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DEVELOPMENT AND CHARACTERIZATION OF NEW CROSSLINKED POLYMER OF CARBOXYMETHYL ARABINOXYLAN-g-METHACRYLIC ACID FOR CONTROLLED DRUG RELEASE

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ABSTRACT

Present work deals with formulation and characterization of a new cross linked polymer of carboxymethyl arabinoxyla-g-methacrylic acid as a drug delivery carrier for controlled drug delivery of highly acid labile drug "rabeprazole sodium". Free radical polymerization technique was employed to prepare new cross linked polymer by using carboxymethyl arabinoxylan (polymer), methacrylic acid (monomer), potassium persulfate (initiator) and N,N methylene bisacrylamide (crosslinker). Prepared crosslinked polymer was evaluated by swelling studies at acidic and basic pH, instrumental analysis (SEM, FTIR and TGA & DSC). pH responsive *in vitro* drug release was also performed by using rabeprazole sodium as model drug.

Prepared hydrogels were subjected to pH responsive swelling analysis and *in vitro* drug release studies. It was observed that by increasing methacrylic acid and carboxymethyl arabinoxylan contents swelling was also increased at basic pH. While with increase in crosslinker contents swelling ratio was decreased. Among nine formulations with varying formulation contents, M6 exhibited more pH sensitive swelling and highest cumulative drug release (90%) at alkaline pH and minimum release (2.93%) at acidic pH.

Results showed that new cross linked polymer carboxymethyl arabinoxylan-g-methacrylic acid can be a best polymer for controlled drug delivery of acid labile drugs.

Keywords: Rabeprazole Sodium, Carboxymethyl Arabinoxylan, pH Sensitive, Graft Copolymer, Swelling Analysis, *in vitro* Release

INTRODUCTION

One of the chief provocations in pharmaceutical research is site targeted dosage form design for challenging drugs. Polymers are aggressively contributed in the architecture of innovative drug delivery carriers, encourage targeted drug release to a particular section in the gastrointestinal tract. Natural polymers are an attractive class of excipients for successful, stable and effective drug delivery system. These are economical and easily available, safe, biodegradable, and ecofriendly and can be modified affording to necessity [1,2].

Polymer modifications are necessary to transform supreme characters to natural materials, such as improve thermal stability, multiphase physical responses, compatibility, impact response, flexibility, rigidity and aqueous solubility [3].

Carboxymethylation is an extensively used technique for polymer modification to produce a variety of promising characters in polymer. Carboxymethylation adds carboxymethyl groups to the natural polymers thereby augmenting their solubility and solution clarity renders more suitable candidate for food, cosmetics and pharmaceutical applications [4]. Graft copolymerization is expected to be a potential tool for polymer modifications to impart desired characteristics [5].

Hydrogels are cross-linked polymeric networks comprise of high number of hydrophilic domains, capable of imbibing large amount of water, but do not dissolve in water at physiological pH and temperature because of their network structure [6]. Smart hydrogels can swell to beneficial rates when placed into an appropriate environment, exhibiting pH-sensitive swelling behavior. Transition in external pH ionize the acidic or basic group, electrostatic repulsion increase uptake of solvent in the network causing expansion of polymer [7].

The seed husk of Ispaghula (Plantagoovata) is chief source of xylan (arabinoxylan) and minor amount of other sugar components Rhap and Galp [8]. The carboxymethylation of arabinoxylane was converted by treatment with sodium monochloroacetate in aqueous alkaline medium into carboxymethyl arabinoxylan. Aqueous solubility of carboxymethyl arabinoxylan depends upon degree of substitution [9]. Carboxymethylation of psyllium arabinoxylan modified its fundamental properties. It reduces viscosity of solution; improve crystallineity and thermal stability of arabinoxylan [10].

Methacrylic acid ordinarily used for enteric/ delayed release drug carrier, controls the hydrolytic and swelling behavior of hydrogels. High contents of methacrylic acid increase swelling of hydrogel in alkaline/ intestinal medium and vice versa [11].

The aim of this research work was to develop smart crosslinked polymeric network by free radical polymerization technique in water. Formulation influencing factors like monomer concentration, polymer concentration and crosslinking agent concentration were scrutinized to comprehend their effect on their swelling, pH responsive behavior and release of model drug (rabeprazole sodium).

MATERIALS AND METHODS

MATERIALS

Rabeprazole sodium (Getz Pharma Islamabad Pakistan), Potassium persulfate (AnalaR, BDH-England), N,N Methylene bisacrylamide (Fluka-Switzerland), Tris (hydroxymethyl) aminomethane (Fluka Switzerland), Potassium dihydrogen phosphate(Merk- Germany), Methacrylic acid (Merk, Germany). *Plantago ovate* (ispaghula) seed husk was purchased from local market of Pakistan. Acetic acid (BDH laboratory England), sodium hydroxide (Sigma Aldrich Lab Riedel-deHaen GmbH).

METHODS

Isolation of arabinoxylan

Arabinoxylan was isolated from the Ispaghola husk by method of Saghir*et al*., (2008). 100 g of Ispaghula seed husk was soaked in 5 liters of distilled water over night. Aqueous sodium hydroxide solution (2.5%) was added to the mixture for pH adjustment at 12 with continuous stirring for 2-3 minutes. Husk was separated from the gel by vacuum filtration. Concentrated acetic acid was used to coagulate the sample. The gel obtained was washed with distilled water until the pH become constant and freeze dried for 1 week.

Carboxymethylation of arabinoxylan

The reported method was adopted after necessary modifications. Arabinoxylan (2.5g) obtained by above procedure was suspended in ethanol. The reaction mixture was vigorously stirred at room temperature for 1 h. After addition of 25% aqueous sodium hydroxide solution, sodium monochloro acetate was added and the temperature of reaction bath was increased to 55°C. The etherification was performed for 5 h. The product was filtered and suspended in 80 % (v/v) water/methanol, neutralized with diluted acetic acid, and washed with ethanol. The product was dried under vacuum [9]. Obtained product was verified by water solubility and FTIR analysis.

Graft copolymer preparation

Calculated amount of Carboxymethyl arabinoxylangiven in Table 1 was dissolved in degassed distilled water at 70 °C to obtain a sticky transparent solution. Then potassium persulfate solution in water was added to Carboxymethyl arabinoxylan solution and stirred at 300 rpm for 10 min at 70 °C to generate radicals. Following this, reaction mixture was cooled down to room temperature. At room temperature, solution containing monomer (methacrylic acid) and cross linker (N,N MBA) was added under magnetic stirring at 300 rpm. The final weight of solution was made by adding distilled water. Air above the solution in the tube or any dissolved oxygen was removed by bubbling nitrogen for 15-20 min which acts as free radical scavenger. For polymerization, solution was heated in water bath at 45 °C for 1 h, 50 °C for 2 h, 55 °C for 3 h, 60 °C for 4 h and 65 °C for 8 h [12]. Hydrogels obtained were cut into discs. 0.1M sodium hydroxide and ethanol were used to remove unreacted monomer and catalyst. These discs were thoroughly washed until the pH of washing water come to neutral. After washing, the discs were dried first at room temperature and then in oven at 45-50 °C till constant weight of hydrogels obtained. These discs were kept in dessicator and further used for characterization and drug release study [13]. Different formulations with varying concentration of polymer, monomer and cross linker were prepared as presented in Table 1.

Table1: Composition of 100g CMAX-g-MAA hydrogel preparation with varying monomer polymer and crosslinker concentration and amount of drug loaded.

Sr. No	Formulation code	CMAX	MAA	Crosslinker % mole ratio of monomer	Amount of Rabeprazole sodium loaded (mg per 0.45g of dry disk)	
					By extraction	By weight
1	M1	0.5	20	0.25	89	90
2	M2	0.5	30	0.25	87	87.9
3	M3	0.5	35	0.25	83	83.7
4	M4	1	25	0.25	90	91.3
5	M5	1.5	25	0.25	94	95
6	M6	2	25	0.25	97	98.4
7	M7	0.5	25	0.45	81	81.8
8	M8	0.5	25	0.65	77	78
9	M9	0.5	25	0.85	71	71.9

Swelling studies

Smart swelling behavior of hydrogels was investigated in buffer solutions at different pH values. Dried hydrogels (0.45 g) were immersed in 100 ml solution of USP phosphate buffer of pH 1.2 and pH 7.4 at 37 °C. The swollen samples were weighed at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 18, 24, 48, 72 hours and excess media were removed by blotting with a piece of filter paper. The studies were performed in triplicate and

average values were taken for data analysis. The swelling of various samples were continued until they attained constant weight [14]. The dynamic swelling ratio Q was calculated using following equation [15].

$q = W_s/W_d$ (1)

Where q is dynamic swelling ratio, W_s is the weight of swollen gel at time t and W_d is the initial weight of dry hydrogel.

pH responsive/Pulsatile behavior

For controlled delivery of drug from graft copolymer, the swelling process must be reversible i.e. release of drug could be initiated and stopped promptly upon change in pH. To investigate reversibility of swelling/deswelling process of polymer networks with respect to environmental pH change, selected hydrogel samples were swollen in a buffer solution of pH 7.4, placed them in a buffer solution of pH 1.2, returned them to a buffer solution of pH 7.4, and finally collapsed them in a buffer solution of pH 1.2 [16].

Drug loading

Samples showed maximum swelling were selected for drug loading and release study. Drug was loaded by incubation after polymerization. Incubation after polymerization removed all non-reacted monomers and decomposed products of the catalyst.

Selected hydrogels were soaked in 0.1 M sodium hydroxide solution containing 1% rabeprazole sodium for time period until swelling equilibrium achieved. Loaded hydrogels were washed after swelling with water to remove surface adhered drug on disc. For drug loading, 0.1 M sodium hydroxide solution was selected due to maximum swelling ratio of hydrogels and drug stability in that solution. The drug loaded hydrogels were freeze dried because drug is unstable at oven drying temperature [17].

Determination of drug loading

Two methods were used for determining drug loading in hydrogels. The first method used to calculate the amount of drug loaded in hydrogel was determined by following equation:

Amount of drug = W_L-W_o (2)

W_o and W_L are the weight of dried hydrogels before and after immersion in drug solution, respectively.

In 2nd method, amount of drug entrapped in hydrogels was calculated by repeatedly extracting the weighed quantity of powdered loaded gels by using 0.1M sodium hydroxide solution. Each time fresh 0.1M sodium hydroxide solution was replaced after specific interval until there was no drug in the solution. Drug concentration

was determined spectrophotometrically at λmax 284 nm. Amount of drug present in all portions was considered as total amount of drug loaded into hydrogel [18].

Sol-gel fraction

The hydrogels prepared by free radical polymerization were dried to measure the gelation. Hydrogels were cut into 4-5 mm thickness and oven dried. Then dried hydrogels were extracted with water at room temperature in order to extract the insoluble parts of hydrogel until the weight became constant. The gel percent in hydrogel was determined from the following equation: The gel fraction was calculated by following equation [19]:

$$\text{Sol fraction } \% = \frac{W_o - W_1}{W_o} \times 100 \ldots. \quad (3)$$

Gel fraction (%) = 100- Sol fraction ….(4)

Where W_o is weight of hydrogel before extraction and W_1 is weight of hydrogel after extraction.

Determination of the equilibrium water content

Dried hydrogel samples were soaked in buffer of pH 1.2 and pH 7.4 at 37 °C to measure water uptake of hydrogel in a thermostatically controlled chamber to the equilibrium state. Fully swollen samples were removed and weighed after removal of excess of solvent with absorbent paper. The equilibrium water content in swollen samples (W_{eq}) was calculated as follows [20].

$$W_{eq}\% = \frac{W_s - W_d}{W_s} \times 100 \ldots\ldots (5)$$

Where W_s is the weight of swollen sample at equilibrium state and W_d is weight of the dry sample.

Instrumental analysis

Scanning Electron Microscopy (SEM)

Surface morphology of crosslinked hydrogel was evaluated by Quanta 250 SEM (FEI), operating at 10 kV with secondary electrons, in low vacuum mode. For a better observation of the pores, swollen hydrogels were previously freeze-dried in freeze dryer (Christ Alpha 1-4 Germany), for 24 hrs at -55 °C. The sample was prepared by cutting the dry hydrogels with a sharp razor blade, in order to expose the internal structures [21].

Fourier Transform Infrared (FTIR) Spectroscopy

Drug polymer interactions and grafting were studied by FTIR spectroscopy. IR spectra for drug and drug loaded hydrogel were recorded in a Fourier transform infrared (FTIR) spectrophotometer (Bruker, Tensor-27, Germany). For FTIR analysis pure components and hydrogel samples were ground to powder. A small quantity of sample was placed in crystal area and pressure arm was locked to push the sample

over zinc slenide crystal. Bands were in the region from 4000 to 400 cm^{-1}[21].

Thermal Gravimetric Analysis and Differential Scanning Calorimetery (TGA & DSC)

Thermal behaviour of the prepared graft copolymers were studied by Thermogravimetric Analyzer model SDT Q 600 series Thermal Analysis System (TA instruments, New Castle DE, UK) from room temperature to 600 ˚C. The hydrogel samples were ground and passed through mesh 40. Sample dry weight was 5-10 mg placed in an open pan (platinum 100 µl) attached to a microbalance. Heating rate of 10°C/min was used under nitrogen atmosphere at a flow rate of 20 mL/min. All measurements were made in triplicate. Thermo grams were recorded by software [22].

Release studies

***In vitro* release/dissolution studies**

The selected in vitro dissolution conditions were in accordance with US Food and Drug Administration, CDER (Center for Drug Evaluation and Research). Drug release studies were carried out using a USP type II dissolution test apparatus (PTCF II Pharma Test, Germany) at 100 rpm for 24hrs in 0.1 N HCl (900 ml) maintained at 37±0.5^{o}C. 5 ml of sample was collected at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 hour with an automated sample collector (PT-DT7 Pharma Test, Germany) after filtering through sinter filters (10 µm). The collected samples were diluted up to 50 ml and analyzed at 284 nm using a UV-spectrophotometer (UV-1600 Shimadzu. Germany)**.** Same studies were conducted with 0.6M tris buffer, pH 8.0 (900 ml) and tested for drug release for 24hrs at same temperature and rotation speed. Samples were taken out and volume of fresh tris buffer pH 8.0 was added to kept volume of dissolution medium constant and samples were analyzed using UV spectrophotometer at 284 nm. The *in vitro* cumulative drug release study was conducted in triplicate [23]. Dissolution profile can be described by different mathematical functions. To obtain a more quantitative understanding of the transport kinetics in hydrogel, the drug release data was analyzed as a function of time. The release models with major application and best describing drug release phenomena are, in general, the Higuchi model, zero order model, first order model and Korsemeyer Peppas model [24].

RESULTS AND DISCUSSION

Swelling studies

Swelling behavior of CMAX-g-MAA hydrogel of varying contents (monomer, polymer, cross linker) was investigated at acidic and alkaline pH. To evaluate the effect

of methacrylic acid contents on swelling pattern series of formulations (M_1, M_2, and M_3) with varying methacrylic acid contents from 20% w/w, 30 %w/w and 35 % w/w respectively were analyzed at pH 1.2 and pH7.4 as given in Table 2. It was observed that at alkaline pH swelling ratio (20.85, 16.70, and 14.28) is higher than at pH 1.2 (5.03, 4.09 and 3.14). pKa values of pH-sensitive polymers and buffer solutions perform major task in the swelling behavior. In literature it has been proposed that at basic pH, carboxyl groups of methacrylic acid repel each other, causing the swelling of the system. At acidic pH the carboxyl groups of methacrylic acid are unionized as a result, the polymer network remains in collapsed state avoid swelling. Phenomenon of electrostatic repulsion can also be explained by Donnan effect. Polymeric network is worthy of attracting counterions, causing a chemical potential gradient, osmotic pressure within the polymer's realm surmounts than that of the external solution, and therefore, the polymer is proficient of swelling. In the past it has been proclaimed, polymeric networks containing methacrylic acid act like hydrophilic systems. Upon crosslinking they happen to insoluble, but are seemly to swelling by protonation/de protonation of carboxyl group [25]. Similar findings have been observed by Khare and Peppas in cross-linked poly (hydroxyethyl methacrylate-co-methacrylic acid) and poly(hydroxyethyl methacrylate-co-acrylic acid) hydrogels [26]. It has been observed that overall swelling (20.85, 16.70, and 14.28; 20 %w/w, 30 %w/w and 35% w/w methacrylic contents respectively) of CMAX-g-MAA reduced by increasing concentration of methacrylic acid. Hydrophobic nature of methacrylic acid is responsible for reduce swelling [27].

Degree of swelling is highly pH dependent and increased by increasing concentration of CMAX. It may be assumed that increased contents of CMAX impart hydrophilicity to hydrogel. As it has been reported that carboxymethylation of Arabinoxylan modified its fundamental properties like hydrophilicity and anionic nature depending on degree of substitution [9].

Equilibrium swelling behavior of CMAX-g-MAA copolymer with varying degrees of cross-linking has been examined as a function of pH as given in Table 2. It was ascertained that changing the degree of cross-linking has a significant effect on the swelling behavior. It has been shown that equilibrium swelling ratio was decreased from 14.28 to 8.97 by increasing N, N MBA concentration from 0.25 %w/w to 0.85 %w/w. Decrease in swelling by increasing

crosslinker contents could be mechanistically due to decreased mesh size of hydrogel and high degree of crosslinking obstruct ionization process. Our findings regarding relationship of swelling and crosslinker contents can be correlated with the results of Khalid *et al*. (2009) who prepared poly (methyl methacrylate-co-itaconic acid) hydrogels with varying contents of cross linker [28].

Pulsatile behavior of hydrogel

CMAX-g-MAA hydrogels are absolute pH sensitive system as shown by pulsatile behaviour given in Figure 1.

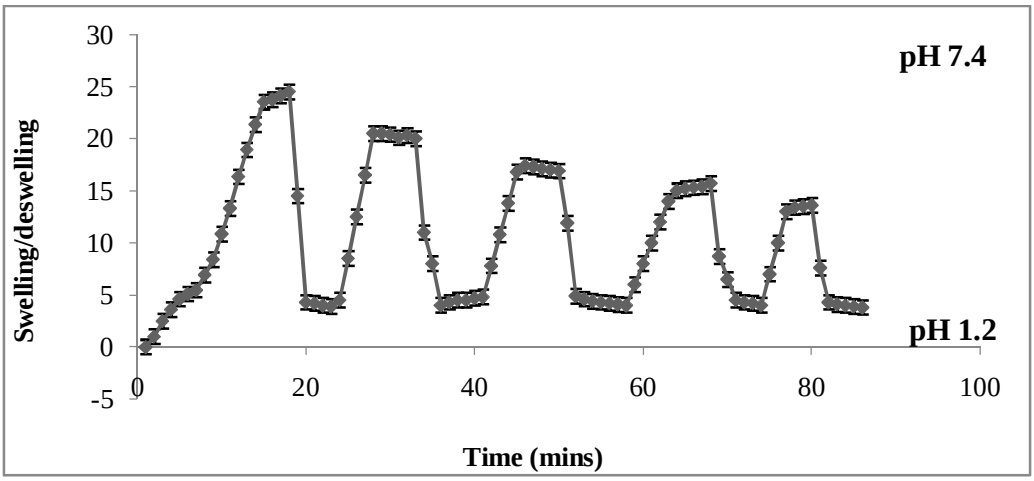

Figure 1: On-off switching behavior as reversible pulsatile swelling (pH 7.4) and deswelling (pH 1.2) of CMAX-g-MAA hydrogel

Swelling equilibrium studies revealed that CMAX-g-MAA hydrogels are absolute pH sensitive system. For controlled drug delivery system swelling process should be reversible to ensure that the release of drug could be triggered and stopped instantly. The proficiency of the contender polymer to manifest reversibility in swelling pattern was examined in the solutions of pH 1.2 and 7.4. It was detected that hydrogel at basic pH swell due to anion-anion repulsion of carboxylate ions, however, on exposing the swelled hydrogel in the solution of pH 1.2 it deswell with in few minutes due to protonation of carboxylate groups. Now, again on immersing the deswelled hydrogel in the solution of pH 7.4 it swells again, thus representing the pulsatile behavior as presented in Figure 1.

This impulsive swelling-deswelling fashion at different pH values renders the system to be highly pH-responsive and thereby it may be a suitable candidate for designing controlled drug delivery systems. Similar pH dependency behavior has also been illustrated by other ionic hydrogels like Starch-Poly (Sodium Acrylate-co-Acrylamide) superabsorbent hydrogel; poly

(acrylamide-comethacrylic acid) grafted Gum ghatti based [29, 30].

Equilibrium water contents and gel fraction

Table 2: Equilibrium water contents and dynamic equilibrium swelling ratio (q) of CMAX -g-MAA hydrogels using different concentrations of MAA, CMAX and crosslinker

Formulation code	Contents %w/w	EWC %	Dynamic equilibrium swelling ratio (q)	
			pH 1.2	pH 7.4
M1	MAA 20	95	5.032	20.855
M2	MAA 30	93	4.095	16.693
M3	MAA 35	91	3.140	14.285
M4	CMAX 1	95	4.658	18.808
M5	CMAX 1.5	95	3.462	22.122
M6	CMAX 2	95	2.770	24.638
M7	MBA 0.45	92	4.005	15.371
M8	MBA 0.65	85	3.342	12.131
M9	MBA 0.85	81	2.696	8.972

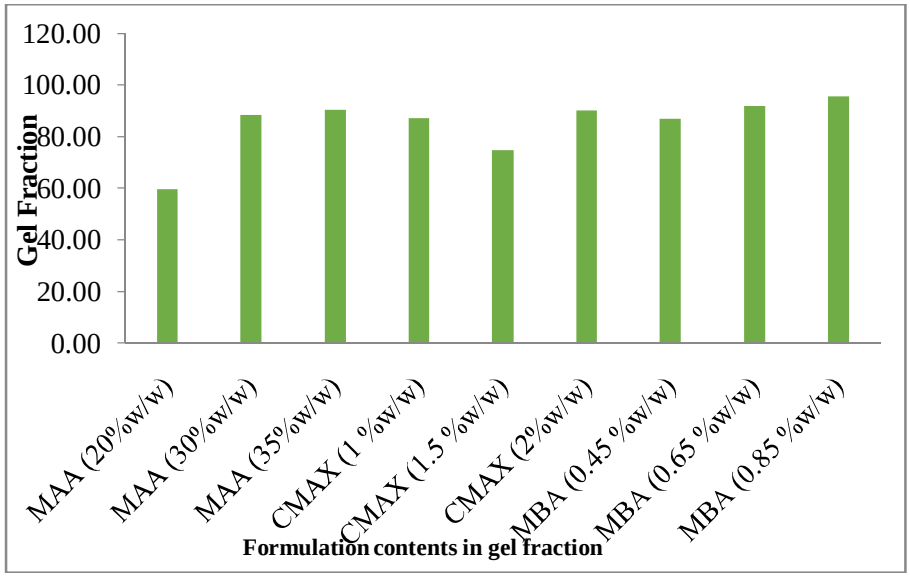

Figure 2: Gel fraction of CMAX-g-MAA hydrogel with different concentrations of MAA, CMAX and crosslinker

It has been observed that the xerogel starts to drink water when it was placed in an aqueous media. Hence, determination of the extent of water gulped within the hydrogel is vital measure for illustrating the hydrogel for biomedical applications and is frequently symbolized equilibrium water contents, directly proportional to hydrophilicity of copolymeric network. Equilibrium water contents of CMAX-g-MAA was evaluated as given in Table 2, revealed the effect of composition of hydrogel effect water absorbing capacity of hydrogels. It was scrutinizes that CMAX contents (1 %w/w.

1.5 %w/w and 2 %w/w) promoted EWC (95 %), but increasing methacrylic acid contents (EWC=95 % -91 %) and crosslinker concentration (EWC= 92 %-81 %) obstruct water diffusion through hydrogels. Amount of water imbibed within the hydrogel impacts the diffusional characteristics of a drug through the hydrogel. Generally, the higher the equilibrium water contents, higher are the diffusion rate of the solute. Micro-architecture of graft copolymer is also one of the major controlling factor of EWC [31].

Figure 2 show the effects of methacrylic acid, CMAX and crosslinking agent (N, N MBA) concentration on the gel fraction of different formulations of CMAX-g-MAA hydrogel. It was ascertained that by raising the concentration of MAA (M1to M3), and N, N MBA (M7 to M9) gel contents increases while sol fraction decreases and by increasing the concentration of CMAX (M4 to M6) gel fraction increase up to 1.5% of polymer contents and above that remain constant. It has been reported that reactivity of the monomers and radicals in copolymerization is determined by the nature of substituent in the double bond of the monomer. The methyl group of methacrylic acid may motivate the double bond, making the monomer more reactive than acrylic acid. Peppas and Klier prepared poly (methacrylic acid-g-ethylene glycol) hydrogels, and narrated that high MAA concentration formed efficient network (high gel contents) due to the higher concentration of reactive vinyl groups in monomer resulting in highly crosslinked matrix [32].

INSTRUMENTAL ANALYSIS

Scanning electron microscopy

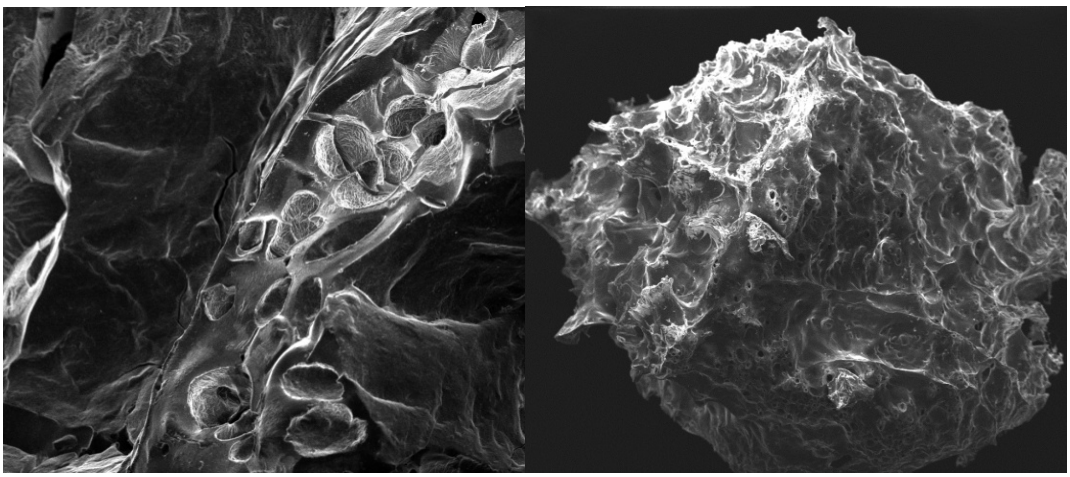

Figure 3: SEM images of lyophilized hydrogels (CMAX-g-MAA) at magnification of 100 X and 300µ, and 500µ scale bar respectively

The surface morphology of CMAX-g-MAA hydrogel was investigated by scanning electron microscopy (SEM). Figure 3 presented SEM micrograph of the polymeric hydrogels. These photomicrographs confirm that synthesized polymer (CMAX-g-MAA) have a porous structure. At high magnification and lyophilized hydrogels (Figure 6) displays a large, open, channel-like structure. Similar porous structure has been reported for crosslinked graft copolymer of methacrylic acid and gelatin. These interconnected pores could be suitable for controlling drug release by diffusion. Porosity of hydrogels depends on diverse factors like nature of monomer, reaction conditions, amount of diluent (water) and crosslinking density [16].

FTIR spectral analysis

For polymer characterization one of preferred method is FTIR spectroscopy. To confirm grafting, FT-IR spectra (CMAX, MAA, and CMAX-g-MAA) was used as given in Figure 4.

The FTIR spectrum of pure carboxymethyl arabinoxylan (Figure 4) shows the characteristic peak at 3301 cm^{-1} due to –OH stretching, –C=O of –COOH at 1629 cm-1 and ether linkage at 1425 cm-1. This can be related to the absorption of carboxymethyl groups in arabinoxylan and peaks at 1334, 1034, 895, 626, 618 cm^{-1} are due to polymer backbone. These results are in accordance with Saghir*et al.*, work, they prepared carboxymethylate darabinoxylan by etherification method and characterized by FTIR spectra [9].

Spectrum of CMAX-g-MAA (Figure 4) shown three new distinctive absorption peaks at 1692, 1536 and 1445 cm^{-1}authenticating the architecture of graft copolymer product. These new bands accredited to carbonyl stretching of the carboxylic acid groups and symmetric and asymmetric stretching modes of carboxylate anions, respectively. Similar findings have been illustrated for poly methacrylic acid grafted onto psyllium for confirmation of grafting [33].

Thermal analysis

TGA/DTG thermogram of CMAX-g-MAA (Figure 5) illustrated that thermal degradation of graft copolymer was accomplished in two steps, 66 ^{o}C to 152 ^{o}C and 435 ^{o}C to 536 ^{o}C with weight loss 21.1%and 31.05% respectively. Middle thermal degradation temperature values, of both steps are 94 ^{o}C and 462 ^{o}C. Complete loss of pure methacrylic acid was detected below 100 ^{o}C. Thermal decomposition of pure polymer CMAX was occurred in two steps initial degradation temperature of first segment is 236 ^{o}C and of second is 431 ^{o}C.Tdf of both

steps are 382 ^{o}C and 562 ^{o}C with 44.5 % and 25% weight loss. Total weight loss of graft copolymer is less than raw polymer, depicted thermal stability of graft copolymer. It has been illustrated in previous studies that weight loss in the range of 150–250 ^{o}C is due to the formation of anhydride with elimination of H_2O molecule from the two neighboring carboxylic group of the grafted chains. The second segment of degradation is credited to the decarboxylation of the anhydrides formed earlier. The change of thermal behaviors confirmed the formation of grafted copolymer. Xanthan gum grafted with methacrylic acid represented such type of thermal behavior [34]

DSC curve of CMAX-g-MAA hydrogel revealed exothermic peak at 401^{o}C and endothermic peak at 517 ^{o}C. These peaks confirm grafting because these are absent in polymer backbone DSC curve. Thermal stability and endothermic–exothermic behaviors of graft copolymer related to the increase of molecular weight and addition of functional groups [35].

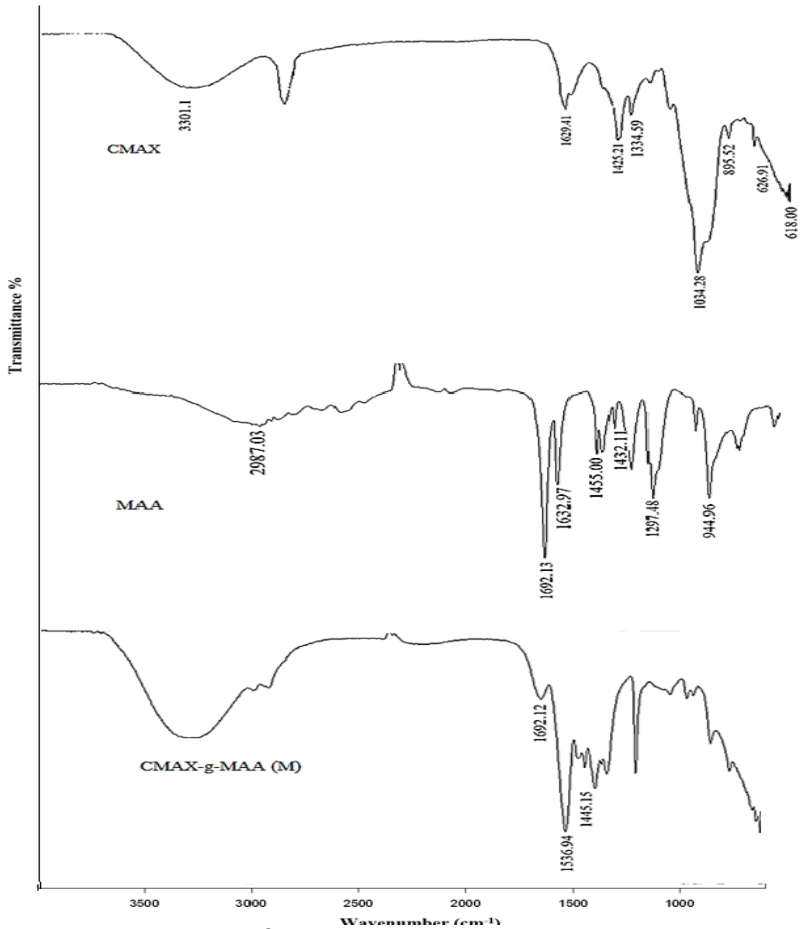

Figure 4: FTIR spectrum of CMAX, MAA and CMAX-g-MAA (M) hydrogel

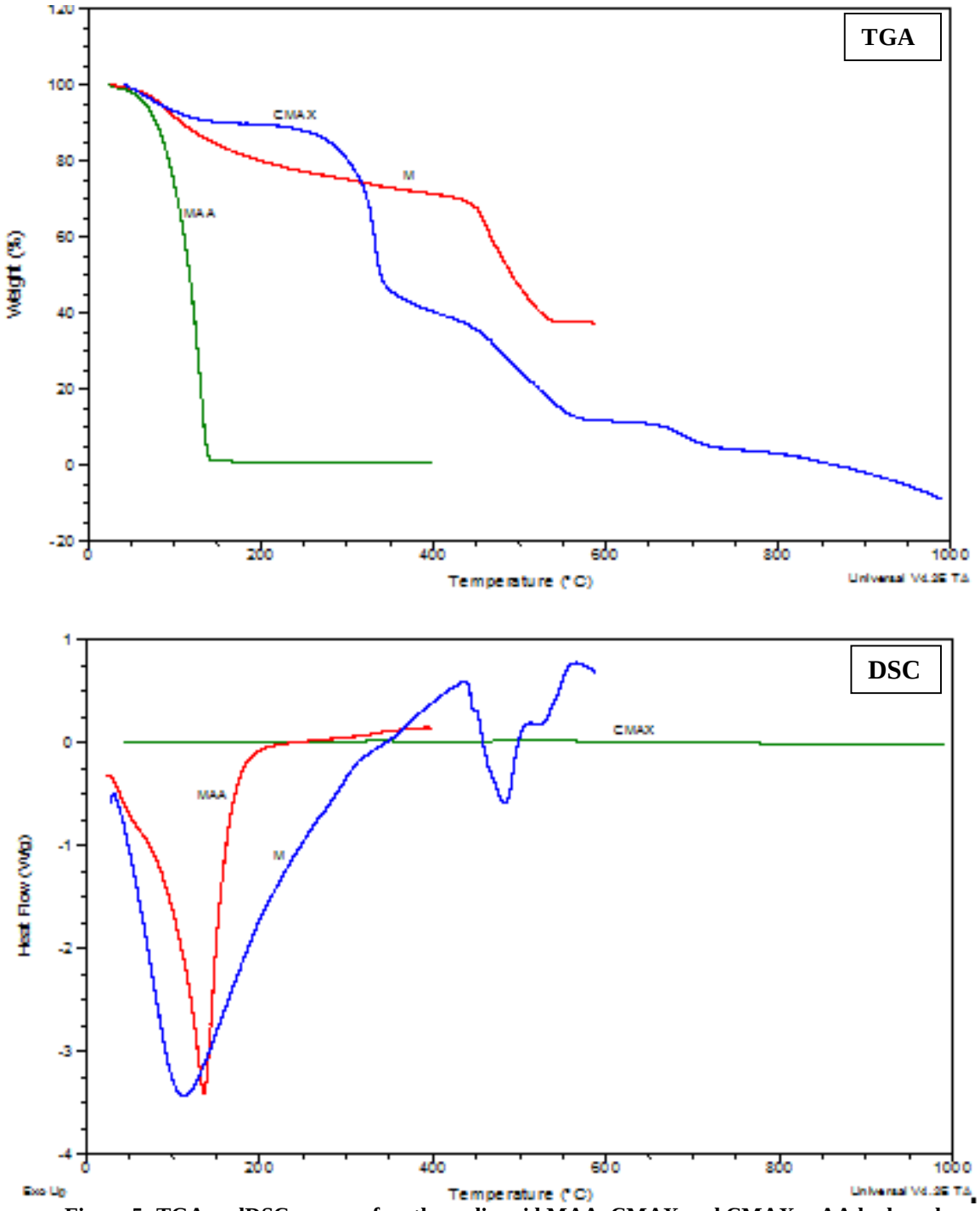

Figure 5: TGA andDSC curves of methacrylic acid MAA, CMAX and CMAX-g-AA hydrogel

***In vitro* release kinetics of Rabeprazole sodium CMAX-g-MAA hydrogel**

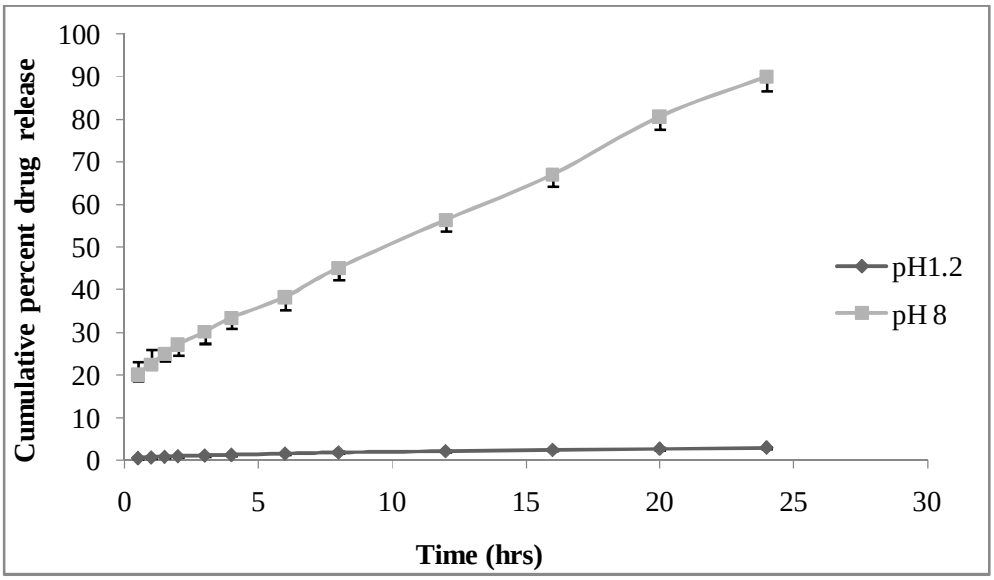

Figure 6: Cumulative percent drug release of Rabeprazole sodium from hydrogel CMAX-g-MAA

Table 3: Kinetic parameters of Rabeprazole sodium release from CMAX-g-MAA hydrogels

Formulation code	Higuchi	First order	Zero order	Korsmayer-peppas	
	R^2	R^2	R^2	R^2	n
M1	0.972	0.480	0.997	0.985	0.819
M2	0.958	0.614	0.999	0.987	0.810
M3	0.970	0.620	0.998	0.994	0.867
M4	0.972	0.461	0.995	0.980	0.846
M5	0.976	0.471	0.996	0.976	0.766
M6	0.972	0.414	0.998	0.984	0.716
M7	0.970	0.531	0.990	0.979	0.960
M8	0.954	0.633	0.997	0.989	1.004
M9	0.968	0.681	0.993	0.984	1.053

We were interested in developing a polymer which shows no swelling at low pH values and maximum swelling at higher pH value. In order to simulate the possible effect of pH on drug release rate, in vitro release studies were performed at acidic and alkaline pH values at physiological temperature of 37 °C. To explain release curves, three main factors have to be taken into account: pH sensitivity, graft copolymer composition and nature of individual constituent and crosslinking density of graft copolymer. In vitro release study has revealed that composition of the graft copolymer absolutely control release of

drug. As contents of methacrylic acid raised (20%, 30% and 35 %), pH sensitivity enhanced (as percent drug release at basic pH was 84.19%, 75.9%, 71.26 % and at acidic pH was 10.3%, 7.7% and 5.33%) but overall swelling reduced so percent cumulative drug release has been declined. Swelling analysis of CMAX-g-MAA hydrogel has been represented that overall swelling reduced by increasing concentration of methacrylic acid. Hydrophobic nature of methacrylic acid is responsible for reduce swelling [27]. The affirmative Rabeprazole sodium release depiction could be accredited to the pH-sensitivity of the hydrogel. Swelling of such hydrogels in the stomach is minimal so drug release consequently low as shown in Figure 6. A similar practical approach has also been narrated by other researchers; pH sensitive methacrylic acid containing hydrogels can bypass the acidity of gastric fluid without liberating substantial amounts of the loaded drug [21].

By increasing concentration of CMAX (1 %, 1.5 % and 2 %) percent cumulative release increased at basic pH was increased (79.78%, 87.93 % and 90.06 % respectively) and become very low at acidic pH (4.91 %, 3.17 % and 2.93 %). These results indicate that by increasing CMAX content of the hydrogels pH sensitivity was enhanced, hence cumulative drug released at basic pH was maximum. This fact may be related with increased hydrophilicity of hydrogel by increasing CMAX contents, could be explained by free volume theory. This theory was suggested that solute diffuses only through aqueous region, so effective free volume available for transport of solute is free volume of water in gel in swollen state [36].

Effect of MBA concentration on release of drug revealed that high crosslinking density lead to low percent cumulative release i.e 55%. This could be due to the fact that at higher crosslinking, reduced free volume of the matrix, thereby obstructing the transport of drug molecules through the matrix [37].

Numerous drug release models were practiced for analyzing rabeprazole sodium release kinetics. Principles for choosing the appropriate model were based on the ideal fit specified by the values of regression coefficient (r) near to 1. Regression coefficient (r) values obtained from CMAX-g-MAA hydrogels at varying contents of MAA, CMAX and N, N, MBA for zero order, first order, Higuchi and Korsemeyar peppas model are given in Table 3. Values of r obtained using zero order release model were viewed higher than other order release model, thus depicting that drug release from

the series of hydrogels at varying amount of MAA, CMAX and N,N MBA was zero order. Release kinetics of drug from hydrogels has been used to describe the relationship between drug dissolution and geometry of hydrogels on drug release patterns mathematically. It is apparent from the literature that no single approach is widely accepted to determine for similar dissolution profiles [38].

CONCLUSION

Among various graft copolymer formulations prepared with varying contents of carboxymethyl arabinoxylan, methacrylic acid and N, N MBA M6 present superior properties in regards with swelling, pulsatie behavior, mechanical strength, sustained, and pH responsive drug release. CMC-g- MAA hydrogels with high methacrylic acid concentration may lead to more efficient network formation (a lower sol fraction) due to the higher concentration of reactive vinyl groups in the polymer mixture. The concept of formulating graft copolymer CMAX-g-MAA containing Rabeprazole sodium offers an appropriate, sensible approach to accomplish a lingering therapeutic outcome by continuously releasing the drug over extended period of time.

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