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RESEARCH ARTICLE

Synthesis and Characterization of Potato Starch Grafted Poly (2-Hydroxyethyl Methacrylate –Co-Acrylic Acid) Hydrogel for Drug Delivery

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ABSTRACT

Hydrogels, three dimensional polymeric networks which swell in water or biological fluids have been explored as a potential carrier for drug(s) in drug delivery systems. The suitability of hydrogel polymer as carrier for drug delivery is attributed to their unique characteristics of imbibing large amounts of fluid, biocompatibility, intelligence of responsiveness to specific stimuli like pH, temperature etc. The potato starch grafted (2-hydroxyethyl methacrylate –co-acrylic acid) hydrogel polymer was synthesized by graft copolymerzation using potato starch (preformed polymer), 2-Hydroxyethyl methacrylate and acrylic acid monomers, Ammonium persulphate (initiator) and N,N-methylene bisacrylamide (crosslinker) with an aim of developing a pH sensitive polymer for drug delivery to GIT. The synthesized polymer was investigated for the effect of change of monomer concentration on the swelling behaviour and characterized by FT-IR, SEM, DSC, Drug loading, swellability and dissolution studies.

KEYWORDS

Hydrogel, potato starch grafted poly (2-hydroxyethyl methacrylate-co-acrylic acid), Acrylic acid, pH sensitive, 2-hydroxyethyl methacrylate

INTRODUCTION

Controlled release drug delivery system provides drug release at a controlled rate over an extended period. Over past three decades the pharmaceutical research is being focussed on development of controlled and sustained drug delivery system which will overcome the disadvantages of conventional dosage forms like the time required for therapeutically effective plasma concentration, dosing frequency, reliability, effectiveness and safety.[1,2] Hydrogels, three dimensional polymeric network, swelling to equilibrium in presence of water or physiological fluids.[3]

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Hydrogels can be synthesized from natural polymers that provide inherent biocompatibility and biodegradability and lacks mechanical strength as well as synthetic polymers which have well defined structure that can be modified for desired function.[4] The swelling of hydrogels is due to the presence of hydrophilic groups and the mechanical strength is because of crosslinking of the polymer chains with the behaviour of swelling dependent upon the nature and concentration of the monomers as well as the degree of cross linking.[5] The crosslinking of the polymer chains can be by physical entanglements, hydrogen bonding , ionic interaction or by formation of covalent bonds. The high water content and the elasticity makes the hydrogel polymer resemble living tissue and hence biocompatible.[6] The application of hydrogel in the drug delivery is

due to the ability to load molecules of different size and release them in the appropriate environment[7] Apart from drug delivery hydrogels also have application in the field of tissue engineering, cosmetology and wound management.[8]

The drug release mechanism through these hydrogel matrices can be diffusion controlled, swelling controlled or chemically controlled.[9] Hydrogels responding to specific stimuli known as stimuli responsive hydrogels have gained attention since many pH and temperature are environmental variables found in body. Also hydrogels responding to specific molecules have been studied extensively.[10] pH sensitive polymers are of great interest in drug delivery to the gastrointestinal tract due the pH variation throughout GIT that is enough to elicit a pH sensitive response. Various pH sensitive polymers studied for delivery are given in Table 1[11]

Table 1: Some pH sensitive polymers studied for drug delivery

POLYMER	DRUG
Tri polymer of N-vinyl 2-pyrrolidone methacrylamide and itaconic acid.	Insulin
Copolymer of cationic guar gum and acrylic acid monomer	Ketoprofen
Copolymer of polymetacrylic acid and polyethyleneglycol	Calcitonin
Polyethyleneglycol	Camphotecin
Poly dimethyl amino ethyl methacrylate	Caffeine

2-Hydroxyethyl methacrylate (2-HEMA) is a neutral monomer that imparts hydrophobicity to the polymer chains and modifies the pH sensitive behaviour of the polymer. 2-hydroxyethyl methacrylate homopolymers and copolymers have been studied for delivery of number of drug. Poly (2- Hydroxyethyl methacrylate-co-methacrylic acid was studied for delivery of the drug timolol maleate.[12] Acrylic acid (AA) is a hydrophhilic monomer containing –COOH group with pKa 5.5. The –COOH groups ionise at higher pH values towards the alkaline side and undergo swelling thus exhibiting a pH dependent swelling behaviour.

MATERIALS AND METHOD

Reagents and Chemicals

The potato starch grafted poly (2-hydroxyethyl methacrylate –co- acrylic acid) hydrogel polymer was synthesized by graft polymerization. The synthesis requires a preformed polymer, cross-linker, monomers and initiator. The polymerizing solvent used was distilled water. The monomer 2-hydroxyethyl methacrylate was obtained from Merck where as other chemicals were obtained from SD fine chemicals Limited. The drug belonging to the class of proton pump inhibitors Rabeprazole Sodium was obtained as a gift sample from Naprod life sciences.

Method of Preparation

1gm of starch was dispersed in 10 ml of distilled water and heated in a three necked reactor placed on a water bath to 68^0 C. The initiater and cross-linker were weighed accurately and dissolved in 2ml distilled water. The solution of the initiater ammonium persulphate was added to the starch solution and heated to achieve 80^0 C with continuous stirring with glass rod. Measured quantities of the monomers were taken into the test tubes. After 20 minutes of addition of the initiater the two monomers 2-Hydroxyethyl methacrylate and acrylic acid were added simultaneously along with the cross linker. The reaction mixture was stirred continuously with temperature maintained between 78^0C-80^0C for one hour. The product obtained was then allowed to cool to room temperature and then soaked in water to remove the unreacted materials for 10 days. The products were then dried in oven at 55^0C till constant weight was achieved. The dried products were then grind and sieved to the

desired particle size. .Different products were synthesized varying the ratio of the monomers as stated in Table 2.

Table 2: Ratios of the monomers 2-Hydroxyethyl methacrylate and acrylic acid

Sr.No.	Hydrogels	2-HEMA: AA ratio
1	Hydrogel1	1:1.5
2	Hydrogel 2	1:2
3	Hydrogel 3	1:2.5

The initiator ammonium per sulphate in the presence of heat forms sulphate anion radical that attacks starch and results in the formation of activated starch species which reacts with the monomers 2-HEMA and AA to form cross-linked polymeric network.

Characterization

FT-IR Spectroscopy

FT-IR spectroscopy was carried out for the identification of the functional groups present in the structure of the synthesized hydrogel and for confirmation of grafting of monomers on the starch backbone. KBr pellet method was used. Well dried sample of hydrogel was crushed in an agate mortar with pestle. Crushed sample was then mixed with potassium Bromide in the proportion of 1:100 and then compressed to obtain a semi transparent disc. The spectrum was recorded in the range of 4000 cm^{-1} – 600 cm^{-1}.

Scanning Electron Microscopy

In order to study the surface morphology and the effect of pH on the morphology of the synthesized hydrogel Scanning electron microscopy studies were carried out. JEOL SEM (JSM-7600F, JAPAN) was the instrument used for the study. The SEM images were recorded after soaking the samples in solutions of pH 1.2 and 7.4 for 30 minutes.

Differential Scanning Calorimetry

The differential Scanning calorimetry studies were carried out to confirm synthesis and drug loading into the synthesized hydrogel. The thermograms for 2-Hydroxyethyl methacrylate, acrylic acid, starch, drug, plain hydrogel and drug loaded hydrogel were recorded using Differential scanning calorimeter (Universal TA Model Q 200).

Dynamic Swelling Study

The dynamic swelling studies were carried out to study the swelling behaviour of the hydrogels. The swelling of the hydrogel has impact on the drug release kinetics. Also the study throws light on the effect of monomer concentration on the swelling behaviour of the hydrogel. 100mg of the weighed hydrogel samples were soaked in the solutions of pH 1.2, 2.5, 4, 7.4, 8. The studies were carried out for 8 hours where the samples were placed onto filter paper and the excess water was removed by tapping it with a dry piece of filter paper at an interval of one hour and weighed. The equilibrium degree of swelling was calculated using the following formula

Equilibrium degree of swelling = Wt – Wo/ Wo

Wt : Weight of swollen hydrogel

Wo : Weight of dry hydrogel

Drug Loading in to Hydrogels

Drug loading is one of the important parameters for the characterization of the hydrogels. Dried hydrogels were soaked in the drug solution of known concentration of drug (1mg/5ml) for about 10 hours. The drug loaded hydrogels were then filtered on a vaccum pump. The products were then dried in the oven at 40^0C until a constant weight was achieved. The drug concentration in the solution was determined by UV spectroscopy at 284 nm.

The entrapment efficiency was calculated using the following formula:

$$\%EE = \frac{\text{Total amount of drug} - \text{Free drug} * 100}{\text{Total drug}}$$

Drug Release Studies

Dissolution studies were carried out to understand the drug release kinetics through the

hydrogels. Drug loaded hydrogel with known amount of the drug was placed in muslin cloth. The dissolution studies were carried out in USP TEST Apparatus II TDT 08L. The muslin cloth filled with the drug loaded hydrogel was tied to the paddle. The studies were carried in acidic buffer pH 1.2 for 2 hours with temperature maintained at 37^0C at 100 rpm and for 8 hours in the phosphate buffer pH 7.4. Aliquots were withdrawn at fixed time intervals and the amount of drug release was estimated using UV spectroscopy.

RESULTS AND DISCUSSION

The potato starch grafted poly (2-Hydroxyethyl methacrylate-co-acrylic acid) hydrogel polymer was satisfactorily synthesized by graft copolymerisation through free radical polymerization.

A simple and convenient UV spectroscopic method was developed for the estimation of drug Rabeprazole sodium and validated as per ICH guidelines Q2 (R1). The method was validated in three solvents Distilled water because of drugs solubility, HCl buffer pH 1.2 and Phosphate Buffer pH7.4 for estimation of the drug release in the acidic and basic buffer. A 20ppm drug solution was scanned and 284 nm was the wavelength of maximum absorption as shown in figure. 1.

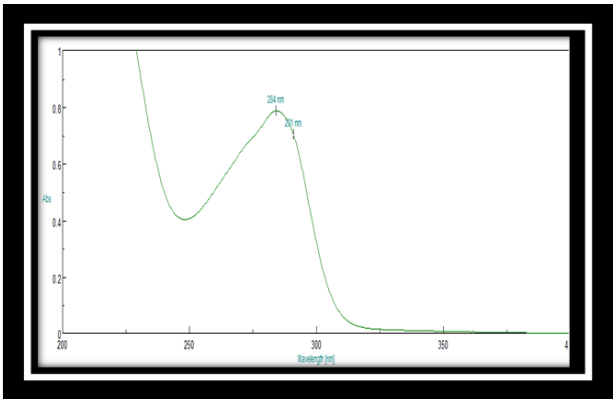


Figure 1: Scan of 20 ppm drug solution

A 100 ppm stock solution was prepared by dissolving 10 mg of rabeprazole sodium n the three solvents. From this stock solutions aliquots of 0.4, 0.6, 0.8, 1.0, 1.2, 1.4 ml were withdrawn and diluted to 10ml with the solvents to obtain standard solution of the concentration of 4, 6, 8, 10, 12, 14 ppm respectively. Absorbance of this solution was recorded as shown in the Table 3, 4, 5. Also graph of absorbance v/s concentration was plotted using Microsoft excel which are shown in Figure 2, 3, 4.

Table 3: Concentration and Absorbance in Distilled Water

Conc. (ppm)	Absorbance
4	0.1305
6	0.2042
8	0.281
10	0.3501
12	0.414
14	0.4731

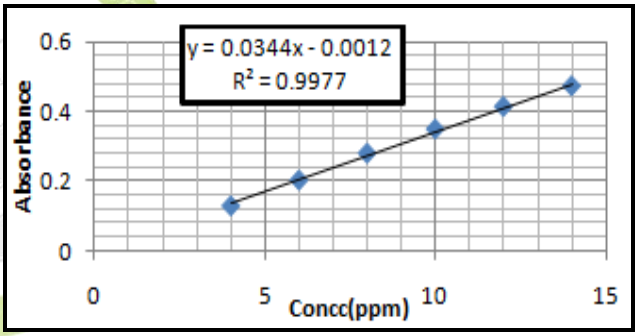


Figure 2: Plot of absorbance v/s concentration in distilled water

Table 4: Concentration and absorbance in pH buffer 1.2

Conc. (ppm)	Absorbance
4	0.1134
6	0.1687
8	0.2389
10	0.2987
12	0.3543
14	0.4098

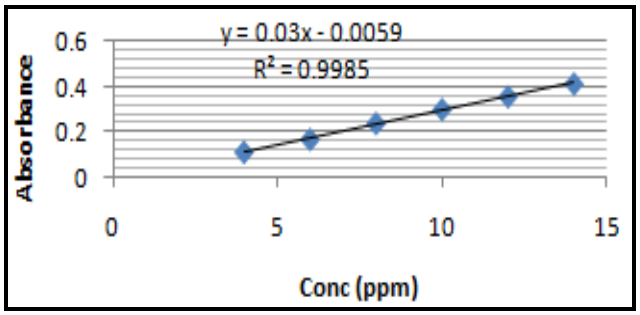


Figure 3: Plot of absorbance v/s concentration in pH buffer 1.2

Table 5: Concentration and absorbance in pH buffer 7.4

Conc. (ppm)	Absorbance
4	0.1538
6	0.2124
8	0.3101
10	0.3617
12	0.4551
14	0.5319

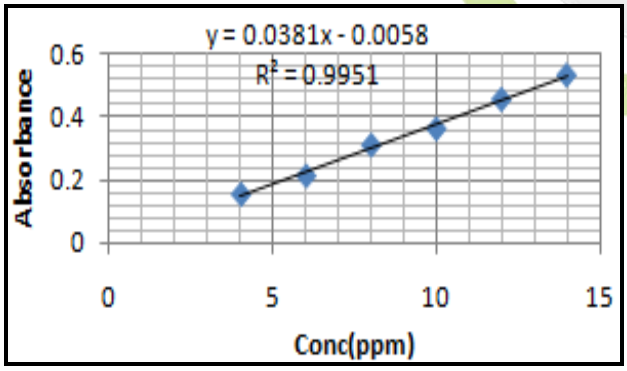


Figure 4: Plot of absorbance v/s concentration in pH buffer 7.4

The method developed was satisfactorily validated and the method was found to be accurate, precise and robust.

Fourier Transformed Infrared Analysis (FT-IR)

The structure of one of the product synthesized was characterized by FT-IR analysis.

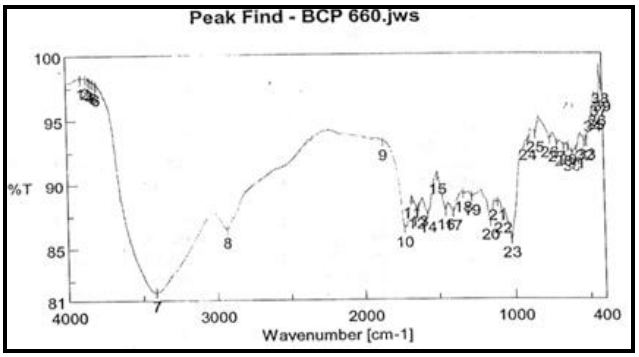


Figure 5: IR Spectrum of the synthesized polymer

Table 6: Frequency in the IR Spectra of the synthesized polymer

Peak position	Wavenumber (cm^{-1})	Functional group
7^{th} position	3413	O-H str
8^{th} position	1730	C=O str (ester)
10^{th} position	1682	C=O str (acid)

The signal at 1730cm^{-1} is due to C=O str i.e. the carbonyl group of ester present in 2-hydroxyethyl methacrylate.

Scanning Electron Microscopy

The SEM microphotographs of the hydrogels in pH 1.2 and pH 7.4 are presented in figure 6 and 7.

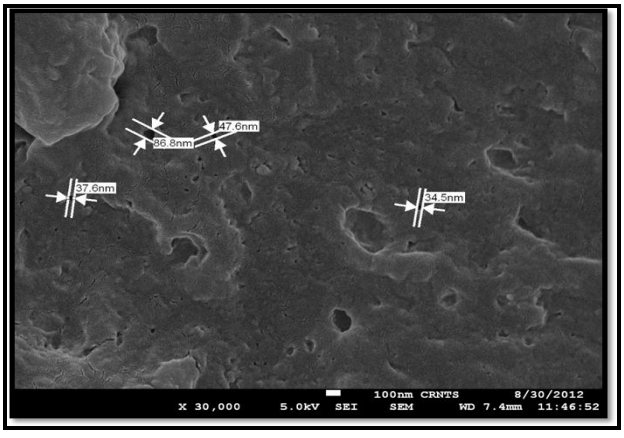


Figure 6: SEM microphotograph of hydrogel in pH 1.2

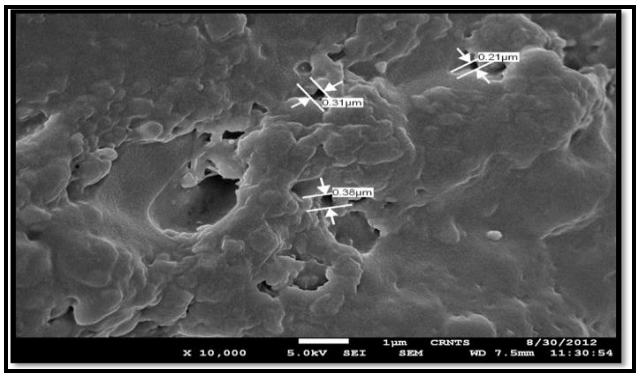


Figure 7: SEM microphotographs of hydrogel at pH 7.4

The SEM microphotographs show that at pH 1.2 the pores are small and the surface plain whereas at pH 7.4 the pore size is more and surface appears to be swollen thus proving that pH has some effect on the synthesized hydrogel.

Differential Scanning Calorimetry

The differential scanning analysis were performed on the monomers, starch, drug, drug loaded hydrogel and the synthesized hydrogel for confirmation of the polymerisation reaction as well as drug loading.

The thermograms are shown in Fig 8, 9, 10, 11, 12, 13.

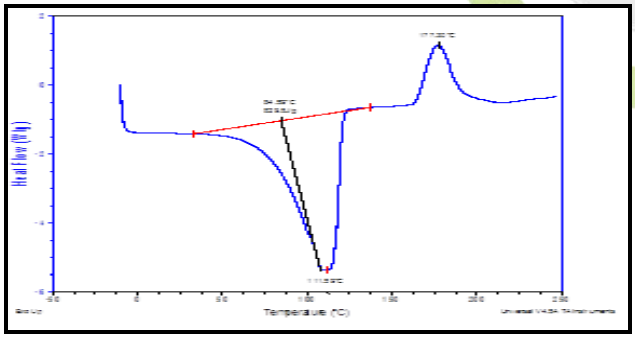


Figure 8: DSC Thermogram of 2-HEMA

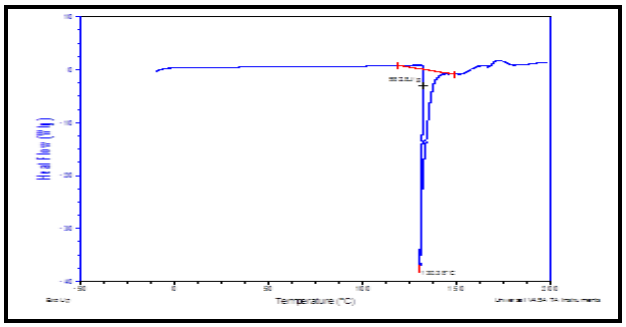


Figure 9: DSC Thermogram of AA

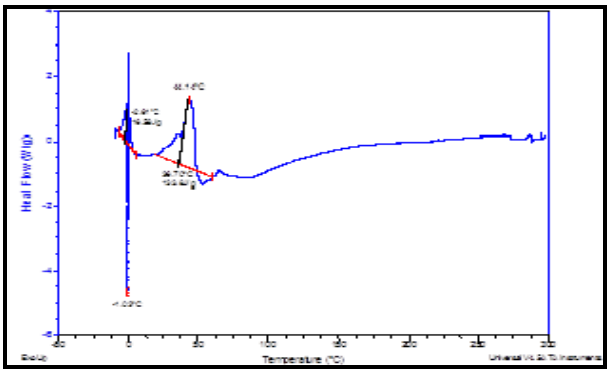


Figure 10: DSC Thermogram of Starch

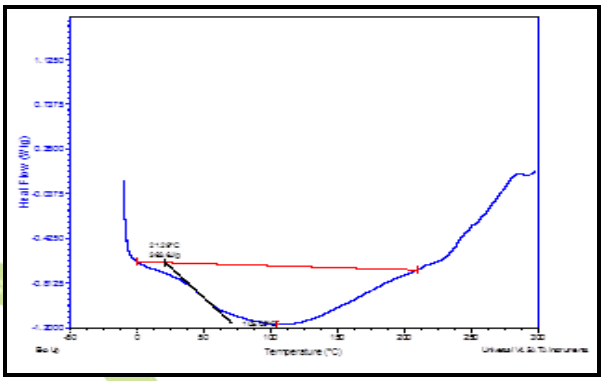


Figure 11: DSC Thermogram of Plain Hydrogel

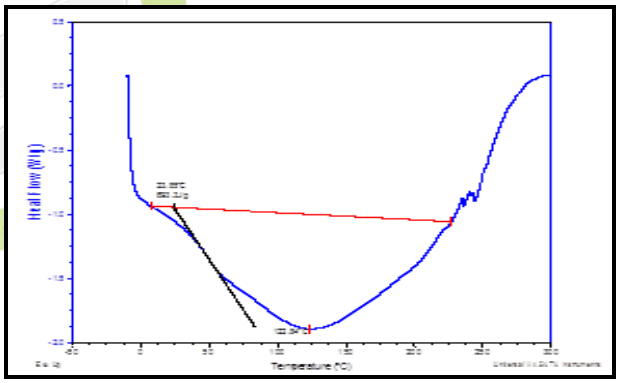


Figure 12: DSC Thermogram of Drug Loaded Hydrogel

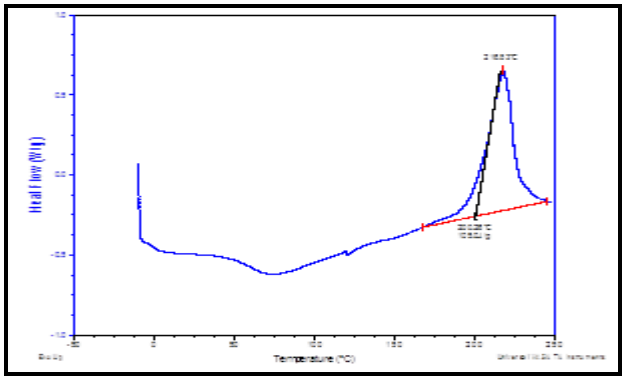
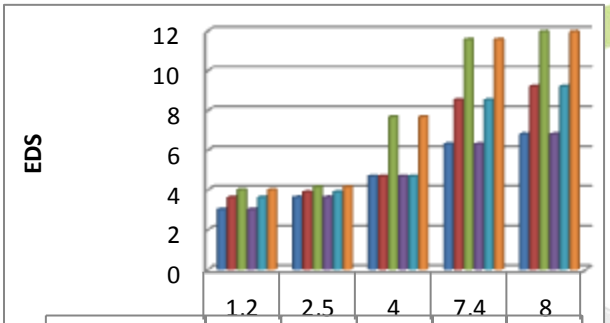


Figure 13: DSC Thermogram of Drug

The thermograms of 2-hydroxyethyl methacrylate show peaks at 84.5^{0}C and 177.30^{0}C and acrylic acid at 130.38^{0}C whereas of starch at 44.14^{0}C which are not observed in the thermogram of plain hydrogel. The thermogram of drug shows peak at 218^{0}C which is not observed in the drug loaded hydrogel indicating the fact that the drug is loaded into the hydrogel.

Dynamic Swelling Studies

The dynamic swelling studies were carried out to determine the pH sensitivity of the synthesized polymer. The synthesized polymers were exposed to different environmental pH to determine the swelling ratio. The plot of equilibrium degree of swelling (EDS) is presented in the figure 14.



	1.2	2.5	4	7.4	8
Hydrogel 1	3.02	3.63	4.68	6.3	6.8
Hydrogel 2	3.62	3.89	4.68	8.52	9.2
Hydrogel 3	4	4.14	7.67	11.56	11.95
Hydrogel 1	3.02	3.63	4.68	6.3	6.8
Hydrogel 2	3.62	3.89	4.68	8.52	9.2
Hydrogel 3	4	4.14	7.67	11.56	11.95

Figure 14: EDS of the Hydrogels at pH 1.2, 2.5, 4, 7.4, 8.

The plot shows that the swelling of the hydrogel increase with increase in the pH is more towards the alkaline side. This is due to the electrostatic repulsion of the ionised carboxylic groups which take place at higher pH. In the acidic pH there is protonation of the free carboxylic groups which result in the formation of hydrogen bonds and hence less swelling. Also hydrogel 3 shows higher swelling as compared to others which can be attributed to its higher acrylic acid content.

Drug Entrapment Efficiency

The drug loaded into the hydrogel was determined by UV spectroscopy at wavelength 284 nm. The entrapment efficiency was determined using the following formula

$$E.E\ \% = \frac{\text{Total amount of drug- free drug}}{\text{Total drug}} \times 100$$

The entrapment efficiency was found to be 70%.

Drug Release Studies

The plot of % drug release v/s time is given in figure 15.

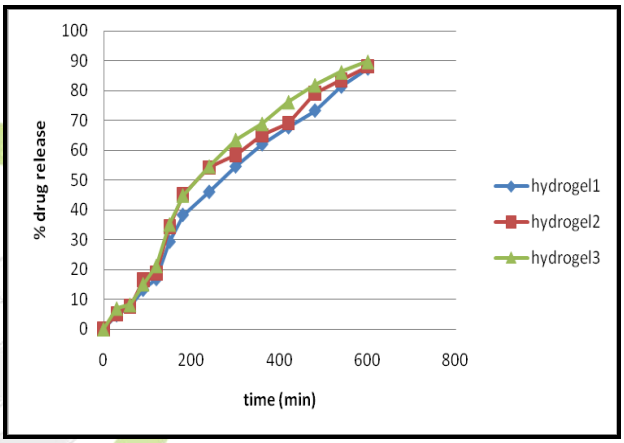


Figure 15: Plot of % Drug Release v/s Time

The drug release study shows that the drug release from all three hydrogels is comparable. The amount of drug release in the acidic pH is less than 20% for all the three hydrogels. Around 80% of the drug is available for release into the intestine. 90% of the total drug release was obtained at the end of the tenth hour. The drug release occurs slowly for a period of 8 hours in the alkaline pH. The release parameters are stated in table.7

The rate of drug release is found to follow first order kinetics since the r^2 value is the closest to 1 as compared to zero order. The r^2 value for Higuchi and Korsmeyer peppas is very close and hence it cannot be concluded that the drug release mechanism follows Higuchi or Korsmeyers peppas or both. But it can be concluded that the mechanism of drug release is diffusion controlled.

Table 7: Release Parameters of Drug Loaded Hydrogel

Sample	Zero order		First order		Higuchi		Korsmeyer-peppas	
	R^2	K (min^{-1})	R^2	K (min^{-1})	R^2	K (min^{-1})	R^2	N
Hydrogel 1	0.9539	0.345	0.9773	0.00322	0.9511	0.539	0.9668	1.026
Hydrogel 2	0.9484	0.350	0.9832	0.00345	0.9526	0.526	0.9578	1.004
Hydrogel 3	0.9480	0.354	0.9922	0.00391	0.9536	0.505	0.9572	0.959

CONCLUSION

Potato starch grafted poly (2-hydroxyethyl methacrylate –co-acrylic acid) polymer was synthesized satisfactorily which has shown to exhibit a pH dependent swelling behaviour. The physical and chemical properties of the hydrogel can be modified so as to optimise their enviroresponsive nature, bioadhesion, biodegradability. The enviroresponsive hydrogels can be used in the drug delivery to the target site due to their ability to respond external stimuli like pH, temperature for which there are enough evidences.

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