



**HYDROXYPROPYL METHYL CELLULOSE BASED HYDROGELS AS AN ORAL
CONTROLLED DRUG DELIVERY SYSTEM; DESIGN AND EVALUATION**

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ABSTRACT

The basic objective of study was to develop and evaluate HPMC-co-AA-HEMA hydrogels as an oral controlled release drug delivery system.

By using technique free radical solution polymerization pH responsive hydrogels were formed. N, N-methylene bis acrylamide (MBA) and potassium persulphate (KPS) were used as cross linker and as initiator respectively. Hydrogels were evaluated by FTIR, TGA & DSC, SEM and XRD. Swelling ratios, percent equilibrium swelling, percent gel content (%g_c), (%P) percent porosity, *in vitro* drug release and pharmacokinetic evaluation were performed.

Swelling ratio was increased by increasing HPMC and AA concentration from 4.127 % to 4.500 % and 5.000 % to 5.784 % (pH 1.2) and 42.618 % to 49.011 % and 47.436 % to 62.270 % (pH 7.4) respectively. While HEMA and MBA showed decreased swelling ratio with increasing weight ratio. %g_c and %P ranges from 82.844 % to 94.413 % and 12.911 % to 38.934 % respectively with different weight ratios of components. *In vitro* release was increased by increasing AA from 75.80 % to 82.82 % while it was decreased by increasing HEMA (67.46 % to 59.64 %) and MBA concentration (60.58 % to 48.37 %).

HPMC-co-AA-co-HEMA hydrogels could successfully be used as an oral controlled release drug delivery system.

Keywords: Hydrogel, *In vitro* drug release, *In vivo* evaluation, Polymer, Controlled release

INTRODUCTION

Polymers have become marvelous icon of interest in many areas, such as the pharmaceutical industry, therapeutic innovation and others. Spreads in polymer science have open new gates to expansion of novel drug delivery systems [1]. Advances in polymers impart unique properties of interest to carrier system. Both natural and synthetic polymers are stand-in an auspicious tool for drug delivery, especially in oral administration therapeutic drugs having challenging issues like poor absorption or short half-life etc [2]. Because of unique properties like compatibility, degradation and nontoxic behavior of biocomposite polymers, these are becoming a tool of tremendous interest for controlled drug delivery. By suitable physical or chemical modification in polymers, properties of interest can be attained or enhanced [3].

This polymeric area invites various modifications in properties of polymer viz. blending, grafting and curing to achieve targeted action. Among these graft copolymers have been extensively used to formulate a number of controlled release systems like hydrogels, microspheres or matrix tablets etc. For oral controlled release drug delivery systems hydrophilic gel forming polymeric systems are in extensive use to

acquire an anticipated drug release profile, cost effectiveness and broad regulatory acceptance [4]. Hydroxy propylmethyl cellulose (HPMC) is a hydrophilic polymers attaining prominence in this regard as these approaches anticipated attributes of an ideal polymer. More over both hydrophilic and hydrophobic variants with different viscosity grades are also available making them more and more suitable candidate for desired release profile[5].

The study was planned to appraise graft polymeric carrier systems for sustained or controlled delivery of potassium channel opener “Nicorandil”. With an elimination half-life of almost 1 hour it is a likely agent for development of controlled release formulations for treatment of hypertension and angina pectoris. To lessen frequency of administration and to improve patient compliance once daily sustained/controlled release formulation of nicorandil was anticipated.

MATERIALS AND METHODS

Materials

Acrylic Acid (99 %) was purchase from Sigma Aldrich-Netherlands, (Hydroxypropyl) methyl cellulose (80-120cP) was purchased from Sigma Aldrich-USA and 2-Hydroxyethyl methacrylate (97 %) was purchased from

Sigma Aldrich-Germany. N, N methylene-bis-] acrylamide (98 %) purchased from Fluka-Switzerland. Potassium persulphate (99%) purchased from Anala R, BDH-England, Potassium dihydrogen phosphate(98-100 %) Merk- Germany, Ethanol Absolute Merk- Germany, Nicorandil (99.8 %) was gifted by Getz Pharma-Pakistan. Acetonitrile HPLC grade was purchased from Wilson Pharmaceuticals, Methanol HPLC grade was purchased from Merck-Germany. Heparin was purchased from Medicare Pharma-Malaysia.

METHODS

Preparation of hydrogel by free radical solution polymerization

Hydrogels were prepared by free radical solution polymerization i.e. a physical cross linking method. Hydroxypropyl methyl cellulose (HPMC) solution was maintained on water bath at 70 °C with stirring at 300 rpm. Solution of initiator potassium persulphate (KPS) was added in drop wise fashion to above solution with continue stirring at 300 rpm and 70 °C for 35min. The mixture was cooled to room temperature. Calculated amount of 2-hydroxyethyl methacrylate (HEMA) solution and acrylic acid (AA) was added to mixture at room temperature and stirred at 300 rpm for 1-2min. N, N, methylen-bis-acrylamide (MBA) solution was

also added drop wise to above mixture at ambient temperature and whole mixture was stirred at room temperature for 2-3min. Final solution was poured into glass test tube and placed in water bath at 80 °C for 3 hours. After that test tube was broken and formulated hydrogel was cut into small discs of 4mm thickness with sharp cutter. To dewater formulation these discs were first washed with distilled water then placed in ethanol:water (50 : 50) solution for 24 hrs. Discs were oven dried at 46 °C till drying equilibrium. These discs were subjected to further *in vitro* and *in vivo* studies. Various weight ratios were used as shown in table 1.

Characterization

Swelling studies

All formulations were subjected to swelling studies at pH 1.2, 5.8 and 7.4 till swelling equilibrium, at predefined time points. For this purpose weighed disc of formulation was soaked in 100 ml phosphate buffer of pH 1.2, 5.8 and 7.4. At predefined time points discs were blot dried and weight by using analytical weight balance.

Dynamic swelling and equilibrium swelling ratios of all formulations were determined by using following equations.

$$q = \frac{W_h}{W_d} \quad \dots (1)$$

Where “q” is dynamic swelling

W_h shows swollen gel's weight at time t

W_d shows initial weight of dried hydrogel disc [6]

Equilibrium swelling measurements (%ES)

The swelling measurement was carried out until equilibrium weight of gel. Percent equilibrium swelling was calculated by following equation.

$$\% ES = \frac{M_{eq} - M_o}{M_{eq}} \times 100 \quad \dots(2)$$

M_{eq} is mass of swollen gel at equilibrium

M_o is mass of dried gel disc [7]

Percent gel content (%g_c)

Freshly prepared hydrogel disc (3-4 mm) was oven dried at 45 °C until a constant weight (W_o) was obtained. Then extraction was performed for 24 hours with deionized water to wash away non reacted polymer/monomer. The disc was again oven dried at 45 °C until constant weight (W_1) was obtained. By using following formula % gel content was determined.

$$\%g_c = [W_1/W_o] \times 100 \quad \dots(3)$$

Where W_1 is the weight of dry gel after extraction in distilled water and W_o is the initial weight of dry gel [8]

Porosity measurement

Computing fraction of voids volume over total volume between 0 and 1 or in case of percent between 0 to 100 % is called as porosity. Solvent replacement method was used to compute porosity measurement. Dried weighed hydrogel disc (W_d) was immersed in absolute ethanol for 24 hrs (till constant weight). After 24 hrs hydrated hydrogel disc was blot dried to remove excess surface ethanol and weighed by using analytical weight balance (W_h). Percent porosity (%P) was calculated by equation 4.

$$\text{Porosity} = \frac{(W_h - W_d)}{\rho V} \times 100 \quad \dots(4)$$

Where ρ refers to density of absolute ethanol and V is hydrogel volume [9].

Drug loading

Absorption method was used for drug loading to hydrogel disc. 1 % drug solution in phosphate buffer of pH 7.4 was prepared. One disc of each formulation was immersed in 100 ml of 1 % drug solution till swelling equilibrium was reached. After swelling equilibrium was achieved discs were removed from solution, washed out with distilled water to remove surplus surface drug. Then allowed to air dry at room temperature first and then oven dried at 40 °C till drying equilibrium [10]. Drug loaded in discs was determined by following formula given in equation 5.

$$\text{Total drug loaded} = W_L - W_u \quad \dots(5)$$

Where W_L is weight of dried drug loaded disk and W_u is weight of dried unloaded disc [11].

Fourier Transform Infrared (FTIR)

Formulation was subjected to fourier transform infrared analyzer (Bruker, Tensor 27, Germany) at 25 °C to confirm grafting of newly formulated hydrogel.

Thermal Gravimetric Analysis and Differential Scanning Calorimetry (TGA & DSC)

Thermal analysis and differential scanning calorimetry of formulations were performed by sealing prior to test and putting them in aluminum pans. Measurements were achieved

at a rate 10 °C per minute, under nitrogen flow of 25 ml per minute, in temperature range of 20 °C to 900 °C. The standard uncertainty of the sample mass measurement was $\pm 1\%$. Equipment calibration was accomplished with calcium oxalate supplied with instrument [12].

Scanning Electron Microscopy (SEM)

Surface morphology of all combinations of hydrogel formulations was determined by scanning electron microscope (Hitachi, S3400N). Samples were coated with gold by Hummer Sputter Coater [13].

In vitro drug release evaluation

In vitro drug release studies of hydrogel discs loaded with nicorandil was performed according to specifications of United States Pharmacopeia by using USP apparatus II. 900 ml of relevant dissolution medium i.e. 0.1 M HCl pH 1.2 and phosphate buffer pH 7.4 were used. Media was stirred at 50 rpm at 37 °C \pm 0.5 °C. 5 ml of aliquot was drawn at intervals of 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 hour with an automated sample collector T-DT7 Pharmatest Germany, after filtering through sinter filters (10µm). At each interval fresh 5 ml medium was added to preserve volume. Collected samples were diluted up to 50 ml with respective buffer and analyzed at 225 nm using a UV-spectrophotometer PTCF II Pharma Test-Germany. The *in-vitro*

cumulative drug release study was calculated in triplicate and reported as mean [14].

In vivo studies

Six healthy male rabbits were enrolled in study weighing 2 ± 0.5 kg in agreement with standard protocols by the Research and Ethical Committee of Faculty of Pharmacy and Alternative medicine (approval certificate number 105-2014/PREC), The Islamia University of Bahawalpur, Punjab, Pakistan. Single dose study was conducted on animal model (rabbits). Each animal received single dose (6.5 mg/kg) orally with the help of a 3 ml syringe having smoothly cut barrel at needle end in view of avoiding damage to oral mucosa of rabbit [15]. 2 ml blood sample was withdrawn from jugular vein of rabbit by 3 ml syringe. Samples were collected into heparinized centrifuge tubes at zero time before dosing and at intervals of 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after dosing. Collected blood samples were centrifuged at 5000 rpm for 10 minutes. Separated plasma samples were frozen at -70 °C in ultra-low freezer (Sanyo-Japan, maximum -86 °C) until assay [16].

Mobile phase of Water and acetonitrile (75: 25 v/v) was transported at flow rate of 1 mL/min at ambient temperature. Injection volume was 20 µL. Detection was achieved at 256 nm. An HPLC system of Agilent consisted of a pump, a

column (BDS hypersil C₈ 4.6 mm x 250 mm) and UV visible detector used to examine prepared plasma samples. The UV detection of nicorandil was set at 256 nm. Mobile phase consisting of water and acetonitrile (75: 25 v/v) was transported at flow rate of 1 mL/min at ambient temperature. Pharmacokinetic parameters were evaluated by non-compartmental pharmacokinetic approach by using pharmacokinetic software, Kinetica version 4.1.1.

RESULTS

Swelling behavior

Dynamic equilibrium swelling ratios and percent equilibrium swelling (%ES) as depicted in table 1 showed that in acidic medium with lower pK_a less swelling was noted as compared to basic medium with higher pK_a where swelling was greater.

Swelling studies showed that with increasing hydroxypropyl methyl cellulose and acrylic acid content swelling ratio and percent equilibrium swelling were increased while both decreases with increase in cross linker concentration and hydroxyethyl methacrylate concentration.

In vitro drug release studies

Over all in vitro drug release studies followed ascending order with respect to pH as pH is increasing from acidic to basic as given in figure 1.

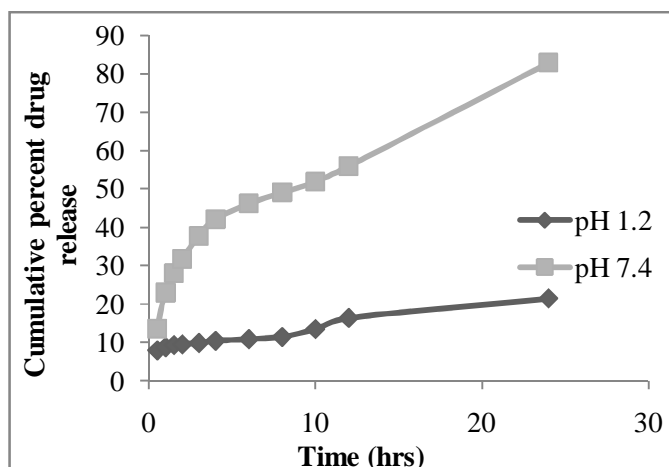


Figure 1 Cumulative percent drug release of HPMC-co-AA-co-HEMA hydrogels

Drug release was greatly affected by varying monomer, polymer and cross linker concentration. At pH 7.4 percent drug release was increased by increasing hydroxyl propyl methyl cellulose and acrylic acid concentration from 69.29 % to 73.38 % and 75.80 % to 82.82 % while it was noted to be decreased by increasing HEMA (67.46 % to 59.64 %) and MBA concentration (60.58 % to 48.37 %).

Percent gel content (%g_c) and %porosity (%P) measurement

Percent gel content (%g_c) and percent porosity (%P) measurements of all formulations covering various concentrations of components computed. Percent gel content ranges from 82.844 % to 94.413 % with different weight ratios. While percent porosity ranges from 12.911 % to 38.934 % with different weight ratios of all components as given in table 2.

Table 1: Composition and comparative swelling ratios of HPMC-co-AA-co-HEMA hydrogels using different concentrations components

Sample Code	HEMA g (%w/w)	AA g (%w/w)	HPMC g (%w/w)	MBA g (%w/w)	Dynamic equilibrium swelling ratio (q)			% Equilibrium swelling (%ES)		
					pH 1.2	pH 5.8	pH 7.4	pH 1.2	pH 5.8	pH 7.4
F19	0.5	7.5	2.5	0.15	5.41	25.28	50.79	71.41	90.74	93.88
F20	1	7.5	2.5	0.15	4.37	23.10	46.48	68.66	89.62	93.25
F21	1.5	7.5	2.5	0.15	3.36	21.97	39.36	66.81	89.08	92.69
F22	0.5	10	2.5	0.15	5.00	26.84	47.43	65.89	89.35	93.33
F23	0.5	12.5	2.5	0.15	5.28	31.25	56.43	67.90	90.18	93.75
F24	0.5	15	2.5	0.15	5.78	36.36	62.27	68.49	90.48	93.90
F25	0.5	7.5	5	0.15	4.12	23.50	42.61	81.59	94.89	97.17
F26	0.5	7.5	7.5	0.15	4.29	25.82	45.60	81.14	96.50	97.56
F27	0.5	7.5	10	0.15	4.50	29.07	49.01	80.35	96.79	97.79
F28	0.5	7.5	2.5	0.20	2.89	16.69	30.39	65.72	89.90	94.08
F29	0.5	7.5	2.5	0.25	2.66	14.97	26.65	64.34	88.87	93.36
F30	0.5	7.5	2.5	0.30	2.32	12.52	21.59	60.45	83.85	92.74

Table 2: Percent gel content (%g_c), percent porosity (%P) measurement of HPMC-co-AA-co-HEMA hydrogels containing different %w/w of components

Formulation Code	Varying Component	%w/w Ratio (g)	% g _c	% P
F19	HEMA	0.5	82.844	19.567
F20		1	86.529	17.278
F21		1.5	90.596	16.473
F22	AA	10	86.352	25.394
F23		12.5	88.354	31.164
F24		15	93.489	38.934
F25	HPMC	5	84.840	20.205
F26		7.5	88.642	23.793
F27		10	93.854	25.383
F28	MBA	0.2	85.372	16.961
F29		0.25	89.196	14.174
F30		0.3	94.413	12.911

FTIR analysis

In this study, attenuated total reflectance (ATR) technology along with OPUS data collection software was employed to compute fourier transform infrared (FTIR) spectra of all samples using Bruker FTIR (Tensor 27 series, Germany) in the range of 500 cm⁻¹ 4000 cm⁻¹. Characteristics band were observed 3247 cm⁻¹ for (NH); 1675 cm⁻¹ for (C=O, CONH) and 1362 cm⁻¹ for (CH₂). FTIR spectra of HPMC-co-AA-co-HEMA hydrogel is given figure 2.

Scanning Electron Microscopy (SEM)

Results of scanning electron microscopy (SEM) of are illustrated in figure 3. SEM

images of HPMC-co-AA-co-HEMA hydrogels have given loose network structure of lamellar shape.

Thermal Gravimetric Analysis and Differential Scanning Calorimetry (TGA & DSC)

Thermal transition behavior of prepared formulation was analyzed by thermal gravimetric analysis and differential scanning calorimeter (DuPont thermal analyzer with 2010 DSC194 module) in temperature range of 20 °C to 900 °C at heating rate of 10 °C/min under nitrogen atmosphere and flow rate of 20 ml/min. Results TGA and DSC of all combinations are illustrated in figure 4.

In vivo studies Pharmacokinetic parameters were evaluated by non-compartmental pharmacokinetic are given in table 3.

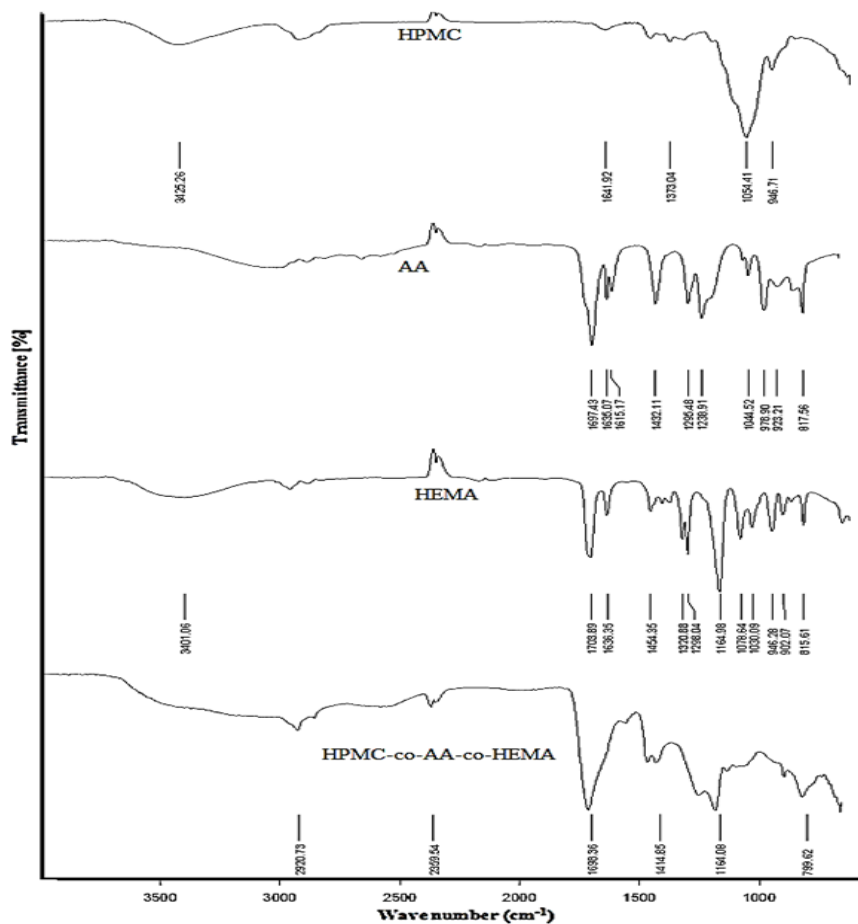


Figure 2 FTIR spectrum of HPMC-co-AA-co-HEMA hydrogels

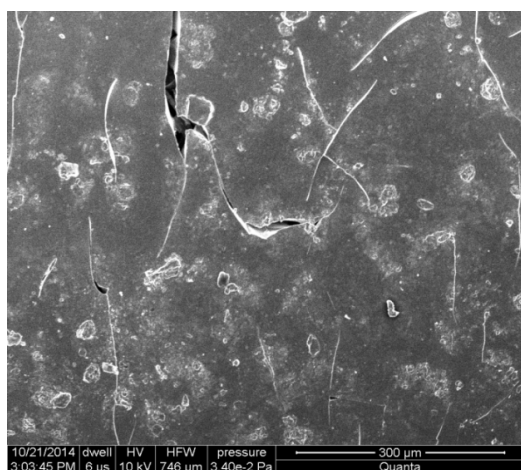


Figure 3: Scanning electron micrographs (SEM) of surface of HPMC-co-AA-HEMA hydrogels at magnification of 200X and 500μm scale bar

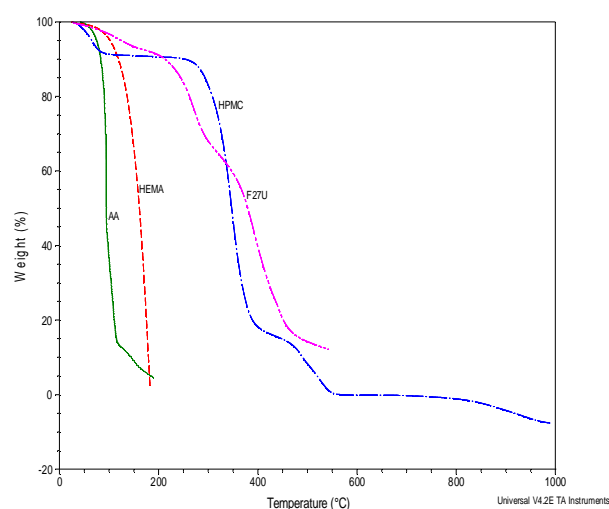


Figure 4: TGA thermogram for HPMC-co-AA-co-HEMA hydrogels

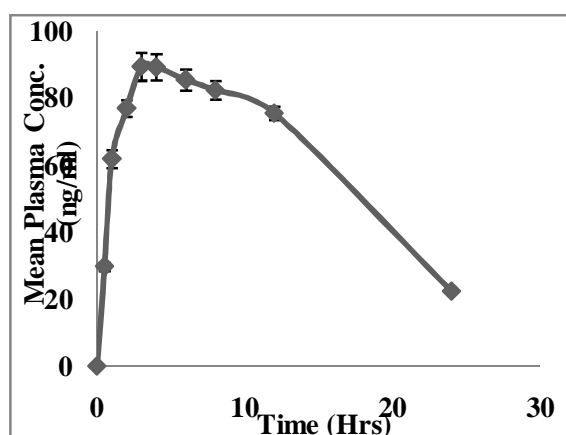


Figure 5 Mean plasma concentration vs. time profile of nicorandil administered in an oral dose of 15 mg in rabbits

Table 3 Pharmacokinetic parameters of nicorandil administered in an oral dose of 15 mg in rabbits

Parameters	Mean \pm SEM
C_{max} (ng/ml)	92.32212 \pm 3.667
T_{max} (Hrs)	3 \pm 0.365
AUC_{tot} (ng.h/ml)	1791.957 \pm 29.630
$AUMC_{tot}$ (ng.h ² /ml)	24340.85 \pm 248.153
MRT (Hrs)	13.60022 \pm 0.245
K_e (Hr ⁻¹)	0.084933 \pm 0.002
$t_{1/2\text{el}}$ (Hrs)	8.192592 \pm 0.226

DISCUSSION

Swelling behavior

Swelling kinetics of HPMC-co-AA-co-HEMA hydrogel

Dynamic swelling as function of concentration for HPMC-co-AA-co-HEMA hydrogels was determined at various pH buffer solution i.e. pH 1.2, pH 5.8 and pH 7.4. Swelling ratio of hydrogel formulation was found to be greatly affected by varying weight ratios of component.

Dynamic equilibrium swelling of HPMC-co-AA-co-HEMA hydrogels was increased with increased monomer concentration i.e. acrylic acid as acrylic acid hydrogel are anionic in

nature [17]. It can be justified as percent swelling of an ionic network greatly depends on concentration of ionizable groups in network [18]. Dynamic equilibrium swelling ratio was increased from 5.000 to 5.784 in pH 1.2 and 47.436 to 62.270 in pH 7.4 by increasing AA concentration from 10 to 15 (% w/w). HPMC-co-AA-co-HEMA hydrogel contains anionic acrylic acid and non-ionic acrylate unit which give adequate polarity, charge and hydrogen bonding responsible for better hydration. Swelling ratio was also increased from 4.127 to 4.500 and 42.618 to 49.011 in buffer solution of pH 1.2 and 7.4 respectively by increasing concentration of HPMC from 5 to 10 (% w/w). The basic reason for this type of swelling of hydrogels was free carboxylic acid groups. These carboxylic acid groups have ability to release proton and have a tendency to dissociate at basic pH resulting in greater hydration and swelling. While at acidic pH great quantities of hydrogen bonds were present due to acrylic acid and acrylate chain. As pH was raised break down of hydrogen bonds occurred, moreover carboxylic acid groups started to ionize resulting in greater inside osmotic pressure and electrostatic repulsion. Overall result was greater expansion of hydrogel at basic pH i.e. 7.4. Present data had depicted that formulated hydrogels have greater

sensitivity towards pH so it can be used for sustained drug delivery through gastro intestinal tract on behalf of different pH environments throughout tract.¹⁹

Similar type of study was conducted by Nihar and Patel in 2014. They formulated pH sensitive poly acrylamide-co-acrylic acid hydrogel for controlled and sustained drug delivery and found that swelling of formulated hydrogels were increased with increased monomer concentration as also depicted by present study [19]. Carboxylic acid groups present in hydrogel structure were thought to be responsible for pH sensitive swelling behaviour. At lower or acidic pH values large quantities of hydrogen bonds formed were found and carboxylic acid remains in form of COOH. While at basic pH (7.4) carboxylic acid groups were present in free state able to lose proton and dissociate. As a result inner osmotic pressure of hydrogels was increased and electrostatic repulsion promoted network expansion [20].

Percent gel content (%g_c) and %porosity (%P) measurement

Percent porosity depends on the volume of the pores present scaffolds of hydrogels and percent gel content depends upon cross linking density.

Porosity decreased with increasing concentration of monomer i.e. HEMA and

cross linker i.e. MBA while percent gel contentment increased due to enhanced cross linking density and greater physical entanglement resulting in compact structure with less pore density. Ultimately swelling ratio or water retention capacity was decreased leading to decreased drug release. While higher concentration of monomer AA led to lesser cross linking density and lesser physical entanglement, as a result more pore volume or greater pore density was observed. Same pattern study was conducted by Shivani in 2013 where he confirmed that percent gel content increased with increase cross linking density and percent porosity was decreased and vice versa [21].

Percent gel content was noted to increase with increasing content of HEMA and HPMC at pH 7.4. In hydrogel preparation free radicals are generated on polymer/monomer leading to formation of cross linked macromolecules. As concentration of polymer/monomer increased macromolecules come closer to each other resulting in more facilitated cross linking which ultimately leads to increase in gel content [22]. Percent gel content was found increasing with increasing feed of monomer HEMA. Percent gel content was found to increase with increasing ratio of AA. This can be attributed to increase in cross linking ratio with increase in monomer concentration.

Similar type of results were reported by Kamal *et al.*, in 2014 where he reported that % gel content was found to increase with increasing concentration of AA. He reported that cross linking density increases with increasing monomer concentration resulting in enhanced gel content [23]. In present study percent gel content was increased with increase in cross linker concentration from 85.372% to 94.413% (F28 to F30) at pH 7.4. Results are in good agreement with studies conducted by Samiullah and Nazar in 2014 where they have reported that percent gel content increases with increase in cross linker concentration because of increase in cross linking density [9].

Percent porosity was noted to decrease with increase in monomer concentration i.e. HEMA while it was noted to increase with increasing concentration of AA and HPMC. Percent porosity was noted to decrease with increasing cross linker concentration. Increase in percent porosity can be justified by fact that viscosity of solution increases in such cases which prevent bubbles from escape and form more interconnected channels. These interconnected channels result in more porous network. While on other hands in cases where porosity is decreased more cross linking occurred resulting in formation of more

entanglement structures as in case of increasing cross linking concentration.

Same kind of results was reported by Samiullah and Nazar in 2014. They reported that percent porosity decreased with increasing concentration of cross linker while it increased with increasing polymer/monomer concentration [9].

In vitro drug release studies

In vitro drug release studies were conducted to find out percentage drug release and drug release mechanism. Analysis of in vitro release data was done by employing various kinetic models like Zero order release model, first order release model, Higuchi model and Corsmayer-Peppas model for better understanding of release mechanism. Value of regression coefficient (r) was used to decide upon best fit model for drug release.

Drug release studies were carried out at acidic pH (i.e. pH 1.2) and basic pH (i.e. pH 7.4). Drug release was found to be less at acidic pH as compared to basic pH following same mechanism as that of percent swelling. Percent drug release was found to be varied with varying concentrations of polymer or monomer. Percent drug release was decreased from 67.46 % to 59.64 % in formulations F19 to F21 by increasing concentration of HEMA from 0.5 to 1.5 (%w/w) as a result of more compact structure formation with less

porosity. Percent release was increased from 69.29 % to 73.38 % and 75.80 % to 82.82 % in formulations F22 to F27 with increasing concentration of HPMC and AA from 5 to 10 and 10 to 15 (%w/w) respectively as more polymer chain relaxation occur leading to more water absorbing and retention capacities.

These formulations were also subjected to kinetic evaluation by applying various kinetic models. Best fit method was decided upon value of regression coefficient (r) keeping in view the fact that as value of regression coefficient (r) approaches more close to 1 model is thought to be the best fit for drug release mechanism for that formulation. Values of regression coefficient (r) lie in range of 0.9673 to 0.988 for Higuchi model and from 0.949 to 0.9885 for Corsmayer-Peppas model and plot of drug released versus square root of time was linear justifying at diffusion controlled drug release. Value of release exponent “n” for increasing concentration of HEMA and crosslinker MBA lie in range of 0.3296 to 0.4186 and 0.2727 to 0.3352 respectively indicating that drug release followed fickian diffusion mechanism as given in table 4.34. Value of release exponent “n” for acrylic acid was greater than 0.5 indicating that that drug release followed non-Fickian or anomalous mechanism.

Sindhu et al., conducted same pattern of studies. Results of his studies were in good support to results of present studies as he stated that percent drug release was increased by increasing concentration of acrylic acid and also release of acrylic acid hydrogels followed non-fickian diffusion controlled mechanism [24]. *In vitro* drug release profile HPMC and acrylic acid hydrogels was studied by Nazar and Umbreen with supportive results to present studies [8].

FTIR analysis

FTIR is an important identification tool for new formulations. FTIR spectra of HPMC-co-AA-co-HEMA hydrogel and of individual components were obtained as shown in figure 2. In pure HPMC spectra a broad peak at 3425.26 cm^{-1} was due to -OH stretching vibrations of the hydroxyl groups and peak at 1641.92 cm^{-1} could be representative of N-H group [25]. In prepared hydrogel a peak obtained at 2920.73 cm^{-1} was representing -CH stretching of methyl and hydroxypropyl groups and peak at 1698.36 cm^{-1} showed N-H deformation bending of hydroxypropyl methyl cellulose. Prepared hydrogel consist of hydroxypropyl methyl cellulose back bone having carboxylate and ester functional groups as side chains which are identified by sharp peak at 1698.36 cm^{-1} . Peak at 1414.85

cm^{-1} could be representative of C=O stretching.

Muhammad in 2010 also conducted same pattern of study with chitosan, acrylic acid and HEMA hydrogel. He has reported peaks of monomer AA and HEMA as found in FTIR spectra of present study like peak at 1414.85 cm^{-1} representative of C=O stretching and peak around 1637 cm^{-1} representing C=O stretching of COOH and at 1116 cm^{-1} . So it can be concluded that results of his study were in good agreement with present study [15].

Scanning Electron Microscopy (SEM)

Via SEM images of freeze dried HPMC-co-AA-co-HEMA hydrogels morphology of the hydrogels was shown in figure 3. Loose network structure of lamellar shape was thought to be responsible for water holding or absorbing capacity. This network structure was considered to be formed as a result of cross linking of polymer/monomer.

Guoat *al.*, also in 2014 worked on various HPMC and AA formulations. He also reported network structure of lamellar shape which is considered to be responsible for functionality of hydrogels [26]. A scientist named Mohammad Sadegh said that microstructure morphology must be considered among the most important properties of hydrogel. His work was based

on same pattern as that of present study. He also reported microporous morphology of hydrogels. He declared that these pores act as regions of water permeation and provides interaction sites of external stimuli [27]. Muhamad and Mojgan also studied scanning electron micrograph of HPMC and AA hydrogel in various formulation and they reported that these hydrogels possess porous structure and have good water absorbing and retention capacities [28].

Thermal Gravimetric Analysis and Differential Scanning Calorimetry

TGA graphs of HPMC-co-AA-co-HEMA hydrogels described its thermal stability as shown in figure 4. Cross linked HPMC-co-AA-co-HEMA hydrogels exhibited three step degradation starting at 200°C . Only 20% weight loss was observed in temperature range of 200°C to 300°C which showed grafted copolymer was more thermostable as compared to individual components i.e. hydroxypropyl methyl cellulose, acrylic acid and HEMA. Significant weight loss i.e. 35% was observed at temperature range of 350°C to 450°C . In comparison AA and HEMA exhibited slight two-step decomposition at temperature range of 75°C to 100°C and 100°C to 175°C respectively with almost 80% weight loss. This fact clearly showed that

grafting has greatly improved thermal stability.

In DSC thermogram of HPMC-co-AA-HEMA hydrogel cleared that formulation exhibited a broad exothermic peak transition peak at temperature range of 223 °C to 545 °C. Thermal degradability of acrylic acid was showed by a sharp endothermic peak at 70 °C. HPMC behaved more stable over temperature of 900 °C. Melting range of HEMA lied in temperature range of 100 °C to almost 225 °C with an endothermic peak at 202 °C. Above data exhibited that formulation was more thermo-degradable than individual ingredient HPMC and more thermostable as compared to AA.

Podko also worked with TGA and DSC of various HEMA hydrogels. His work is in good support with present study [29]. Results of study conducted by Monica *et al.*, in 2014 were also in good agreement with results of present study [30].

Pharmacokinetic Evaluation

Desired drug delivery system with controlled release profile was achieved by formulating hydrogels of various components that delivered therapeutic agent at a desired rate for a specified period of time. Nicorandil was used as model drug to evaluate prepared hydrogels systems. For conventional immediate release dosage forms reported C_{\max}

of nicorandil was 300 ng/ml approximately in humans for a dose of 20 mg b.i.d. C_{\max} is attained rapidly within 30 min after administration for immediate release dosage forms. Nicorandil show extensive metabolism and kidney is major route of elimination [31]. Various pharmacokinetic parameters like C_{\max} (ng/ml), T_{\max} (Hrs), AUC_{tot} (ng.h/ml), $AUMC_{\text{tot}}$ (ng.h²/ml), MRT (Hrs), K_e (Hr⁻¹) and $t_{1/2 \text{ el}}$ (Hrs) of model drug nicorandil were determined for HPMC-co-AA, HEMA-co-AA, HPMC-co-AA-co-HEMA hydrogels and oral solution after administering 15 mg.

From pharmacokinetic data obtained it was found that mean plasma concentrations was 92.32212 ± 3.667 ng/ml for HPMC-co-AA-co-HEMA(F24) hydrogels. From pharmacokinetic data it was observed that the time taken to reach peak plasma concentration T_{\max} was 3 ± 0.365 hrs HPMC-co-AA-co-HEMA hydrogels. Similarly mean elimination half life $t_{1/2}$ for HPMC-co-AA-co-HEMA hydrogels was 0.084933 ± 0.002 hr⁻¹. The mean AUC_{tot} value was 1791.957 ± 29.630 (ng.h/ml) HPMC-co-AA-co-HEMA hydrogels.

So on behalf of these stated results HPMC-co-AA-co-HEMA considered a good controlled release drug delivery system as it provided a prolonged and controlled *in vivo* delivery of model drug.

Same pattern of in vivo studies were conducted by a researchers named Hemant and Shivakumar on controlled release hydrogel formulations. He also made comparison of two different hydrogel formulations and found that one gave more sustained release profile so gave better results [32].

CONCLUSION

Nicorandil was successfully given in a hydrogel formulation resulted in less dosing frequency and thus improving patient compliance.

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