

SYNTHESIS, CHARACTERIZATION AND *IN VIVO* EVALUATION OF PH SENSITIVE HYDROXYPROPYL METHYL CELLULOSE-GRAFT-ACRYLIC ACID HYDROGELS FOR SUSTAINED DRUG RELEASE OF MODEL DRUG NICORANDIL

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ABSTRACT

Background: Anti hypertensive drugs like “Nicorandil” require frequent dosing due to their shorter half-life. Such drugs are also pH sensitive, due to which greater portions of these drugs are degraded in acidic pH of stomach resulting in lesser bioavailability. The objective of this study was to formulate graft polymeric carrier system for sustained delivery of nicorandil to minimize dosing frequency and enhance patient compliance.

Materials & Methods: This animal model study was conducted in Department of Pharmacy, Islamia University of Bahawalpur, Pakistan. Hydroxypropyl methyl cellulose-graft-acrylic acid hydrogels were synthesized by free radical solution polymerization with diverse weight ratios of polymer, monomer and cross linker. Total duration of study was 1.5 years from March 2013 to August 2015. The N, N-methylene bis acrylamide and potassium persulfate were used as crosslinker and initiator respectively. Hydrogels were characterized for swelling ratio, equilibrium swelling, gel content, porosity and *in vitro* drug release. The surface morphology of synthesized hydrogels was evaluated by using Scanning Electron Microscopy. Thermal properties of hydrogels were evaluated by Thermogravimetric Analysis and Differential Scanning Calorimetry whereas FTIR was done to examine chemical compatibility. Finally, *in vivo* evaluation of prepared hydrogels was carried out in rabbits using simple parallel study design to estimate various pharmacokinetic parameters.

Results: HPMC-co-AA hydrogels had good pH sensitivity whereas; they demonstrated maximum and minimum swelling at pH 7.4 and 1.2 respectively. Swelling ratio, gel fraction and cumulative percent drug release were decreased with increasing crosslinker concentration while these parameters were increased with increasing AA and HPMC concentrations. A porous network was observed in the SEM images. All formulation ingredients of prepared hydrogels showed good compatibility as determined by FTIR. Results of *in vivo* study proved the pH sensitivity and sustained drug release of prepared hydrogels.

Conclusion: The HPMC-graft-AA hydrogels showed good pH-sensitivity and sustained-release profile for model drug nicorandil.

KEY WORDS: Polymers; Hydrogel; Drug Delivery; Drug Release; Bioavailability; Controlled Release; Half-life; pH sensitive.

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1. INTRODUCTION

Polymeric hydrogels have gained enormous attention for drug delivery due to their biocompatibility.¹ Hydrogels can be described as water swollen polymeric cross linked network formulated by reaction of one or more monomers/ polymers² that can efficiently grasp ample amount of water without being dissolved. Water absorption ability of hydrogels can be attributed to hydrophilic functional groups pres-

ent on polymeric backbone while their resistance to dissolution is attributed to crosslinking between polymeric network chains.^{3,4}

Among polymers, natural ones have considerable importance in drug delivery due to various useful properties including low density, biocompatibility and biodegradability.⁵ Cellulose is a natural and excessively available linear homopolymer composed of D-glucopyranose units linked together by β -(1 \rightarrow 4) glycosidic bonds.⁶ It possess remarkable physical and chemical attributes like hydrophilicity, reactive hydroxyl groups and aptitude to form supra structures that are employed in various areas⁷ such as fibers, coatings, laminates, optical films, sorption media, pharmaceuticals and cosmetics.⁸ Modification of natural polymers by using various means like grafting has great significance in achieving desired formulations with preferred physicochemical properties.

Nicorandil (IUPA name; 2-(pyridine-3-carbonylamino) is a derivative of niacinamide that is a vasodilator indicated for management of angina. At therapeutic concentration, it leads to K⁺ATP channel opening that results in decreased coronary vascular resistance.⁹ Nicorandil is comprehensively metabolized and rapidly eliminated through kidneys resulting in short elimination half-life of 1 h requiring frequent dosing.¹⁰

The objective of this study was to formulate graft polymeric carrier systems for sustained delivery of nicorandil to minimize dosing frequency and enhance patient compliance.

2. MATERIALS AND METHODS

2.1 Materials

This animal model study was conducted at the Department of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Pakistan from March 14, 2013 to August 10, 2014.

Acrylic acid (99%) was purchased from Sigma-Aldrich, Netherlands, (hydroxypropyl) methyl cellulose (80-120cP) from Sigma-Aldrich, USA, N, N methylene-bis-acrylamide (98%) from Fluka, Switzerland, potassium persulphate (99%) from AnalaR, BDH-England, potassium dihydrogenphosphate (98-100%), ethanol absolute and methanol HPLC grade from Merck, Germany, acetonitrile HPLC grade from Wilson Pharmaceuticals, Islamabad, Pakistan and heparin from Medicare Pharma, Malaysia. Nicorandil (99.8%) was provided by the Department of Pharmacy, The Islamia University of Bahawalpur.

2.2. Methods

2.2.1 Preparation of HPMC-graft-AA hydrogel

HPMC-graft-AA hydrogels were formulated by free radical polymerization. Hydroxy propyl methyl cellulose solution was placed on hot plate magnetic stirrer at 70°C and stirring was performed at 300

rpm. Initiator (KPS) solution was added drop wise to above solution at same temperature and stirring speed. The process was continued for 10 min. Then solution is kept to cool up to room temperature. Required quantities of acrylic acid and N, N, methylen-bis-acrylamide solution were added to above mixture. Final solution was stirred at 300 rpm for 1-2 min. Final mixture was placed at 80°C for 3 h in a water bath to perform polymerization. Formulated hydrogel was sliced into tiny discs of 4 mm thickness with sharp cutter. Discs were washed with distilled water then put in ethanol: water (50:50) solution for 24 h. Formulation was subjected to oven drying at 46°C till equilibrium was achieved.

2.2.2 Swelling studies

Swelling studies were planned at pH 1.2, 5.8 and 7.4 at preset time points unless swelling equilibrium was achieved. For swelling study, weighed disc of formulation was flooded in 100 ml buffer of appropriate pH. At definite time points, discs were spot dried and weighed at analytical weight balance.

Dynamic swelling and equilibrium swelling ratio of all formulations were calculated by following equation 1.

$$q = W_t/W_d \quad \text{(Equation.....1)}$$

Where "q" is dynamic swelling

W_t shows swollen gel's weight at time t

W_d shows initial weight of dried hydrogel disc¹¹

2.2.3 Percent gel content (%g_c)

Freshly prepared hydrogel discs (3-4 mm) were placed for drying in a vacuum oven at 45°C until constant weight (W_0) was achieved. The dried gel disc was subjected to extraction with deionized water for 24hr for washing of non reacted polymer/monomer. The washed disc was again dried in oven at 45°C till constant weight (W_1). By using below mentioned formula % gel content was determined.

$$\text{Percent gel content (\%g}_c) = \frac{W_1}{W_0} \times 100$$

(Equation.....2)

Where W_1 is the weight of dry gel after extraction in distilled water and W_0 is the initial weight of dry gel.¹²

2.2.4 Porosity measurement (%P)

Voids volume over total volume is described as porosity and its value lies between 0 to 1 or 0 to 100%. Solvent replacement method was preferred to measure porosity. Dried weighed hydrogel disc (M_d) was soaked in absolute ethanol for 24 hrs (till constant weight). After 24 hrs, hydrated hydrogel disc (W_h) was blot dried to eliminate surplus surface ethanol and weighed on analytical weight balance. Percent porosity (%P) was determined by equation 3.

$$Porosity = \frac{(Mh - Md)}{\rho V} \times 100$$

(Equation.....3)

Where ρ refers to density of absolute ethanol and V is hydrogel volume.¹³

2.2.5 Characterization

Surface morphology of HPMC-graft-AA hydrogel (F12) was determined by scanning electron microscope (Hitachi, S3400N). Samples were coated with gold by Hummer Sputter Coater.¹⁴

Fourier transform infrared analyzer (Bruker, Tensor 27, Germany) was used to determine FTIR spectra of HPMC-graft-AA hydrogel (F12), polymer and monomer at 25°C.

Thermal transition characteristic of optimized formulation was observed by thermal gravimetric analysis (TGA) and differential scanning calorimeter (DSC) (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 at flow rate of 20 ml/min with temperature range of 0°C to 1000°C. The standard uncertainty of sample mass measurement was ± 1%. Equipment calibration was accomplished with calcium oxalate supplied with instrument.¹⁵

2.2.6 In vitro drug release studies

In vitro drug release of hydrogel discs loaded with nicorandil was performed according to specifications of United States Pharmacopeia by using USP apparatus II at both pH 1.2 and 7.4. Composition of dissolution media was 0.1 M HCl pH 1.2 and phosphate buffer pH 7.4. Stirring of media was continued at 50 rpm at 37°C±0.5°C. Aliquots of 5 ml were taken at intervals of 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 hour with an automated sample collector after filtering through sintered filters (10 µm). After each sample, fresh medium (5ml) was added to maintain sink conditions. Collected samples were diluted up to 50ml with respective buffer and analyzed at 225 nm

using a UV-spectrophotometer. The in vitro cumulative drug release study was carried out in triplicate.¹⁶

2.2.7 In vivo studies

Six (6) healthy male rabbits were taken and enrolled in study. The weight of rabbits was 2±0.5 kg in agreement with standard protocols by Pharmacy Research Ethics Committee of Department of Pharmacy (No. 105-2014/PREC), The Islamia University of Bahawalpur. Single dose study was carried out on animal model (rabbits). Single dose was administered to each animal (6.5 mg/kg) orally and 2 ml blood sample was withdrawn from jugular vein of rabbit in 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. Centrifugation of collected blood samples were done 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.¹⁷ An HPLC system of Agilent consisted of a pump, a column (BDS hypersil C₈, 4.6 mm x 250 mm) and UV visible detector was engaged to observe prepared plasma samples. Mobile phase of water and acetonitrile (750:250 v/v) was used and flow rate was 1 mL/min at ambient temperature. Injection volume was 20 µL and detection was achieved at 256 nm.

Pharmacokinetic parameters were determined by non-compartmental pharmacokinetic approach. Maximum concentration (C_{max}), time to reach peak plasma concentrations (T_{max}) and other pharmacokinetic parameters (AUC_{0-∞}, AUMC_{0-∞}, t_{1/2}, Ke and MRT) were computed by using pharmacokinetic software, Kinetica version 4.1.1.

3. RESULTS

3.1 Swelling studies, percent gel content (%g_c) and percent porosity (%P)

Results of varying concentrations of HPMC, AA and MBA on swelling ratio, percent gel content (%g_c) and percent porosity (%P) are presented in table 1. Swelling ratio was noted to be increased with

Table 3.1: Composition and comparative swelling ratios of HEMA-co-AA hydrogels using different concentrations components

Formulation code	HPMC (%w/w)	AA g (%w/w)	MBA g (%w/w)	Dynamic equilibrium swelling ratio (q)			% g _c	% P
				pH 1.2	pH 5.8	pH 7.4		
F10	0.6	12.5	0.15	5.412	22.974	51.033	85.614	27.037
F11	0.9	12.5	0.15	5.878	27.902	55.027	90.866	30.698
F12	1.2	12.5	0.15	6.245	31.327	69.647	93.990	33.157
F13	0.3	7.5	0.15	6.395	17.640	37.716	86.352	32.771
F14	0.3	10	0.15	6.457	19.927	40.668	83.291	32.607
F15	0.3	12.5	0.15	6.719	25.963	47.380	80.468	29.670
F16	0.3	7.5	0.20	5.434	19.606	35.379	82.180	28.708
F17	0.3	7.5	0.25	5.303	16.741	31.230	84.764	24.506
F18	0.3	7.5	0.30	5.091	14.631	28.633	88.268	21.860

increasing concentration of HPMC and AA while it was decreased with increasing concentration of MBA. Formulation F12 showed maximum swelling ratio. Percent gel content and percent porosity was also increased by increasing the concentration of polymer, monomer and cross linker. (Table 3.1)

3.2 Characterization

3.2.1 Scanning Electron Microscopy (SEM)

To observe morphology of optimized formulation (F12), scanning electron microscopy was performed. Scanning electron micrographs (SEM) of surface of HPMC-graft-AA hydrogels at magnification of 100X and 200X and 500µm scale bar and 300µm scale bar were observed and it demonstrated uneven pores (size and shape) distribution. (Figure 3.2.1)

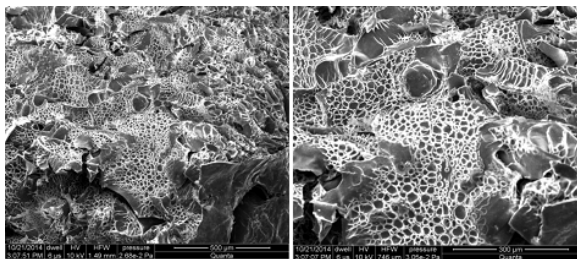


Figure 3.2.1: Scanning electron micrographs of surface of HPMC-co-AA hydrogels at 100X and 200X (left to right) and 500µm and 300µm scale bar respectively.

3.2.2 FTIR analysis

In this study, attenuated total reflectance (ATR) technology along with OPUS data collection software was used to compute fourier transform infrared (FTIR) spectra of all samples in the range of 500 cm⁻¹ 4000 cm⁻¹. Characteristic bands were seen at 3247 cm⁻¹, 1675 cm⁻¹ and 1362 cm⁻¹ that represent stretching of NH, C=O/CONH and CH₂ respectively. FTIR spectra of pure components and formulation are demonstrated in Figure 3.2.2.

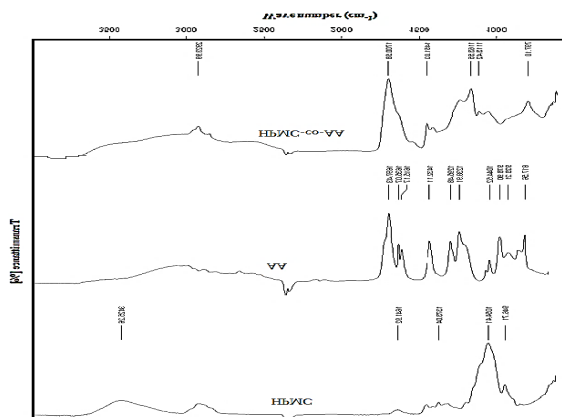


Figure 3.2.2: FTIR spectrum of HPMC-graft-AA hydrogels

3.2.3 Thermal gravimetric analysis and differential

scanning calorimetry (TGA and DSC)

Thermograms of TGA and DSC of formulation F12 are depicted in Figures 3.2.3. HPMC and AA demonstrated less thermal stability as compared to grafted copolymer. HPMC illustrated four phases of decomposition. First decomposition was observed at 301°C with 10.2% weight loss whereas, second phase was of great decomposition as approximately 70% weight loss was noted at narrow temperature range of 301 °C to 350 °C. For acrylic acid nearly 90% weight loss was noted at temperature range of 90 °C to 100 °C.

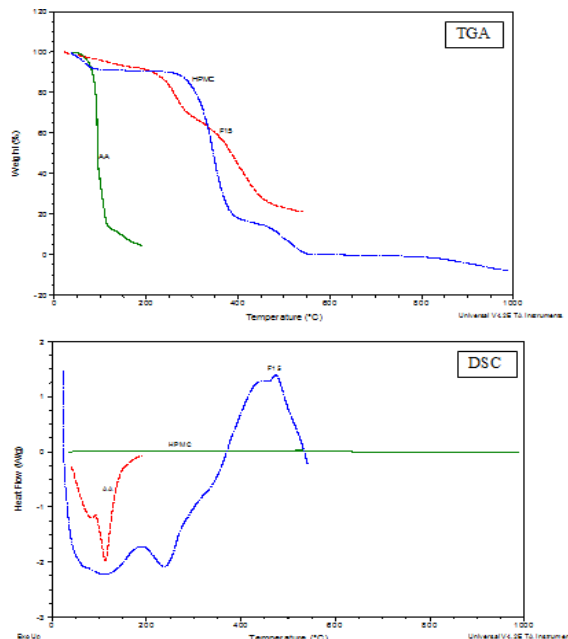


Figure 3.2.3: TGA and DSC thermogram for HPMC-graft-AA hydrogels.

3.3 In vitro release studies

The results of *in vitro* drug release study demonstrated that drug release was significantly higher at pH 7.4 as compared to pH 1.2. Drug release was affected by changes in polymer, monomers and cross linker concentration. At pH 7.4, drug release was increased with increasing concentration of HPMC and AA from 89.817% to 92.878% and 75.78% to 84.93% respectively. While percent drug release was decreased from 66.63% to 56.26% with increasing concentration of MBA. Patterns of cumulative percent drug release at pH 1.2 and pH 7.4 is given in Figure 3.3.

3.4 In vivo evaluation

Among various formulations, formulation F12 resulted in maximum swelling and *in vitro* drug release. So F12 was chosen to perform *in vivo* evaluation. Pharmacokinetic parameters were computed by non-compartmental pharmacokinetics as given in Table 3.4, while mean plasma concentration vs. time profile of nicorandil is demonstrated in Figure 3.4.

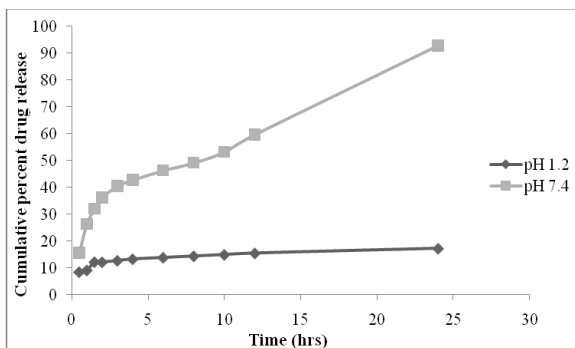


Figure 3.3: Cumulative percent release of Nicorandil from HPMC-graft-AA hydrogels

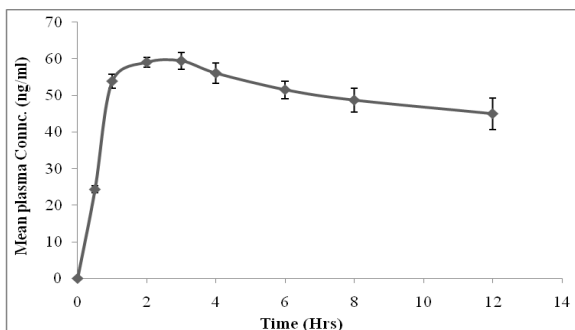


Figure 3.4: Mean plasma concentration vs. time profile of nicorandil administered in an oral dose of 15 mg in rabbits (n=6)

4. DISCUSSION

4.1 Swelling studies & percent gel content.

Dynamic swelling of formulations F10 to F18 was noted till swelling equilibrium achieved in buffer solution of different pH i.e. 1.2, 5.8 and 7.4 keeping in view the pH variations throughout gastrointestinal tract. Over all swelling ratio is increased in basic medium as compared to acidic medium because of higher pK_a value of basic medium.

By addition of pendant acidic or basic functional groups to a polymer chain, pH sensitivity can be imparted to polymer backbone. This addition of acidic or basic functional groups made network to either release or accept protons in different pH medium. As a result electrostatic repulsion is produced which eventually controls porosity of network. Ionic hydrogels having carboxylic acid groups that result in swelling changes in different pH medium. Polymer networks having more pendant acidic groups show more electrostatic repulsions ensuing in greater porosity and swelling at high pH (pH 7.4) while networks with basic pendant groups demonstrate electrostatic repulsion at low pH values (pH 1.2). In present study HPMC-graft-AA hydrogel has more acidic pendant groups from acrylic acid, that's why these hydrogels showed greater swelling at pH 7.4 (basic pH) as compared to acidic pH 1.2. Similar report is from Rizwan, et al.,¹⁸ where they explained the role of acidic pendant group in pH sensitive hydrogels.

Similar results were reported by Nesrinne and Djamel¹⁹ in 2017 where they formulated poly (acrylamide-co-acrylic acid) hydrogel and studied their swelling behavior at different pH. Their results reveal that more swelling was observed at basic pH as compared to acidic pH. Moreover, swelling ratio was increased with increase in acidic content i.e. acrylic acid. This study is in good support with results of present study.

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

4.2 Percent porosity

Porosity was decreased by increasing the concentration of cross linker i.e. MBA while percent gel content increased due to enhanced cross linking density and greater physical entanglement resulting in compact structure with less pore density. Eventually swelling ratio or water retention capacity was suppressed

Table 3.4: Pharmacokinetic parameters of nicorandil administered in an oral dose of 15 mg in rabbits (n=6)

Variables	Mean	SD	Minimum	Maximum	Range	95% CI of Mean	
						Lower	Upper
C_{max} (ng/ml)	108.3883	5.7275	100.494	116.247	15.753	102.3776	114.3989
T_{max} (Hrs)	3	0.6324	2	4	2	2.3363	3.6636
AUC_{tot} (ng.h/ml)	2101.51	98.0136	1944.85	2229.96	285.11	1998.6510	2204.3689
$AUMC_{tot}$ (ng.h ² /ml)	27665.4	2326.912	24640.9	31016.2	6375.3	25223.4556	30107.3443
MRT (Hrs)	13.1786	1.1464	12.0371	14.7084	2.6713	11.9755	14.3816
K_e (Hr ⁻¹)	0.0884	0.0113	0.0731	0.1035	0.0304	0.0765	0.1003
$t_{1/2el}$ (Hrs)	7.8270	1.1587	6.6955	9.4842	2.7887	5.9832	9.6707

leading to lesser drug release. While higher concentration of HPMC and AA led to lesser cross linking density and lesser physical entanglement, as a result more pore volume or greater pore density was depicted. Similar study was reported by Nair, et al.,²⁰ in 2014 where the author confirmed that percent gel content was increased and percent porosity was decreased with increase in cross linking density.

Percent gel content was seen to be improved with increasing content of HPMC at pH 7.4. In hydrogel preparation free radicals are produced on polymer/monomer leading to formation of cross linked macromolecules. As concentration of polymer/monomer is increased, macromolecules come close to each other resulting in more facilitated cross linking which eventually leads to increase in gel content. Similar studies were reported by Narjary, et al.,¹³ in 2012.

4.3 Characterization

4.3.1 Scanning Electron Microscopy

SEM micrograph of HPMC-graft-AA hydrogel at magnification of 100X and 200X depicted uneven pores in size and shape distribution. This porous network was responsible for entrapment of aqueous media. Parida and Mishra²¹ also reported that SEM image of hydrogel have porous structure with smooth surface. His results were in good conformity with present study. Another scientist Pitta worked with acrylic acid and HPMC hydrogels and demonstrated that prepared formulations have porous morphology that is responsible for water retention capacities. The results are also in good agreement with the study of Hu, et al.,²² reported in 2015.

4.3.2 FTIR Analysis

In FTIR spectra of HPMC-graft-AA hydrogel absorption band that appears at 3419 cm^{-1} refer to OH group stretching while absorption band at 1617 cm^{-1} correspond to CH=CH stretching. In FTIR spectra of pure HPMC, peak at 2922.90 cm^{-1} is representative of methyl and hydroxypropyl group responsible for -CH stretching of these groups. More over peak at 1641.92 cm^{-1} is representative of C-O stretching.²² In FTIR spectra of HPMC-graft-AA hydrogel peak at 1697.92 cm^{-1} could be representative of C=O stretching of carboxylic group. Peak at 1450.52 cm^{-1} in formulated hydrogel refers to C-H deformation of alkane. Peak at 1163.16 cm^{-1} in hydrogel could be representative of C-O stretching in C-O-C group. These peaks show presence of representative functional groups of HPMC and acrylic acid after synthesis of HPMC-co-AA hydrogels. Parida²¹ and Hu²² also prepared HPMC and AA hydrogels and reported FTIR peaks around 1637 cm^{-1} and 1116 cm^{-1} representing C=O stretching and C-O stretching respectively. Their results are in good agreement with present study.

4.3.3 TGA Analysis

Thermograms (TGA) were obtained by plotting percentage residual weight against temperature. End of first straight line portion of curve was used to find out initial decomposition temperature. Thermogram of HPMC-graft-AA hydrogel depicted greater stability as compared to its components. On behalf of these results we can conclude that formulated hydrogel was more thermostable as compared to individual ingredients.

4.3.4 DSC Analysis

Results of DSC demonstrate that formulation is more thermo-degradable than individual ingredients. DSC data of present study was in good conformity with DSC studies performed by Parida²¹ in 2012 and Hu²² in 2015 respectively, where they studied thermal stability of HPMC-graft-AA hydrogel by TGA and DSC. They reported that HPMC and AA hydrogel are more thermostable as compared to individual component. Grafting is observed to improve thermal stability of formulation. Their results are in support with results of present study.^{21,22} Osiris and Manal also reported increased thermal stability of HPMC after hydrogel preparation which was also in good agreement with present study.¹⁵

4.3.5 *In vitro* drug release studies

Drug release depends upon swelling mechanism and chemical architecture of hydrogels. All formulations of HPMC-graft-AA hydrogels (F10-F18) were subjected to *in vitro* release study in both acidic and basic media at pH 1.2 and pH 7.4 to simulate conditions of gastric fluid (SGF) and intestinal fluid (SIF), respectively. Percentage drug release in acidic media at pH 1.2 was less for varying polymer, monomer or cross linker concentrations. Reason for less drug release in acidic media can be explained by less hydrogel swelling due to anionic regions that form more compact arrangement resulting in low polymer chain relaxation and less water holding capacity. Drug release at basic media was greater as function of time for different polymer, monomer or cross linker concentrations due to increased polymer chain relaxation leading to more water penetration and release. Drug release was increased with increasing concentration of AA and HPMC while drug release was decreased with increasing cross linker concentration. Reason for less drug release by increasing cross linker concentration was increased crosslink density in polymeric structure. Similar results were reported by Eswaramma, et al.,¹¹ where authors stated that drug release was enhanced in basic media as compare to acidic media and their results are in good agreement with the results of present study.

4.4 Pharmacokinetic evaluation

Nicorandil was used as model drug to assess prepared hydrogels systems. For conventional immediate release dosage forms reported C_{max} of nicorandil was approximately 300 ng/ml in humans for a dose of 20mg b.i.d. The C_{max} is attained rapidly within 30 min after administration for immediate release dosage forms. Nicorandil show extensive metabolism and kidney is basic route of elimination.¹⁰

Various pharmacokinetic parameters like C_{max} (ng/ml), T_{max} (Hrs), AUC_{tot} (ng.h/ml), $AUMC_{tot}$ (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 hydrogel and plain drug solution (equivalent to 15 mg) administered orally. The enhanced mean plasma concentrations of HPMC-co-AA hydrogel compared to plain drug solution can be explained on the basis of greater cross linking density and greater porosity of hydrogel. It also had more water retention and controlled release capacities.

5. CONCLUSIONS

HPMC-co-AA (F12) hydrogel could be designated as superior formulation compared to oral solution. Optimized hydrogel formulation demonstrated better *in-vitro in-vivo* release profile and desired sustained release effect at predetermined rate over prolong period of time. However, these findings are preliminary and studies can proceed to further investigations.

REFERENCES

- Gao S, Tang G, Hua D, Xiong R, Han J, Jiang S. Stimuli-responsive bio-based polymeric systems and their applications. *J Mater Chem* 2019;5:1-22. <https://doi.org/10.1039/C8TB02491J>
- Ahmed EM. Hydrogel: Preparation, characterization, and applications: a review. *J Adv Res* 2015; 6(2):105-21. <https://doi.org/10.1016/j.jare.2013.07.006>
- Klotz BJ, Gawlitta D, Rosenberg AJWP, Malda J, Melchels FPW. Gelatin-methacryloyl hydrogels: towards biofabrication-based tissue repair. *Trends Biotech* 2016;34(5):394-407. <https://doi.org/10.1016/j.tibtech.2016.01.002>
- Caló E, Khutoryanskiy V V. Biomedical applications of hydrogels: A review of patents and commercial products. *Eur Polymer J* 2015; 65: 252-7. <https://doi.org/10.1016/j.eurpolymj.2014.11.024>
- Shit SC, Shah PM. Edible polymers: challenges and opportunities. *J Polym* 2014 May; 1-13. ID 427259. <https://doi.org/10.1155/2014/427259>
- Shak KPY, Pang YL, Mah SK. Nanocellulose: Recent advances and its prospects in environmental remediation. *Beil J Nanotech* 2018; 9: 2479-98. <https://doi.org/10.3762/bjnano.9.232>
- Bhatia S, Bhatia S. Natural Polymers vs synthetic polymer. *N Poly Drug Del Syst* 2016; 9: 95-118. https://doi.org/10.1007/978-3-319-41129-3_3
- Jabbour L, Bongiovanni R, Chaussy D, Gerbaldi C, Beneventi D. Cellulose-based Li-ion batteries: A review. *Cellulose* 2013; 20(4): 1523-45. <https://doi.org/10.1007/s10570-013-9973-8>
- Buckley JF, Singer M, Clapp LH. Role of KATP channels in sepsis. *Cardiovascular Res* 2006;72(2): 220-30. <https://doi.org/10.1016/j.cardiores.2006.07.011>
- Mannhold R. KATP Channel openers: structure-activity relationships and therapeutic potential. *Med Res Rev* 2004;24(2): 213-66. <https://doi.org/10.1002/med.10060>
- Eswaramma S, Reddy NS, Rao KSVK. Phosphate crosslinked pectin based dual responsive hydrogel networks and nanocomposites: Development, swelling dynamics and drug release characteristics. *Int J Biol Macromol* 2017; 103: 1162-72. <https://doi.org/10.1016/j.ijbiomac.2017.05.160>
- Morselli D, Bondioli F, Sangermano M, Roppolo I, Messori M. Epoxy resins reinforced with TiO₂ generated by nonhydrolytic sol-gel process. *J Appl Polym Sci* 2014; 131(13): 1-9. <https://doi.org/10.1002/app.40470>
- Narjary B, Aggarwal P, Singh A, Chakraborty D, Singh R. Water availability in different soils in relation to hydrogel application. *Geoderma* 2012; 187(188): 94-101. <https://doi.org/10.1016/j.geoderma.2012.03.002>
- Luo Y, Teng Z, Wang X, Wang Q. Development of carboxymethyl chitosan hydrogel beads in alcohol-aqueous binary solvent for nutrient delivery applications. *Food Hydrocoll* 2013; 31(2): 332-39. <https://doi.org/10.1016/j.foodhyd.2012.11.011>
- Franklin DS, Guhanathan S. Influence of chain length of diol on the swelling behavior of citric acid based pH sensitive polymeric hydrogels: A green approach. *J Appl Polym Sci* 2015; 132(5): 1-9. <https://doi.org/10.1002/app.41403>
- Vinod R. Formulation and evaluation of nicorandil sustained release matrix tablets using natural gum *Mangifera indica* as release modifier. *Asian J Biomed Pharm Sci* 2013;3(18):1-9.
- Naeem M, Pervaiz F, Nawaz Z, Yousuf M, Ali A, Khalid N, et al. A quality by design approach: Fabrication, characterization and evaluation of optimized transdermal therapeutic system for antirheumatic lornoxicam. *Acta Pol Pharm-Drug Res* 2017; 17(1): 249-66.
- Rizwan M, Yahya R, Hassan A, Yar M, Azzahari AD, Selvanathan V, et al. pH sensitive hydrogels in drug delivery: brief history, properties, swelling, and release mechanism, material selection and applications. *Polymers* 2017; 9(12): 137-48. <https://doi.org/10.3390/polym9040137>
- Nesrinne S, Djamel A. Synthesis, characterization and rheological behavior of pH sensitive poly(acrylamide-co-acrylic acid) hydrogels. *Arab J Chem* 2017; 10(4): 539-47. <https://doi.org/10.1016/j.arabjc.2013.11.027>

20. Nair SS, Zhu JY, Deng Y, Ragauskas AJ. Hydrogels prepared from cross-linked nanofibrillated cellulose. ACS Sustain Chem Eng 2014; 2(4): 772-80. <https://doi.org/10.1021/sc400445t>
21. Parida P, Mishra C. Synthesis, crosslinking and evaluation of graft polymer for biomedical use. Res Rev J Pharm Sc 2012; 3(1): 37-45.
22. Hu X, Wei W, Qi X, Yu H, Feng L, Li J, et al. Preparation and characterization of a novel pH-sensitive Salecan-g-poly(acrylic acid) hydrogel for controlled release of doxorubicin. J Mater Chem B 2015; 3(13): 2685-97. <https://doi.org/10.1039/C5TB00264H>

CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

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Acquisition, Analysis or Interpretation of Data:	AR, URT, FMI, NSM, AE
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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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