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Formulation and evaluation of pH sensitive poly(acrylic acid-co-hydroxy ethyl methacrylate) hydrogels for specific site drug delivery

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ABSTRACT

The aim of the present study was to formulate the hydrogels of hydroxyethyl methacrylate (HEMA) and acrylic acid (AA) with two drugs namely; disopyramide phosphate (DSP) and propafenone hydrochloride (PPH) for pH sensitive drug delivery systems. These monomers were polymerized by free radical polymerization method and crosslinked with ethylene glycol dimethacrylate (EGDMA). The dynamic swelling and deswelling behaviors of the prepared hydrogels were studied by changing the pH from 1.2 to 7.4, varying copolymer compositions and crosslinker content. It was observed that with change in pH from 1.2 to 7.4, a considerable increase in swelling of about 70 % was observed for all formulations. It was also found that the degree of swelling increased with an increase in acrylic acid concentration and decreases with increase in EGDMA content. The drug loaded hydrogels were characterized by Fourier transmission infrared (FT-IR) spectroscopy, differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). The prepared drug loaded hydrogels have been further evaluated for drug content, in vitro drug release and stability studies. The in vitro drug release profiles of both the drugs were almost similar indicating that release is independent of the drug used and also the formulations showed stability for about 30 days.

Keywords: Acrylic acid, drug release profiles, EGDMA, pH sensitive hydrogels.

INTRODUCTION

For many decades, pharmaceutical dosage forms like tablets, capsules, creams, liquids, and injectables as drug carriers have mostly accomplished treatment of acute disease. Even today, these conventional drug delivery systems are primary pharmaceutical products, known to provide prompt drug release. Thus, to achieve and maintain a therapeutically effective drug concentration range it is necessary to take these drugs several times a day. This results indicates that significant fluctuation of drug levels and side effects i.e., they suffer from minimal synchronization between the required time for therapeutically effective drug concentration and actual drug release profile exhibited by dosage form [1].

The oral drug delivery holds a plethora of importance because of its ease of administration and patient compliance. Though the conventional oral drug delivery achieves both local and systemic effects, there is no control over drug release forms that may lead to local or systemic toxicity [2, 3]. Moreover, the rate and extent of absorption from these drugs may vary depending on physico-chemical properties of drug and excipients and other factors like presence or absence of food, pH of gastro intestinal tract (GIT) etc., These limitations shifted the focus of pharmaceutical scientists towards idealized drug delivery, wherein the required amount of bioactive agent is made available at desired time and site of action in the body. The low development cost and time required to introduce a novel drug delivery system, as compared to a new chemical entity further fortifies this shift. These systems allow

maintenance of plasma concentration within therapeutic range, which minimizes side effects and also reduces frequency of administration.

One such novel approach is the administration of drug in hydrogel polymer network. Hydrogels can be formulated sensitive to several stimuli, of which the pH sensitive drug delivery system are gaining importance specially in the oral route of administration considering the variation in pH along the GIT [4] with reduced side effects and increased patient convenience. In a medium of optimum pH and ionic strength, the pendant groups ionize and develop fixed charges on the gel and also swelling force in the gel [5]. Thus swelling force increases in the gel due to localization of fixed charges on the pendant groups and as a result, the mesh size of the network changes with small change in pH.

The model drugs used in the present investigation are disopyramide phosphate (DSP) and propafenone hydrochloride (PPH). Disopyramide phosphate is a drug of choice for cardiac disease due to its narrow therapeutic index; a controlled release microsphere is highly desired [6]. Propafenone hydrochloride is a well known anti-arrhythemic drug and lipophilic in nature due to short half life [7]. Hydroxyethyl methacrylate (HEMA) is the most widely studied system for biomedical application [8]. HEMA gels are very resistant to high temperature, acid and alkaline hydrolysis and they have low reactivity with amines. Since the gels of HEMA are considered non-ionic, pH sensitive swelling behavior involve modified HEMA, copolymerized with acrylic or methacrylic acids. Acrylic acid is easily incorporated, producing anionic polyelectrolyte gels whose ionization is a function of pH.

The dynamic equilibrium swelling, structural characterization and solute transport in swollen HEMA gels crosslinked with tripropylene glycol diacrylate was studied at varying concentrations of crosslinker by Ferreira *et al* [8]. Through swelling studies it was found that on changing pH from 6.5 to 12, a large increase in swelling occurred. Franson *et al*., have studied the influence of co-polymer composition on non-Fickian water transport through glassy copolymers [9]. Atul *et al* have studied the release behavior of bioactive agents from pH-sensitive hydrogels using controlled release systems and have reported lowest drug release rate was observed from non-ionized polymer networks in agreement with relationship between ionization, swelling and drug release [10].

Soppimath *et al* and Bajpai *et al* have studied the water sorption dynamics of binary copolymeric hydrogel of HEMA. The water uptake of poly(2-hydroxyethyl methacrylate) has been improved by co-polymerizing HEMA with acrylamide in presence of hydrophilic polymer such as polyethylene glycol (PEG) [11-12]. Shrivastava *et al* have studied the water sorption dynamics of hydrophobic, ionizable copolymer gels [13]. The diffusion of water, solute and protein in physiologically responsive hydrogels of poly(methacrylic acid-g-ethylene glycol) using a range of compositional changes was investigated by Bell *et al* [14] and Lisa Brannon Peppas *et al* [15]. The drug diffusion and binding in ionizable poly(vinyl alcohol)/poly (acrylic acid) (PVA/PAA) interpenetrating polymer networks (IPNs) was investigated by Wright *et al* [16].

Diclofenac sodium releasing pH sensitive monolithic devices were recently synthesized by copolymerization of HEMA with acrylate based co-monomers. Results indicate that in the stomach pH, swelling degree of acrylic acid containing gels is low (< 5%), while as high as 97.5% in the intestinal pH [17-18]. *In vitro* swelling and release studies of ocular pharmaceutical agents by silicon-containing hydrogels have been studied by Karlgard *et al* [19]. Release of amoxicillin from polyionic complexes of chitosan and PAA was carried in order to evaluate polymer-polymer and polymer-drug interactions [20]. Recently pH responsive hydrogels of poly(N-vinyl-2-pyrrolidone-polyethylene glycol diacrylate)-chitosan for oral drug delivery was reported [21-24].

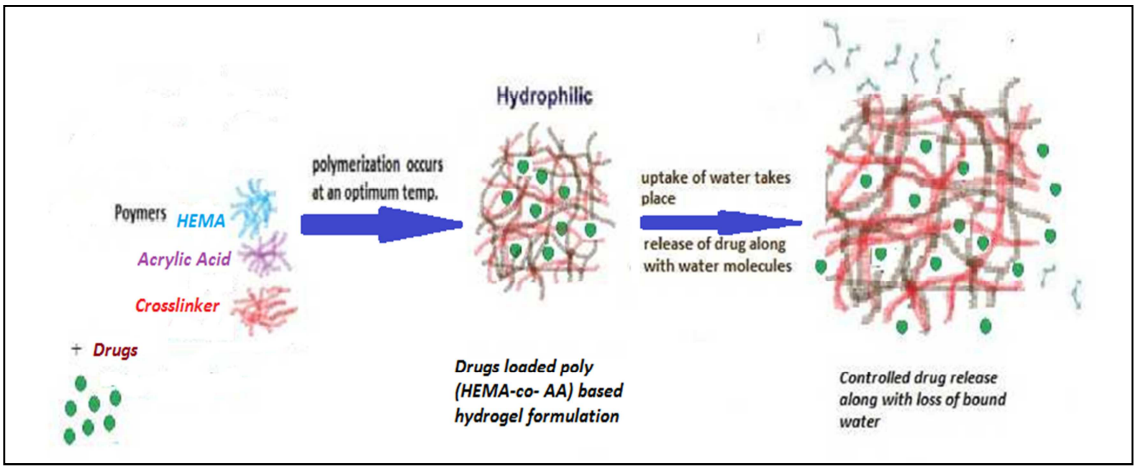
In the present research investigation, using Disopyramide phosphate and Propafenone HCl as drugs and hydroxyethyl methacrylate-co-acrylic acid hydrogel as carriers, an attempt has been made to design pH sensitive drug delivery system.

MATERIALS AND EQUIPMENTS

The drugs disopyramide phosphate and propafenone hydrochloride were obtained from Micro Labs, Bangalore, India. Hydroxy ethyl methacrylate (HEMA), ethylene glycol dimethacrylate (EGDMA), potassium persulphate and sodium metabisulphate were purchased from Sigma - Aldrich, USA. Acrylic acid and potassium dihydrogen phosphate were obtained from Loba Chemie, Mumbai. All other chemicals of analytical grade were obtained from Ranbaxy Fine Chemicals, Mumbai, India.

The prepared hydrogels were characterized for drug-carrier interactions by Fourier Transform Infrared (FT-IR) [25, 27] and differential scanning calorimetry (DSC). Fourier Transmission Infra Red Spectroscopy (FT-IR) analysis was carried out by KBr pellet method using FT-IR spectrometer, model 8033 Shimadzu, USA. DSC analysis was

performed using 2010 DuPont TA instrument, Germany. The dried samples were sealed into an aluminium pan and the dynamic DSC scans are recorded under in the temperature range 25°C - 300°C, at a heating rate of 10°C/min. The DSC scans recoded under argon gas purge at a flow rate of 80 ml/min. The drug content released from the hydrogel was estimated by spectrophotometric method using UV-visible spectrophotometer, 1601 model, Shimadzu, Japan and by automated dissolution tester USP XXI (TDL 08L) type II apparatus. Scanning electron microscopy (SEM) studies have been carried out using Joel SEM instrument, Japan.



Preparation of Poly(AA-co-HEMA) Hydrogels

The typical hydrogel formulations and designations of the prepared copolymeric hydrogels of both disopyramide phosphate and propafenone hydrochloride is tabulated in Table **1**. For all the formulations HEMA and AA were used, where HEMA is a non-ionic monomer and AA is the pH sensitive monomer.

The specific monomer ratios have been taken in water and temperature was raised to 65°C-70°C and stirred for 15 mins for pre-polymerize. Water (approx. 20ml) was chosen as the common solvent in which both the monomers are soluble. The free radical co-polymerization process has been carried out using 0.04 M redox couple (potassium persulphate and sodium meta bisulphate) initiator. The calculated dose of the drug was added and stirred for 5 mins to get uniform dispersion of drug in hydrogels. About 0.5 % of EGDMA crosslinker was added and mixed well. The reaction mixture was poured into petridish and allowed for 4 h. The formed copolymeric gel was removed from the mold and kept in desiccators for 2-3 days for complete drying. The dried hydrogels were crushed and passed through sieve #85/120 and used for further studies. In formulations M6, M7, G6 and G7 the initiator concentration and the ratios of monomer composition (HEMA : AA (40:60)) are kept constant and vary the EGDMA content from 1 to 1.5%.

Table 1. Typical formulations of disopyramide phosphate and propafenone hydrochloride loaded poly(AA-co-HEMA) hydrogels

Disopyramide phosphate formulations							
Ingredients	Sample Code						
	G1	G2	G3	G4	G5	G6	G7
DSP (mg)	4.92	4.92	4.92	4.92	4.92	4.92	4.92
HEMA (%)	100	80	60	40	20	40	40
AA (%)	0	20	40	60	80	60	60
SMBS (molar)	0.4	0.4	0.4	0.4	0.4	0.4	0.4
KPS (molar)	0.04	0.04	0.04	0.04	0.04	0.04	0.04
EGDMA (% v/v)	0.5	0.5	0.5	0.5	0.5	1	1.5
Propafenone hydrochloride formulations							
Ingredients	Sample Code						
	M1	M2	M3	M4	M5	M6	M7
PPH (mg)	492	492	492	492	492	492	492
HEMA (%)	100	80	60	40	20	40	40
AA (%)	0	20	40	60	80	60	60
SMBS (molar)	0.4	0.4	0.4	0.4	0.4	0.4	0.4
KPS (molar)	0.04	0.04	0.04	0.04	0.04	0.04	0.04
EGDMA (% v/v)	0.5	0.5	0.5	0.5	0.5	1	1.5

Determination of λ_{max} for drugs

The UV spectra were recorded for the 10 µg/ml of Disopyramide phosphate and Propafenone hydrochloride drug stock solutions in pH 7.4 phosphate buffer solution in the wavelength range 200 - 400 nm. The absorption maximum

was found to be 268 nm and 304 nm for disopyramide phosphate or propafenone hydrochloride respectively and these wavelengths were utilized for quantitative analysis of drug delivery.

Swelling and De-swelling Studies

The pH dependent swelling behaviors of the poly(AA-co-HEMA) hydrogels have been studied in both 0.1N HCl (pH 1.2) and pH 7.4 phosphate buffer. About 200 mg of hydrogels were placed in 20 ml of 0.1N HCl for the first 2 hr, and then the hydrogels were transferred to pH 7.4 phosphate buffer solution and change in weight was monitored. At every 1 hr interval, the hydrogels were taken out and surface adhered water was removed by blotting with tissue paper and their weights were recorded. The swelling studies of hydrogels were carried out till 10 hr. The percentage of water uptake (S) was calculated by the following equation;

$$S = \frac{\text{Weight of swollen hydrogel} - \text{Weight of dry hydrogel}}{\text{Weight of dry hydrogel}} \times 100 \quad (1)$$

De-swelling study is performed to confirm the pH sensitivity and also to check whether the pH sensitivity is reversible. The swollen poly(AA-co-HEMA) hydrogels for 10 hr were blotted with tissue paper to remove surface adhered water and their weights were recorded. These were transferred to 20 ml of 0.1N HCl. The weights were recorded for every 1 hr after blotting the surface of the hydrogels with soft tissue paper [28, 29]. The percentage decrease in swelling was determined using the equation mentioned above.

Drug Content

The drug, DSP (150 mg- equivalent weight) and PPH drug (225 mg- equivalent weight) were extracted from the hydrogels using water as comment solvent. Both extracts were suitably diluted and drug contents were estimated by UV spectrophotometric method at 268 nm and 304 nm for DSP and PPH respectively.

In vitro drug release and stability studies

In vitro drug release from the poly(AA-co-HEMA) hydrogels have been carried out in triplicate at 37 ± 1°C in a USP II rotating paddle dissolution apparatus at a rotation speed of 50 rpm. The dissolution media was maintained at 37 ± 0.5^{0}C and stirred at 100 rpm. Drug release from the formulations were determined by withdrawal of 10 ml samples using guarded pipette at 30 min intervals for the first 4 h and 1 h interval for the remaining 4 h. Drug content was estimated after appropriate dilution. Effect of ageing on drug release studies were carried out for the selected batches of the formulations. The selected formulations were stored at 25^{0}C and 60% RH in desiccators for a period of 4 weeks. Each batch formulation of 100 mg was taken on 1st, 2nd, 3rd and 4th week and was subjected to *in vitro* drug release studies.

RESULTS AND DISCUSSION

Differential Scanning Calorimetric (DSC) Studies

To understand the compatible state of the drug and copolymer hydrogel carriers, DSC studies have been carried out on pure DSP, PPH, DSP loaded hydrogel formulation (G5) and PPH loaded hydrogel formulation (M5). The obtained DSC thermograms are shown in Figures 1 (a)-(b). The melting point range of pure drug, DSP was lies in the range 211.6 - 216.9 ^{0}C with a sharp endothermic peak at 213.8 ^{0}C. Similarly the melting range of the pure PPH was lies in the range 171.4 - 177.4 ^{0}C and exhibits a sharp endothermic peak at 173.4 ^{0}C. It was observed that presence of the endothermic peak of DSP at 213.4 ^{0}C in formulation, G5 and PPH at 172.3 ^{0}C in formulation, M5 indicated that the presence of DSP and PPH drug in the hydrogels respectively. The melting points of the drugs were in good agreement with the DSC data reported elsewhere [30].

FTIR Studies

FT-IR spectra were obtained for poly(AA-co-HEMA) hydrogel, DSP and its hydrogel formulation G5 and PPH and its hydrogel formulation M5 (Figures 2 (a)-(c)). FTIR spectra showed that the characteristics bands of pure DSP drug were not altered after successful encapsulation without any change in their position, indicating no chemical interaction between DSP and poly(acrylic acid-co-2-HEMA). The characteristic IR absorption peaks of the G5 formulation (Fig. 2(b)) were noticed at, 3479 cm^{-1} is due to amide stretching, 3295 cm^{-1} is due to N-H stretching, 1643 cm^{-1} is due to -$CONH_2$ stretching, 1598 cm^{-1} is due to benzene and pyrimidine ring vibration and 945 cm^{-1} is due to H_3PO_4 stretching.

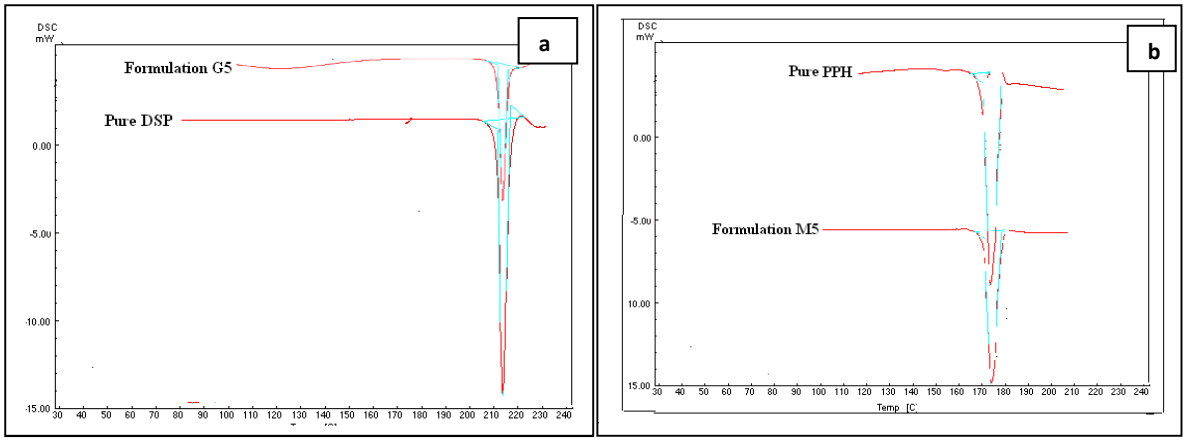
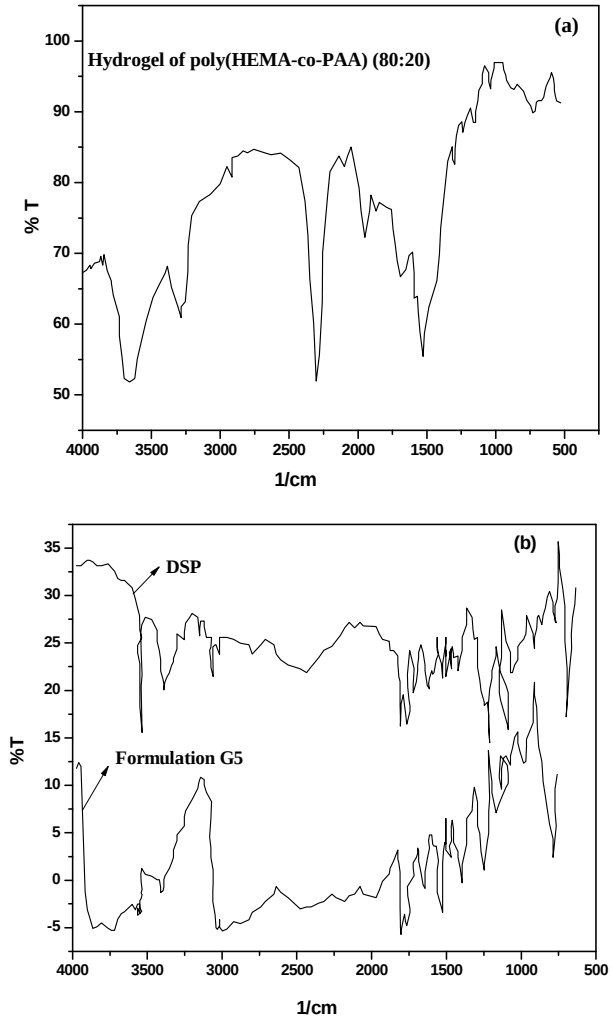


Figure 1. DSC thermograms of (a) pure DSP & formulation, G5 and (b) pure PPH & formulation, M5



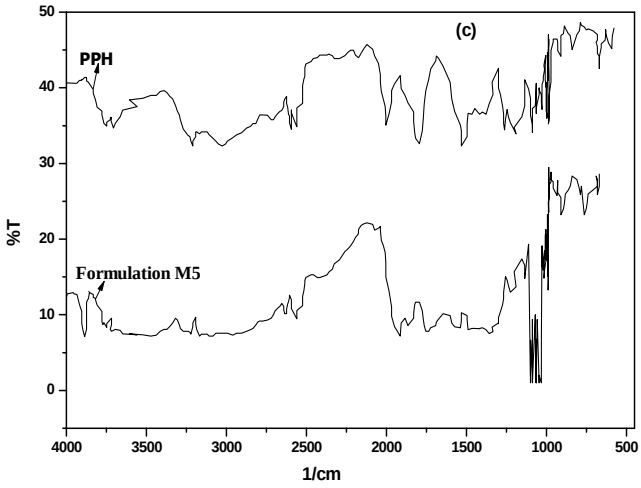


Figure 2. FTIR spectra of (a) Hydrogel of poly (acrylic acid- co-hydroxy ethylmethacrylate) (20/80), (b) pure DSP and formulation, G5 and (c) pure PPH and formulation, M5

FT-IR spectra were obtained for PPH and PPH loaded hydrogel are presented in Figure 2(c). FTIR spectra showed that the characteristics bands of pure drug PPH were not altered after successful encapsulation, indicating no chemical interaction between PPH and poly(acrylic acid-co-hydroxy ethyl methacrylate). The characteristic absorption peaks of IR spectra of PPH formulations were noticed at 3420 cm^{-1} is due to hydrogen bonded -OH stretching, 3317 cm^{-1} is due to secondary amine stretching, 2972 cm^{-1} is due to aliphatic C - H stretching, 1662 cm^{-1} is due to keto group stretching, 1593 cm^{-1} is due to aromatic ring, C - C stretching and 1030 cm^{-1} is due to C - O group stretching. A comparison and interpretation of this region is in good agreement with the reported data elsewhere [31].

Morphological Behaviors

SEM analysis was performed to study the morphological behaviors of swollen hydrogels in water, solutions at pH 1.2 and 7.4. The SEM photomicrographs of swollen hydrogels at neutral, pH 1.2 and pH 7.4 are shown in Figures 3 (a)-(c) respectively. It was observed that the hydrogels in water were coarse and when compared with pH 1.2 and pH 7.4 buffer solution the surface image of hydrogels shows more swollen with respect to pH 7.4 buffer solution than in 1.2 pH solution. This could be attributed to the increased swelling of the hydrogel in alkaline pH confirming its pH sensitivity [32].

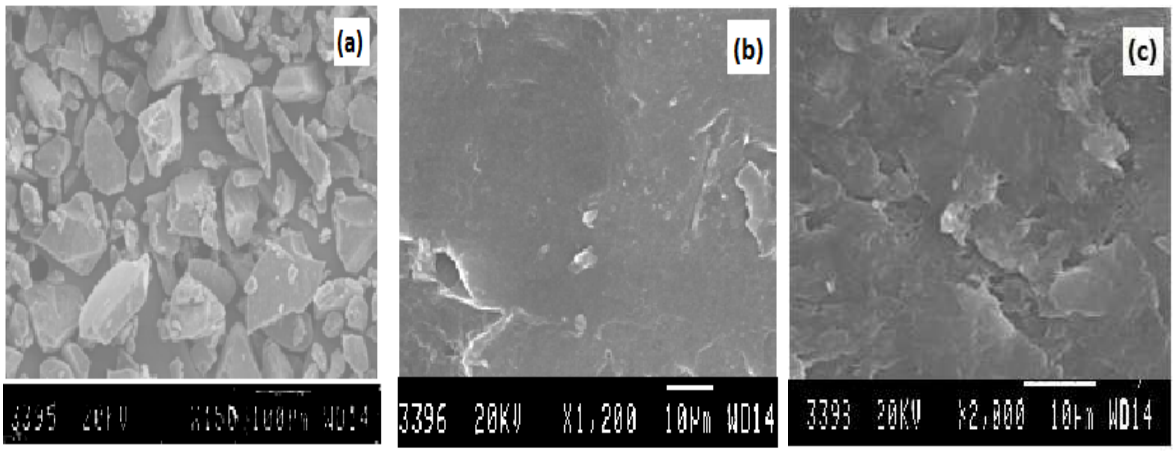


Figure 3. SEM photomicrographs of swollen poly(AA-co-HEMA) hydrogel particles (a) in neutral medium, (b) at 1.2 pH and (c) at 7.4 pH

Drug Content in Poly(AA-co-HEMA) Hydrogel

The measured percent of drug content in poly(AA-co-HEMA) formulations were lies in the range 19.25 - 20.33 % and 19.3 - 20.4 % for DSP and PPH systems respectively. Drug content was found to be almost same in both DSP and PPH loaded hydrogel formulations which are tabulated in Table 2. Although a slight change in the drug amount was observed in the hydrogels indicating that a slight variations in the ratios between the drug and carrier used. This result clearly indicates that the drug is uniformly distributed in all hydrogel formulations [33-34].

Table 2. Content Uniformity Data of DSP and PPH loaded Poly(AA-co-HEMA) Hydrogels

Disopyramide phosphate based formulations							
Formulation Code	G1	G2	G3	G4	G5	G6	G7
Average mean*(mg) ± S.D	19.6±0.52	19.2±0.25	19.7±0.38	19.2±0.52	19.2±0.52	19.6±0.5	19.4±0.9
Propafenone hydrochloride based formulations							
Formulation Code	M1	M2	M3	M4	M5	M6	M7
Average mean*(mg) ± S.D	19.6±0.42	19.8± 0.40	19.8±0.2	19.7±0.1	20.4± 0.50	19.3±0.5	20.4± 0.44

Swelling Studies of Poly(AA-co-HEMA) Hydrogels

The effect of monomer compositions in the copolymers and crosslinker content on the swelling behaviorus of hydrogels has been studied. The swelling studies of hydrogels (without drugs, designated as S1, S2, S3, S4, S5, S6 and S7) were carried out for first 2 h in acidic pH (0.1N HCl) to mimic the stomach conditions. For the next 8 h, swelling was determined in basic pH (pH 7.4, phosphate buffer) to mimic the intestinal conditions. The plots of percentage swelling of hydrogels as a function of time are shown in Figures 4 (a)-(b).

The Figures 4 (a)-(b) indicate that with change in pH from 1.2 to 7.4, a drastical increase in swelling was observed for all hydrogel formulations. This is due to the ionization of carboxylic groups at higher pH range [36]. From S1 to S5 formulations, the acrylic acid concentration increases from 0% to 100%. The concentration of EGDMA remains constant at 0.5% in all the above formulations.

Swelling behaviors of hydrogels strongly depends on the extent of crosslinking. As the EGDMA content is increased from 0.5% to 1.5 %, the percentage swelling was found to decrease from 420.3 % to 281.4%. This is due to the fact that increase in crosslink content increases the polymeric structure stability which is due to more number of crosslink points in the polymeric cage [37]. At lower cross-linking density, the network is loose packing with a greater hydrodynamic free volume, so that the chains can accommodate more of the solvent molecules resulting in higher swelling. This clearly indicates that the crosslinker content have a remarkable effect on the swelling behavior of the drug loaded hydrogel [38].

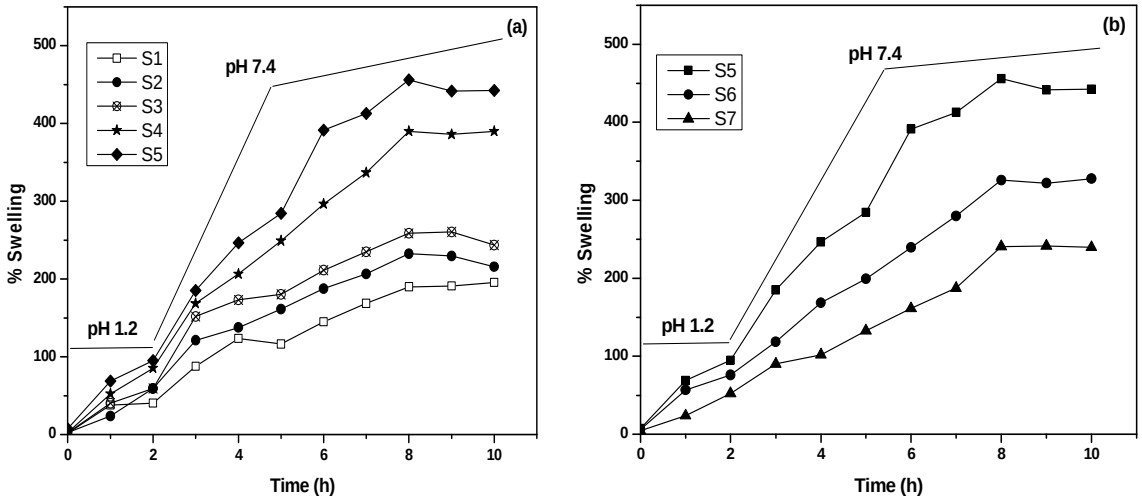


Figure 4. The effect of (a) monomer content and (b) crosslinker content on swelling behaviours of poly(AA-co-HEMA) hydrogels

Deswelling Studies

Hydrogels swell differently at different pH media; hence, their pH dependent deswelling behaviors were investigated. The prepared hydrogels were allowed to swell for 10 h by placing in pH 7.4 phosphate buffer solution and deswelling behavior is monitored by transferring the gels into 0.1N HCl solution for 8 h [39 , 40] (Figure 5). At every one hour the hydrogels were taken out from the buffer solution, surface water was blotted and the weights were recorded. The effect of monomer (AA) content on the deswelling behaviors of hydrogels is shown in Figures 5 (a). From the figure it was noticed that as increase in AA content the deswelling behaviour of hydrogels is increases. The trend of deswelling behaviors of hydrogels is same as swelling behaviors.

Effect of crosslinker content on the deswelling behaviours of the hydrogel formulations has been studied by increasing the EGDMA content from 0.5% to 1.5% (Figure 5(b)). The rate of deswelling behavior was reduced as increase in crosslink density of the polymeric structure. It can also be noticed that the duration of swelling behavior was 10 h and but it is shorter for deswelling studies (8 h).

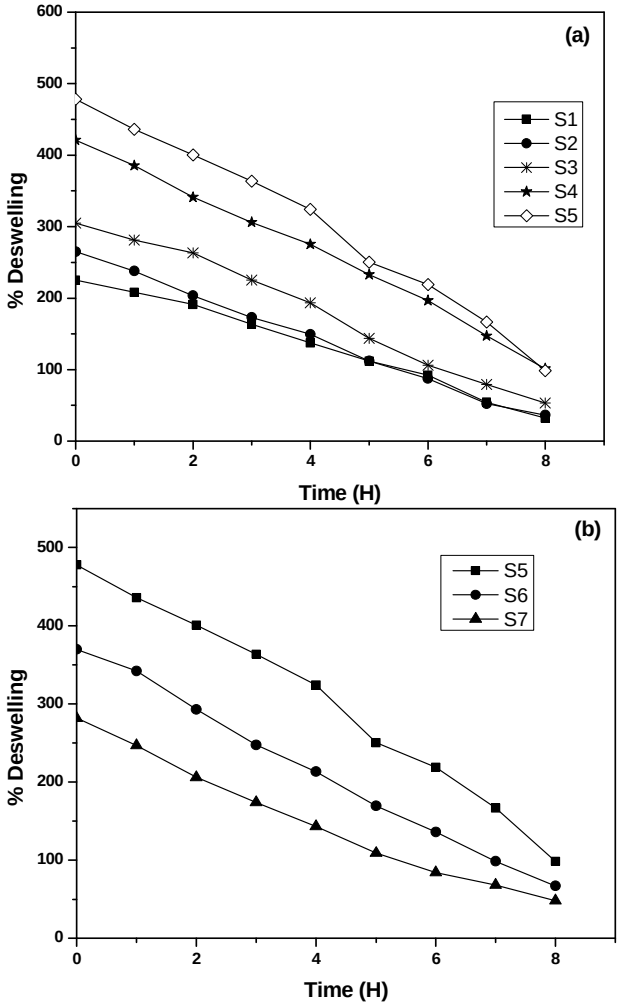


Figure 5. The effect of (a) monomer content and (b) crosslinker content on deswelling behaviours of poly(AA-co-HEMA) hydrogels

In vitro Release Studies

The *in vitro* release studies were carried out for all the formulations (G1 to G7 and M1 to M7) in both acidic and basic media. The release studies were carried out in the simulated gastric fluid (SGF) for first 2 h, to mimic the acidic conditions prevailing in the stomach. For the next 8 h, the release studies were carried out in simulated intestinal fluid (SIF), mimicking the alkaline conditions of the intestine. The *in vitro* release data for the hydrogels of DSP and PPH formulations are shown in Figure 6 (a)-(b) and Figure 7 (a)-(b) respectively. The release profiles of the drugs from their formulations were almost similar with initial burst occurring in the acidic solution showing slightly higher drug release content from PPH loaded hydrogels than in the DSP loaded formulations. Hence, it can be stated that release is independent on the nature of drug used.

Effect of pH on the drug release profiles of poly(AA-co-HEMA) hydrogels have been carried out by changing the pH of the solution from acidic (pH 1.2, HCl solution) to slight basic (pH 7.4 phosphate buffer). For the initial 2 h i.e., in the SGF, the percentage drug release was found to be low (on comparing to a conventional tablet) for about only 15% of the complete drug for all the formulations; this can be attributed to the fact that the hydrogel swells less in the acidic medium thereby showing very less release profile . When the dissolution medium was changed to SIF i.e., at pH 7.4, the release was found to increase as a function of time.

Variations in the monomer composition also have a significant effect on the drug release rate from the hydrogel formulations. This effect has been studied by varying the ratio of acrylic acid and HEMA in the formation of hydrogels. For all the formulations from M1 to M5 and from G1 to G5, it was noticed that the percentage release of the drug increases to about 85% with increase in acrylic acid concentration in the poly(AA-co-HEMA) hydrogel formulations.

The effect of crosslinker, EGDMA content on the drug release behavior of the hydrogel formulations has been studied (Figure 6(b)). As the EGDMA content increased from 0.5% to 1.5%, the percentage drug release were found

to decrease from 100% (G5) to 85% in G6 and 77% in G7 respectively in DSP loaded hydrogel formulations. Similarly in PPH loaded hydrogel formulations with increase in EGDMA content, the percentage drug release showed a decrease from 98% (M5) to 88% in M6 and 80% in M7 respectively. The effect is due to the increased crosslink density in the polymeric structure leading to sustained drug release. This result clearly indicates that crosslinked hydrogels can be preferred tool for the controlled drug release.

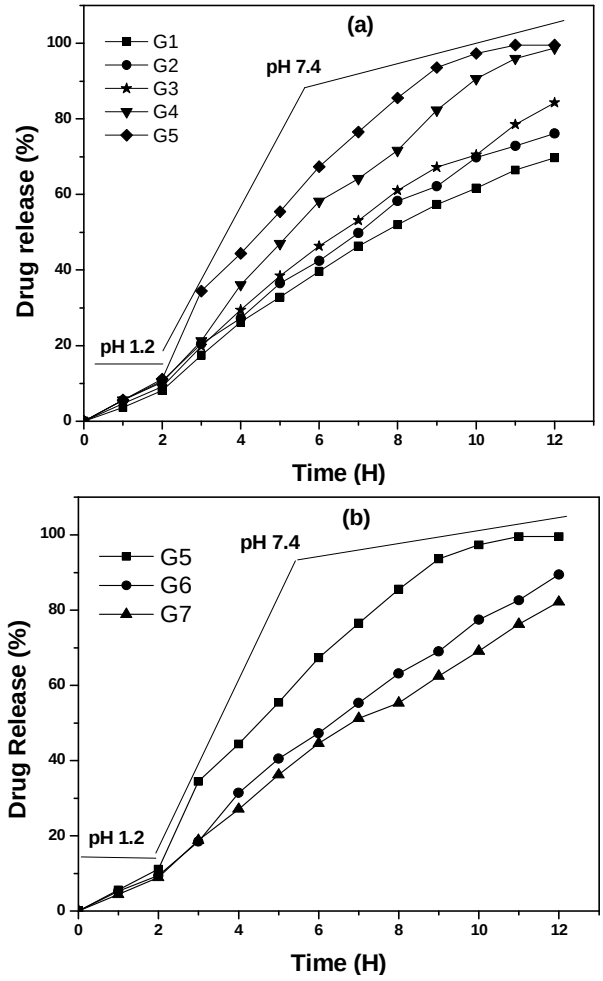
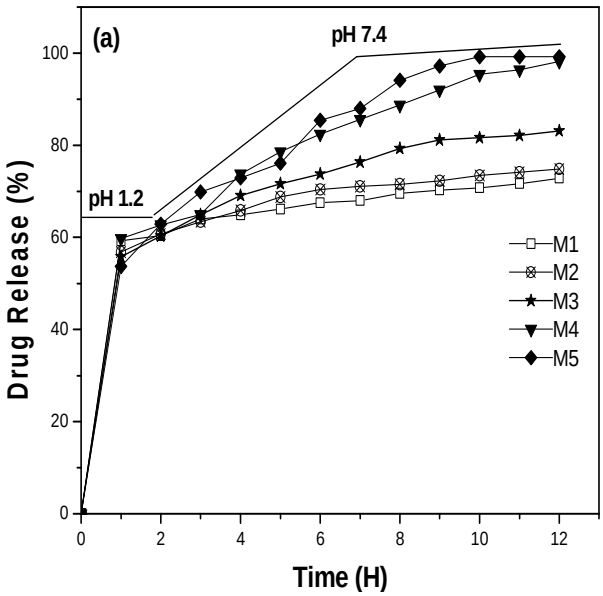


Figure 6. *In-vitro* DSP release profiles from poly(AA-co-HEMA) hydrogel; (a) effect of monomer (AA) content and (b) effect of corsslinker content



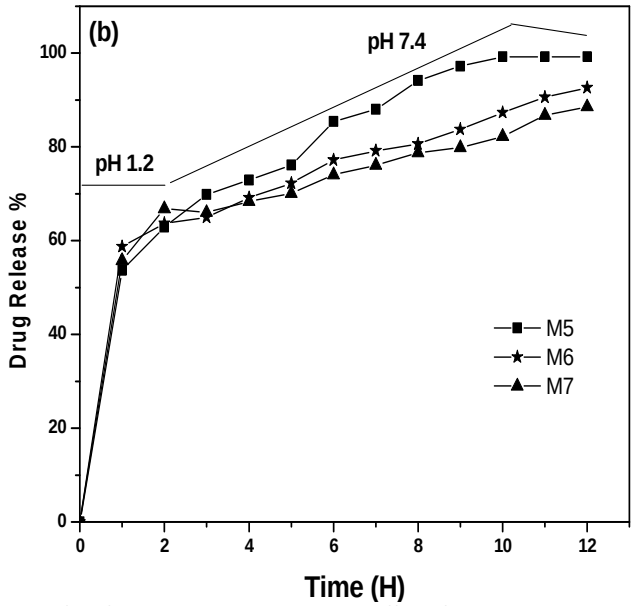


Figure 7. (a) *In-vitro* PPH release profiles from poly(AA-co-HEMA) (a) effect of monomer (AA) content and (b) effect of crosslinker content

Mathematical Model Fitting of Obtained Drug Release Data Using pcp-Disso-V2.08 Software

The *in vitro* release studies data for both DSP loaded and PPH loaded formulations was quantified using PCP-Disso-v2.08 Software. This software was used to determine the percentage release of drug and also to determine the release mechanism. Parameters like 'n' the time exponent and 'K' the release rate constant were calculated which are tabulated in Table 3. The value of n determined from Korsmeyer-Peppas equation was in the range 0.8-1.2, which indicates that the drug release from the hydrogels follows non-Fickian or anomalous mechanism (relaxation controlled) and Super case II transport respectively.

Table 3. n and K Values of DSP and PPH loaded Poly(AA-co-HEMA) Hydrogel Formulations obtained from Best Fit of Peppas Model

Sample codes	G1	G2	G3	G4	G5	G6	G7	G8
n	0.9	0.8	0.9	0.9	1.0	0.9	1.1	1.2
K	1.1	1.4	1.2	1.9	2.0	1.72	2.15	1.86
Sample codes	M1	M2	M3	M4	M5	M6	M7	M8
n	0.98	0.92	1.2	1.04	0.9	0.97	1.1	1.06
K	1.3	1.42	1.1	1.16	2.2	2.05	1.98	2.1

Stability studies

Stability studies of the DSP and PPH loaded formulations namely, G5 and M5 were subjected to ageing at 25^0C, 60% RH for about 30 days. After ageing G5 and M5 formulations were evaluated for drug content at regular intervals of time (for a period of 4 weeks) and drug content results obtained are presented in Table 4. The results obtained indicate that there was no significant change in drug content of the hydrogels after ageing. Based on the result it can be concluded that the formulation containing DSP and PPH were stable.

Table 4. Stability Studies of the Drug Content from Formulations G5 and M5

Formulation	Time (week) mean ± SD*			
	0	1	2	4
G5*	20.33 ± 0. 18	20.19 ± 0.23	20.11 ± 0.09	20.09 ± 0.32
M5*	20.40 ± 0.12	20.35 ± 0.19	20.31 ± 0.15	20.28 ± 0.30

CONCLUSION

FT-IR studies indicated that there is no interaction between the polymers and drugs in both formulations and the key characteristic peaks of the drugs were not altered. From the DSC thermograms, it was evident that the decomposition temperatures of both the drugs and their hydrogel formulations are closer; hence no significant interactions exist between drug and polymers. The results obtained from the drug content studies, indicates that the drugs are uniformly distributed in all the hydrogel formulations.

From the results of swelling studies, it was observed that with change in pH from 1.2 to 7.4, an exceptional increase in swelling was observed for all hydrogel formulations, confirming the pH sensitivity of the hydrogels. The swelling

behavior strongly depends on the monomer concentration and crosslinker content. The results obtained from deswelling studies indicate that upon changing the medium from basic to acidic, there is a decrease in swelling, confirming the reversibility of the system.

The *in vitro* drug release profiles of both the drugs were almost similar and concluded that release is independent of the nature of drug used. The release profiles were dependent on the change in pH, crosslinker content and ratio of monomers used in the hydrogels. Drug release from the hydrogels followed non-Fickian or anomalous mechanism (relaxation controlled) and super case II transport respectively. Based on the drug release results it can be concluded that the formulations G5 and M5 are optimized hydrogels.

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