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Synthesis of Novel Hydrogels based Poly(4-Hydroxyphenylazo-3-N-(4-hydroxyphenyl)maleimide) for Specific Colon Delivery of Chemotherapeutic Agent

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ABSTRACT

In recent years azo functionalized polymeric hydrogels are very interesting; it is due to their promising applications in various fields especially in the colon drug delivery. 4-Hydroxyphenylazo-3-N-(4-hydroxyphenyl) maleimide (HPM) was synthesized and used for development of hydrogels by free radical polymerization with acrylamide (Am) and N,N-methylene bis acrylamide. Synthesized poly(Am-co-HPM) (PAH) hydrogels were used for encapsulation of 5-fluorouracil (5-FU) an anticancer drug. Structural, thermal, morphological and drug distribution of PAH hydrogels were characterized by Fourier transform infrared spectroscopy, scanning electron microscopy and X-ray diffraction techniques, respectively. Maximum percentage of encapsulation efficiency i.e. 78.25±1.3 was observed for AZ1 PAH hydrogels. 5-FU release studies were performed by in vitro method in simulated gastro intestinal fluids (pH 1.2 & 7.4). To support the 5-FU release mechanism from PAH hydrogels, swelling and deswelling kinetics were studied in doubly distilled water.

INTRODUCTION

The specific colon delivery of drugs by various systems, such as prodrugs, polymeric drug and polymeric matrices has great interest in the recent years (Saffran *et al.*, 1998; Kopeček and Kopečková, 1992; Tozer *et al.*, 1991). Considering the requirement of specific colon drug delivery there are three approaches to reach the drug into the colon such as utilizing pH changes in the gastrointestinal tract (GIT) (Ashford *et al.*, 1993; Kuethe, 1992), timed release capsules (Davis *et al.*, 1986; Sudhakar *et al.*, 2013), and polymeric carriers degraded by the microflora located in the colon (Brown *et al.*, 1983). The mechanism of these colon-specific drug delivery systems is presumed to take place due to enzymatic cleavage by the normal colonic microflora. The rich microflora of the human colon is responsible for the conversion of laxatives such as suhstine and sennosides to active therapeutics. There are only a few studies performed on polymeric systems that could carry a variety of drugs to the colon. A more universal approach to utilize bacterial degradation of the azo bond to achieve specific release has been the synthesis of a polymer suitable for coating (Saffran *et al.*, 1986; Prabhakar *et al.*, 2013), and the use of hydrogels with azoaromatic cross-links (Brondsted and Kopecek, 1992; Mallikarjuna *et al.*, 2013).

To reduce the side effects and increasing bioavailability, colon formulation approach has been used (Philip *et al.*,2008). The specific site targeted drug delivery to the colon is most important in the treatment of colonic diseases such as inflammatory bowel diseases, irritable bowel syndrome and colon cancer.

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Hence it is essential to enhance the release rate of drug and absorb drug at colon for chemotherapy. Other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction (Davis, 1990). The most critical challenge in such drug delivery approach is to preserve the formulation and also preserve the drug from degradation, release and/or absorption in the upper portion of the GIT (Ashford and Fell, 1994; Chandra Sekhar *et al.*, 2014).

To achieve successful colon targeted drug delivery, a formulation need to produce controlled release in the proximal colon. The drug formulations such as therapeutic proteins and peptides which are susceptible to chemical and enzymatic degradation in the upper GIT are suitable for colonic delivery (Luck and Crabb, 2000).

In the present investigation attempts were made to develop novel azo functionalized polymeric hydrogels from 4-hydroxyphenylazo-3-N-(4-hydroxyphenyl) maleimide (HPM) and acryl amide (Am) free radical polymerization for colon drug delivery. This poly(Am-co-HPM) hydrogels were characterized by FTIR, DSC, XRD and SEM. The in vitro release studies of the incorporated 5-fluorouracil (5-FU) were carried out in simulated gastric and intestinal fluids.

MATERIALS AND METHODS

Materials

Acrylamide (Am), Potassium persulphate (KPS), 4-amino phenol and maleic anhydride purchased from s.d. Fine chemicals. N,N-methylene-bis-acrylamide (MBA), 5-Fluorouracil (5-FU), were purchased from Aldrich chemicals Mumbai, India. All other chemicals were analytical grade and were used as received without further purification. 4-hydroxyphenylazo-3-N-(4-hydroxyphenyl) maleimide was synthesized as reported in literature (Mohammed and Mustapha, 2010). Double distilled (DD) water was used throughout the experiments.

Preparation of PAH hydrogels

poly(Am-co-HPM) hydrogels were prepared by free radical copolymerization. Monomers (Am and HPM) were dissolved in 4 mL of distilled water, to this solution 1 mL of crosslinking agent (2 wt %, MBA), 1mL of potassium per sulfate solution (5 wt %).

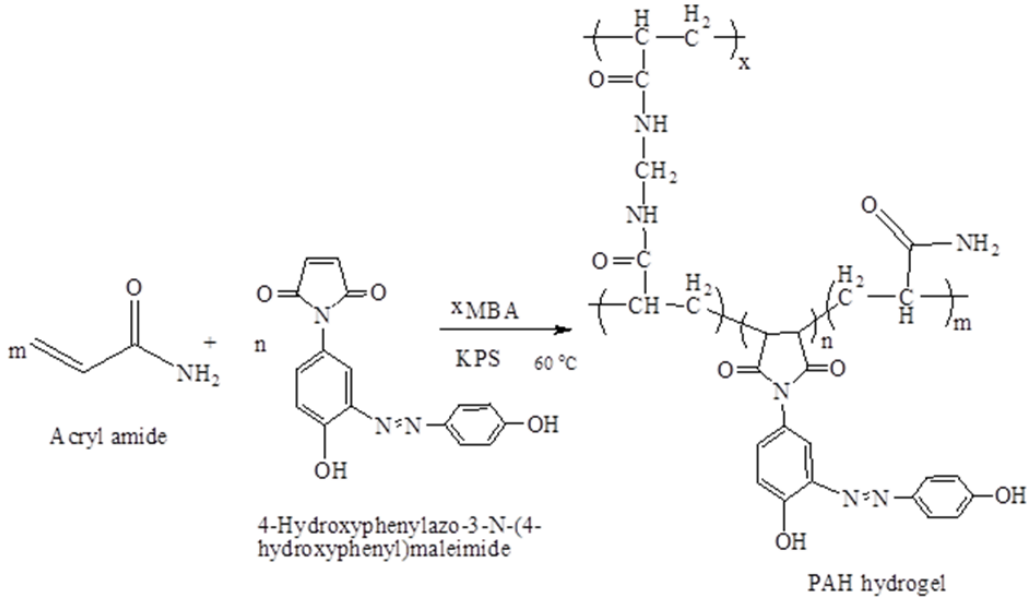
The free-radical polymerization was carried out in a 50 mL beaker maintained at 60^{o}C temperature in order to complete matrix formation. The schematics of chemical reaction of PAH hydrogel has given in Scheme I. The digital photographs of synthesized PAH hydrogels are shown in Figure 1.

Swelling studies of PAH hydrogels

The percentage of swelling is the most important parameter for characterization of hydrogels (Omidian *et al.*, 1994). Swelling and deswelling kinetics of the PAH hydrogels were studied in DD water by mass measurements at 37^{o}C. The percentage of swelling ratio (%SR) and equilibrium swelling ratio (%ESR) was calculated by following Equation.

$$\%\ \text{Swelling ratio of PAH hydrogels} = \left(\frac{m_t - m_d}{m_d}\right) \times 100 \quad ..1$$

Where m_t and m_d are weight of swollen PAH hydrogels for a given time t and dried PAH hydrogels, respectively.



Scheme I. Schematic representation of PAH hydrogels.

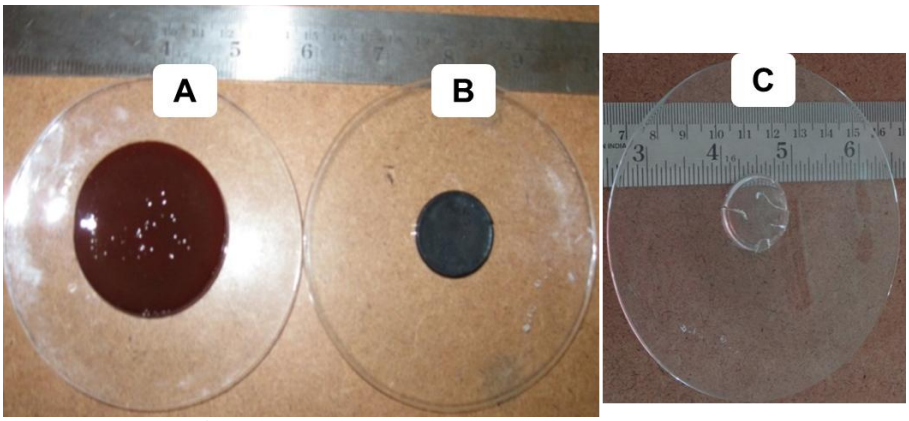


Fig. 1: A digital photograph of (A) swollen, (B) dried poly(Am-co-HPM) hydrogels and (C) poly(Am) dried hydrogels

Table 1: Results of % encapsulation efficiency of PAH hydrogels loaded with 5-FU and Release kinetic parameters of different formulations.

Code	Am (g)	HPM (g)	MBA (ml)	APS (ml)	%EE	*n*	r^2	*k*
AZ1	1	0.5	1	1	78.25±1.3	0.473	0.987	0.4819
AZ2	1	0.5	2	1	63.76±1.8	0.672	0.986	0.1276
AZ3	1	0.25	1	1	62.09±0.9	0.745	0.979	0.4415
AZ4	1	0.1	1	1	53.87±2.1	0.672	0.986	0.1288
AZ5	1	0.5	3	1	42.03±1.1	0.653	0.948	0.4570

5-FU loading and encapsulation efficiency of PAH hydrogels

The anticancer drug 5-FU loaded into PAH hydrogels by equilibrium swelling method. The known concentration of 5-FU drug solution was prepared and allowed to swell the PAH hydrogels for 24h at 37°C. The 5-FU loaded PAH hydrogels were placed in 10 mL of buffer solution and stirred vigorously for 24h to extract 5-FU drug from the PAH hydrogels. The solution was filtered and assayed by UV spectrophotometer (LAB INDIA, UV-3092) at fixed λ_{max} value of 270 nm. The results of % 5-FU loading and encapsulation efficiency (% EE) were calculated using Eqs. (2) and (3) respectively. These data are compiled in Tables 1, respectively.

$$\%\,5\text{-FU loading} = \left(\frac{\text{Amount of 5-FU in PAH hydrogels}}{\text{Amount of PAH hydrogels}}\right)\times 100 \quad \ldots 2$$

$$\%\,5\text{-FU encapsulation efficiency} = \left(\frac{\text{Actual 5-FU PAH loading}}{\text{Theoretical 5-FU PAH loading}}\right)\times 100 \quad \ldots 3$$

In-vitro release study of PAH hydrogels

Dissolution was carried out using the fully automated dissolution system (DS 8000, LAB INDIA) equipped with eight baskets. Dissolution rates were measured at 37°C under 100 rpm speed. Drug release from the PAH hydrogel was studied in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4) at 37°C. At periodic intervals of time, aliquot samples were pipetted out and assayed using LAB INDIA, UV-3092, UV-Vis spectrophotometer. After each sampling an equal volume of fresh buffer solution was added to the release medium.

Characterization

The chemical structure of PAH hydrogels were analyzed by Fourier transform infrared spectroscopy (FTIR) using Perkin Elmer, Spectrum Two model. The PAH hydrogels were finely ground with KBr to prepare the pellets under a hydraulic pressure of 392.2 dynes/m^2 and spectra were scanned between 4000 and 500 cm^{-1}. Differential scanning calorimetry (DSC) curves of the pristine 5-FU, placebo PAH hydrogels and 5-FU loaded PAH hydrogels were recorded using DSC 200F3 Maia. The analysis was performed by heating the samples at the rate of 10 °K/min under nitrogen atmosphere and temperature range between 0-580°C.

The X-ray diffractograms of pure 5-FU, PAH hydrogels and 5-FU loaded PAH hydrogels were recorded on X-ray diffractometer (Philips, PW1830) equipped with a Ni-filtered CuKα radiation (λ =1.5418A˚). The PAH hydrogels were mounted on a sample holder and XRD scans were recorded in the 2θ range of 0-80° at the speed of 5°/min to estimate the crystallinity of the PAH hydrogels.

The morphological characteristics of the PAH hydrogels were studied using scanning electron microscopy (model: MIRA\\TESCAN).

RESULTS AND DISCUSSION

Characterisation of 4-Hydroxyphenylazo-3-N-(4-hydroxyphenyl)maleimide

The FTIR and ^{1}H-NMR spectrum of 4-Hydroxyphenylazo-3-N-(4-hydroxyphenyl)maleimide is shown in Figure 2 and 3.; Color: yellow brown; yield: 78%; melting point: 215-218 °C; FTIR (KBr disc): 3,310 cm^{-1} (O-H), 3,170 cm^{-1} (HC=CH), 1,715 cm^{-1} (C=O), 1,610 cm^{-1} (aromatic ring) and 1,575 cm^{-1} (N=N), 830 cm^{-1} and 716 cm^{-1}; ^{1}H-NMR (D6 DMSO): 7.17-7.57 (aromatic), 6.96-7.21 (HC=CH of maleimide), 6.31-6.51 (HC=CH) ppm.

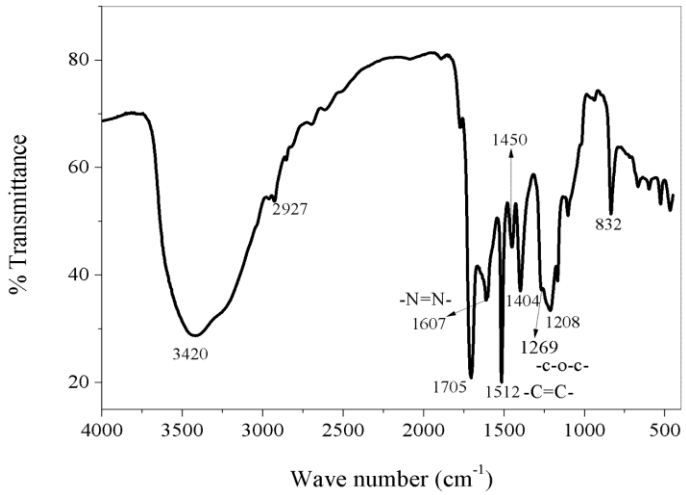


Fig. 2 FTIR Spectra of 4-hydroxyphenylazo-3-N-(4-hydroxyphenyl) maleimide.

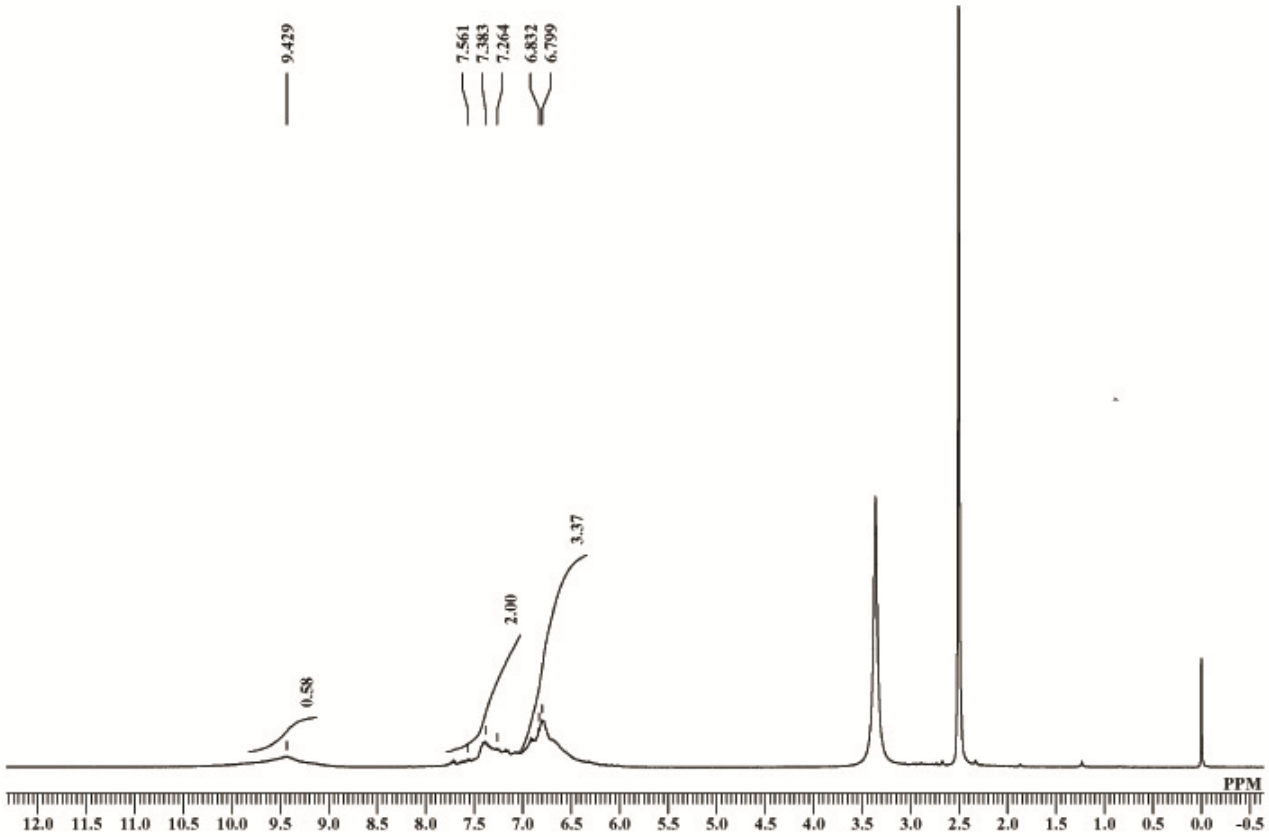


Fig. 3 ^{1}H NMR spectra of 4-hydroxyphenylazo-3-N-(4-hydroxyphenyl) maleimide.

FTIR Spectra analysis of PAH hydrogels

The FTIR spectra of PAH hydrogels of AZ1 formulation, 5-FU loaded AZ1 and pure 5-FU drug and the spectra of the same presented in figure 4. From figure 4a, pure 5-FU shows the characteristic peak at 3125 cm^{-1} for N-H stretching (free) and also peaks at 1729, 1648, 1247, and 1175 cm^{-1} for carbonyl stretching (C=O), C-N stretching, C-F stretching and C-O stretching vibrations appear in pure 5-FU also in drug loaded hydrogel respectively. The FTIR spectra of AZ1 hydrogels in figure 4 (b), the N–H stretching vibration in methylene bis(acrylamide) appear at 3420 or amide groups of acrylamide in hydrogels appear at 1660 cm^{-1} and hydroxyl group merged in 3420cm^{-1} region. The peat for alkene group (HC=CH) appear at 3030 cm^{-1}. The presence of the azo (N=N) group band in 1594 cm^{-1} range confirmed the HPM copolymerized with acrylamide and formation of PAH hydrogels. In the case of pure 5-FU the bands at 3130, 1245 cm^{-1} gives information of N-H stretching (free) and –C-F band after drug loading some of the bands disappear and N-H stretching (free)

appear at same, –C-F band appear at 1245 cm^{-1}. This indicate that the 5-FU is molecularly dispersed in to the PAH hydrogels. The interactions between functional groups in interpenetrating polymer networks are great potential use in pharmaceutical preparations, especially in drug delivery systems.

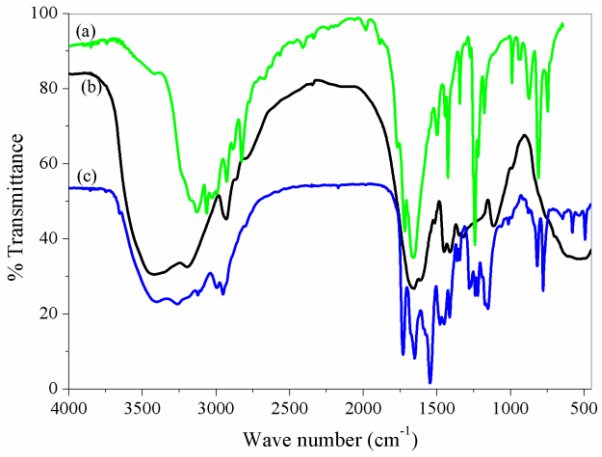


Fig. 4: FT-IR spectra of (a) pure 5-FU (b) PAH hydrogel (c) drug loaded PAH hydrogels (sample AZ1).

Differential Scanning Calorimetry (DSC)

The DSC thermograms of pure 5-FU, placebo PAH and drug loaded PAH hydrogels is as depicted in figure 5. The DSC of pure 5-FU showed a sharp melting endotherm was observed at 282 ºC followed by decomposition those reported previously (Rama Subba Reddy *et al.*, 2014; Chandra Sekhar *et al.*, 2014). The DSC of PAH hydrogels shows three staged weight loss.

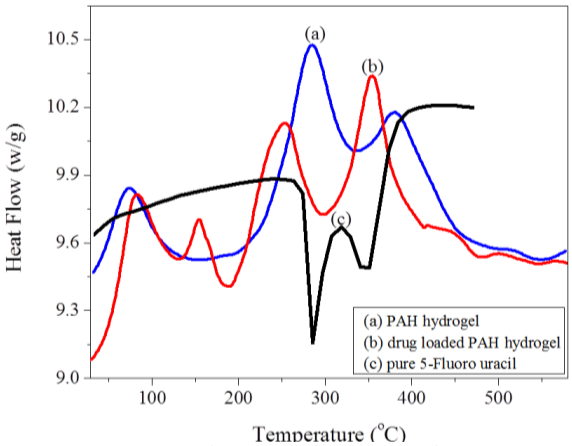


Fig. 5: DSC thermograms of PAH hydrogels for AZ1 formulation.

The melting exotherms were observed at 73.04, 285.40 & 380.16°C and two melting endotherms were observed at 157.30, 336.52°C. The broad endothermic peak was observed around 150°C can be explained by the evaporation of water from the hydrogels. The DSC analysis of 5-FU loaded PAH hydrogels showed three melting endotherms at 130.22, 187.02 and 296.92°C. The first endotherm corresponds to melting of the acrylamide chains, for 4-hydroxyphenylazo-3-N-(4-hydroxyphenyl)maleimide melting endotherms at 187.02° C and we observed the DSC thermogram of 5-FU drug at 282°C had changed in the DSC thermogram of the 5-FU loaded PAH hydrogel at 296.92°C indicating that the 5-FU drug had been successfully loaded in the hydrophobic core of the hydrogel network.

X-ray diffraction analysis (XRD)

XRD diffractograms of PAH hydrogel, 5-FU loaded PAH hydrogel and pristine 5-FU are displayed in Figure 6, indicates that the crystalline nature of the drug before and after encapsulation in the hydrogel. The 5-FU has shown characteristic intense peak at 2θ of 29◦ due to its crystalline nature. However, these peaks have disappeared in 5-FU loaded hydrogels, since molecular level dispersion in the hydrogel network, as no crystals were found in the 5-FU loaded hydrogel network.

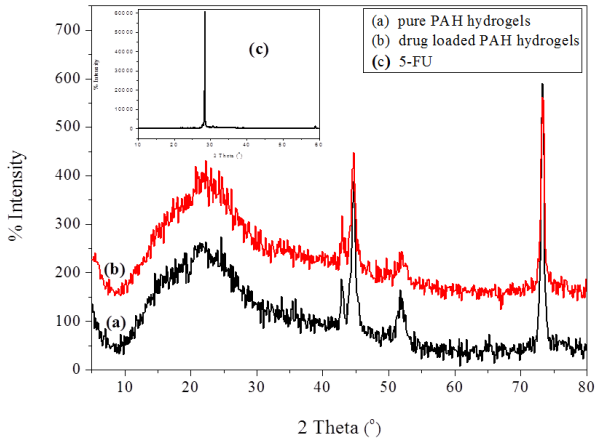


Fig. 6: XRD pattern of the (A) pure 5-FU, (B) PAH hydrogel and (C) drug loaded PAH hydrogels for AZ1 formulation.

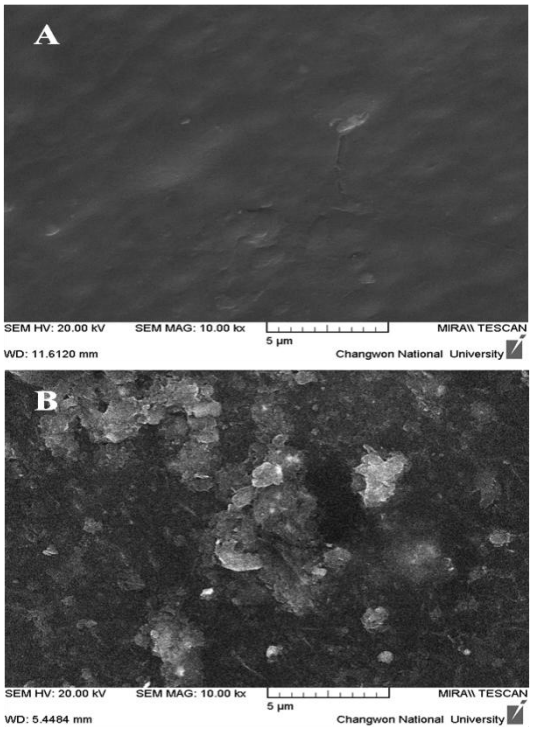


Fig. 7: Scanning electron microscopy images of (A) AZ1 PAH hydrogels and (B) AZ1 PAH hydrogels after drug release.

Scanning Electron Microscopy (SEM)

SEM studies were performed for PAH hydrogel of AZ1 formulation, before and after drug release the SEM images are presented in figure 7A and 7B.The SEM image of pure AZ1 shows smooth surfaces and less pore size but in the case of AZ1 hydrogels after drug release in the alkaline environment; the surface appeared rough having pore size. The hydrogel is exposed to pH environment the size of pore was affected this indicates that the hydrogel have a good pH-responsibility, it is useful for colon drug delivery.

Swelling studies

The swelling and deswelling kinetic studies of the PAH hydrogels with different HPM and MBA concentrations are shown in figure 8A. The swelling data shows that the rate of swelling is increased with increasing amount of HPM content in the PAH hydrogel matrix this is due to hydrophilic nature of hydroxyl and amide functional group. While in the case of AZ1, AZ2 and AZ5 formulations the swelling ratio decreases due to increasing cross linker content (MBA) from 0.0013mol to 0.0038mol. The cross-linked PAH hydrogels swelled to about 80% at equilibrium, reached after 42 h. The percentage swelling at equilibrium increased with the increase in pH from acid to alkaline range. The same trend follows in the case of deswelling kinetics (figure8B) of PAH hydrogels.

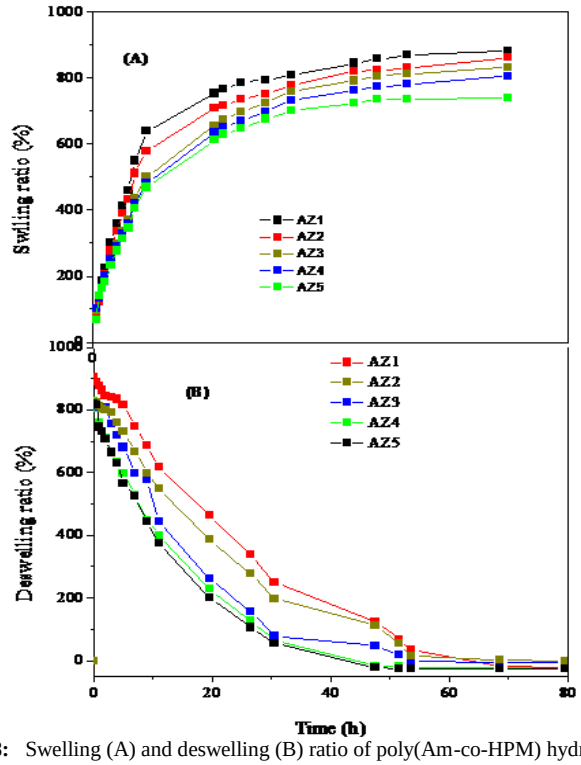


Fig. 8: Swelling (A) and deswelling (B) ratio of poly(Am-co-HPM) hydrogels

In vitro release kinetic studies

Figure 9a. shows the *in vitro* release profiles of 5-FU from the PAH hydrogels in pH =1.2. There was about 40% drug release with in 3h and about 42% release at the end of 5h from AZ1 hydrogel. In the case of AZ3 hydrogel there was about 20% release in 3h and 30% drug release after 5h where as it was 10% and 18% in the case of AZ4 hydrogels at the end of 3h and 5h, respectively.

In the first 3h there was an initial burst release and this was followed by near zero order patterns up to 16h. The cumulative release profiles of 5-FU from the PAH hydrogels in pH =7.4 phosphate buffer are shown in figure 9b. The AZ1 hydrogels released about 40% of 5-FU in 3h and about 46% of 5-FU entrapped in 5h. The drug released from AZ3 hydrogels was about 19% in 3h and 29% after 5h, whereas it was 10% in 3h and 18% at the end of 5h from AZ4 hydrogels.

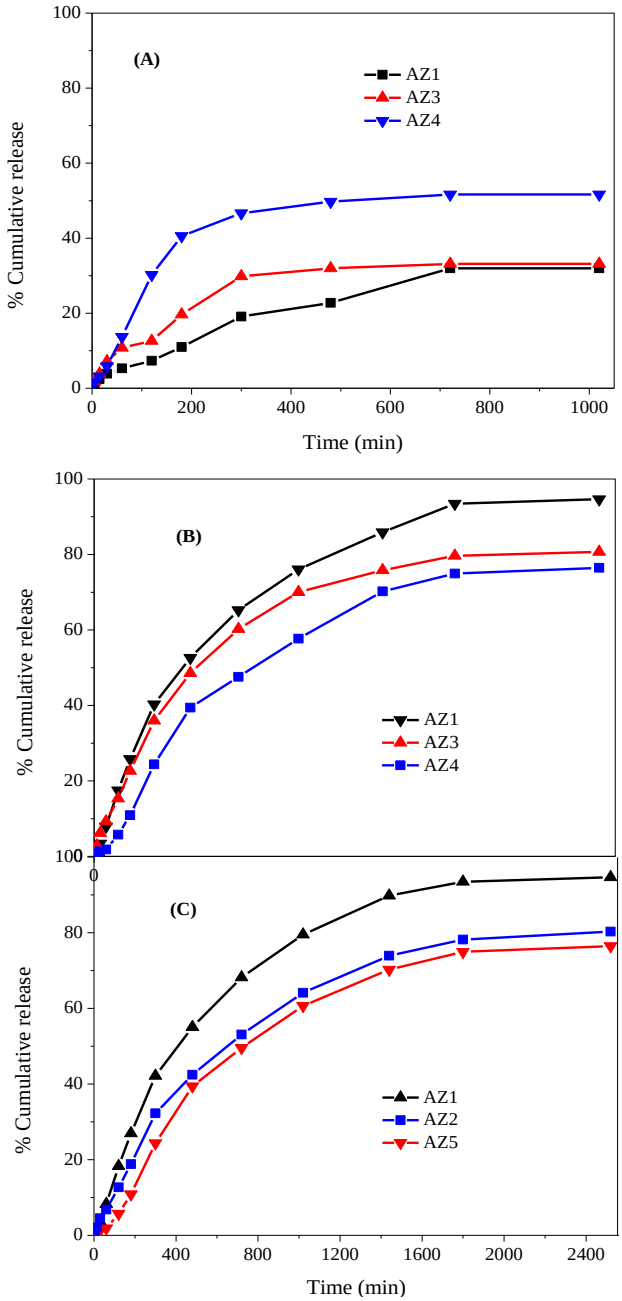


Fig. 9: % Cumulative release of monomer variation in (a) pH 1.2 (b) pH 7.4 and (c) MBA variation of poly(Am-co-HPM) hydrogels in pH 7.4.

The cumulative release of 5-FU influenced by MBA (cross linker) concentrations and the release profiles are shown in figure 9c. The AZ1 hydrogels released about 27% of 5-FU in 3h and about 43% of 5-FU released in 5h. In the case of AZ2 hydrogels 18% drug release in 3h and 33% release in 5h. The AZ5 hydrogels only 10% in 3h and 25% drug release in 5h. This indicates that the cross linker concentration increases rigidness of the matrix increases and the free volume available for penetrant diffusion decreases. As the concentration of MBA increases from 0.0013mol to 0.0038mol, the mobility of the polymeric chains decreases dramatically.

The kinetics of the synthesized PAH hydrogels was studied at 37°C, in aqueous buffer solutions of pH = 1.2 and 7.4. The total buffer concentration was maintained 0.05 M, and the ionic strength (m) is 0.5 for phosphate buffer. The release of 5-FU was monitored by UV-Vis spectrophotometer and using above data % cumulative release calculated and fitted into the following peppas equation (Li *et al.,* 2006). The diffusion parameters k, n and r^2 value were calculated and presented in Table 1.

$$\frac{m_t}{m_\infty} = kt^n \quad \ldots 4$$

Where m_t and m_∞ is the amount of drug released at time t, and the total drug release at equilibrium in the PAH hydrogels, m_t/m_∞ is the fractional release of the drug, k is the release rate constant and n is the release exponent, indicating the mechanism of type of drug release. The release exponent, release rate constant and correlation coefficients for the PAH hydrogels containing 5-FU are presented in Table 1. The type of release mechanism is given by the *n* value in peppas equation, where $n \leq 0.5$ indicates Fickian diffusion; while $0.5 < n < 1$ indicates non-Fickian diffusion (anomalous mass transfer). Based on release data the highest correlation coefficient was observed for AZ1 hydrogels this indicates that 5-FU is released from PAH hydrogels by Fickian diffusion that means diffusion rate of the PAH hydrogels is much lower than the relaxation time. At the same time we demonstrate based on peppas equation the release exponent is 0.47 or very close to 0.5.

Mechanism of 5-FU Release

The 5-FU was entrapped into the PAH hydrogels and the action of 5-FU release was observed in pH 1.2 and 7.4 phosphate buffer media. The percent (%) of swelling ratio of PAH hydrogel is less in the region of pH 1.2, while in the case of pH 7.4 the % of swelling ratio is more due to hydrophilic nature of PAH networks present in the hydrogel. Based on the swelling ratio, the cumulative release of 5-FU in PAH hydrogels follows and when the drug loaded PAH hydrogel reached the stomach, the hydrogels will be exposed to acidic environment (pH = 1.2) and the release of 5-FU from PAH hydrogels very low, this is due to the release of the surface entrapped 5-FU drug only. The cumulative release of 5-FU from PAH hydrogels in pH 7.4 increases slowly due to alkaline environment present in the large intestine and also contributes to the swelling of PAH hydrogels and the azo bond will be accessible for cleavage. The swollen hydrogels are easy to cleaving the azo bond and causes release of the 5-FU in the colon by loosening the PAH hydrogel matrices.

CONCLUSION

The poly(Am-co-HPM) hydrogels containing azo aromatic copolymers were developed for colon targeting by simple free radical polymerization method and were cross-linked with N,N-methylene bis acrylamide. The 5-FU release rate decreases with increasing MBA concentration in the PAH hydrogels. The slowest % cumulative release was obtained for the most viscous cross-linked AZ5 PAH hydrogels. The rate of 5-FU release can be controlled by the HPM concentration, and crosslinking agent. The PAH hydrogels were characterized by FTIR, DSC, XRD and SEM. The percentage of swelling studies were carried out in deionized water and *Invitro* release studies of 5-FU entrapped in the hydrogels were carried out in SGF and SIF. The maximum encapsulation efficiency of 5-FU is 78.25% and the release of 5-FU from PAH hydrogels is more in alkaline environment when compared to acidic media.

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