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Synthesis of acryloyl guar gum and its hydrogel materials for use in the slow release of L-DOPA and L-tyrosine

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ABSTRACT

Acryloyl guar gum (AGG) and its hydrogel materials were synthesized for use as carriers and slow release devices of two pro-drugs, L-tyrosine and 3,4-dihydroxy phenylalanine (L-DOPA). To evaluate their structure-properties relationship, these were characterized by scanning electron micrography (SEM), FTIR spectroscopy and swelling studies. The hydrogel materials responded to the change of pH of the swelling medium, and exhibited reversible transitions in 0.9% saline solution. These were loaded with two pro-drugs, and their cumulative release behavior was studied at pH 2.2 and pH 7.4. The hydrogel materials exhibited structure-property relationship in the release of these pro-drugs. The % cumulative release of L-tyrosine was the maximum from the AGG-*g*-poly(methacrylic acid), while the maximum release of L-DOPA was observed from AGG-*g*-poly(AAc) in both the media. On the other hand, the AGG-*g*-poly(2-hydroxyethyl methacrylate) and AGG-*g*-poly(2-hydroxypropyl methacrylate) retained 42.33% and 49.05% of the drug even after 12 h.

1. Introduction

Guar gum is a natural hetero-polysaccharide obtained from the endosperm of the guar plant, *Cyamopsis tetragonolobus,* which has been extensively used in various industrial applications. It is a high molecular weight hydrocolloidal hetero-polysaccharide composed of galactan and mannan units. It possesses several attractive and industrially useful properties. Guar gum has been modified by derivatization, grafting and network formation to improve its property profile for a wide spectrum of end-uses. The grafting of methacrylamide (Behari, Kumar, Tripathi, & Pandey, 2001), acrylamide (Singh, Tiwari, Tripathi, & Sanghi, 2004), acrylonitrile (Trivedi, Kalia, Patel, & Trivedi, 2005) and acrylic acid (Pandey, Srivastava, Tripathy, & Behari, 2006; Taunk & Behari, 2000) has been reported to affect its water retention properties. Shi and Zhang (2007) grafted poly(*N*-isopropylacrylamide) on *O*-carboxymethyl-*O*-hydroxypropyl guar gum and investigated the temperature induced phase transition behavior of the graft copolymers. The modification of guar gum has been reported by network formation as single component (Barbucci, Pasqui, Favalorob, & Panariello, 2008) or with the other polymer component such as poly(acrylamide) (Soppimath, Kulkarni, & Aminabhavi, 2001) or alginate (George & Abraham, 2007). The introduction of guar gum in the network with poly(*N*-isopropylacrylamide) results in the reduction of the total solid weight needed for the gel formation. The reversible thermo-responsive characteristics of a hydrogel such as deswelling rates and the final water retention are reduced even at the low guar gum contents (Li, Wu, & Liu, 2008).

Guar gum is inherently biodegradable and biocompatible. Hence, it has been used 'as such' or in the modified forms to design drug delivery carriers and release devices, especially, colon specific drug delivery systems. The pH-sensitive microgels of guar gum with the partially hydrolyzed poly(acrylamide) were loaded with anti-hypertensive drugs diltiazem hydrochloride and nifedipine, and their transport was observed to be non-Fickian in the simulated gastric and intestinal pH conditions (Soppimath et al., 2001). The pharmacokinetic studies of the guar gum-entrapped mebendazole (Krishnaiah et al., 2003a) and 5-fluorouracil (Krishnaiah et al., 2003b) have been reported *in vivo* on healthy human volunteers by oral administration. The *in vitro* colon specific drug delivery of 5-fluorouracil has also been evaluated using guar gum-xanthan gum based delivery devices. A highly retarded drug release proportionate to the ratio of the gums used was observed even after 24 h of the tablets dissolution (Sinha, Mittal, Bhutani, & Kumira, 2004). The drug release from the pH-sensitive alginate–guar gum hydrogels has been reported to be the minimal at pH 1.2, and maximum at pH 7.4. The presence of guar gum and glutaraldehyde as the

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crosslinking agent increases the entrapment efficiency of drug and slows down the dissolution of alginate in higher pH of the intestine, ensuring a controlled release of the entrapped drug (George & Abraham, 2007). The release of *in situ* loaded ketoprofen from pH-sensitive polyelectrolyte hydrogel mainly followed the non-Fickian diffusion kinetics in pH 7.4 buffer solution, as the drug release was mainly affected by polymer erosion (Huang, Yu, & Xiao, 2007). The carboxymethyl guar films formulations have been reported as the transdermal therapeutic systems for the release of terbutaline sulphate (Murthy, Rani, Hiremath, & Paranjothy, 2004).

In view of the above, and in continuation to our earlier work on the preparation of stimuli responsive biopolymers based hydrogels (Chauhan & Chauhan, 2008; Chauhan, Chauhan, Chauhan, Kumar, & Kumari, 2007; Chauhan, Guleria, & Sharma, 2005; Chauhan & Mahajan, 2002), in this article we report synthesis of acryloyl guar gum (AGG) and its hydrogel materials for use in the drug delivery applications. We have not come across any report on the derivatization of guar gum to its acryloyl form. AGG was functionalized by the grafting reaction using four vinyl monomers, viz. acrylic acid (AAc), methacrylic acid (MAAc), 2-hydroxyethyl methacrylate (HEMA) and 2-hydroxypropyl methacrylate (HPMA). The hydrogels materials were characterized by FTIR, SEM and water uptake studies and were used as carriers and release devices for L-tyrosine and 3,4-dihydroxy phenylalanine (L-DOPA) as the model pro-drugs. L-tyrosine is involved in the synthesis of neurotransmitters in brain. It is a precursor to L-DOPA, nor-epinephrine and epinephrine. The concentrations of these neurotransmitters in brain are dependent upon the intake of tyrosine. The deficiency of tyrosine has been associated with depression and L-tyrosine or its precursor phenylalanine serve as valuable adjunctive therapy in the treatment of Parkinson's disease (Yehuda, 2002). L-DOPA is an intermediate in dopamine biosynthesis. It is used as a pro-drug to increase dopamine levels for the treatment of Parkinson's disease, since it is able to cross the blood–brain barrier whereas dopamine itself cannot. It is also the precursor molecule for the catecholamine neurotransmitters (dopamine, nor-epinephrine or noradrenaline) and the hormone epinephrine (adrenaline). L-DOPA is the drug of choice for the neurodegenerative Parkinson's disease; however, it has drawback of the low water solubility, low permeation, and sensitivity to chemical and enzymatic oxidation and peripheral decarboxylation (Cestelli et al., 2001). L-DOPA and L-tyrosine are also precursors to the biological pigment melanin. There is scanty information on the release of these pro-drugs by using active hydrogels. The release of L-DOPA from a polymeric pro-drug α-β-poly(*N*-hydroxyethyl)-DL-aspartamide-L-DOPA adduct microencapsulated in alginate–chitosan microspheres has been reported (Filipovic-Grcic, Maysinger, Zorc, & Jalsenjak, 1995). A relatively slow release of L-DOPA in rat has also been reported from the liposomal formulations (Stefano et al., 2004). In this study we report release of these two pro-drugs form AGG-based hydrogel materials.

2. Materials and methods

2.1. Materials

Guar gum (courtesy Lucid Colloids, Jodhpur, India), sodium hydroxide, iso-propanol, AAc, thionyl chloride, MAAc, HEMA, (Merck, Schuchardt, Germany), L-tyrosine, L-DOPA (HiMedia), ammonium persulphate, copper sulphate and sodium potassium tartarate, potassium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate (S.D Fine, Mumbai, India) were of all analytical grade and used as received.

2.2. Synthesis of AGG

Guar gum was dissolved in 18% sodium hydroxide solution and then extracted with 2-propanol. Sodium salt of guar gum was washed thoroughly with 2-propanol and then dried in oven at 40 °C. To it was slowly added acryloyl chloride that was prepared by the direct reaction of AAc with thionyl chloride under controlled conditions in an ice bath. A thick gelatinous precipitate of AGG was obtained. This gelatinous precipitate was repeatedly washed with methanol to wash-off any unreacted acryloyl chloride trapped in the gel. There after, the product was dried under vacuum.

2.3. Functionalization of AGG by graft copolymerization

Grafting reaction of AGG with various monomers was carried out in an aqueous medium by using ammonium persulphate (APS) as an initiator. In a standard set of reaction, AGG (1 g), AAc (1 g) and APS (0.5% of the total weight of AGG and AAc) were taken in 2.5 mL of water, and the reaction was carried out at 60 °C for 1 h. The same procedure was used for the grafting of other monomers. The graft copolymers (hence after referred as hydrogel materials) were separated from the respective homopolymers by fractional precipitation using acetone as non-solvent. These were vacuum dried and the % polymer add-on or graft yield (P_g) was calculated as % weight increase with respect to the initial weight of the backbone (AAG) as follows:

$$P_g = \frac{W_2 - W_1}{W_2} \times 100$$

where W_2 is the weight of the hydrogel material and W_1 is the initial weight of the AGG.

2.4. Characterization of hydrogels

The hydrogel materials were characterized by using SEM and FTIR to obtain the evidence of monomer incorporation on the backbone polymer. Surface morphology was observed by scanning electron microscopy. The samples were mounted onto stubs, sputter coated with gold in a vacuum evaporator, and photographed using scanning electron microscope. FTIR spectrum was recorded on Nicollette 5700 in transmittance mode in KBr. Swelling studies were carried as a function of time (30–480 min), pH (2.0 and 7.4 pH), and in 0.9% NaCl solution at 37 °C following an earlier reported method (Chauhan & Chauhan, 2008). Percent swelling (P_s) of the hydrogel materials was evaluated as follows:

$$P_s = \frac{\text{Weight of swollen hydrogel} - \text{weight of dry hydrogel material}}{\text{Weight of dry hydrogel material}} \times 100$$

2.5. Loading and release of L-DOPA and L-tyrosine

Loading and release of L-DOPA and L-tyrosine was carried at 37 °C. Different hydrogel materials (0.1 g) were separately immersed in the solution of L-tyrosine and L-DOPA (1000 ppm each) made in a buffer solution (pH 7.0) for 1 h at 37 °C. These were removed from the solutions, and the solutions were analyzed for the concentration of the L-DOPA and L-tyrosine on the UV/vis spectrophotometer (Carey 100, Varian Inc., USA) by Lowry method, which is described as follows. To 1.0 mL of the test solution was added 3 mL of alkaline copper reagent which was prepared fresh by adding 2% Na_2CO_3 (w/v) solution in 0.1 M NaOH, 1% $CuSO_4$ (w/v) solution and 1% sodium potassium tartrate (w/v) solution in 98:1:1 ratio, respectively. After 15 min 0.3 mL of Folin–Ciocalteau reagent diluted with distilled water in 1:1 ratio

was added and mixed well. The test tubes were put into water bath for 30 min at 37 °C, and then, the optical density values were observed from the UV–vis spectrophotometer. The hydrogel materials loaded with drugs were washed with distilled water to remove drug attached on the surface. These were dried in air oven at 37 °C. These were used to study the release kinetics of the drugs in 10 mL of the buffer solutions of 2.2 and 7.4 pH at 37 °C. The aliquots were removed from the solutions from time to time and analyzed on the UV/vis spectrophotometer for the released amount of the drugs. The concentration of tyrosine and DOPA released from was assessed from their respective standard curves prepared in different medium (distilled water, pH 2.2 or pH 7.4).

3. Results and discussions

AGG was synthesized in a facile process using the sodium guar gum as the precursor. Four biocompatible hydrogel materials were synthesized by the APS initiated free radical grafting in a limited aqueous medium. Apart from the presence of hydroxyl groups as grafting sites on the galacto-mannan of the AAG backbone, the unsaturated acryloyl groups are easily accessible as the grafting and crosslinking sites to generate a three dimensional network structure (Hamcerencu, Desbrieres, Khoukh, Popa, & Riess, 2008). The incorporation of the polymers onto AGG backbone was affected by the hydrophilicity of the monomers. P_g of 89 and 70 was obtained in AGG-*g*-poly(AAc) and AGG-*g*-poly(MAAc), respectively, while the less hydrophilic methacrylates poly(HEMA) and poly(HPMA), were grafted to a lesser extent with a P_g of 60 and 53, respectively (Table 1).

3.1. Characterization of hydrogel materials by SEM, FTIR and swelling

Characterization of the hydrogel materials was carried out by SEM and FTIR spectroscopy. The evidence of synthesis of AGG and grafting was obtained by analyzing the characteristics peaks of the functional groups present in the respective hydrogel materials. The spectra of candidate hydrogel materials are presented in Fig. 1. In the case of guar gum, important peaks are observed at 3365.8 cm^{-1}, 2928.5 cm^{-1}, 1015 cm^{-1} and 1152 cm^{-1} due to the associated O–H stretching, C–H stretching, and hydroxylic C–O single bond and C–O–C stretching, respectively (Fig. 1(a)). The evidence of the formation of AGG was obtained from its spectrum that has peaks at 1565 cm^{-1} (C=C stretching), and a shoulder peak at 1710 cm^{-1} (C=O stretching). Apart from these peaks, the change in the intensity and the position of the peaks of guar gum are shifted. The peak due to the O–H stretching is sharper as compared to that seen in its precursor as on derivatization, the polymeric association is broken and also some hydroxylic groups are also consumed in the formation of AGG (Fig. 1(b)). In the spectra of the hydrogel materials, the additional peaks diagnostic of the polymer grafted on guar gum can be observed along with the peaks of AGG. The spectra of AGG-*g*-poly(AAc) and AGG-*g*-poly(MAAc) have broad peaks at 1718.2 and 1701 cm^{-1} (due to C=O stretching of acid and ester), respectively, with a medium intensity peak at 1454 cm^{-1} in the spectrum of the latter (due to $-CH_3$ asymmetric bending) (Fig. 1(c)). In the spectra of AGG-*g*-poly(HEMA) and AGG-*g*-poly(HPMA) a strong band is present at 1727 cm^{-1} and 1725 cm^{-1} (due to C=O stretching of ester group), respectively. The hydrogel materials have distinct surface morphologies as can be observed from Fig. 2. SEM of AGG is presented in Fig. 2.1. It has porous structure. A porous network structure is also revealed from the SEMs of AGG-*g*-poly(AAc) and AGG-*g*-poly(MAAc). The SEM of the latter has well defined network with pores of uniform size and shape (Fig. 2.2). Such morphology is desirable for the biomedical applications. The well defined network in this case resulted from the strong interactions between the strongly hydrophilic monomer and AGG during synthesis. The surface morphology of AGG-*g*-poly(HEMA) and AGG-*g*-poly(HPMA) revealed that pores are of small size and the grafted polymer chains form aggregates at the surface as a result of low level of interactions between the less hydrophilic poly(HEMA) or the surface active poly(HPMA) with the AGG backbone (Fig. 2.3). Swelling behavior was studied as a function of swelling time, pH of the medium and in the presence of 0.9% NaCl solution at 37 °C. The water uptake was very less in the medium of 2.2 pH, but for AGG-*g*-poly(HPMA) which exhibited an increase in P_s with the increase of time before attaining equilibrium after 360 min (Fig. 3.1). Such behavior of AGG-*g*-poly(AAc) and AGG-*g*-poly(MAAc) is explained by the formation of a transient network in the stronger acidic medium, and the result is shrinking and consequent poor swelling (Chauhan & Chauhan, 2008). The same is also true in the case of AGG-*g*-poly(HEMA) where its primary hydroxyl group interacts to form interpolymeric associations. However, the same does not operate in the case of AGG-*g*-poly(HPMA) as the grafted polymer is surface active in nature and that does not allow the polymer chains to collapse in the medium of low pH. It also exhibited pH-independent swelling behavior at pH 7.4, as the nature and the extent of swelling were almost same as observed at pH 2.2. In other cases, P_s increased with the increase in the swelling time and these exhibited the maximum P_s at 240 min and attained equilibrium thereafter (Fig. 3.2). The high swelling of AGG-*g*-poly(AAc) and AGG-*g*-poly(MAAc) in the medium of pH 7.4 resulted from the ionization of the unionized carboxylic groups to more water interacting carboxylate groups. In 0.9% NaCl solution, the water uptake by the AGG-*g*-poly(AAc) and AGG-*g*-poly(MAAc) was appreciable, while the other two hydrogels exhibited high salt sensitivity as very low swelling was observed (Fig. 3.3). The pre-swollen hydrogels were also subjected to deswelling in 0.9% NaCl (Fig. 3.4). The maximum deswelling and salt sensitivity was observed in AGG-*g*-poly(HEMA) and AGG-*g*-poly(HPMA), as these lost most of the absorbed water within initial 10 min. On the other hand, AGG-*g*-poly(AAc) and AGG-*g*-poly(MAAc) exhibited good salt tolerance as these retained high amount of water even after 120 min. In the pre-swollen hydrogels the polymer matrix is opened-up by the absorbed water, and when in contact with the saline solution, it looses the water due to ex-osmosis (Chauhan & Chauhan, 2008). This is more vividly expressed in the case of AGG-*g*-poly(HEMA) and AGG-*g*-poly(HPMA) which by their low hydrophilic nature cannot hold much water in the saline solution, hence rapid deswell was observed in these two cases as compared to the other two hydrogels.

Table 1
P_g for modified biopolymers.[a]

Monomer	Hydrogel materials	P_g
CH_2=CHCOOH (AAc)	AGG-*g*-poly(AAc)	89
CH_2=C(CH)$_3$COOH (MAAc)	AGG-*g*-poly(MAAc)	70
CH_2=C(CH)$_3$COOCH$_2$CH$_2$OH (HEMA)	AGG-*g*-poly(HEMA)	60
CH_2=C(CH)$_3$COOCH$_2$CH(OH)CH$_3$ (HPMA)	AGG-*g*-poly(HPMA)	53

[a] Agg (1 g): monomer (1 g) in 1:1 ratio by weight, water = 2.5 ml, temperature = 60 °C, time = 1 h.

3.2. Loading and release behavior of L-DOPA and L-tyrosine

The concentration of L-DOPA and L-tyrosine was determined by Lowry's method, which is based on colorimetry. This method is particularly sensitive because as it employs two color-forming reactions: (i) It uses biuret reaction in which peptide bond coordinate with alkaline copper to give a deep blue color and (ii) in

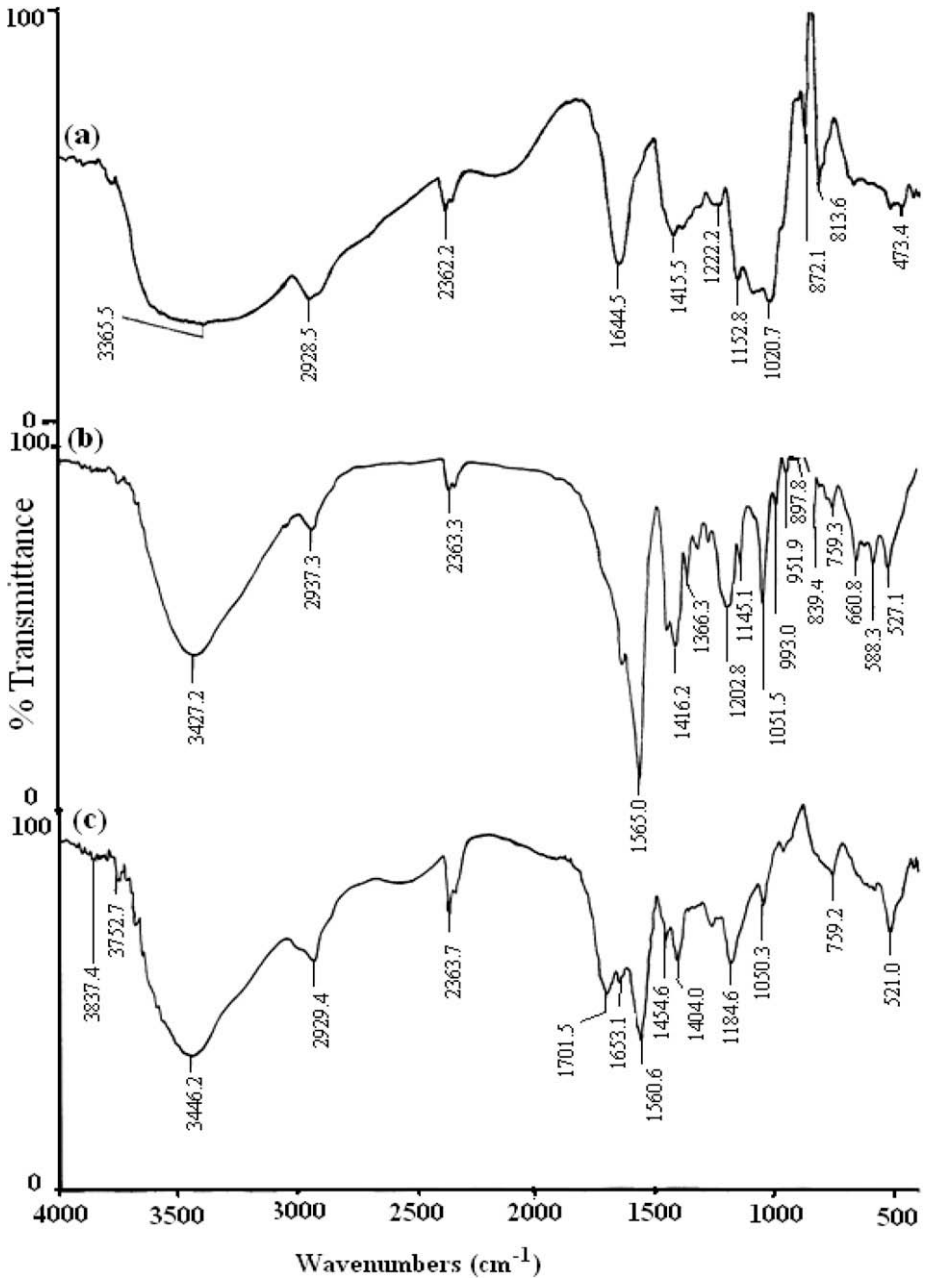
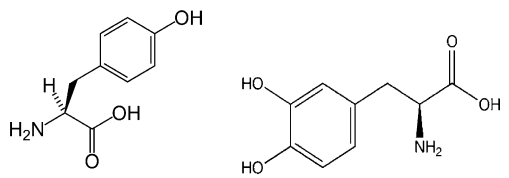


Fig. 1. FTIR spectra of (a) guar gum (b) AGG and (c) AGG-*g*-poly(MAAc).

addition, it uses Folin–Ciocalteu chemistry, in which the reduction of the Folin–Ciocalteu reagent (phosphomolybdate phosphotungstate) by amino acid tyrosine and tryptophan takes place to give an intense blue-green color. The combination of these two reactions gives a method that is more sensitive than either reaction alone. L-tyrosine (I) and L-DOPA (II) have the following structure.



(I) (II)

These were loaded from their respective solutions (1000 ppm) at pH 7.0 and 37 °C. From the surface morphology of the hydrogel materials, the uptake of these two pro-drugs is expected to be both by the pore mechanism and also by surface adsorption. All the hydrogel materials exhibited almost equal efficiency in the uptake of L-tyrosine, but there was selectivity in the case of L-DOPA as the lesser amount was loaded on those comprising of methacrylates than those having $-CO_2H$ groups (Table 2). The highest uptake of L-tyrosine (10.85%) and L-DOPA (11.24%) was observed on AGG-*g*-poly(AAc) and AGG-*g*-poly(MAAc), respectively. It is proposed that the pro-drugs are held on the hydrogel materials by the ionic–ionic and ionic–dipole interactions in the case of AGG-*g*-poly(AAc) and AGG-*g*-poly(MAAc), and by the ionic–dipole and dipole–dipole interactions in the other two hydrogel materials. The structural differences of the hydrogel materials are well pronounced in the release behavior of the pro-drugs. The release

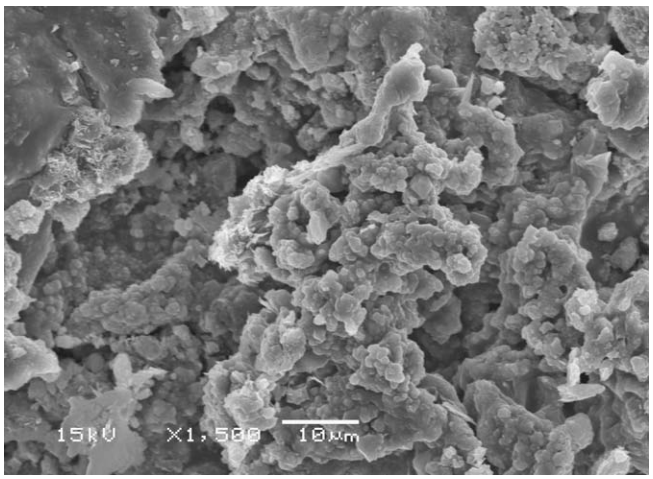


Fig. 2.1. SEM of AGG.

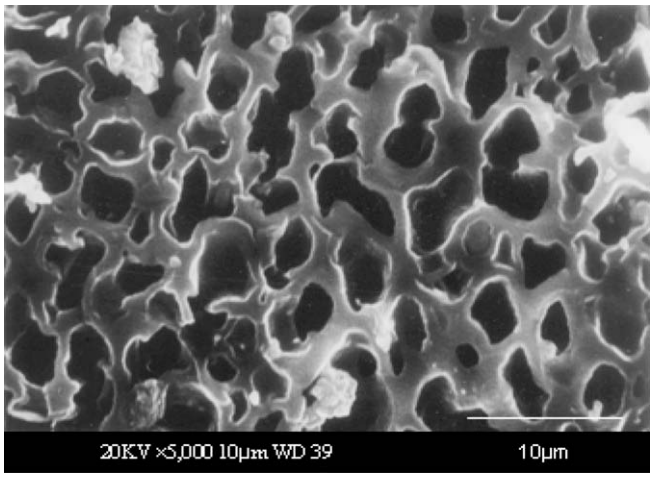


Fig. 2.2. SEM of AGG-*g*-poly(MAAc).

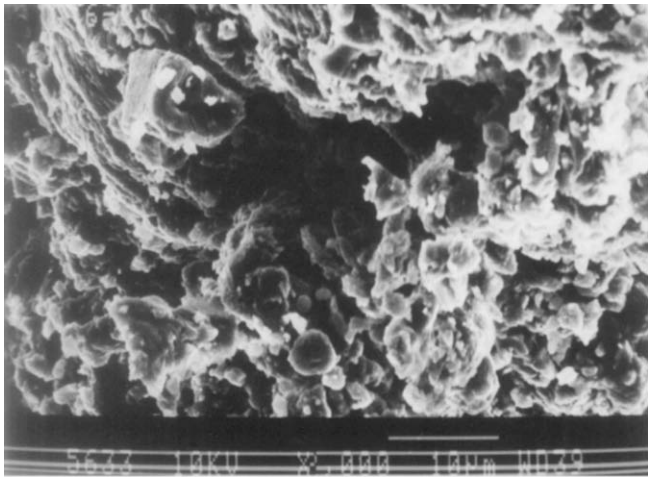


Fig. 2.3. AGG-*g*-poly(HPMA).

behavior of L-tyrosine at pH 2.2 and pH 7.4 is presented in Figs. 4.1 and 4.2. The % cumulative release of L-tyrosine is the maximum (84.9) from the AGG-*g*-poly(MAAc) in the medium of pH 2.2, as well as also (11.7) in the medium of pH 7.4. The AGG-*g*-poly(AAc)

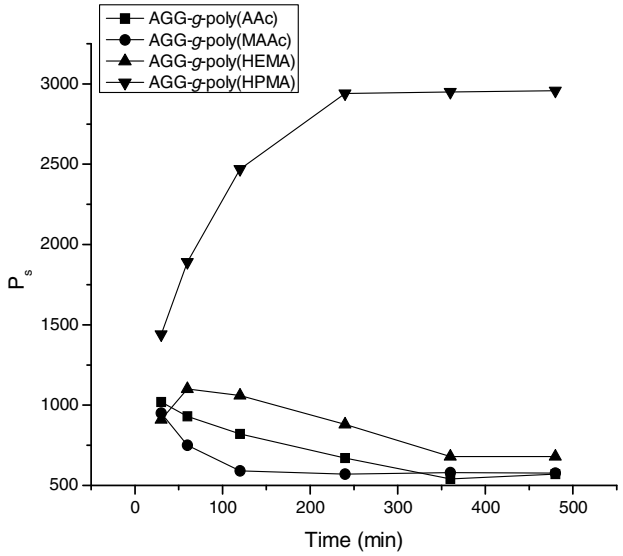


Fig. 3.1. P_s of hydrogels as a function of time at 37 °C in medium of 2.2 pH.

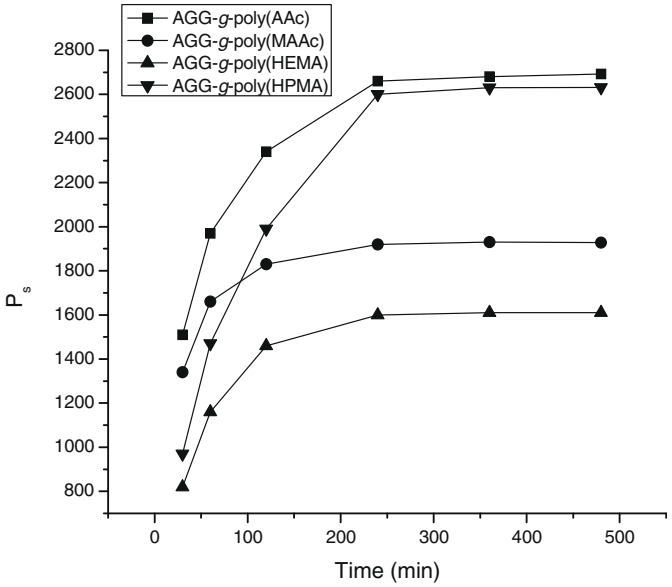


Fig. 3.2. P_s of hydrogels as a function of time at 37 °C in medium of 7.4 pH.

released L-tyrosine in a more controlled manner in both the media. Despite high % release of the drug in the medium of pH 2.2, both AGG-*g*-poly(HEMA) and AGG-*g*-poly(HPMA) retained 42.33% and 49.05% of the drug after 12 h. The release behavior in this case was almost independent of time after 120 min in the medium of 7.4 pH. The release behavior of the L-DOPA was also dependent on the structure of the hydrogel materials with AGG-*g*-poly(AAc) exhibiting the highest release in both the media. However, the release from the AGG-g-poly(HEMA) and AGG-*g*-poly(HPMA) was slow, but regulated over 4 h (Table 3, Fig. 4.3 and 4.4). The polymers show high release of L-DOPA in the acidic medium (pH 2.2) in contrast to the basic medium (pH 7.4). The maximum % release of 71.08 in pH 2.2 and 25.47 in pH 7.4 was observed from AGG-*g*-poly(AAc), while it was again far low in both the media in the case of those containing methacrylates. From the perusal of these results it is revealed that the drugs are released by a slow mechanism. The uptake of pro-drugs was very high though the maximum amount of these was bound on the surface which was

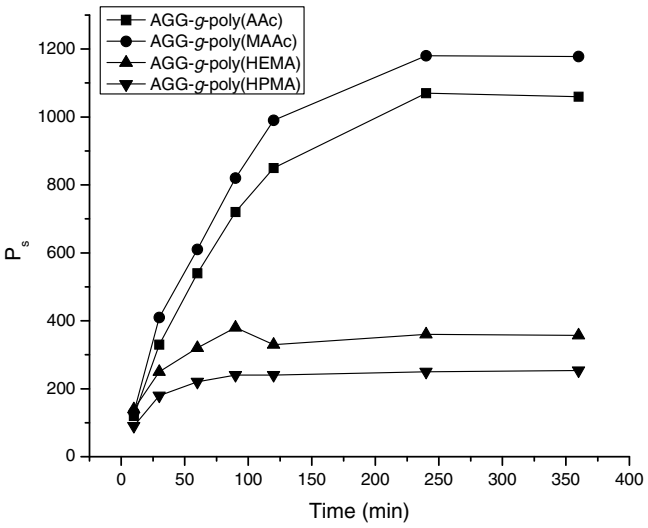


Fig. 3.3. P_s of hydrogels as a function of time at 37 °C in 0.9% NaCl solution.

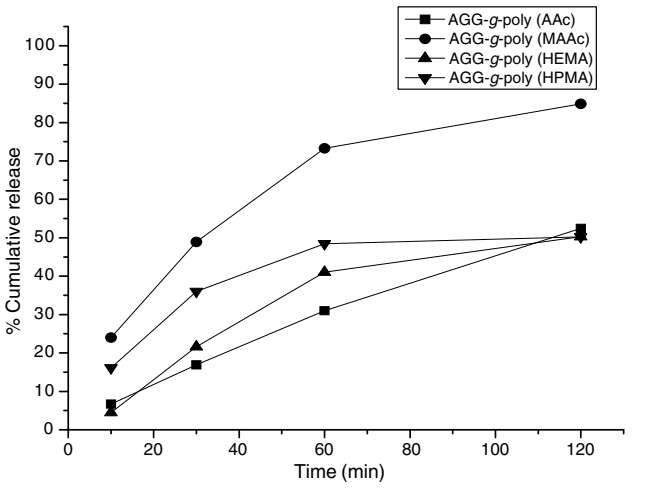


Fig. 4.1. % Cumulative release of L-tyrosine as a function of time at 37 °C in medium of pH 2.2.

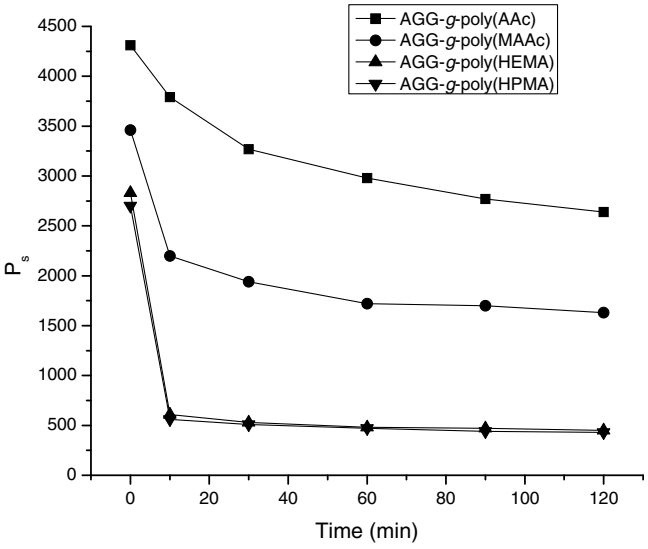


Fig. 3.4. P_s of pre-swollen hydrogels as a function of time at 37 °C in 0.9% NaCl solution.

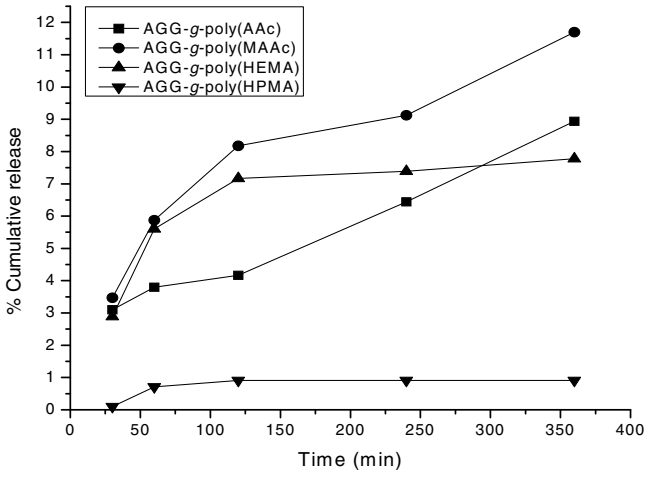


Fig. 4.2. % Cumulative release of L-tyrosine as a function of time in medium of pH 7.4 at 37 °C.

released easily in the acidic medium, where the hydrogel shrivel and surface is exposed to the strong acidic medium. Though the amount of pro-drug released in the present study was low in the medium of 7.4 pH, yet it was far higher than that has been reported for L-DOPA (Filipovic-Grcic, Maysinger, Zorc, Jalsenjak, 1995). However, the technological significance of these hydrogel materials as the release devices of these bioactive molecules lies in the slow release and high retention even after a period of 12 h.

4. Conclusions

The acryloyl guar gum and hydrogel materials synthesized from it were characterized by FTIR, SEM and swelling studies. These hydrogel materials exhibit unique swelling behavior, and respond well to the physiological stimuli such as pH and the ionic strength. The high loading of L-tyrosine and L-DOPA was achieved on these hydrogel materials. The release behavior was slow, especially, in the medium of pH 7.4. There exists structure-property relationship in the release of both these pro-drugs, as the hydrogel materials having poly(AAc) and poly(MAAc) released the highest amount of

Table 2
Loading of L-tyrosine and L-DOPA at 37 °C.[a]

Hydrogel materials	L-tyrosine		L-DOPA	
	Uptake (ppm)	Uptake (mg/g of Hydrogel materials)	Uptake (ppm)	Uptake (mg/g of Hydrogel materials)
AGG-*g*-poly(AAc)	542.6	108.52	525.75	105.15
AGG-*g*-poly(MAAc)	535.2	107.04	562.25	112.45
AGG-*g*-poly(HEMA)	542.4	108.40	414.00	82.80
AGG-*g*-poly(HPMA)	523.2	104.64	469.75	93.95

[a] pH = 7.0, standard tyrosine concentration = 1000 ppm, time = 30 min.

Table 3
The maximum release of L-tyrosine and L-DOPA at 37 °C.

Hydrogel materials	Total % release of tyrosine		% Retention (after 12 h)	Total % release of L-DOPA		% Retention (after 12 h)
	pH 2.4 (4 h)	pH 7.4 (8 h)		pH 2.4 (4 h)	pH 7.4 (8 h)	
AGG-*g*-poly(AAc)	52.43	4.44	43.13	71.08	25.47	03.45
AGG-*g*-poly(MAAc)	84.90	11.7	3.7	61.61	8.35	30.04
AGG-*g*-poly(HEMA)	50.28	7.39	42.33	28.26	0.79	70.95
AGG-*g*-poly(HPMA)	50.25	0.70	49.05	20.25	3.66	76.09

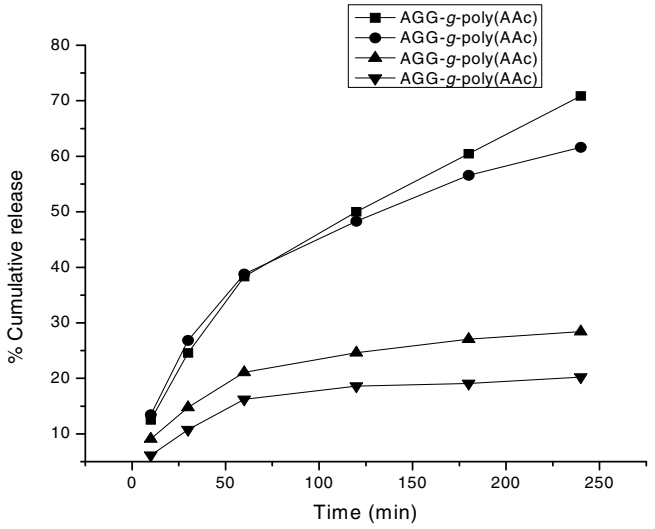


Fig. 4.3. % Cumulative release of L-DOPA as a function of time at 37 °C in medium of pH 2.2.

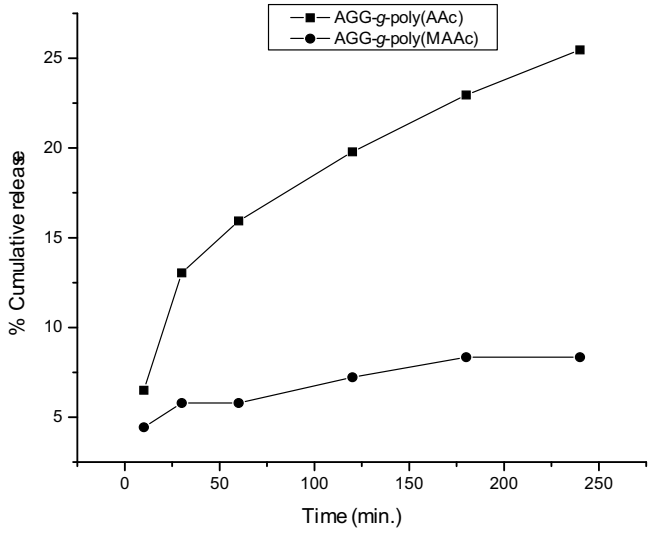


Fig. 4.4. % Cumulative release of L-DOPA as a function of time in medium of pH 7.4 at 37 °C.

L-tyrosine and L-DOPA, respectively, in both the media. The slow release behavior of all the hydrogel materials in the medium of pH 7.4, and the high retention of both the pro-drugs by those based on methacrylates even after 12 h period are two important points those emerged from this study. These aspects when considered together make these hydrogel materials useful release devices for transdermal applications for the treatment of disease like vitiligo and Parkinson's disease. We are currently investigating the release behavior of these pro-drugs from the methacrylates based hydrogel materials over a long period of time.

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