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Novel Drug Binder From Biomaterials: Synthesis and Characterization

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ABSTRACT

The developments in the field of polymeric superabsorbent over the past decade are presented in the paper. Special attention has been paid to the preparation methods to emphasize the new synthesis strategies developed in the recent years. Superabsorbent copolymers form as a result of the phase separation during the free radical cross linking copolymerization of sodium acrylate, methyl acrylate and methyl methacrylate monomers in the presence of inert diluents. It has been established that a variety of absorbent structures can be achieved during or after the cross linking by varying the independent parameters of the polymer synthesis, i.e. the degree of the polymer interactions, the amount of the cross linker and the diluents as well as the initiator concentration or the polymerization temperature. The most important reaction parameter to superabsorbent polymer synthesis is a ternary system composed of a polymer network, soluble polymers and low molecular compound. All concentrations of polymeric mass and properties of the monomers of the system change continuously during the cross linking process. Synthetic polymeric hydrogels represent a group of materials, used in various biomedical regulations, and are still developing for new promising applications. There has been extensive development in the clinical and pharmacological precincts of hydrogels for drug delivery applications but imperative challenges remain. Here we also discuss the current movement in overcoming these challenges, specifically with regards to successfully delivering hydrogels inside the body without implantation, prolonging the release kinetics of drugs from hydrogels, and increasing the nature of drugs which can be delivered via hydrogel based approaches. They have been effectively used as superabsorbent materials and in drug delivery, cell encapsulation and tissue repair due to their high water content and subsequent biocompatibility.

Keywords: Starch, Carboxyl Propyl Starch, CPS-acrylate, CPS-methyl acrylate, CPS-methyl methacrylate.

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INTRODUCTION

During the past decades, most of the pharmaceutical research activities have focused on the discovery or synthesis of the novel drugs and drug administration systems. In this way, controlled release drug delivery systems (DDS) have an outstanding place [1]. Among various kinds of polymeric systems, which have been used as drug containers or release rate controlling barriers, hydrogels have gained considerable interest and reviewed from different points of view. Hydrogels are a unique class of macromolecular networks that may contain a large fraction of aqueous solvent within their structure. They are particularly suitable for biomedical and tissue engineering applications because of their ability to simulate biological tissues [2]. The hydrophilicity of the network is due to the presence of chemical residues such as hydroxylic, carboxylic, amidic, primary amidic, sulphonic, and others that can be found within the polymer backbone or as lateral chains [3]. Nevertheless, it is also possible to produce hydrogels containing a significant portion of hydrophobic polymers, by blending or copolymerizing hydrophilic and hydrophobic polymers. Considering various advantages, such as biocompatibility, ability to respond to external stimuli under various physiological conditions, and the fact that water retention in the hydrogels provides a suitable drug diffusion pathway [4-6].

One of the most studied natural polymers is starch. Starch is the most abundant and renewable biopolymer in nature. It is the main constituent of plant cell walls, fungi, some algae and several bacteria has the ability to produce extra-cellular starch as their metabolites [7-10]. Starch is a carbohydrate homopolymer consist of 1,4-alpha glycosidic unit's joint together by 1, 4-alpha glycosidic bond. Starch fibrils are highly insoluble and inelastic. Their molecular configuration making the tensile strength of starch comparable to that of steel and this unique feature provide mechanical support to the tissues which it resides. Starch normally used in conventional drug binders [solubility of starch]. In present paper using chemically modified starch and graft with acrylates prepared hydrogels and use as a drug binder. By means of, hydrogels represent polymeric networks capable of absorbing large quantities of water, yet remaining insoluble due to chemical or physical crosslinks between individual polymeric chains. It's has biocompatible and non-toxic properties.

Thus, looking above background in mind and importance of the hydrogels the present communication comprises intensive investigation of the synthesis and characterization of CPS hydrogels is carried out. We are also focus on recent developments addressing three key clinically relevant issues regarding the use of hydrogels for drug delivery facilitating the

in vivo application of drug eluting hydrogels, extending their duration of drug release, and broadening the range of drugs which they effectively deliver.

MATERIALS AND METHOD

Materials

Paracetamol was received from Ahmedabad, Gujarat, India. Lactose, Mg-stearate and talc were procured from SD fine chemicals, Mumbai. All other chemicals and reagent used were of L. R. grade.

Methods

Extraction of Starch

Starch was extracted from 5-15 cm depth of 400 gm Indian potatoes having 5.6-6.2 pH using standard protocol described by Sinha, 1990 [11]. Mature potatoes were thoroughly rinsed in running tap water cut into small slices and kept in saline water (0.1M NaCl) to prevent bacterial contamination. The slices were crushed in a mixer with an excess of saline water. Obtained milky pulp was filtered through nylon cloth to collect the separated granules, Residual material was crushed and filtered repeatedly to collect a maximum of starch. Filtrate thus collected contained starch granules and fine lighter impurities were removed by numbers of saline water washing. To remove portentous matters associated with starch, the suspension in saline water was mechanically stirred with toluene for an hour. Starch was allowed to settle and then the supernatant containing toluene with soluble and insoluble portentous matter of water-toluene interface was siphoned out. The process was repeated till portentous matter was completely removed. The complete removal of portentous matter was ensured when the water-toluene junction had no such extracted matter. Finally, the starch (figure 1) was washed within saline water and stored in a cool place. Sodium chloride was removed by repeated washings with distilled water to obtained 68% yield of Starch.

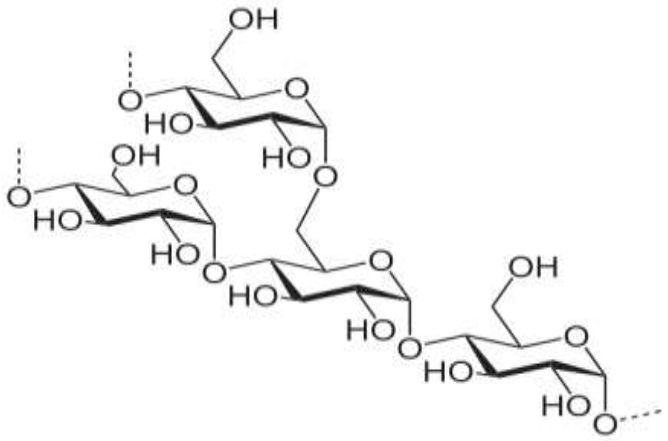

Figure 1: Chemical structure of starch

Preparation of sodium salt of Partly CarboxylicPropyl Starch (Na-PCPS)

Carboxylic propyl starch (figure 2a) was prepared according to Abdel-Akher et al. [12]. In three necked flask equipped with condenser, stirrer and gas inlet tube, affixed amount of starch was suspended in a known volume of isopropyl alcohol. The mixture was stirred for thorough mixing and 50% sodium hydroxide solution was added in a span of half an hour at 40 ºC. 3-Chloro propionic acid was then added at once. The reaction mixture was stirred for4 hours and was controlled 55 ºC temperature through constant temperature bath and the reaction was carried out under nitrogen atmosphere. And then the isopropyl alcohol over the reaction mixture was produced 90% aqueous methanol to remove of excess of Soult and dry 35 ºC under vacuum.

Graft co-polymerization with PCPS

The following three different acrylates were used to induce hydrogel formulation Grafting acrylate with PCPS was prepared as reported method [13]. Specific amount of carboxylic propyl starch (CPS) was dissolved in an aqueous solution with continuous mechanical stirring until a homogeneous viscous mixture was obtained. Then different concentrations from three various acrylates namely, sodium acrylate, methyl acrylate and (figure 2b) methyl methacrylate were added separately drop wise to CPS solution with continuous stirring. The formed paste, was transferred to the Petri dish, dried in an oven at 65 ºC for 45 min the resulting carboxylic propyl starch-acrylate graft copolymer was then washed in cold water bath and separated using a centrifuge to remove engrafted Starch and (figure 2c) acrylates then cured for (25-55 min) at different temperatures (120-140 ºC).

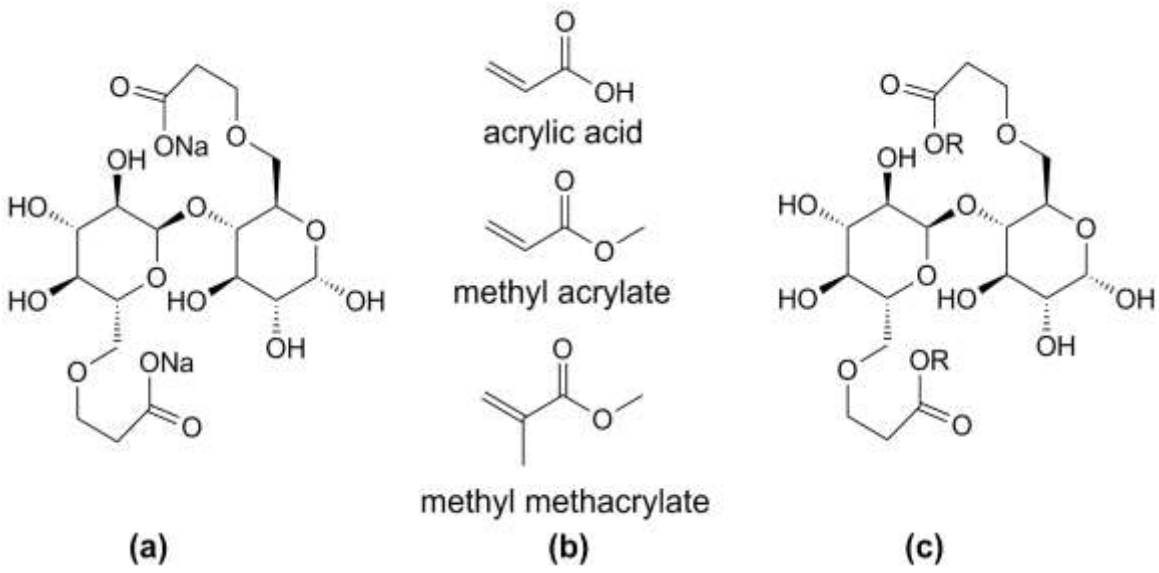

Figure 2: (a) Structure of sodium salt of etherified starch (b) Structure of various acrylates (c) Structures of grafted co-polymerization with PCPS [R= acrylic acid, methyl acrylate, methyl methacrylate]

Preparation of Matrix Tablets

Solid dosage formulation of Paracetamol drug was prepared using the wet granulation method. The steps involved in wet granulation were, Weighing, Mixing, Granulation, Screening the damp mass, Drying, Dry screening, Lubrication and Compression. The active ingredients of Paracetamol, diluents and disintegrants were mixed. A batch of 20 tablets was prepared. The ingredients Paracetamol (71.4%), Lactose (11.6%), Binder (10%) and Starch (5%) were grinded using mortars 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. If the granulation is over wetted the granules will be hard, requiring considerable pressure to form the tablets. If the powder mixture is not wetted sufficiently the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression. The wet granulation is forced through a 6 or 8 mesh screen. The moist materials was placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. Then prepared granules were dried at 55 ºC for one hour in an oven. Then dried granules were passed through sieve 44 #. To these dry granules the lubricants such as 1% Mg stearate and 1% Talc were added and mixed thoroughly [14, 15]. Tablets were prepared using different binder by tablet punching machine. The prepared three different types of tablets name given C_A, C_{MA}, and C_{MMA}.

Weight of Tablets

With a tablet designed to contain a specific amount of drug in a specific amount of tablet formulation, the weight of the tablet being made is routinely measured to help ensure contains the proper amount of drug . In practice, composite samples of tablets (usually 20) are taken and weighed throughout the compression process.

The Weight (mg) of each of the 20 individual tablets was found out by dusting each tablet off and putting it along an electronic balance [16].

Thickness of Tablets

For thickness measurement jaw of the gauge was opened, tablet was inserted between the jaws and then by moving the display head to the left the jaws it was closed and reading on the digital display was noted. The individual thickness of the tablets was determined by DIGITAL CALIPER MODEL 500. The instrument is designed to accept tablets and similar samples up to a maximum of 150 mm (6”) and to an accuracy of 0.01 mm (0.0005”) [17].

Friability Test of Tablets

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. 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 were recorded and the percent friability was estimated [18].

Disintegration Test of Tablets

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 Tablets

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. 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 [19]. The test was performed on manual hardness tester Model HT-1 Systronic India PVT, Ltd.

In Vitro Dissolution Studies of Tablets

The dissolution test was carried out for tablets using 900ml phosphate buffer pH 7.8 as the medium and rotating the paddle at 50 rpm for 30 min. A suitable volume of the sample was withdrawn and filtered first few ml of filtrate was rejected and the remaining were diluted with some solvent. Absorbers of the resulting solution at the maximum at about 249 nm were measured using UV 1800 Shimadzu. Similarly, absorbance of a solution of a known concentration of the paracetamol reference standard was measured. The content of $C_8H_9NO_2$ relative to the declared content of $C_8H_9NO_2$ in paracetamol reference standard was determined [20,-23].

Fourier transfer infrared Spectroscopy

Fourier transfer infrared (FTIR) Spectroscopy absorption of sample were taken in KBr pellets, using an ABB bomem MB- 100 FTIR Spectrophotometer (SICART V.V.Nagar) at room temperature.

X-ray diffraction

The raw materials and the patches were subjected to X-ray diffraction (XRD-PW 1700, Philips, INDIA) using CuKα radiation generated at 40 KV and 40 mA; the range of diffraction angle was 10.00-70.00^o 2θ.

RESULTS AND DISCUSSION

FT-IR Analysis

The IR spectra of CPS, CPS-acrylate, CPS-methyl acrylate and CPS-methyl methacrylate are shown in the figure 3 to figure 7. The Starch peaks at 1162.28 cm^{-1} and 2926.64 cm^{-1} are attributed to the C–O–C of ether linkage (1,4-alpha glycosidic bond) of starch and C–H stretching respectively while the prominent peak at 3438.68 cm^{-1} correspond to O–H stretching of intermolecular hydrogen bonding in figure 3. The CPS IR in spectrum has shoulders 1559.93 cm^{-1} representative of COO group stretching in figure 4. CPS-acrylate spectra showed distinctive peaks at 1639.76 cm^{-1} correspond to C=C stretching. The prominent peak at around 1700 cm^{-1} is assigned to C=O stretching and broad peak at 3040-2340 cm^{-1} refers to O–H stretching in figure 5. CPS-methyl acrylate showed distinctive peaks at C=O 1700 cm^{-1} and characterization peak of PMA at 1549.37 and 1216.36 cm^{-1} from IR data it is clear that the CPS-methyl acrylate was grafted in fig. 6. Indicates the details of functional groups present in the CPS-methyl methacrylate in fig. 7. A sharp intense peak at 1731 cm^{-1} appeared due to the presence of ester carbonyl group stretching vibration. The broad peak ranging from 1260-1000 cm^{-1} can be explained owing to the C–O (ester bond) stretching vibration. The broad band from 950-650 cm^{-1} is due to the bending of C–H the broad peak ranging from 3100-2900 cm^{-1} is due to the presence of stretching vibration [24, 25].

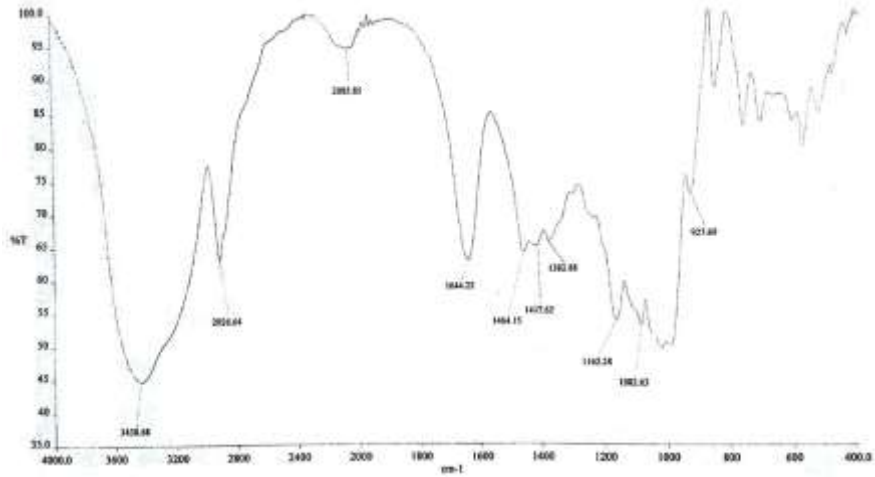

Figure 3: FTIR Spectra of pure starch

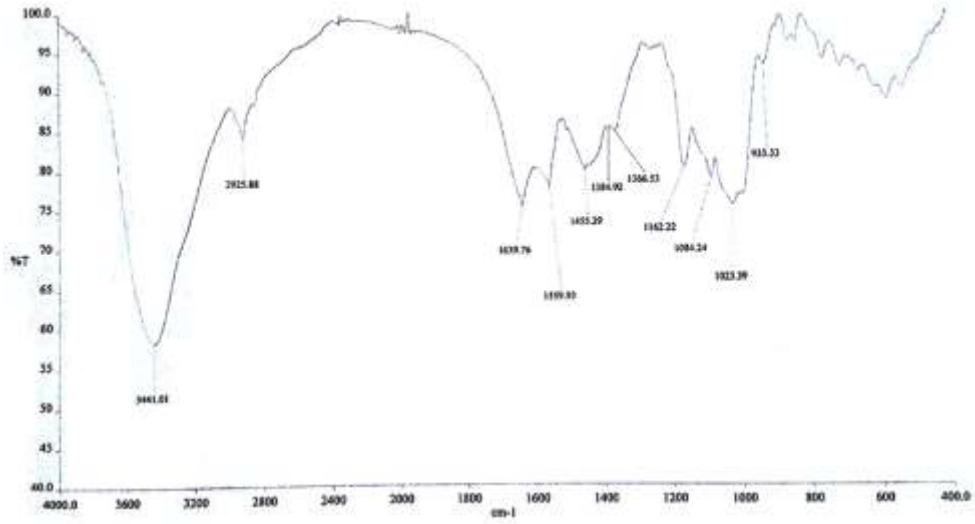

Figure 4: FTIR Spectra of PCPS

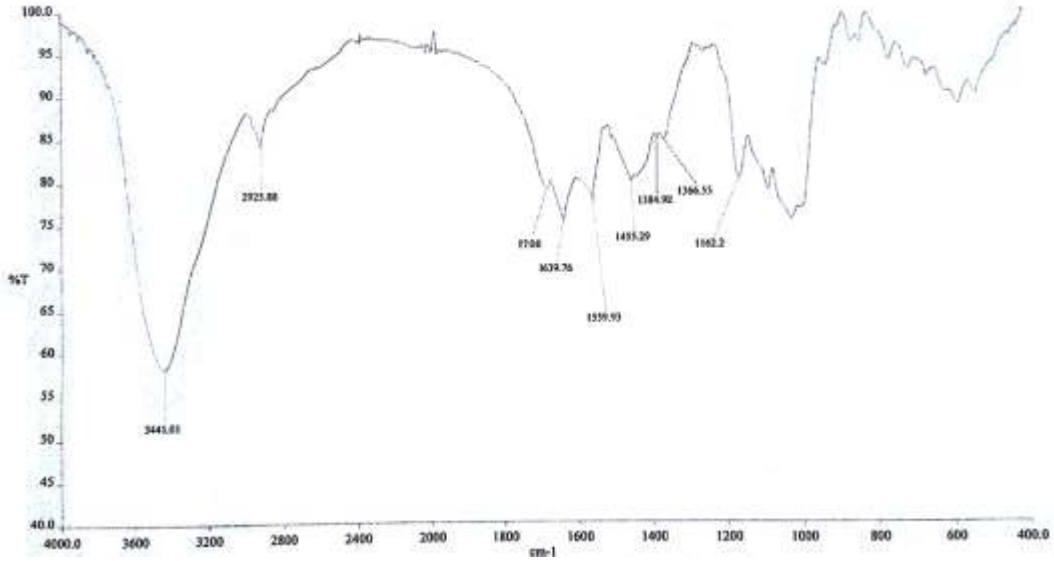

Figure 5: FTIR Spectra of PCPS-g-acrylate

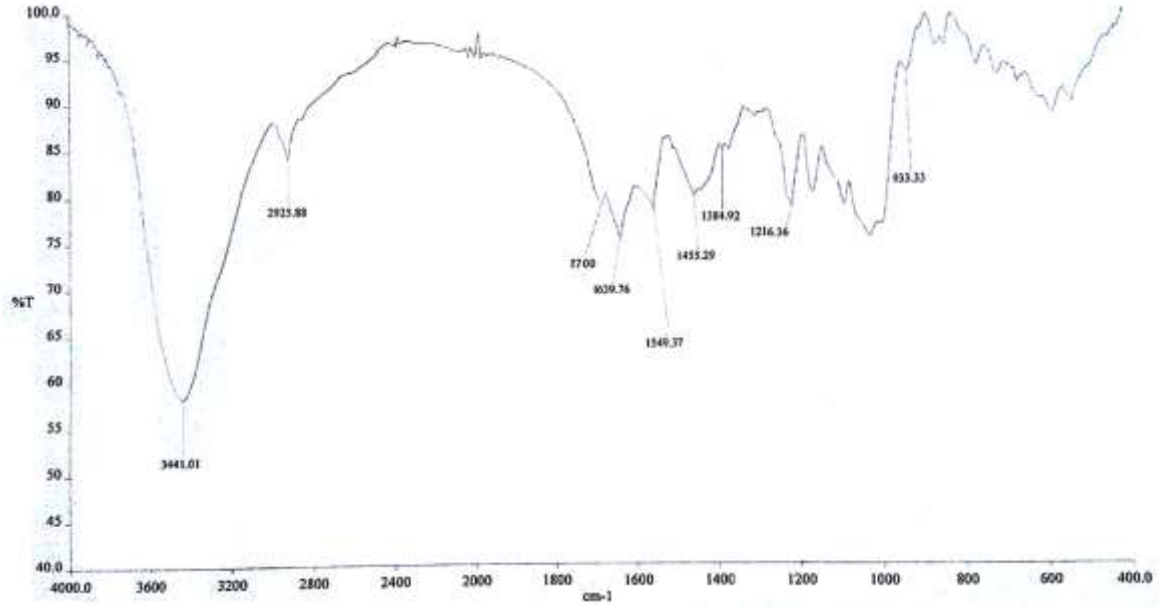

Figure 6: FTIR Spectra of PCPS-g-methyl acrylate

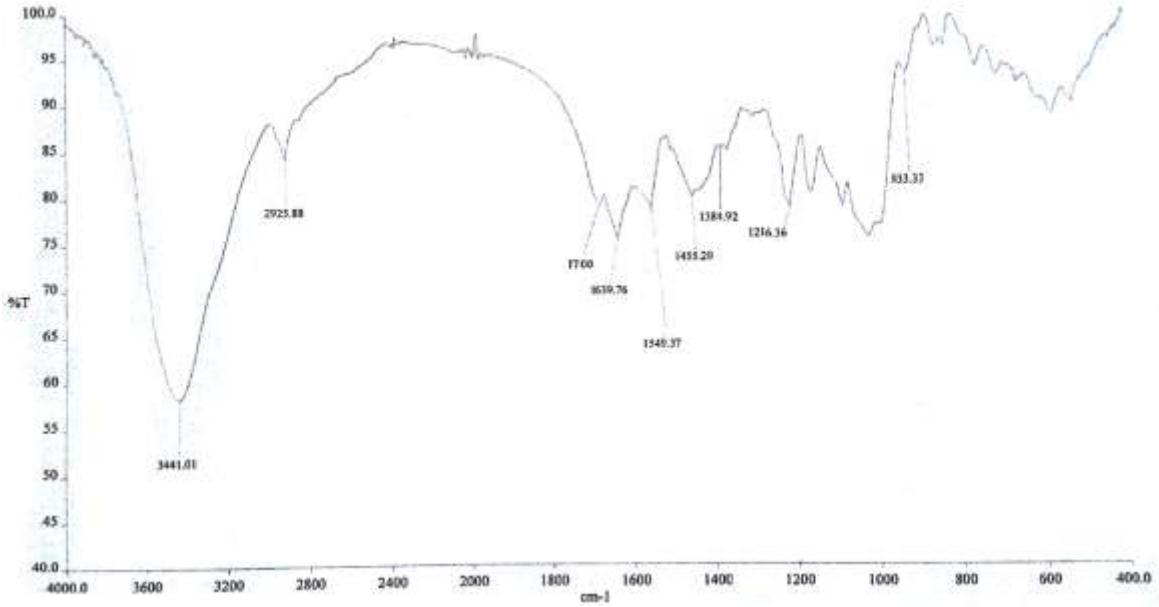

Figure 7: FTIR Spectra of PCPS-g-methyl methaacrylate

X-ray diffraction (XRD) Analysis

A diffractogram of the CPS is shown in figure 8, and diffractograms of the hydrogels formed from CPS- acrylate in given figure 9 (a) CPS, (b) CPS- acrylate, (c) CPS-methyl acrylate and (d) CPS-methyl methacrylate. Upon transformation of the CPS into the form of hydrogels membranes structure changes are shown in figure 9. The effect of polymer concentration on structural properties of the membranes produced from acrylate is shown in figure 9. The XRD patterns showed that crystallinity of the membranes depends on polymer concentration in the solution.

Hydrogel of CPS membranes reveal better ordering than the initial homopolymers. Pure CPS used in this study exhibits rather amorphous properties.

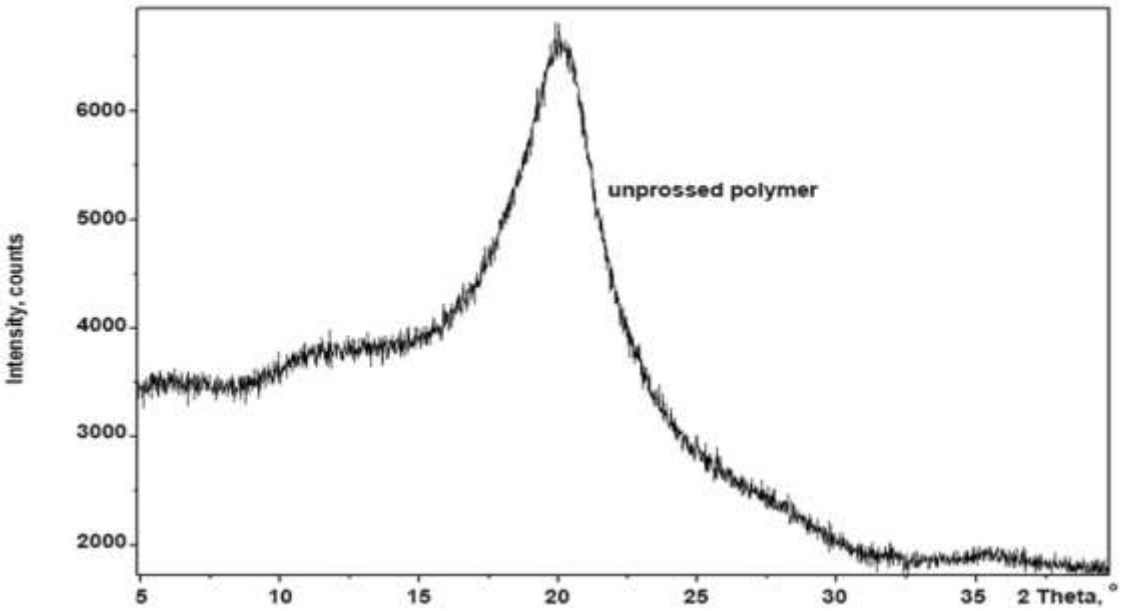

Figure 8: X-Ray deflection spectroscopy of PCPS

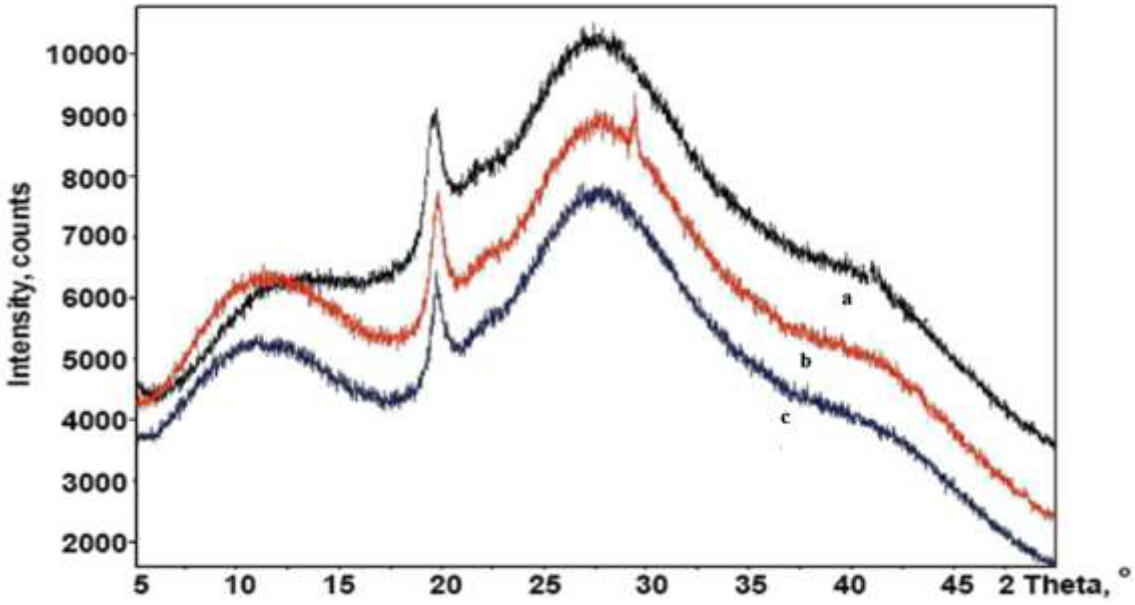

Figure 9: X-Ray deflection spectroscopy of (a) PCPA, (b) PCPMA, (c) PCPMMA

Properties of Polymeric Paracetamol Tablet

The choice of polymeric excipients is of obviously important to get the desired release profile. Table 1 given the result of the tablets prepared by direct pressing. They have successfully passed the test for weight uniformity, hardest testing and Friability test which should be below then 2%.

Clearly observe the discuss release of the drug amount as compared to the reference standard in table 2.

Table 1: Paracetamol tablet testing

Sr. No.	Disintegration [a] (minutes)	Friability [a] (Percent)	Hardness [a] (Kg)	Weight Variation [a] (mg)	Thickness [a] (mm)
C_A	16.20±0.25	1.20±0.02	6.0±0.08	507.1±0.021	2.78±0.012
C_{MA}	15.45±0.47	1.30±0.01	6.3±0.09	499.4±0.010	2.77±0.031
C_{MMA}	16.22±0.37	1.30±0.02	6.5±0.10	503.2±0.013	2.80±0.022

[a] = all experiment are in triplicate and mean value are given in table with SD

C_A= CPS-acrylate, C_{MA}= CPS-methyl acrylate, C_{MMA}= CPS-methyl methacrylate

Drug Release Study

Observation from the graphical representation of the drug release study of standard tablet and polymeric tablet were display in figure 10 to figure11. The standard tablet immediately release in short period of time so the drug leave in the blood forthcoming beyond the toxicity level. In compeer the polymeric drug provide an immediate release of drug which on time produces the desired therapy, followed by gradual and continual release of additional amounts of drug to maintain this effect over a predetermined period of time. So the drug level maintain in the blood is parallel to therapeutic level. The resulting benefits of the polymeric drug are extended release tablets or capsules are commonly taken only once or twice daily compared with the conventional dosing of 2 to 4 times daily. The need for night dosing of drugs may be eliminated. There was no any side effect by polymeric drug.

Table 2: Release study of paracetamol from standard tablet and varies batches

Time (min)	% Drug Release [a]			
	C_A	C_{MA}	C_{MMA}	Standard Paracetamol Tablet
15	4±0.09	3±0.06	3±0.07	15±0.15
30	6±0.12	4±0.07	5±0.09	20±0.21
45	8±0.16	7±0.14	8±0.11	24±0.37
60	11±0.19	10±0.19	12±0.19	28±0.60
75	16±0.27	12±0.25	14±0.24	33±0.60
90	22±0.34	17±0.27	20±0.29	37±0.90
105	26±0.42	20±0.32	24±0.34	40±0.82
120	29±0.49	24±0.38	28±0.39	45±0.91
135	33±0.57	28±0.42	31±0.60	48±1.21
150	37±0.59	30±0.49	34±0.57	53±0.98
165	43±0.61	33±0.54	38±0.61	58±1.16
180	45±0.64	35±0.57	40±0.72	62±1.23
195	48±0.67	38±0.61	40±0.73	65±1.41
205	52±0.72	38±0.60	40±0.71	68±1.75
220	52±0.71	38±0.64	40±0.74	73±1.59
235	52±0.73	38±0.62	40±0.72	75±1.89

250	52±0.70	38±0.63	40±0.71	80±1.68
265	52±0.72	38±0.65	40±0.72	83±2.01
280	52±0.70	38±0.61	40±0.74	87±1.97
295	52±0.72	38±0.63	40±0.73	92±2.04
305	52±0.71	38±0.62	40±0.71	94±2.30
320	52±0.70	38±0.59	40±0.72	100±1.93

[a] = all experiment are in triplicate and mean value are given in table with SD

C_A= CPS-acrylate, C_{MA}= CPS-methyl acrylate, C_{MMA}= CPS-methyl methacrylate

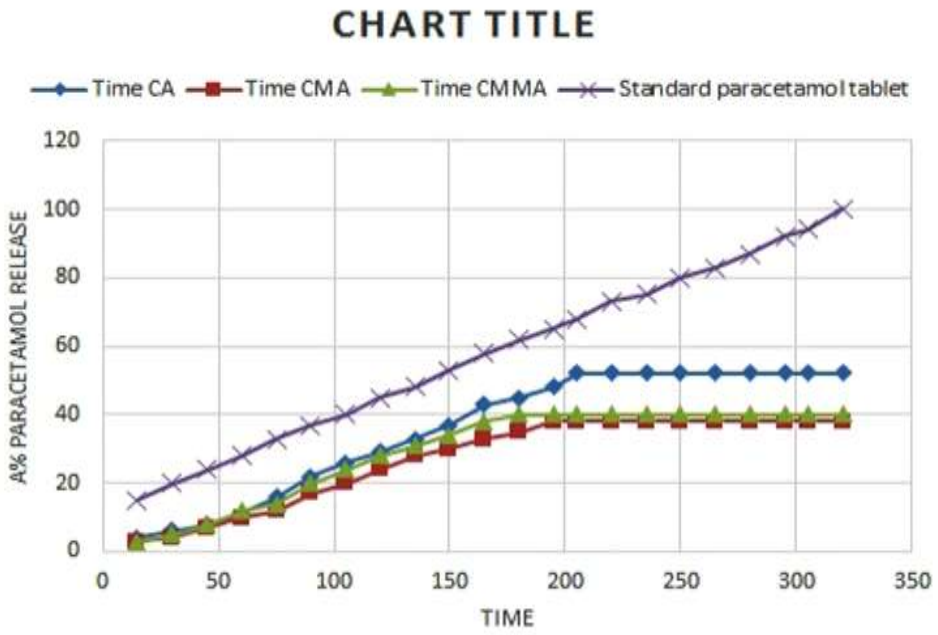

Figure 10: Drug release profile of paracetamol and polymeric drug

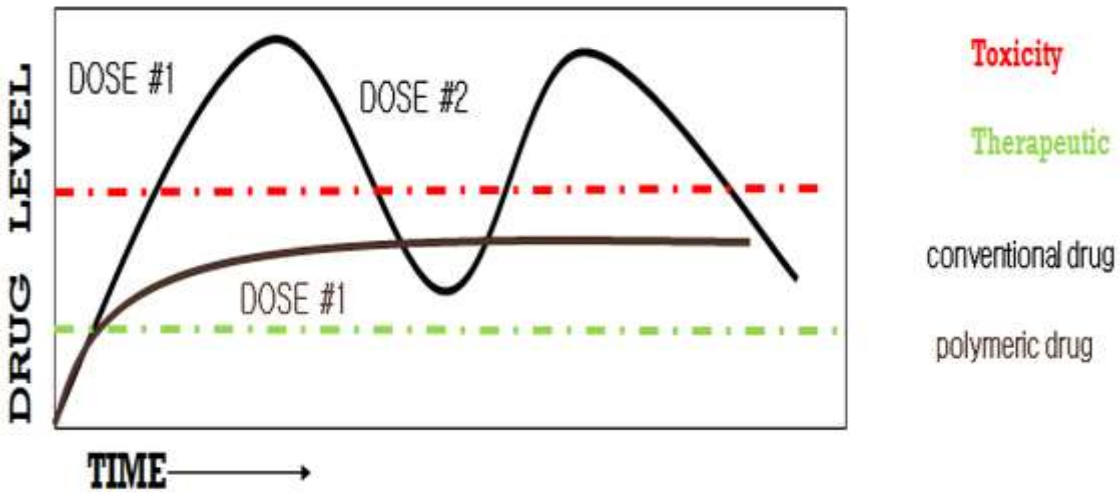

Figure 11: Toxicity and therapeutic effect of drug release profile of paracetamol and polymeric drug

CONCLUSION

Carboxylic Propyl Starch of varied degree of substitution was prepared. The degree of substitution of ether group onto starch moiety was measured using titration method. Low degree of substitution product was preferred for acrylic grafting. The starch ether thus prepared was successfully grafted with acrylic monomers in heterogeneous medium. Confirmation of grafting was done using spectroscopic methods such as FTIR and XRD. Starch gains hydrophilic or hydrophobic character depending on the monomer grafted. Therefore, Starch graft copolymers have many applications. Thus prepared polymeric binder was used in place of starch to prepare the tablet formulation of Paracetamol. The release pattern of the prepared tablets were studied and plotted. In comparison of drug release form C_A, C_{MA}, $C_{MMA,}$ the C_{MA} was considered to be an ideal.

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CONFLICT OF INTERESTS

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

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