



Synthesis and characterization of polymeric hydrogels for drug preparation and its release study

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ABSTRACT

The objective of this research is preparation of novel starch based hydrogel polymer. First extracted starch from the potato and purified. The etherification of starch was done by using mono chloro propionic acid. This improved controlled drug release property of etherified starch, the prepared gel have high water holding capacity, biocompatible and biodegradable on grafting with monomers 3-(acryloyloxy) 2-hydroxypropyle (2, 3- dihydroxypropyle) succinate monomer and 2-(acryloyloxy) propanoic acid resulted in etherified starch polymer matrix (hydrogel). The resulting hydrogel was used as drug carrier with loading a specific drug. The structure of hydrogel was conformed by using SEM and FTIR. Mass spectra for monomer reaction formation. ¹³C NMR of monomer for structure conformation. The results obtained in this research work clearly indicated improved drug life in the body for long period of time compared to ordinary drug.

Keywords: 2-(acryloyloxy) propanoic acid, grafting, hydrogel, starch.

INTRODUCTION

Natural polymers derived from renewable resources are widely distributed in nature. These materials exhibit a large diversity of structures, different physiological functions and, may offer a variety of potential applications in the field of tissue engineering due to their various properties, such as pseudo plastic behavior, gelation ability, water binding capacity and biodegradability.¹ Many of these polymers forms hydrogels that can respond to external stimuli. Hydrogels look like natural living tissue more than any other class of synthetic biomaterials due to their high water content and soft consistency which is similar to natural tissue.²⁻⁴ Furthermore, the high water content of these materials contributes to their biocompatibility and can be used as contact lenses, coatings for artificial hearts, materials for artificial skin, membranes for biosensors and drug delivery devices. In this paper, we focused used of hydrogel in drug release formulation. Hydrogels are three-dimensional, cross-linked networks of water-

Absorbent polymers. Hydrogels can be made from virtually any water-soluble polymer, encompassing a wide range of chemical compositions and bulk physical properties. Still, hydrogels can be formulated in a variety of physical forms, including lumps, micro particles, nanoparticles, coatings, and films. Above this hydrogel properties in twenty first century, we focused on drug release formulation. General problem for all the oral dosage forms that is the gastric residence time is low for this reason different types of problem faced by humans like Multiple administrations necessary to maintain the drug in therapeutic amounts in the blood stream, tissue burning, Exceed the toxicity level, Side effects, Increased cost of pharmaceuticals. Now a day increase requirement of analgesic drug in the 21st century of the static data (fig.1) has increased death rate and consuming rate parallels pharmaceutical cost also increased. Solve these problems in present scenario for this,^{5,6} researchers focused towards the novel control drug delivery technologies to enhance drug residence time for solved the above problem like reduced multiple doses, no side effect, reduced pharmaceutical cost, decrease rate of death and reduces consuming analgesic drugs. Face the problem Prepared biodegradable, biocompatible, increase drug release time and high water absorption polymeric membered. In normal oral doses tablets used starch as a binder since long period of time to solve above problem in this paper, we make a modification in starch and improve its water holding properties.⁷⁻⁸ This portent can be explained by the presence of hydrophilic functional groups in their

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structure, such as -OH, -COOH, -CONH₂, and -SO₃H, capable of absorbing water without undergoing dissolution.⁹⁻¹¹ In this work using such kind of functional group and prepared 3-dimensional net-work of super porous hydrogel. It's a hydrophilic polymer which absorbs a large amount of water in a very short period of time.

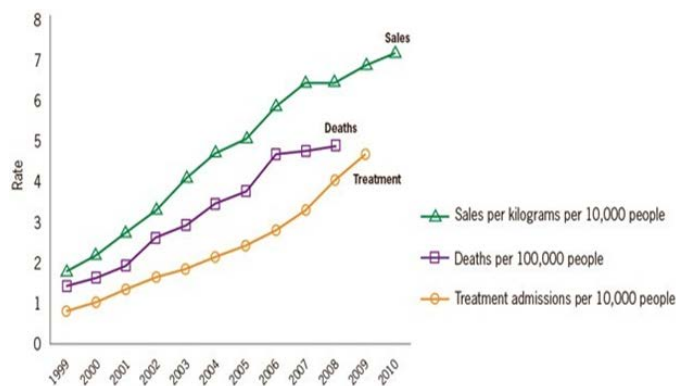


Figure 1 : Prescription painkiller overdoses graph

MATERIAL AND METHOD

Materials

Paracetamol was received from Ahmedabad, Gujarat, India. Lactose, Mg-stearate talc and Acrylic acids were purchased from SD fine chemicals, Mumbai chemicals analytical grade purity 99%. The dibasic acids (succinic) and sulphuric and Glycerol, from Sigma Aldrich product with purity >99% were used without further purification. All solvents used throughout this study were of the chemically pure grade and were fractionally distilled just before use. The water used in the surfactant tests was purified by water purification system.

Apertures

Infrared (IR) spectra were obtained on 1600 FTIR Perkin Elmer-Spectrum in the 400–4,000 cm⁻¹ range using KBr pellets. Scanning electron microscopy (SEM) analysis.

Extraction of starch

Starch was extracted from potatoes using standard protocol.¹² Mature potato was thoroughly washed and all foreign materials were removed. The potato was peeled, weighed and washed. The washed potato was pulverized, using with a mixture. Add require amount of water into the pulp, which was then passed through an 180µm sieve. The filtrate was allowed to settle and for separation of starch and proteins add 0.1N Sodium hydroxide was added as well as to neutralize the prevailing slight acidity. Excess sodium hydroxide was removed by washing several times with distilled water. The clear supernatant fluid was poured away while sedimented starch was collected in a tray and air-dried on a table at room temperature. Using pestle and mortar the dried starch lumps were ground and fine powder passed through 180µm sieve.

Preparation of Sodium salt of Partly Carboxylic Propyl Starch (Na-PCPS)

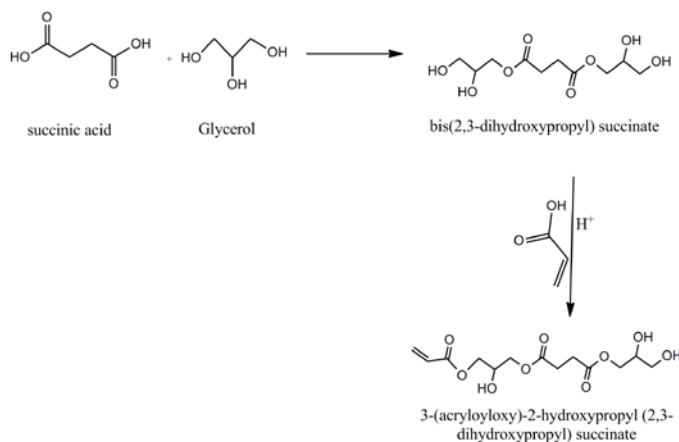
Carboxylic propyl starch was prepared according to published method.¹³ In three necked flask equipped with condenser, stirrer and gas inlet tube, affixed amount 5g of palm Starch was weighed and added to 250 ml Schott bottle followed by 100 ml of

isopropanol. 20 mL of 17.5% aqueous sodium hydroxide was added drop-wise while it is stirred for an hour at 30 °C. After alkali treatment, etherification reaction was continued by adding 6g of sodium monochloroacetate (SMCA) in reaction mixture and placed in a water bath with horizontal shaker. The reaction mixture was heated up to reaction temperature of 50 °C and shaken for 2 hours of reaction time. Longer time of reaction will increase degradation of polymer and will reduce the DS value as well. The slurry was then soaked in methanol for overnight. On the next day, the slurry was neutralized with 90% of acetic acid until reach pH 6-8 and then filtered. CMS was purified by washing with 70% ethanol for five times to remove undesired byproduct. Then the CMS was filtered and dried at 60o C in an oven for 24 hours.

Preparation of monomers

3-(acryloyloxy) 2-hydroxypropyle (2, 3- dihydroxypropyle) succinate

Esterification was performed in a 250-mL three-necked flask fitted with a reflux condenser, thermometer, and a sampling port. The reaction condition was heated the flask at 80 °C with constant starring by magnetic stirrer. The reagents used were in a molar ratio, 4 moles of glycerol to 1 mole of succinic acidand the reaction was catalyzed by 0.1% w/w H₂SO₄ (of total) [14].The culmination of the reaction, the reaction mixture was washed with water and the glycerol ester extracted with Chloroform. Analogous synthetic procedures were performed for the synthesis of bis (2,3-dihydroxypropyl) succinate. Cool at room temperature, then added acrylic acid 1 mole with catalyst 0.1% w/w H₂SO₄ (of total) stared 3 to 4 hours at 35 to 40 °C temperature (scheme 1).

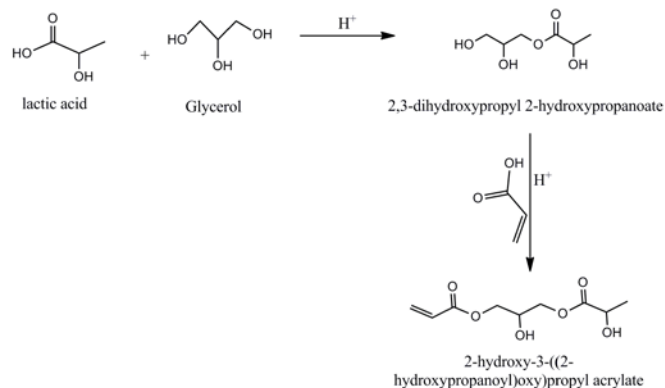


Scheme 1. Reaction scheme of 3-(acryloyloxy) 2-hydroxypropyle (2, 3- dihydroxypropyle) succinate

2-hydroxy-3-((2-hydroxypropanoyl)oxy)propyl acrylate

Esterification was performed in a 250-mL three-necked flask equipped with a reflux condenser, thermometer, and a sampling port. The reaction condition was heated the flask at 80 °C with constant starring by magnetic stirrer. The reagents used were in a molar ratio, 1 mole of glycerol to 1 mole of lactic acidand the reaction was catalyzed by 0.1% w/w H₂SO₄ (of total). Completion of the reaction, the reaction mixture was washed with water and the glycerol ester extracted with Chloroform. Analogous synthetic procedures were performed for the synthesis

of 2-hydroxy-3-((2-hydroxypropanoyl)oxy)propyl acrylate. Cool at room temperature, then added acrylic acid 1 mole with catalyst 0.1% w/w H₂SO₄ (of total) stored 3 to 4 hours at room 35 to 40 °C (scheme 2).



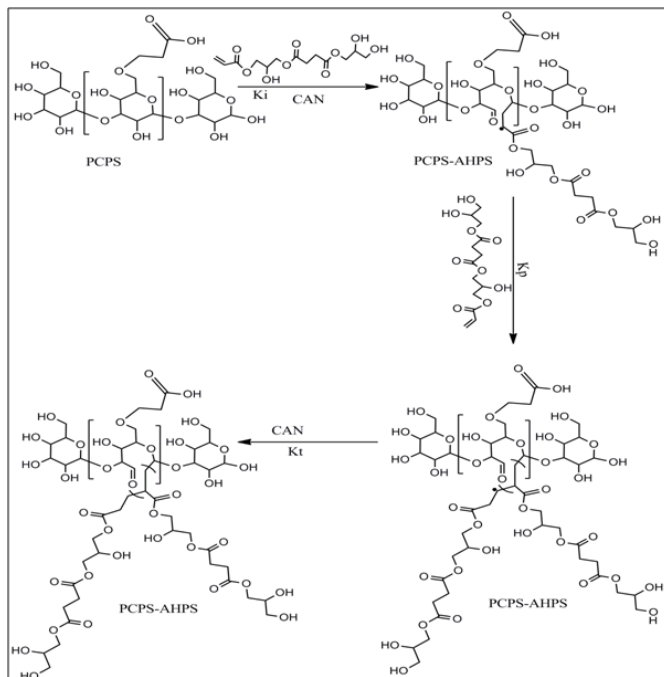
Scheme 2. Reaction scheme of 2-hydroxy-3-((2-hydroxypropanoyl)oxy)propyl acrylate

Graft co-polymerization PCPS-g-3-(acryloyloxy) 2-hydroxypropyle (2,3-dihydroxypropyle) succinate (AHPS)

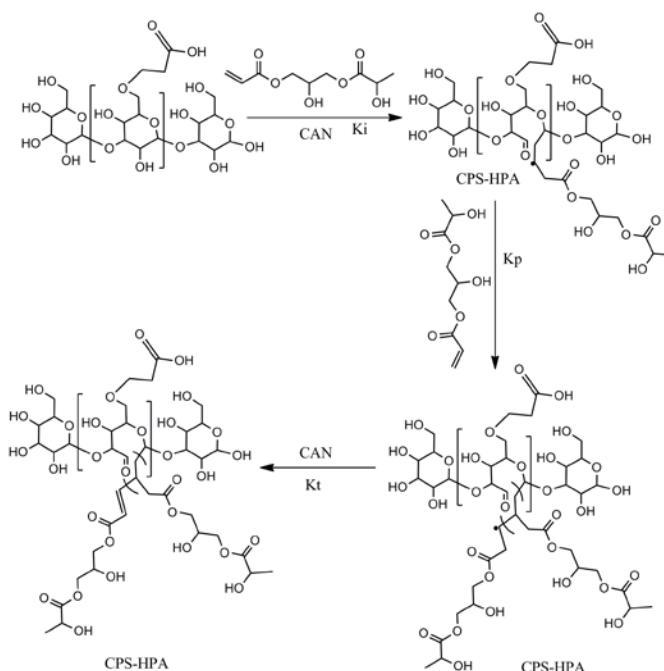
A one step preparative method was used for synthesis of PCPS-g-3-(acryloyloxy) 2-hydroxypropyle (2,3-dihydroxypropyle) succinate (AHPS) hydrogel. PCPS (2 g) was added to 35 ml of doubly distilled water in a three-neck reactor equipped with a mechanical stirrer at 45 to 50 C°. Add the ceric ammonium nitrate to initiate the reaction, then add specific amount of monomer (AHPA) mixture was allowed to stir for certain times (120 min). The pasty mixture was allowed PCPS-g-3-(acryloyloxy) 2-hydroxypropyle (2,3-dihydroxypropyle)succinate (AHPS) to cool to room temperature and neutralized the resulting product upto pH 8.0. Then the gelled product was scissored to small pieces and poured in ethanol (200 ml) to dewater for 5 h. The hardened particles were filtered and dried in vacuum oven (50 °C, 10 h). After grinding, the powdered super absorbent hydrogel was stored away from moisture, heat and light. Crosslinking graft copolymerization of 3-(acryloyloxy) 2-hydroxypropyle (2,3-dihydroxypropyle) succinate (AHPS) shown in (Scheme 3).

Graft co-polymerization PCPS-g-2-hydroxy-3-((2-hydroxypropanoyl)oxy)propyl acrylate (HPA)

A one step method for grafting of PCPS-g-3-(acryloyloxy) 2-hydroxypropyle (2,3-dihydroxypropyle) succinate (AHPS) hydrogel. PCPS (2 g) was added to 35 ml of doubly distilled water in a three-neck reactor equipped with a mechanical stirrer at 45 to 50 °C. Add the ceric ammonium nitrate for initiate the reaction, then add a specific amount of monomer (AHPA) mixture was allowed to stir for certain times (120 min). The pasty mixture was allowed to cool to room temperature and neutralized the resulting product upto pH 8.0. Then the gelled product was scissored to small pieces and poured in ethanol (200 ml) to dewater for 5 h. The hardened particles were filtered and dried in vacuum oven (50 °C, 10 h). After grinding, the powdered superabsorbent hydrogel was stored away from moisture, heat and light. Crosslinking graft copolymerization of 2-hydroxy-3-((2-hydroxypropanoyl)oxy)propyl acrylate (HPA) shown in (Scheme 4).



Scheme 3. Reaction scheme of synthesis PCPS-g-3-(acryloyloxy) 2-hydroxypropyle (2,3-dihydroxypropyle) succinate (AHPS) hydrogel.



Scheme 4. Reaction scheme of PCPS-g-3-(acryloyloxy) 2-hydroxypropyle (2,3 dihydroxypropyle) succinate (AHPS) hydrogel.

Drug loading in polymeric membrane (hydrogel)

Solid dosage formulation of the Ibo profane, drug was prepared using the wet granulation method. Prepared Ibo profane salt and 500 mg API dissolved in distill water.^{16,17} The hydrogel deep in API solution, for 6 to 7 hours. Totally water absorbed by hydrogel dry under vacuum 60 to 65 °C temperature for 6 to 7 hours and crush in fine powder. A batch of 20 tablets was prepared. The ingredients were grinded using mortar and pestle. Various trials batches were prepared using graft co-polymer in various

concentrations with a fixed quantity of drug. Mixing all the ingredients and pass through a sieve 60 #. For above prepare mixture isopropyl alcohol quantity sufficient to produce wet mass was added with constant mixing. And the wet mass produced was passed through sieve 60 # to produce granules. Then prepared granules were dried at 55 °C for one hour in an oven. Then dried granules were passed through sieve 44 #. To these granules 1% Mg stearate and 2% Talc were added and mixed thoroughly. Tablets were prepared by tablet punching machine. The prepared two different types of tablets name given T_{AHPS} and T_{HPA}

RESULTS AND DISCUSSION

Study of water absorption properties

In the experiment, 1 g sample was immersed in excess dis-tilled water and kept undisturbed to reach swelling equilibrium.¹⁸ Then swollen samples were filtered through a 100-mesh gauze to separate from unabsorbed water and weighted. The water absorption amount Q_{eq} (g/g) was calculated as follows:

$$\text{Water absorption (A)} = H_2 - H_1$$

Where H₁ (g) and H₂ (g) are the weights of the dry and wet sample, respectively (A) Water absorption by hydrogel.

$$\% \text{ Water absorption} = \frac{H_2}{H_1} \times 100$$

Friability test of tablet

To measure the friability, tablets were placed in the rotary plastic drum revolving at 25 rpm and dropping them to six inches at every revolution.¹⁹⁻²⁰ Normally, a pre weighed tablet sample are placed, which is then operated for 100 revolutions. The tablets are dusted off and reweighed. Conventional compressed tablets that lose less than 0.5% to 1% of their original weight are generally considered acceptable. When capping is observed in friability testing, the tablet should not be considered for commercial use, regardless of the percentage of loss observed. Tablet friability may be influenced by the moisture content of finished tablets. It also depends on the shape and the condition of the punches used in tablet preparation.

It was determined by weighing fifteen tablets after dusting, placing them in a friability test and rotating the basket vertically at 25 rpm for 4 min (100 drops). After the total remaining weight of the tablets was recorded and the percent friability was estimated.

$$\% \text{ Friability} = \frac{\text{Original weight} - \text{Final weight}}{\text{Original weight}} \times 100$$

Disintegration test of tablet

The test was performed with disintegration tester S-1 (Systronic, India) according to European Pharmacopoeia 7.0. Distilled water (approximately 900 mL) was used as a disintegration medium. Six tablets were placed into the tubes of the disintegration apparatus. The disintegration time was measured semi-automatically.

Hardness test of tablet

Tablets require a certain amount of hardness and resistance to friability, to withstand mechanical shocks of handling during manufacture, packaging and shipping. Tablet hardness has been

defined as the force required breaking a tablet in a diametric compression test. In short, hardness is termed the tablet crushing strength. Hardness of a tablet is a function of die, fill and compression force.²¹ At a constant die fill the hardness value increases and thickness decrease as additional compression force is applied. At a constant compression force, hardness increases with increasing die fills and decreases with lower die fills. To evaluate tablet hardness, mostly Monsanto hardness tester is used.

The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with tablet, and a zero reading is taken. The plunger is then forced against a spring by turning a threaded bolt until tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate force. The force of fracture is recorded, and zero force reading is deducted from it. The test was performed on manual hardness tester Model HT-1 Systronic India PVT, Ltd.

Properties study of hydrogel and its matrix tablets

Friability test of tablet, Disintegration test of tablet, Hardness test of tablet and water absorption study of hydrogel data in table 1. The resulting hydrogel absorption high amount of water in short period of time fig. 2.



Figure 2. Water absorption by hydrogel

Table 1. Properties study of hydrogel and its matrix tablets. (T_{AHPS}: 3-(acryloyloxy) 2-hydroxypropyle (2, 3- dihydroxypropyle) succinate) graft matrix tablet, T_{HPA}: 2-hydroxy-3-((2-hydroxypropanoyl) oxy) propyl acrylate graft matrix tablet.)

Weight	Disintegration (minutes) ^a	Friability (%) ^a	Hardness (Kg) ^a	Variation (mg) ^a	Water absorption (%) ^a
T _{AHPS}	16.22±0.24	1.22±0.02	6.0±0.07	503.1±0.012	1500±0.10
T _{HPA}	15.43±0.48	1.31±0.01	6.2±0.09	492.4±0.011	1100±0.15

^amean±SD, n = 3.

FTIR results 3-(acryloyloxy) 2-hydroxypropyle (2, 3-dihydroxypropyle) succinate, 3-((2-hydroxypropanoyl) oxy) propyl acrylate monomers

The FTIR spectrums of them were shown in (fig. 3) of 3-(acryloyloxy) 2-hydroxypropyle (2, 3-dihydroxypropyle) succinate monomer which had similar characteristic absorption peaks. Comparing with the FTIR spectrum of at 3328.05 cm⁻¹ (O H stretching vibration influenced by hydrogen bond), 2930.46 cm⁻¹ for CH alkenes, 1726.38 C=O ester, 1635.20 C=C alkynes 1110.95 C-O ester group, 854.43 =C-H functional is present, respectively. In (fig.4), the appeared absorption bands at 3426.13 cm⁻¹ (OH stretching), 1738.00 cm⁻¹ (C O stretching vibration of COOH) and the disappeared absorption bands at 2927.46 cm⁻¹

(C-H) and 2927(C=C) absorption of 3-((2-hydroxypropanoyl) oxy) propyl acrylate monomer.

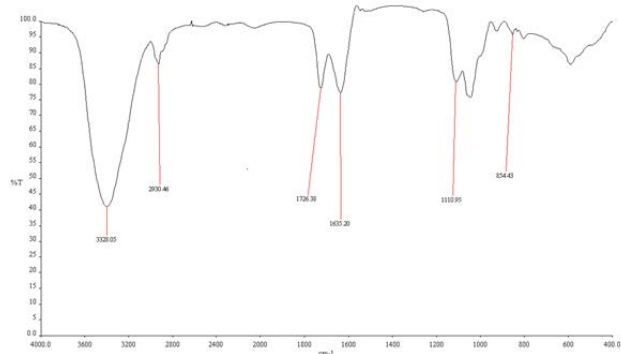


Figure 3. FTIR Spectra of 3-(acryloyloxy) 2-hydroxypropyle (2, 3-dihydroxypropyle) succinate monomer

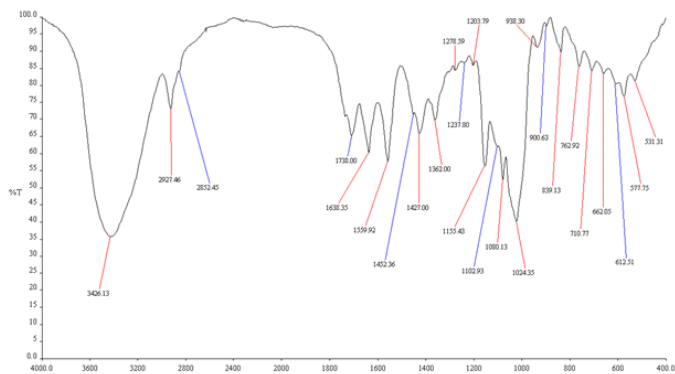


Figure 4. FTIR Spectra of 3-((2-hydroxypropanoyl) oxy) propyl acrylate monomers

FTIR results PPCS-g-AHPS and PCPS-g-HPA

The FTIR spectrums of them were shown in figure 5, which indicate reaction of PCPS-g-2-hydroxy-3-((2-hydroxypropanoyl) oxy) propyl acrylate. Furthermore, the absorption peaks of PCPS-g-2-hydroxy-3-((2-hydroxypropanoyl) oxy) propyl acrylate hydrogel are 3397.9 cm^{-1} O-H stretch, alcohols present, 1731.27 cm^{-1} absorption peaks of C=O esters group may be presented, 1457.59 cm^{-1} C-H bend alkanes may be presented, 1228.8 cm^{-1} C-O stretch alcohols, carboxylic acids, esters, ethers may be present. were larger than PCPS-g- 3-(acryloyloxy) 2-hydroxypropyle (2, 3-dihydroxypropyle) succinate hydrogel, which was assigned to the grafting occurred between PCPS and the grafted given monomer the absorption peaks are 3394.22 cm^{-1} O-H stretch, H-bonded alcohols present, 2959.38 cm^{-1} , 1725.38 cm^{-1} C=O stretch esters present, 1230.16 cm^{-1} C-O stretch alcohols, carboxylic acids, esters, ethers present. 677.68 C-H rock alkanes present results obtained from FTIR analysis showed that PCPS-g- 3-(acryloyloxy) 2-hydroxypropyle (2, 3-dihydroxypropyle) succinate hydrogel (fig.6), and 2-hydroxy-3-((2-hydroxypropanoyl) oxy) propyl acrylate hydrogel was prepared during the polymerization process.

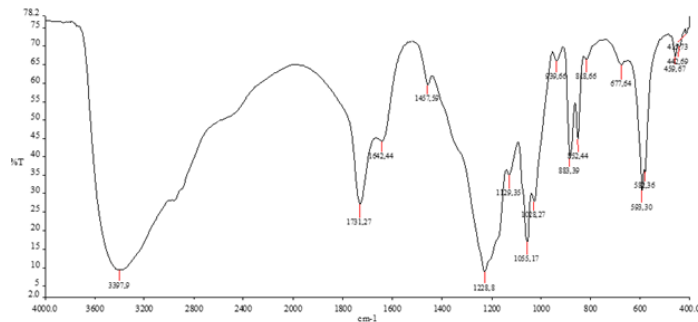


Figure 5: FTIR spectra of PCPS-g-2-hydroxy-3-((2-hydroxypropanoyl) oxy) propyl acrylate

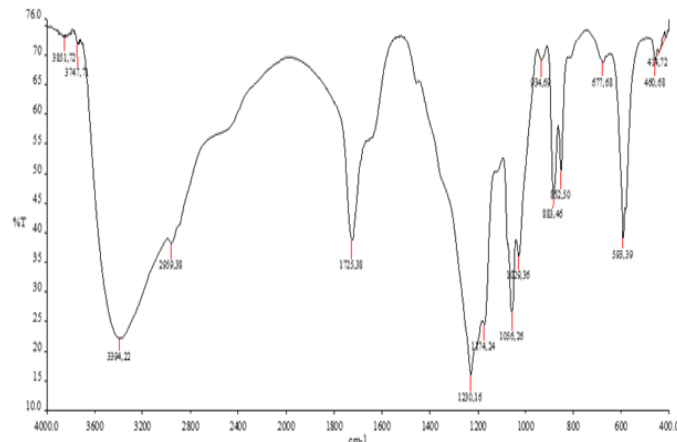


Figure 6. FTIR Spectra of PCPS-g- 3-(acryloyloxy) 2-hydroxypropyle (2, 3-dihydroxypropyle) succinate hydrogel

¹³C NMR spectra analysis of 3-(acryloyloxy) 2-hydroxypropyle (2, 3- dihydroxypropyle) succinate and 2-hydroxy-3-((2-hydroxypropanoyl) oxy) propyl acrylate

The ¹³C NMR spectra of 3-(acryloyloxy) 2-hydroxypropyle (2, 3- dihydroxypropyle) succinate and 2-hydroxy-3-((2-hydroxypropanoyl)oxy)propyl acrylate were shown in (fig.7) and (fig.8) It was found from the ¹³C NMR spectra of 3-(acryloyloxy) 2-hydroxypropyle (2, 3- dihydroxypropyle) succinate (fig.7) The Carboxyl carbon at 173.41 ppm, 165.79 ppm Carboxylic carbon attach alkyne carbon, 65.10-67.25 ppm CH₂ Oxygen containing carbon, carbon of CH₂ and CH in the region of 70.48-62.42 ppm, 28.39 carbon attached carboxylic carbon and obvious ethylene carbon peak at 131.33-129.92 ppm all corresponded with the characteristic structure of 3-(acryloyloxy) 2-hydroxypropyle (2, 3- dihydroxypropyle) succinate monomer. And for 2-hydroxy-3-((2-hydroxypropanoyl) oxy) propyl acrylate (fig.8) the Carboxylic carbon at 173.57-165.74 ppm, carbon of CH₂ and CH in the region 65.07-68.21 ppm Observable 129.92 ppm peak of CH ethylene, 131.33 ppm CH₂ ethylene carbon, 18.81 ppm of CH₃ carbon all related with the characteristic structure of 2-hydroxy-3-((2-hydroxypropanoyl) oxy) propyl acrylate is conformed.

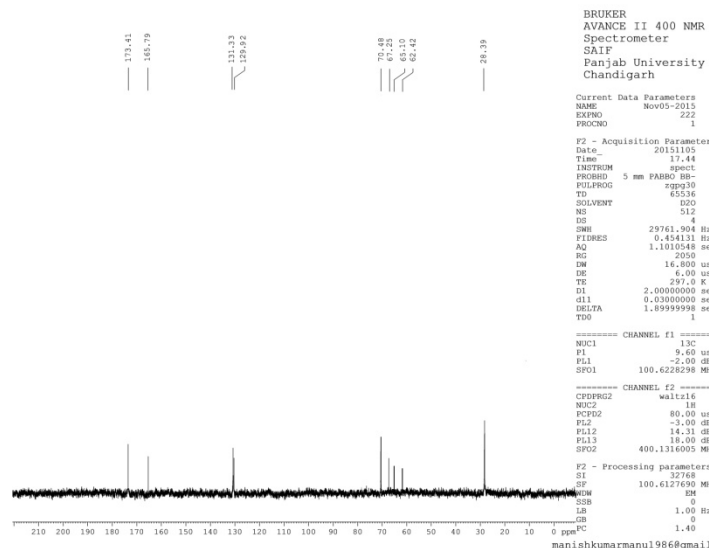


Figure 7. C13 NMR of 3-(acryloyloxy) 2-hydroxypropyle (2, 3-dihydroxypropyle) succinate

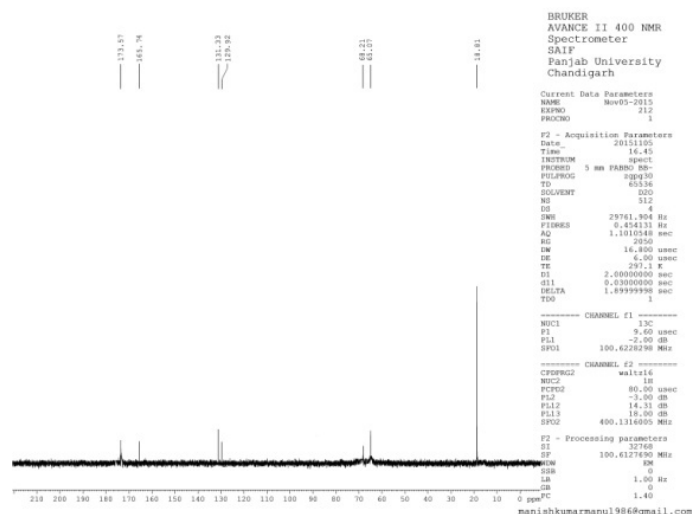


Figure 8: C13 NMR of 2-hydroxy-3-((2-hydroxypropanoyl) oxy) propyl acrylate

Mass Spectra of AHPS and HPA

The mass spectra of 3-(acryloyloxy) 2-hydroxypropyle (2,3-dihydroxypropyle)succinate (AHPS) (fig.9) enumerates a molecular ion peak at 321.1 peak which conforms molecular weight of AHPS. Another monomer mass specters (fig.10) enumerates a molecular ion peak 219.108 which is conforms 2-hydroxy-3-((2-hydroxypropanoyl)oxy)propyl acrylate (HPA).

SEM results

As a widely employed technique, in this paper, SEM was used to investigate and identify the differences of surface morphology, size, shape and porosity of PCPS, PCPS -g-HPA and PCPS-g-AHPS hydrogel (fig. 11(a) (b) and (C)). It was observed that the PCPS after grafting AHPS and HPA monomer with increase the pour sizes of PCPS-g- AHPS, PCPS -g-HPA, The cross-linked densities were higher and net-work structure was more observable than PCPS. This porous microstructure increased surface area and was useful for water penetrating into the network of hydrogels,

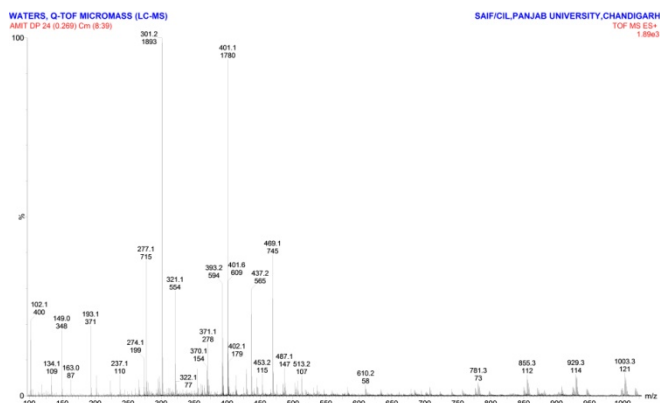


Figure 9. Mass Spectra of 3-(acryloyloxy) 2-hydroxypropyle (2,3-dihydroxypropyle)succinate

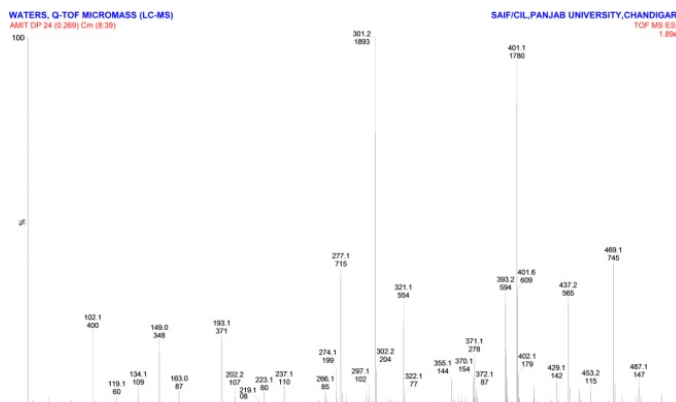


Figure 10. Mass Spectra of 2-hydroxy-3-((2-hydroxypropanoyl)oxy) propyl acrylate

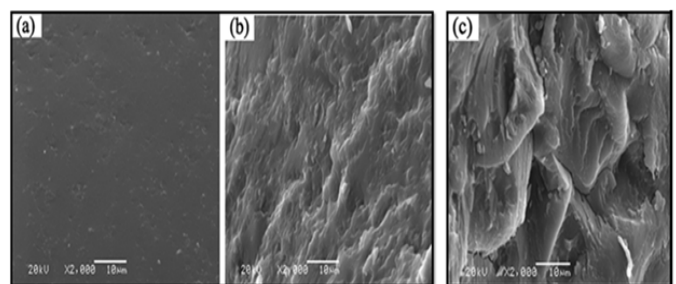


Figure11 : SEM of (a)PCPS,(b) PCPS -g-HPA and (C) PCPS-g-AHPS.

which was conducive to the improvement of water absorbency. Due to numerous interconnected pores in the hydrogel network, water molecules can easily diffuse in hydrogel.

In vitro drug release

The explanation by the release study graph clearly (fig.12) indicated the released of drug amount slowly compare to standard drug (fig.12) a, Observed the graph B and C they both are polymeric tablet deference in % release depend on pour size of polymeric member [22]. The polymeric tablet have more pour size then the diffusion rate become high compare to low pour size so more pour size tablet the % drug release of drug is high.

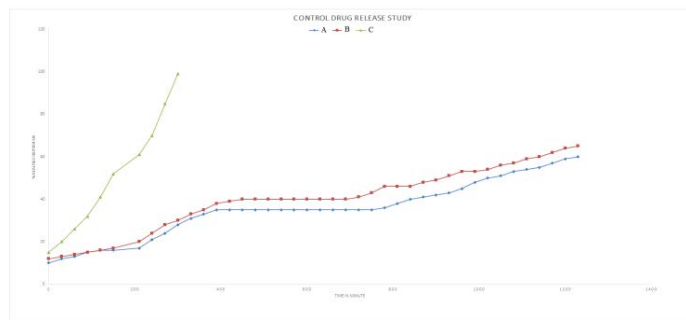


Figure 11. Control drug release study of C- Standard Tablet, B- PCPS-g-HPA Tablet (2-hydroxy-3-((2-hydroxypropanoyl)oxy)propyl acrylate), A- PCPS-g-AHPS Tablet (3-(acryloyloxy)-2-hydroxypropyl (2, 3- dihydroxypropyl) succinate)

CONCLUSION

Observe the in vivo release study graph standard ibuprofen drug release 100% in 5 hour and the hydrogel matrix tablet release time more than 24 hour. In conclusion we may assess the good quality tablet may be prepared from the hydrogel polymer are obtain from sustain release matrix tablet. The prepared with graft copolymer PCPS-g-AHPS and PCPS-g-HPA hydrogels used for oral drug delivery and growing the range of drugs and kinetics which can be achieved using a hydrogel-based tablet compare to normal ibuprofen (Analgesic) drug. Appropriate design of hydrogel for Sustain delivery system it has vast clinical benefits, like maintain a therapeutic drug levels in body for long period of time, reduction of consuming analgesics drug and there side effects, reduction of multiple dosage, reduced cost of pharmaceuticals.

Starch based hydrogel is nontoxic, biocompatible and low cost to compare other hydrogel like cellulose, gelatin and chitosan. Raw material for starch, potato starch available in market and excretion process is also simple. The nontoxic and biocompatible of preparation of tablet used modified grafted starch and the ordinary starch used for preparation of conventional tablets as a binder so it is nontoxic.

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