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Synthesis, Crosslinking and Evaluation of Graft Polymer for Biomedical Use

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ABSTRACT

The objective of this research was focused on grafting of acrylic acid (AA) with hydroxypropyl methylcellulose (HPMC) to obtain copolymers of hydrogels with improved properties for ease of administration and reducing the dose frequency, improved patient compliance and comfort of sustained release medication. Water-absorbing polymers for hydrogels, the swellable polymeric materials have been widely investigated as the carrier for drug delivery system. These are the advanced polymer systems that hold special advantages for delivery of biological drugs and enhancing the biocompatibility of implantable devices. Here polysaccharides fabricated into hydrophilic matrices remain popular biomaterials for controlled release dosage forms. Hydrogel was prepared by in situ emulsifier-free emulsion polymerization using benzyl peroxide as an initiator through primary stage grafting. Acrylic acid could intercalate into layers of HPMC forms graft polymer composite. FTIR spectroscopy helps in determining the backbone functional groups. From Dynamic thermal gravimetric analysis (TGA) temperature is measured using differential scanning calorimetry (DSC).

Keywords: *Graft polymer, acrylic acid, HPMC, FTIR, DSC*

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1. INTRODUCTION

The driving force for the absorption or swelling process is generally a balance of three forces of osmotic, electrostatic and entropy-favored dissolution of polymer in water. Elastic forces are tailor-made into the hydrogel structure to control the entropy of the dissolution process. In other words, the densities of cross-links in the hydrogel structure will prevent the hydrogel from infinite dissolution in water [1]. Hydrogels are presently under investigation as a delivery system for bioactive molecules, because of their similar physical properties as that of living tissue which is due to their high water content, soft and rubbery consistency and low interfacial tension with water or biological fluids. Hydrogels are three-dimensional cross-linked polymer chains, which have the ability to imbibe and hold water within the cross linked structures. They are used for various biomedical applications such as soft contact lenses, wound dressing, super-absorbents and drug delivery systems due to their hydrophilic nature [2, 3]. Hydrogel swells but does not dissolve in an aqueous environment.

They swell by absorbing water and shrink on drying [4]. With ongoing research in advanced drug delivery formulations, to provide stable and economical drug delivery systems, which require a biocompatible, convenient and stable drug delivery system for molecules as small

[5]. Drug release mechanism hydrogels have a unique combination of characteristics that make them useful in drug delivery applications. Due to their hydrophilicity, hydrogels can imbibe large amounts of water. These models are based on the rate-limiting step for controlled release and are therefore categorized as diffusion-controlled, swelling-controlled, and chemically-controlled [6]. Swelling-controlled release occurs when diffusion of drug is faster than hydrogel swelling. The modeling of this mechanism usually involves moving boundary conditions where molecules are released at the interface of rubbery and glassy phases of swollen hydrogels [7].

The release of many small molecule drugs from (HPMC) hydrogel tablets is commonly modeled [7, 8]. Chemically-controlled release can be further categorized according to the type of chemical reaction occurring during drug release. Generally, the liberation of encapsulated or tethered drugs can occur through the degradation of pendant chains or during surface erosion or bulk-degradation of the polymer backbone [6, 9, 10]. Hydrogels are a unique class of macromolecular networks that can hold a large fraction of an aqueous solvent within their structures. They are particularly suitable for controlled drug delivery because of their ability to simulate biological tissues [11].

Hydrogels can be used for topical, oral and rectal drug delivery [12]. A more comfortable way of administration allows easy and safe administration at home by nonmedical personnel, increased stability and prolonged duration of action with increased therapeutic efficacy due to viscosity of the gel matrix [13]. It helps to increase drug candidate solubility in biofluids such as intestinal fluid, increase drug stability in the formulation and in biofluids, increase in drug candidate permeability across biomembranes, such as the small intestinal membrane, increase drug candidate delivery to the pharmacological target, decrease drug candidate metabolism, and/or decrease its elimination [14].

HPMC is a methylcellulose modified with a small amount of propylene glycol ether groups attached to the anhydroglucose of the cellulose. The dry product contains 19% to 30% of methoxyl (-OCH3) groups and 3% to 12% of hydroxypropyl ($-OCH_2CHOHCH_3$) groups. The chemical name is Propylene glycol ether of methylcellulose Hydroxypropyl methylcellulose [15].

Acrylic acid (AA) ($CH_2 = CHCO_2H$), less commonly referred to as propenoic acid, is a colorless, slightly water-soluble carboxylic acid with an acid odor. Functionally, acrylic acid may be regarded as a derivative of ethylene in which one hydrogen atom has been replaced with a carboxyl group (though this is not the basis of its synthesis). Acrylic acid is produced from propylene, a gaseous product of oil refineries [16]. It was prepared by treating benzoyl chloride with barium peroxide

or benzoyl peroxide is usually prepared by treating hydrogen peroxide with benzoyl chloride. The oxygen-oxygen bond in peroxides is weak. Thus benzoyl peroxide readily undergoes homolysis forming free radicals. Benzoyl peroxide is used as a radical initiator to induce polymerizations [17–20].

2. Experimental Methods

2.1 Materials

HPMC (Emami India Ltd.), acrylic acid (HiMedia Laboratories Pvt Ltd.), benzoyl Peroxide (Loba Chemie Pvt Ltd.), solvents-Benzene (Finar Chemicals Ltd.), doubled distilled water (Nice Chemicals Pvt. Ltd,), pyrogalol (Merk Ltd.), potassium permanganate (Glaxo Laboratories), silica crystals (provided by Merck Specialities Pvt. Ltd.).

2.2. Instrumentation for Synthesis Specially

designed nitrogen distillation flask setting for inert atmosphere, nitrogen gas system for inert atmosphere, magnetic stirrer provided by Remi equipments Pvt. Ltd., lyophilizer of Zindal model no. SM1114, water bath provided by Sonu Instruments, rotary shaker provided by Remi Equipments Pvt Ltd., digital balance by Adair Dutt Instruments Pvt. Ltd, model-AD50B , hot air oven of Secor India Ltd., melting point apparatus of Sisco India Ltd, 30 no sieve, glassware (all provided by Borosil Ltd.), (reaction vessels, beakers, pipette, funnel, measuring cylinder, test tube, watch glass etc.).

2.3 Analytical Instrumentation

2.3.1. Field Emission Scanning Electron Microscopy (FESEM)

The morphology of samples was examined by FE scanning electron microscopy, FESEM QUANTA 200FEG model (FEI Netherland make) with operating voltage ranging from 200 V to 30 kV and with 2 nm resolution and 1000 KX magnification. FESEM micrographs were taken after coating the surfaces of samples with a thin layer of gold by using BAL-TEC-SCD-005 Sputter Coater, BAL-TEC AG, Balzers, Liechtenstein, Germany, under argon atmosphere to make the sample conducting.

2.3.2. Fourier Transform Infrared Spectroscopy (FTIR)

Dried samples were ground into powder and mixed and crushed with KBr for homogenization. The KBr to polymer ratio was between 1:20 and 1:50. A Nicolet economy sample press was used to obtain optically clear pellets. Pellets were analyzed using transmission FTIR using a Thermo Nicolet Avatar 370 FT-IR Spectrometer System. Dry air was used as the chamber purge stream for all samples. The scanning resolution was set to 1 nm with a total of 1024 scans per sample. The FTIR spectra were obtained at room temperature over a spectra frequency range of 400–4000 cm^{-1}. IR bands were expressed in terms of frequency (cm^{-1}). The background was obtained against a pure KBr pellet and the data was analyzed by

Omnic software. The liquid base product was measured by making a homogenized mixture by taking NaCl instead of KBr. Functional groups were present and thus the structure of base products and prepared sample could be determined.

2.3.3. Thermal Studies (TGA, DTG & DSC)

TGA, DTG and DSC were carried out simultaneously by using a PYRIS Diamond TG/DTA thermal analyzer, supplied by Perkin Elmer and the data was processed and analyzed by PYRIS Muse Measure and standard analysis software (v. 3.3U, 2002 Seiko Instruments Inc.).

The sample was kept in alumina pan, the reference material was alumina powder and study was carried out at various heating rates such as 10, 20, 30, 40, 50 ° C/min under 200 ml/min flow rate of air or nitrogen atmosphere. Indium and gallium were used as standards for temperature calibration. The measurements were run from room temperature to 600 ° C. The glass transition temperature (T_g) and the percent crystallinity were recorded from the second and first heating curves, respectively. Percent crystalline values for different samples were calculated from the heat of fusion. By integrating the normalized area of the melting endotherm, melt enthalpy and crystallization enthalpy were determined, and rating it to the reference 100% crystalline polymer (93.6 J/g), the relative crystallinity of the polymer was assessed.

2.4. Methods

2.4.1. Preparation of Inert Atmosphere by Nitrogen Gas

In the beginning nitrogen gas was passed through three nitrogen distillation flasks connected in series through a rubber pipe. The first one was filled half with required quantity of pyrogalol, the second flask was filled with required quantity of silica crystals (coarse blue pellets) of size 160 and the third one was left empty. The nitrogen gas that came out after passing through the three nitrogen titration flasks was pure nitrogen gas, free from any impurity, which gave inert atmosphere. The uniform pressure of nitrogen gas flow was regulated by a pressure regulator attached at the neck of nitrogen gas cylinder. Pyrogalol and potassium permanganate solution acted as oxygen scavenger.

2.4.2. Preparation of Solution

HPMC-5% solution with distilled water-26 mL and acrylic acid-2 mL was prepared with the help of a rotary shaker at 150 rpm for two and a half hour and then kept in a refrigerator. A 5 ml solution of benzoyl peroxide with benzene at 1% ratio was prepared immediately before the synthesis.

2.4.3. Synthesis of Graft-Polymers

The synthesis of graft-polymers was done in a previously sterilized reaction vessel. The chemical contents like HPMC solution and acrylic acid were taken in the vessel as for the mentioned ratio above and with a magnetic bit

and capped tightly. Then the vessel was connected to nitrogen atmosphere for 15 min to make an inert atmosphere. Then it was immediately plugged at its both openings after removing the nitrogen supply. Then the preloaded vessel was kept within a beaker of water (water bath) on the magnetic stirrer to make the bit to mix homogeneously the contents and adjusted the temperature at 80 ° C and 350 rpm. (Water bath is to maintain the temperature). After 15 min of through mixing the initiator solution, i.e., benzoyl peroxide 3 ml was added with a syringe to initiate the reaction. Two vapor exit canals were made to evacuate the vapor from the vessel with the help of two needles. The reaction was carried out for 3 hr while maintaining a temperature of 80 ° C. After the reaction, the resultant content was taken out to a watch glass and washed with double distilled water thoroughly. Then these were filtered and dried by lyophilization.

2.4.4. Yield

After freeze drying, a white gummy/gelatinous/rubbery mass was obtained whose yield was measured to be 4.190 g. The powdered products were subjected to general physical property study.

3. RESULTS AND DISCUSION

3.1. General Physical Properties

Physical state – semi-crystalline powder, color – ivory to smoke white, odor – odorless, taste – mucilaginous, solubility – water, methanol, ether, benzene, DMSO, pyridine, piperidine, hydrogel formation occurs in all the above solvents, melting point – measured approximately 128 ° C with the help of melting point apparatus, charring temperature – 240 ° C, approximate density (calculated by applying Archimedes principle) – 0.664 g/cm^2.

3.2. SEM Micrography

The SEM image of the base product HPMC before formation of graft polymer (Figure 1) and the image of formed graft polymer of HPMC-G-AA are shown in Figure 2. The surface of HPMC was found to be smooth but there were some porous spots appearing on it which were effective for entrapment of aqueous media. The formed graft polymer image showed a rough and nonuniform surface which was due to the grafting of the acrylic acid molecules.

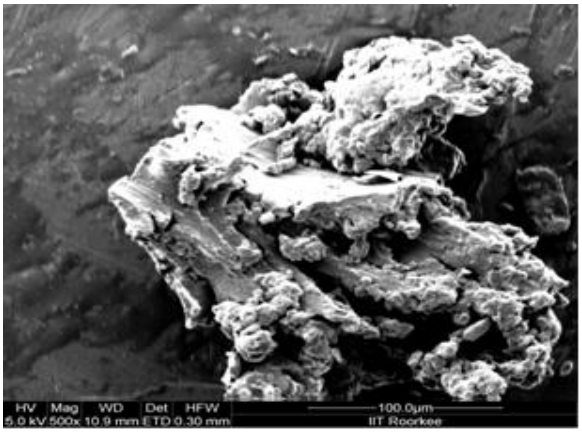

Fig. 1: *Micrograph of HPMC.*

Table I: *FTIR of HPMC.*

Peaks (cm-1)	Groups	Peak Assignment
2978	Methyl and hydroxypropyl gr.	-CH stretching of methyl and propyl gr.
2890	Hydroxyl group	O-H stretching, Intermolecular H-bonding
2660	Hydroxyl group	O-H stretching vibration
1689 and 1615	Six membered cyclic	Stretching of C–O,
1410 – 1400	Cyclic anhydrides	Stretching of C–O–C
1297	Epoxides	Stretching of C–O–C, cyclic epoxide
1059 – 985	Pyranose ring	Ring stretching
813	CH_2 group	Rocking mode of CH_2 group

Table II: *FTIR of HPMC-g-AA.*

Peaks (cm-1)	Groups	Peak Assignment
3419	Hydroxyl	OH vibrational stretching, Chelate H-bridge
1637 – 1617	Alkene	Stretching of C = C
1384	Alkene	C-H stretching
1116	Ethereal	Stretching vibration of ethereal C–O–C
878	CH_2 group	Rocking mode of CH_2 group

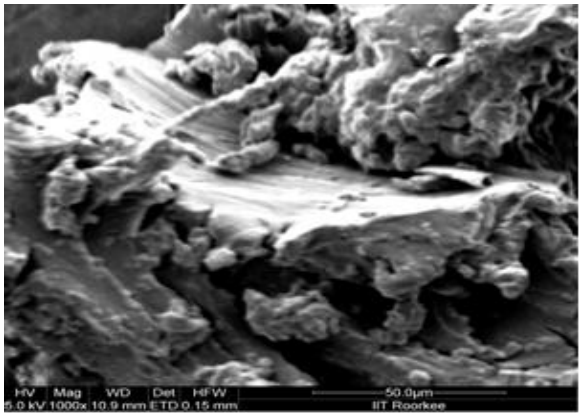

Fig. 2. *Micrograph Images of HPMC-g-AA.*

3.2 FTIR Spectroscopic Study

3.2.1. FTIR Interpretation

From the FTIR analysis, it was obtained that the prominent peaks show the presence of OH group vibrational stretching at 3419 cm^{-1}, hydroxyl group at 1637 – 1617 $cm^{-1}$with C–O group for six-membered cyclic rings (Figure 3)**.**

Stretching of C–O–C of cyclic anhydrides were at 1384 cm^{-1}, ethereal C–O–C groups at 1116cm^{-1}(Figure 4). These functional groups wear identified showing the presence of identical functional groups of HPMC after the synthesis of HPMC-g-AA.

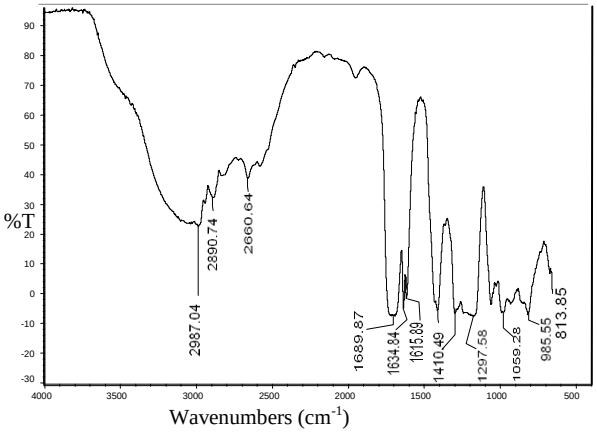

Fig. 3: *FTIR of HPMC.*

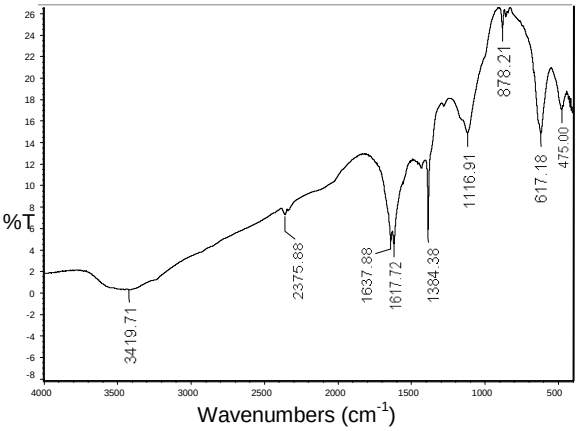

Fig. 4: *FTIR of HPMC-g-AA.*

3.3. Thermogravimetric Study

Table III: *DSC of HPMC.*

Exothermic Peak	Exothermic Peak Area	Heat of Enthalpy(H)
77 ° C	1.26 µW	27.1 µJ/mg
332 ° C	17.47 µW	17.7 µJ/mg
356 ° C	17.46 µW	11.8 µJ/mg

Table IV: *DSC of HPMC-g-AA.*

Exothermic Peak	Exothermic Peak Area	Heat Of Enthalpy(H)
72 ° C	1.67 µW	31.1 µJ/mg

Table V: *DTG Data of HPMC.*

Temperature	Mass Remains
82 ° C	95.6%
275 ° C	92.4%
324 ° C	87.7%.
400 ° C	12.2%
500 ° C	10.1%

Table VI: *DTG Data of HPMC-g-AA.*

Temperature	Mass Remains
100 ° C	94.8%
175 ° C	93.2%
274 ° C	72.7%
325 ° C	46.3%
425 ° C	25.1%

Table VII: *TGA Result for HPMC.*

Temperature	Product Degrade (mg/min)
69 ° C	0.21
357 ° C	3.260

Table VIII: *TGA Result for HPMC-g-AA.*

Temperature	Product Degrade (mg/min)
67 ° C	0.131
247 ° C	0.310
306 ° C	0.679
387 ° C	0.265

3.3.1. Thermal Interpretation

Thermo gravimetric analyses (TGA) were carried out in order to evaluate the effect of the chemical modification on the thermal stability of HPMC. Primary thermograms were obtained by plotting the percentage residual weight against the temperature. The initial decomposition temperature was calculated

from the end of the initial straight-line portion of the curve from where the actual decomposition is believed to have occurred. HPMC thermogram shows a broad exothermic peak transition peak at 77 ° C (Figure 5). The decrease in initial decomposition temperature of HPMC after grafting copolymerization indicates that the chemical change in HPMC has occurred upon grafting and the thermal stability of the acrylic acid grafted HPMC has been found to be lower in comparison to the pure HPMC as is clear from the TGA curves (Figure 6). The above data shows that the formed polymer is more thermo-degradable than the base product. By comparing the two DSC graphs, it was known that the enthalpy required to increase the temperature of the formed sample was enhanced. At the endothermic process, the sample melts to a liquid and requires more heat flowing to sample than it was the phase transition period.

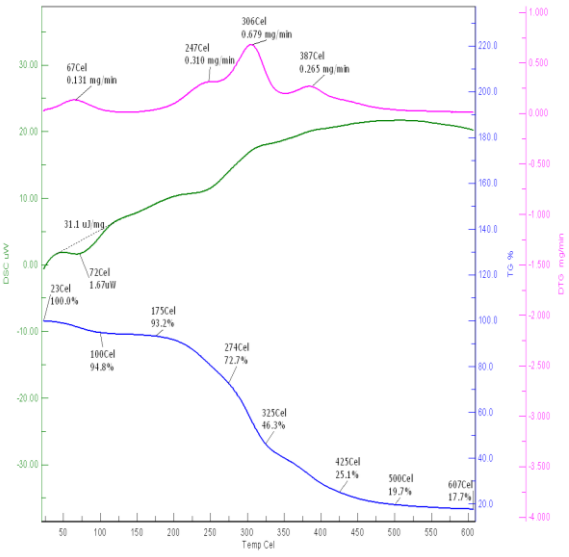

Fig. 5: *Thermogram of HPMC.*

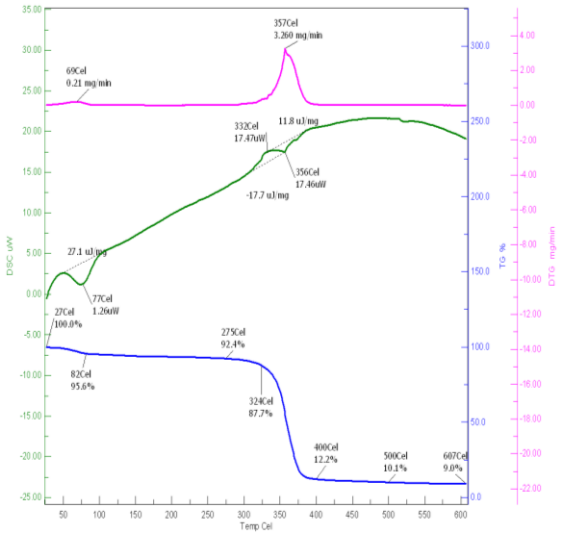

Fig. 6*: Thermogram of HPMC-g-AA.*

4. CONCLUSIONS

Graft polymer of HPMC-g-AA following a novel method of synthesis for hydrogel having very good interaction shows etherification and intermolecular hydrogen bonding, by virtue of which a hydrogel would be produced. Under the experimental conditions from FTIR analysis, it was identified that the HPMC-g-AA resulted in changes in functional groups. The utility of the present work was to improve the delivery rate, biodegradation and site-specific targeting of such hydrogel and which would be properly monitored and controlled. The temperature-dependent physico-mechanical properties of HPMC and Hpmc-g-AA have been measured by the DSC and TGA. The DSC profile Hpmc-g-AA revealed thermal events, an exothermic peak probably due to a solid restructuration before melting. Enthalpy of vaporization calculated by DSC for Hpmc-g-AA was 31.1 µJ/mg.

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