. Peppas, R. Gurny, E. Doelker, P. Buri, *J. Membr. Sci*.,**1980**, 7, 241.
[25] R. Morita, R. Honda, Y. Takahashi, *J. Control. Rel*.,**2000**, 63,297.
[26] M. Kojim, H. Nakagami, *J. Control. Rel*., **2002**, 82, 335.
[27] Y. Hirakawa, E P Patent E P 0671, 167, A1 13 September.
[28] C.R. Gardner, U S Patent 9, 737, 641, 16 October.
[29] Y. Hirakawa, E P Patent E P 0671, 168, B1 13 September.
[30] J. Chen, U S Patent 9, 850, 019, 12 November.