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RESEARCH ARTICLE

Synthesis and Evaluation of Poly (Acrylamide-Co-Acrylic Acid) Hydrogel for Intestinal Delivery of the Drug Naproxen Sodium

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ABSTRACT

Hydrogels are three dimensional polymeric networks. They have the capability to imbibe large amounts of water which results in swelling of the hydrogels. They resemble biological tissue because of their high water content. They are capable of responding to various stimuli such as temperature, pH, light, glucose, electric stimuli etc. The purpose of the research was to synthesize pH sensitive hydrogel for drug release into the intestine. pH sensitive Poly (Acrylamide-co-acrylic acid) hydrogel, poly(AAm-co-AA), was synthesized by free radical crosslinking copolymerization method. N,N'-Methylene bisacrylamide (MBAAm) was used as crosslinking agent. A combination of Ammonium persulphate (APS) and Sodium metabisulphite was used as redox initiators. Naproxen sodium was the drug incorporated into the synthesized hydrogel. The hydrogels were evaluated by Fourier Transform Infrared Spectroscopy (FT-IR), Scanning Electron Microscopy (SEM), drug loading, dynamic swelling and dissolution parameters.

KEYWORDS

Hydrogel, Poly (Acrylamide-Co-Acrylic Acid), pH Sensitive, Naproxen Sodium

INTRODUCTION

Hydrogels have been used extensively in the development of the smart drug delivery systems.[1] "Stimuli responsive" and "self-regulating" drug delivery systems have captured the imagination of researchers, in large part because they suggest a means to mimic the physiological homeostatic feedback mechanisms that are essential for health.[2]

Hydrogels are three-dimensional polymer networks that are able to retain a large amount of water in their swollen state.[3] In comparison with smart hydrogels, ordinary hydrogels undergo only the swelling - deswelling process depending on the availability of water in the environment.

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It is the additional properties over the basic swelling–deswelling property that makes a hydrogel smart. The environmental factors, also referred to as external stimuli, can be physical (temperature, electricity, magnetic field, ultrasound, and pressure), chemical (pH, ion type, ionic strength, and solvent) and biological (enzyme, antibody, and glucose).[4] Hydrogels resemble living tissues closely in their physical properties because of their relatively high water content, soft and rubbery consistency.[5]

Hydrogels can protect the drug from hostile environments, e.g. the presence of enzymes and low pH in the stomach. They can also control drug release by changing the gel structure in response to environmental stimuli. Hydrogels containing such 'sensor' properties can undergo reversible volume phase transitions or gel–sol phase transitions upon only minute changes in

the environmental condition. The types of environment sensitive hydrogels are also called 'Intelligent' or 'smart' hydrogels.[6]

Hydrogels can be prepared from natural or synthetic polymers. Hydrogels made from natural polymers may not provide sufficient mechanical properties and may contain pathogens or evoke immune/inflammatory responses. They do offer several advantageous properties such as inherent biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities. Synthetic hydrogels, on the other hand, do not possess these inherent bioactive properties. Synthetic polymers usually have well-defined structures that can be modified to yield tailorable degradability and functionality.[7]

In the area of oral delivery, a growing attention has been focused over the past few decades on the design and manufacturing of advanced formulations intended for release of bioactive compounds to selected regions of the gastrointestinal (GI) tract. By controlling the site of drug liberation throughout the gut, it would be possible to limit the tolerability issues associated with treatments that mainly affect specific GI districts.[8]

Weak acids and bases like carboxylic acids, phosphoric acid and amines, respectively, exhibit a change in the ionisation state upon variation of the pH. This leads to a conformational change for the soluble polymers and a change in the swelling behaviour of the hydrogels when these ionisable groups are linked to the polymer structure. Various drugs delivered through pH responsive hydrogels are given in the Table 1.

The present study focuses on the synthesis of poly (acrylamide-co-acrylic acid) hydrogels having varying concentrations of acrylamide. Acrylic acid swells in water and is a typical pH sensitive hydrogel that exhibits volume phase transitions in response to pH changes at around pH 7.4. Acrylamide is a hydrophilic monomer. It improves the mechanical strength of the hydrogel.

Table 1: Drugs delivered through pH-responsive hydrogels

Drug	Polymer	Application
Methyl prednisolone	Carboxymethyl chitosan and Carbopol 934	Intestinal drug delivery
Clarithromycin	Chitosan and N,N′-methylenebisacrylamide	Helicobacter pylori infection treatment
Indomethacin	Poly (hydroxyethylmethacrylate-co-acrylic acid)	Enteric drug delivery
Terbinafine	Poly(acrylamide /maleic acid)	Candida albicans infection treatment

MATERIALS AND METHOD

Poly (acrylamide-co-acrylic acid) was synthesized by free radical crosslinking copolymerization method. N,N'-Methylene bisacrylamide was used as the crosslinker. Combination of ammonium persulphate and sodium metabisulphite was used as the redox initiator for initiation of copolymerization reaction. The polymerizing solvent used was distilled water. A gift sample of the drug Naproxen sodium was obtained from Cipla Ltd. The monomers, crosslinker and other reagents were obtained from SD Fine Chemicals Ltd. The hydrogels synthesized with different monomer ratios as mentioned in Table 2.

Table 2: Ratios of the monomers Acrylamide and acrylic acid

Sr No.	Sample	Acrylic acid : Acrylamide
1	H1	1:1
2	H2	1:1.5
3	H3	1:2
4	H4	1:2.5
5	H5	1:3

Method of Preparation

Hydrogels were prepared by free radical cross-linking co-polymerization procedure in distilled water, which was the solvent for all components of the mixture. APS- Sodium metabisulphite act as redox initiators and help in the formation of free radicals.

The monomers (AA and AAm), cross-linker (MBAAm), initiator (APS) and antioxidant (sodium metabisulphite) were accurately weighed using High Precision Balance.

AAm and AA monomers, MBAAm, APS and sodium metabisulphite were dissolved separately in distilled water in stoppered glass test tubes. Acrylamide was triturated properly before dissolving in distilled water. The glass test tubes were shaken vigorously till clear solutions are obtained.

Different amounts of AAm were then added to AA solution. Free radical copolymerization of hydrogels was carried in stoppered glass test tubes at room temperature using initiator APS and antioxidant sodium metabisulphite. The cross-linking was carried out using MBAAm.

The mixture was poured into a wide mouthed container which was sealed with a cap. This mixture was then placed in a sonicator for a period of 10-15 min in order to completely dissolve the ingredients. During the process of sonication excess of heat was released. It was then taken out and kept aside, without disturbing for 15-25 min during which period it cooled down to form transparent viscous gel having a firm structure.

The synthesized hydrogel was then taken out and cut into pieces and kept for air drying. The hydrogels were immersed in distilled water at room temperature for 72 hrs and the water was refreshed every several hours in order to remove the unreacted chemicals. Finally extracted gels were air dried.

Drug Loading in the Hydrogel

The presynthesized dry hydrogels were loaded by swelling to equilibrium in a suitable drug solution. For drug loading into the synthesized hydrogel a simple and convenient swelling loading technique was used.10 mg of the drug, Naproxen sodium was dissolved in 50 ml of distilled water in which 200 mg of the hydrogel was soaked for a period of 48 hrs. This mixture was stirred during regular intervals. The drug loaded hydrogels were taken out and air dried.[9]

Entrapment Efficiency

20mg of the accurately weighed drug loaded hydrogel was soaked in 30 ml of pH 7.4 buffer solution for the duration of 48 hrs. The buffer solution containing the drug loaded hydrogel was stirred at regular intervals.[10,11] The supernatant solution was analysed by using UV visible spectroscopy at 231 nm to determine the entrapment efficiency.

The percent entrapment efficiency was determined by the following formula,

$$\% \text{ EE} = \frac{\text{Actual amount of drug in the hydrogel} \times 100}{\text{Theoretical amount}}$$

FT-IR Spectroscopy

The IR spectrometry is used qualitatively as well as quantitatively, but its major application is in qualitative analysis to identify the functional groups.

KBr pellet method was used. Well dried sample of the hydrogel was crushed in an agate mortar with pestle. Crushed hydrogel was then mixed with potassium bromide in the proportion of 1:100 and compressed to obtain a semi-transparent disc. The spectrum was recorded in the range of 4000 cm^{-1} – 600 cm^{-1}.[12]

SEM

Scanning Electron Microscopy (SEM) was employed to investigate morphology of the synthesized hydrogel.[13] The advantages of the scanning electron microscope evolve from the fact that the surface of a solid specimen is available for experimentation, including simple observation, at a resolution much better than that of the optical microscope and with a depth of field that is orders of magnitude greater.[14] JEOL SEM (JSM-7600F, JAPAN) was the instrument used for the study.

Dynamic Swelling Studies

100 mg of the dried hydrogel samples were soaked in solutions of pH 1.2, 2.4, 4, 7.4 and 8. The studies were carried out for 8 hrs. The soaked samples were then withdrawn at a regular interval of 1 hr. The excess water was removed with the help of tissue papers. The samples were then weighed and the weight was noted down.

Equilibrium degrees of swelling values are the maximum swelling values of the samples.

EDS was determined by the following formula,

$$EDS = \frac{W_t - W_0}{W_0}$$

Wo - initial dry weight

Wt - weight of swollen hydrogel at time t

Drug Release Studies

Drug loaded hydrogel with known amount of drug was placed in the muslin cloth. The cloth was tied with the help of a thread to the paddle of USP Test Apparatus II. The paddle was introduced into the Dissolution Test Apparatus, TDT06T USP. The hydrogel was stirred in acidic buffer pH 1.2 placed in dissolution flask for 2 hrs with temperature maintained at 37°C at 100rpm and aliquots were drawn at an interval of 30 min. The dissolution studies were carried in phosphate buffer pH 7.4 with temperature maintained at 37°C and 100rpm. 5ml of aliquots were withdrawn at an interval of 60 minutes and replaced by a 5ml of the phosphate buffer pH 7.4. The drug released in each 5ml aliquots were analyzed by UV spectroscopy at wavelength of maximum absorption 231 nm. The drug release studies in phosphate buffer pH 7.4 were carried out for 8 hours.

RESULTS AND DISCUSSION

A simple, reproducible, cost effective UV spectroscopy method was developed and validated for the drug Naproxen sodium. The method was validated in three solvents. The drug is freely soluble in water. The hydrogel should not release the drug in the acidic environment of pH 1.2 but in the intestine having a pH of 7.4. Hence HCl buffer pH 1.2, phosphate buffer pH 7.4 and distilled water are used for analytical method development and validation of the drug. A 2 ppm drug solution was scanned and the wavelength of maximum absorption was found to be 231 nm as shown in the Figure 1.

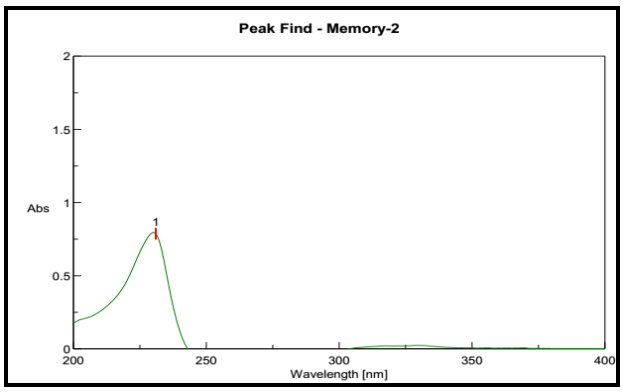

Figure 1: Scan of 2 ppm drug solution

A 100 ppm stock solution was prepared by dissolving 10 mg of Naproxen sodium in all the three solvents in 100 ml volumetric flasks. From this stock solution, aliquots of 0.1, 0.12, 0.14, 0.16, 0.18 and 0.2 ml were withdrawn in 10 ml volumetric flasks and diluted to volume with distilled water to obtain standard solutions of the concentrations 1, 1.2, 1.4, 1.6, 1.8 and 2 ppm respectively.

The absorbance of these solutions were recorded as shown in the Table 3, 4 and 5. Graph of Absorbance v/s Concentration was plotted using Microsoft Excel as shown in the Figures 2, 3 and 4.

Table 3: Concentration and Absorbance in Distilled Water

Sr. No.	Concentration (ppm)	Absorbance
1	1	0.3325
2	1.2	0.4422
3	1.4	0.5027
4	1.6	0.6134
5	1.8	0.6975
6	2	0.7869

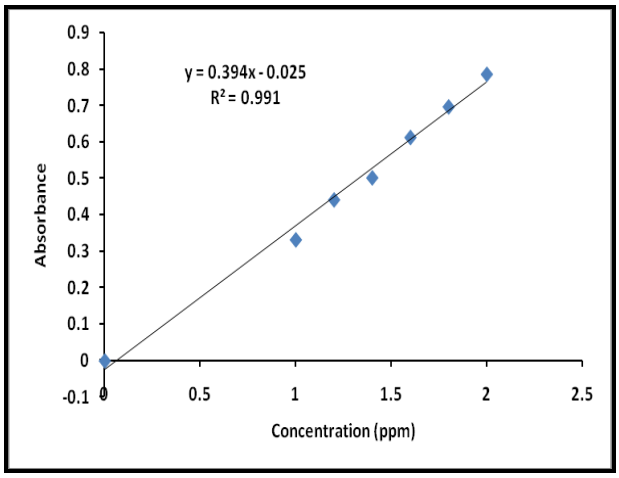

Figure 2: Plot of absorbance v/s concentration in distilled water

Table 4: Concentration and Absorbance in pH buffer 7.4

Sr. No.	Concentration (ppm)	Absorbance
1	1	0.2841
2	1.2	0.3404
3	1.4	0.4405
4	1.6	0.5034
5	1.8	0.5668
6	2	0.6753

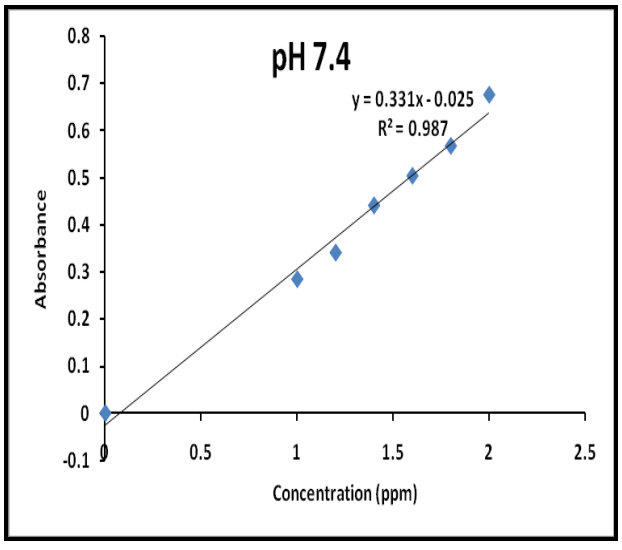

Figure 3: Plot of absorbance v/s concentration in pH 7.4

Table 5: Concentration and Absorbance in pH buffer 1.2

Sr. No.	Concentration (ppm)	Absorbance
1	1	0.2014
2	1.2	0.2430
3	1.4	0.2767
4	1.6	0.2908
5	1.8	0.4071
6	2	0.4284

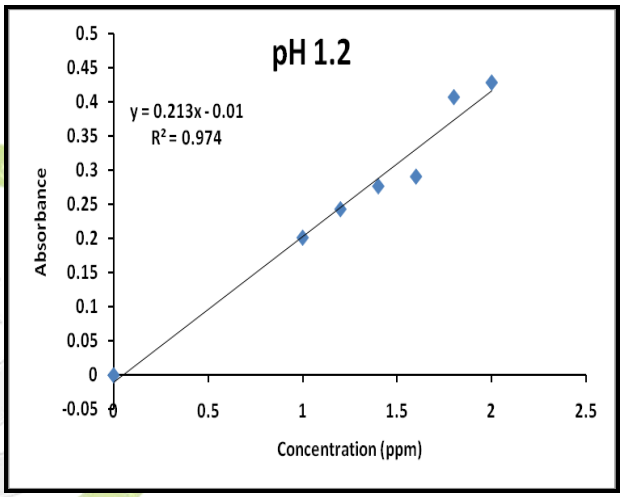

Figure 4: Plot of absorbance v/s concentraton in pH 1.2

FT- IR

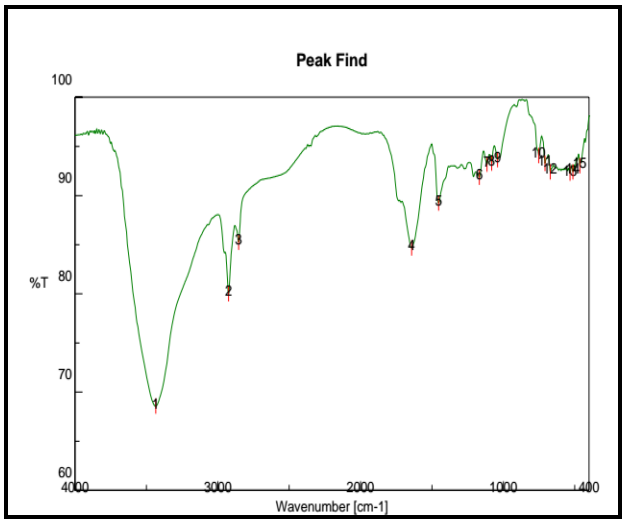

Figure 5: IR spectrum of synthesized polymer

The structure of the compounds was characterized by recording their IR spectra given in the Figure 5. The Table 6 shows the frequencies in the IR spectra of the synthesized hydrogel.

Table 6: Frequencies in the IR Spectra of the synthesized hydrogel

Peak position	Wavenumber (cm^{-1})	Functional group
1st position	3434.6	O-H (s)
2nd position	2924.52	C-H str
4th position	1642.09	C=O str
5th position	1453.1	COO^- str

C=O group connected to the amide group gives absorption peak at 1642.09 cm^{-1}. Symmetric stretching of COO^- was found at 1453.1 cm^{-1}. C-H stretching was found at 2924.52 cm^{-1}. O-H stretching at 3434.6 cm^{-1} because of carboxylic group.

SEM

The synthesized hydrogel was characterised for its surface morphology and pH sensitivity by SEM analysis. SEM analysis monitored the pore sizes.

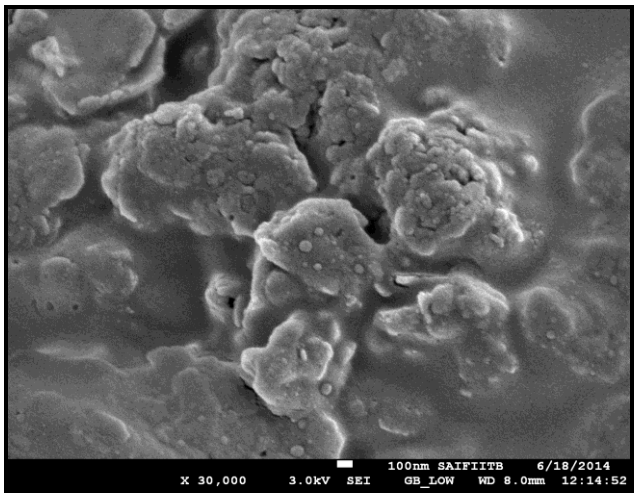

Figure 6: SEM microphotograph of hydrogel in pH 1.2

The differences in the pore size when the hydrogel was allowed to swell at two different pH values pH 1.2 and 7.4 were observed.

The SEM microphotographs of the hydrogel in pH 1.2 and 7.4 are presented in the Figures 6 and 7 respectively.

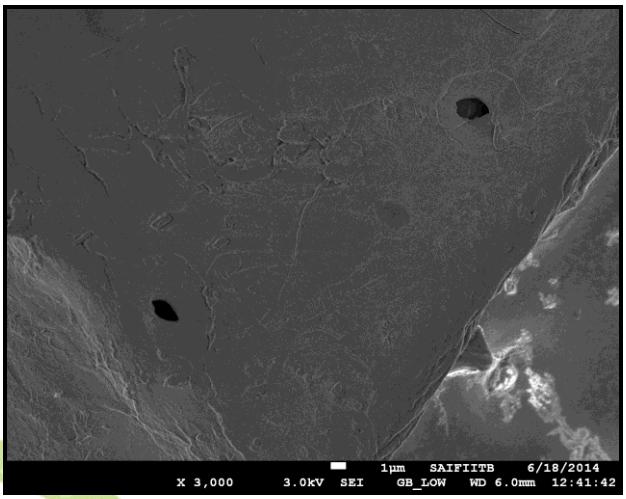

Figure 7: SEM microphotograph of hydrogel at pH 7.4

The SEM microphotographs show the presence of pores in the synthesized hydrogel. The hydrogel kept in pH 1.2 showed pores which were in nanometer size range (approximately 35-45 nm). The hydrogels kept in pH 7.4 showed pores which were in the micrometer range. This clearly shows that the hydrogels exposed to pH 7.4 have bigger pores than those exposed to pH 1.2. The pores were not uniformly distributed throughout the surface, which helps to conclude the hydrogels were not very porous.

The bigger pore size shown by the hydrogel when exposed to pH 7.4 is because the hydrogels swell more at alkaline pH. The main reason for swelling is the carboxylic acid groups of hydrogel loose protons and tend to ionize at pH > 4. The electrostatic repulsion within the hydrogel network is the reason for swelling of the hydrogel.

Dynamic Swelling Studies

The main reason for swelling of the poly (acrylamide-co-acrylic acid) hydrogel was the free carboxylic acid groups of hydrogel which

loses the proton and tends to dissociate at a pH 4.0 results in swelling. In low pH value, most carboxylic acid groups were in the form of COOH and large amounts of hydrogen bonds formed by acrylamide and acrylic acid chain. The hydrogen bond breaks as the environmental pH value rises to 7.4 when carboxylic acid groups began to ionize. The electrostatic repulsion causes the network to expand. So, higher EDS values are obtained for the co-polymeric hydrogel samples at higher pH values. The data shows that the synthesized hydrogels have high sensitivity to pH.

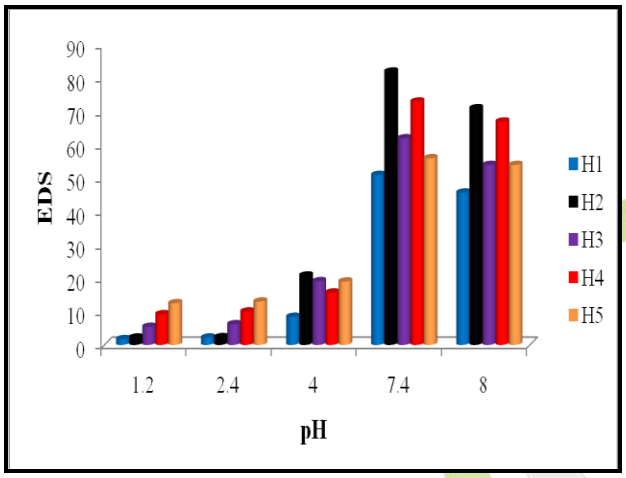

Figure 13: Plot of Equilibrium degree of swelling at various pH of different hydrogels

Table 7: Equilibrium degree of swelling data

pH	1.2	2.4	4	7.4	8
Hydrogel 1	1.7	2.2	8.4	51	45.7
Hydrogel 2	2.2	2.3	20.8	82	71
Hydrogel 3	5.4	6.2	19.1	62	54
Hydrogel 4	9.2	10	15.7	73	67
Hydrogel 5	12.5	13	19	56	54

The Figure 13 shows a plot of the Equilibrium degree of swelling at various pH of different hydrogels. The Table 7 gives the equilibrium degree of swelling data.

The plot shows that the hydrogels swell more as the pH increases i.e. as the pH becomes more alkaline. Among all the five hydrogels it is seen that hydrogel 2 swells more in alkaline pH compared to all the other hydrogels. Hydrogel 4 a bit more than hydrogels 3 and 5 whose swellings are comparable.

Hydrogel 2 has less concentration of acrylamide as compared to hydrogels 3, 4 and 5. Hence it shows a higher degree of swelling.

Hydrogels swell more in alkaline pH because, at pH > 4 the free carboxylic acid groups loose proton and ionisation takes place due to which there is electrostatic repulsion and thus swelling occurs.

Drug Entrapment Efficiency

Since the hydrogel swells maximum at pH 7.4 it was used for the determination. At pH 7.4 pore sizes of the hydrogels increases and the entrapped drug will be able to release from the hydrogel as completely as possible.

Drug loading was carried out using hydrogels 2, 3 and 4 since they swell the most in alkaline pH. The entrapment efficiency in the three hydrogels 2, 3 and 4 were found to be 78.4, 61.4 and 62 % respectively.

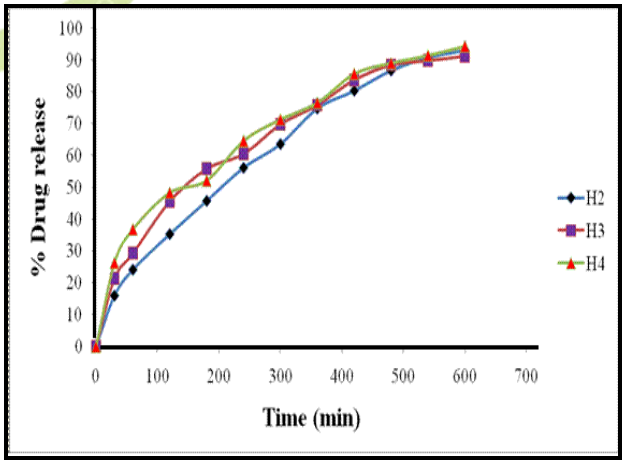

Figure 14: Plot of % Drug release v/s Time

Drug Release Studies

The drug release studies shown in the Figure 14 depicts that the drug release from all the three hydrogels were comparable. The amount of drug released in acidic pH was around 25 %. 90

– 95 % of the total drug release was attained at the 600th minute in the alkaline pH.

The drug release is more in the alkaline pH because the hydrogels swell more in the alkaline pH due to the electrorepulsive forces.

CONCLUSION

Poly (acrylamide-co-acrylic acid) hydrogel was synthesized successfully and it exhibited a pH dependent swelling. By changing the monomer and crosslinker concentration hydrogels with the best physical and chemical properties can be synthesized. Drugs can be released in different parts of the GIT in a targeted manner because of the synthesis of such pH sensitive hydrogels. 25% of the drug was found to release in the acidic pH of the stomach and 90 – 95 % was released in the alkaline pH of the intestine.

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