In-Vitro Release Kinetic Study of Paracetamol from Sustained Release Matrix Tablet Containing Gum acacia and acrylic acid hydrogels

Md Mateen M Shaikh, Anand A Wardole, Gavisiddappa S. Gokavi, Shrikant V Lonikar

***Abstract*— Hydrogels that are pH sensitive were synthesized by ceric ion initiated graft copolymerization of acrylic acid onto gum acacia in aqueous medium in the presence of varying amount of N, N–methylene bisacrylamide as a crosslinking agent. The copolymers were characterized by FTIR spectroscopy and swelling measurement. These hydrogels were used for the in vitro drug release studies using paracetamol as the model drug. The drug release were studied as a function of pH. At pH 1.2 the release of drug was insignificant in first 3 hrs for all the hydrogels which may attribute to the matrix compaction and stabilization through hydrogen bonding at lower pH. At pH 7.4 the amount of drug release was 80 – 90% in 12 hr. The kinetic study shows that the release of the drug from hydrogels was probably controlled by the swelling and relaxation of the polymers indication a super case II transport. These results indicate that the hydrogels may be useful to overcome the harsh environment of the stomach and can be used as excipient in colon targeting matrices.**

***Index Terms* - acrylic acid, gum acacia, paracetamol, pH sensitive hydrogels.**

I. INTRODUCTION

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids. The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), or physical crosslinks, such as entanglements or crystallites The latter provide the network structure and physical integrity. These hydrogels exhibit a thermodynamic compatibility with water which allows them to swell in aqueous media [1]-[5].

There are numerous applications of these hydrogels, in particular in the medical and pharmaceutical sectors [6]-[8]. Hydrogels resemble natural living tissue more than any other class of synthetic biomaterials. This is due to their high water contents and soft consistency which is similar to natural tissue [6]. Furthermore, the high water content of the materials contributes to their biocompatibility. Thus, hydrogels can be used as contact lenses, membranes for biosensors, linings for artificial hearts, materials for artificial skin, and drug delivery devices [6]-[10]. In the present investigation we have used a natural polysaccharide material i.e. *Gum Acacia* also known as *Gum Arabic* which was modified by acrylic acid with methylene bisacrylamide as a crosslinker. Gum arabic is a branched, neutral or slightly acidic, complex polysaccharide obtained as a mixed calcium, magnesium, and potassium salt. The backbone consists of 1,3-linked β-D-galactopyranosyl units. The side chains are composed of two to five 1,3-linked β-D-galactopyranosyl units, joined to the main chain by 1,6-linkages. Both the main and the side chains contain units of α- L-arabinofuranosyl, α-L-rhamnopyranosyl, β-D-glucuronopyranosyl, and 4-O-methyl- β-D-glucuronopyranosyl, the latter two mostly as end-units [11]. Gum arabic has excellent emulsifying properties, artificial sweeteners, in chewing gum as a coating agent and as a pigment stabilizer. In aerated confectionery products, such as marshmallows, nougats, and meringues, gum arabic acts as a whipping and stabilizing agent. It is still used as a suspending agent, emulsifier, adhesive, and binder in tabletting and in demulcent syrups. Gum arabic functions as a stabilizer in lotions and protective creams, where it increases viscosity, imparts spreading properties, and provides a protective coating and a smooth feel. It is used as an adhesive agent in blusher and as a foam stabilizer in liquid soaps. Gum arabic is also used in the preparation of etchingand plating solutions in the lithography industry. It is used as a dispersant in paints and insecticidal/ acaricidal emulsions [12]. In this investigation, we have grafted acrylic acid onto gum acacia using ceric ammonium nitrate (CAN) as an initiator in aqueous medium and with varying the amount of crosslinker N,N'-methylene bis acrylamide. These hydrogels were used as matrix for the study of release rate of paracetamol as a model drug, at two different pH, 1.2 and 7.4.

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II. EXPERIMENTAL

A. Materials

Gum acacia (s.d. Fine chemicals, India) was used. Acrylic acid (Thomas Baker, India), was freshly distilled under reduced pressure before use. Ceric ammonium nitrate (Qualigens, Germany) was dried at 110 C for 1 h. N,N'-methylene bis acrylamide (Thomas Baker, India) Paracetamol (Gift sample from Vamsi Labs, India) and other chemicals were used as such.

B. Preparation of hydrogels

Gum Acacia (2g) was dissolved in distilled water with constant stirring for 1h at 70ºC under nitrogen atmosphere. It

was allowed to cool and ceric ammonium nitrate (0.005M in 1M HNO_3) was added over a period of 15 minutes, followed by addition of required amounts of distilled acrylic acid and crosslinker N, N–methylene bisacrylamide. The reaction was proceeded under N_2 atmosphere for 3h at 37ºC. After completion of the reaction the hydrogel was washed 2-3 times with distilled water to remove homopolymers, if any, and filtered through sintered crucible. The final product was dried under vacuum until constant weight. A series of hydrogels were prepared by varying the amount of crosslinker (0.5, 2.0 and 5.0 mole %).

C. *IR spectral analysis*

IR spectra of gum acacia (GA), poly (acrylic acid) (PAA) and the graft copolymer were taken on Perkin Elmer FTIR spectrum BS spectrophotometer using KBr pellet technique.

D. *Swelling studies*

The equilibrium swelling was measured according to a conventional ''tea bag'' method. The completely dried preweighed hydrogel sample was placed in 200 mL of distilled water and buffer solution of desired pH at 37°C, respectively. The swollen gel was taken out at regular time intervals, wiped superficially with filter paper to remove surface water, weighed, and then placed in the same bath. The mass measurements were continued until the attainment of the equilibrium. The percentage of mass swelling (SM) was determined using the following expression [13].

$$\%SM = \frac{Mt - Mo}{Mo} \times 100$$

where Mo and Mt are the initial mass and mass at different time intervals, respectively. All the experiments were carried out with three samples and the average values have been reported in the data.

E. *Tablet preparation*

Two hundred milligrams of hydrogel and paracetamol (200 mg) were mixed until homogenous mixture was obtained and directly compressed in hydraulic press using a 12-mm flat faced punch of a force of 90 kg/cm ^{2} to obtain tablets.

F. *In vitro drug release studies*

To study the release of the drug from the tablets, the tablets were placed in 50 mL of phosphate buffer solution of pH 7.4 (USP XXIII) at 37°C under unstirred condition as well as in simulated gastric fluid pH 1.2 (2 g NaCl + 7 mL conc. HCl, diluted to 1 L by distilled water, USP XXIII). After predetermined time interval, the aliquot was removed and its absorbance was measured on Shimadzu UV–vis spectrophotometer at λ_{max}=299 nm.

G. *Statistical analysis*

All the data are the means of results from three experiments ±SD. Statistical data analysis was per-formed using the one-way variance with P<0.05 as the minimum level of significance.

III. Result and Discussions

Gum acacia-based copolymer hydrogels were synthesized by free radical copolymerization of acrylic acid onto the gum using methylene bis acrylamide as crosslinker.

A. *Spectral Analysis*

Figure 1 shows the FTIR spectra of the gum acacia (GA) (a), poly (acrylic acid)(PAA) (b), and GA-acrylic copolymer (c). As indicated in Figure 1(c), characteristic bands of both the gum and of the poly(acrylic acid), are present in the spectrum of hydrogel. The strong, broad peak at 3427 cm^{-1} is related to the OH stretching of the carboxylic and hydroxyl groups of acrylic and polysaccharide parts. The medium peaks at 1030–1070 cm^{-1} , due to stretching vibration of C–O–C and C–O–H bonds, confirm the polysaccharide structure of the hydrogel. The very sharp peak at 1717 cm^{-1} is attributed to the carboxyl groups (>C=O stretching) of PAA and the IR spectra also shows a shoulder at 2179 cm^{-1}, which is due to the presence of the –C–N– group of the crosslinking agent (N,N–methylene bisacrylamide). Since the copolymers had already been extracted to remove the soluble contents, its FTIR analysis proved that it is not a physical mixture but chemical linkages have been formed during the free radical polymerization reaction.

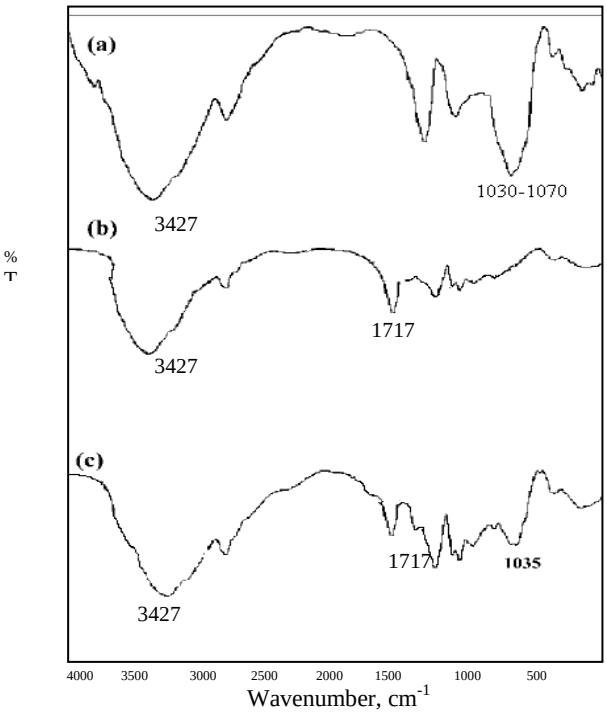

Figure 1: IR spectra of (a) Gum acacia (b) poly (acrylic acid) (c) gum acacia – poly(acrylic acid) graft copolymer hydrogel.

B. *Swelling Kinetics*

The swelling characteristics of a crosslinked polymer depend not only on the hydrophilic-hydrophobic balance but also on the degree of crosslinking. The different graft copolymer prepared by varying the mole percent of crosslinking agent are listed in Table 1 along with equilibrium swelling in distilled water and media of pH 1.2 and 7.4. The graft copolymer hydrogels prepared from gum acacia and acrylic acid undergo a sharp volume phase transition with the change in pH of the swelling medium from an acid to an alkaline one, thus suggesting that diffusion of the entrapped drug will be greatly enhanced with a change in pH of the medium. The amount of crosslinker also influences the water uptake of hydrogels. Finally, the hydrogels seems to have potential to be used for colon targeted drug delivery through oral administration.

Table No:I Gum acacia –acrylic acid graft copolymer hydrogels[a]

Sr. No	Crosslinker (N,N–methylene bisacrylamide) (mole%)	Equilibrium swelling S_e		
		in distilled water	at pH 1.2	at pH 7.4
1	0.5	1010	143	1189
2	2	870	100	677.8
3	5	706	78.84	504.4

a: Gum acacia: 2g, acrylic acid: 4 ml, initiator: ceric ammonium nitrate, (0.005M in 1M HNO_3), 10 ml; medium: water, total volume: 100 ml, temperature: 37˚C, time: 3h.

C. In vitro drug release studies

Figures 2 and 3 show the release profiles of paracetamol from the hydrogels containing different amount of crosslinker at two different pH (pH 1.2 and 7.4). The transit time in the stomach and small intestine is almost 2–3 h and the colonic residence time is about 20–30 h.

At pH 1.2 the amount of drug released within 3 h is near about 15% in GA-PAA1, 13% in GA-PAA2 and 14% in GA-PAA3 (Fig. 7). As discussed earlier, the extent of swelling at pH 1.2 in 3 h was found to be less than 20%. This observed ‘‘induction period’’ suggests that GA–PAA form a more compact matrix than either of the polymers alone. At lower pH, the carbonyl groups are undissociated and involve in hydrogen bonding with hydroxyl groups of gum acacia, which results in stabilization/compaction of the matrix. It may be noted that the pH of gastrointestinal fluid in stomach is 1–3 and the residence time is 2–3 h, which means that all the hydrogels would be useful as matrix to protect the drug from the harsh environment of stomach.

Figure 2 also shows that in the case of hydrogel GA-PAA at pH 1.2, the release of drug loaded was 42% for GA-PAA1 , 35% for GA-PAA2 and 32 % for GA-PAA3 after 24 hr. At the end of 30 hr the release of drug loaded was 54%, 42% and 41%, respectively for GA-PAA1, GA-PAA2 and GA-PAA3. From the results it may concluded that due to the more crosslink structure may results in higher extent of hydrogen bonding and compaction of matrix.

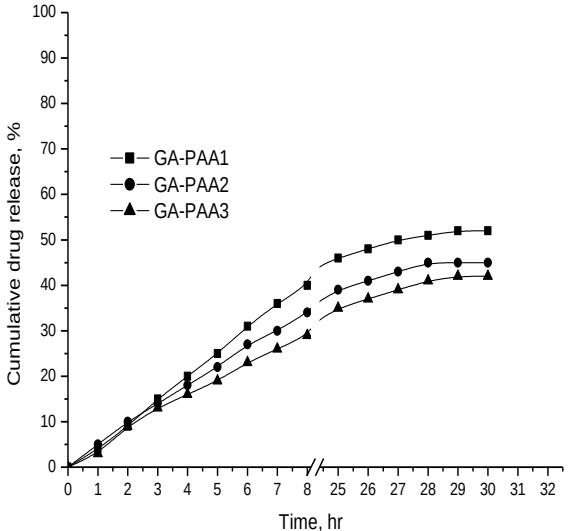

Figure 2 Release of paracetamol from GA-PAA tablets as a function of time at pH 1.2. Values are mean SD of at least three experiments.

Figure 3 shows that in the case of hydrogel GA-PAA at pH 7.4, the release of drug loaded after 3 hr was 52% for GA-PAA1, 38% for GA-PAA2 and 31 % for GA-PAA3, whereas in 6 hrs the release of drug was 57-77% for GA-PAA1, GA-PAA2 and GA-PAA3, respectively and a complete release of drug was in case GA-PAA1 after 12 hr. It is seen that in both pH initial release of drug is very slow, that is, upto 1–3 h, which is also the transit time of stomach and small intestine. So, it can be inferred that the matrix can be designed in such a way that the major amount of the drug loaded can reach the colon.

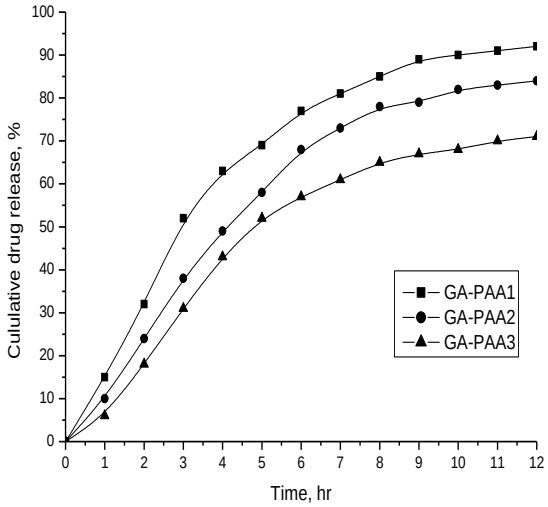

Figure 3 Release of paracetamol from GA-PAA tablets as a function of time at pH 1.2. Values are mean SD of at least three experiments.

D. Release kinetics of the hydrogels

In order to determine the exact mechanism of drug release from the hydrogels, the in vitro drug release data was analyzed according to zero order kinetics, first order kinetics, Higuchi model, Korsemeyer Peppas equation and Hixon – Crowell model. The criterion for selecting the most appropriate model was on the basis of goodness of best fit. Based on the summary of results given in table 2 and figure 4 to 13.

Table II. Release kinetics of hydrogels at pH 1.2

Hydrogels	Zero order	First order	Higuchi model	Korsemeyer – Peppas		Hixon Crowell
	R^2	R^2	R^2	R^2	n	R^2
GA-PAA1	0.9831	0.9957	0.7935	0.9938	0.812	0.9870
GA-PAA2	0.9734	0.9901	0.8856	0.9873	0.822	0.9862
GA-PAA3	0.9784	0.9925	0.8533	0.9889	0.876	0.9905

Table III. Release kinetics of hydrogels at pH 7.4

Hydrogels	Zero order	First order	Higuchi model	Korsemeyer – Peppas		Hixon Crowell
	R^2	R^2	R^2	R^2	n	R^2
GA-PAA1	0.9363	0.9791	0.7333	0.9609	0.953	0.9538
GA-PAA2	0.9689	0.9912	0.8013	0.9814	0.983	0.9834
GA-PAA3	0.9665	0.9817	0.8402	0.9701	0.848	0.9800

The release kinetics for all the graft hydrogels is shown in Table 2 and Table 3. In this study, the drug release data for GA-PAA hydrogels showed good fit into first-order with the highest correlation coefficient (r = 0.9957) for pH 1.2 and (r =0.9912) for pH 7.4. The rate constants were calculated from the slopes of the respective plots. The data obtained were also put in Korsemeyer– Peppas model in order to find out "n" value, which describes the drug release mechanism. The graft copolymer of acrylic acid showed linearity (r=0.9938 to 0.9889) with slope (n) values ranging from 0.812 to 0.876, similarly at pH 7.4 the linearity (r=0.9609 to 9701) with slope (n) values ranging from 0.953 to 0.848, indicating that diffusion is the dominant mechanism of drug release with these formulations. This indicates a first order release controlled by Super case II transport diffusion.

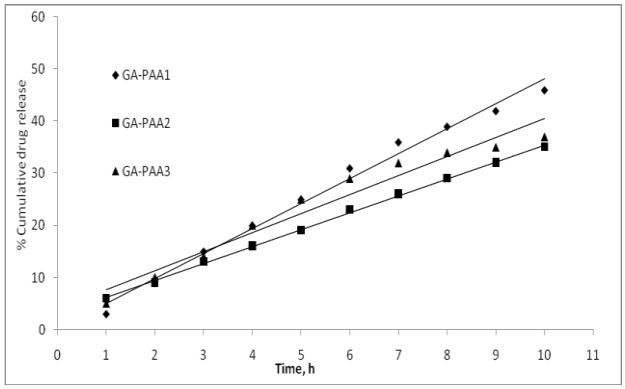

Figure 4 Zero order release of GA-PAA at pH 1.2

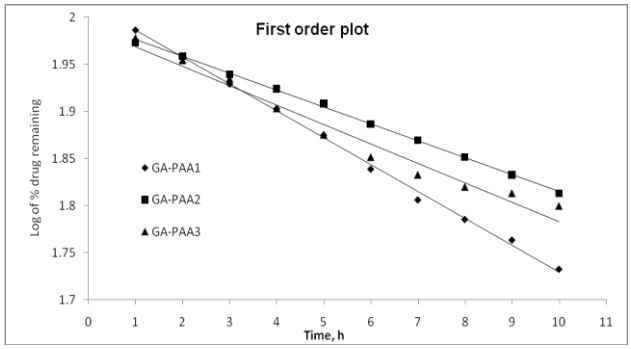

Figure 5 First order release of GA-PAA at pH 1.2

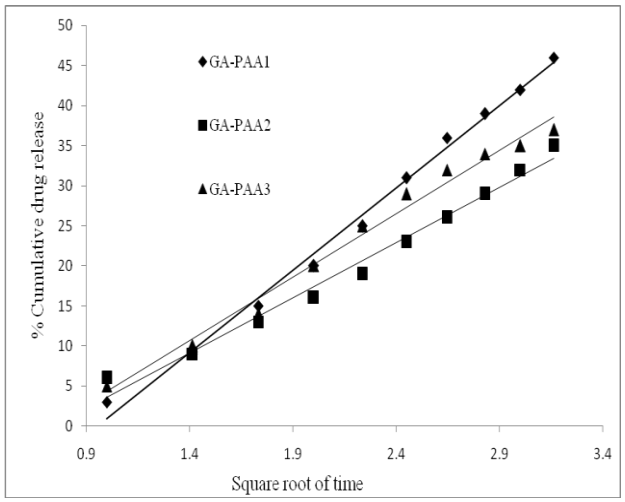

Figure 6 Higuchi release of GA-PAA at pH 1.2

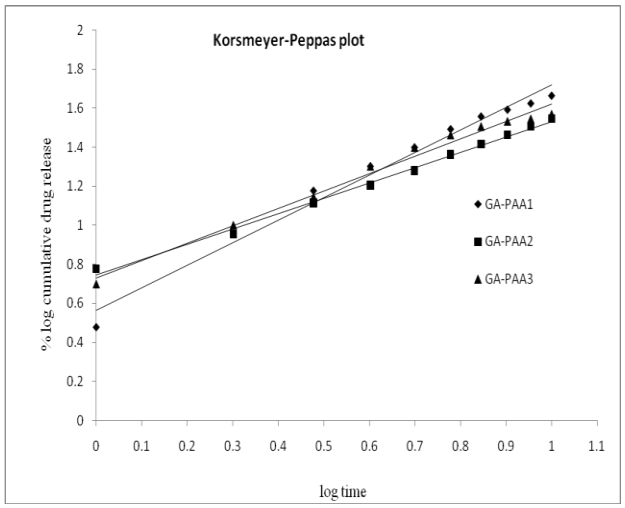

Figure 7 Korsemeyer– Peppas release of GA-PAA at pH 1.2

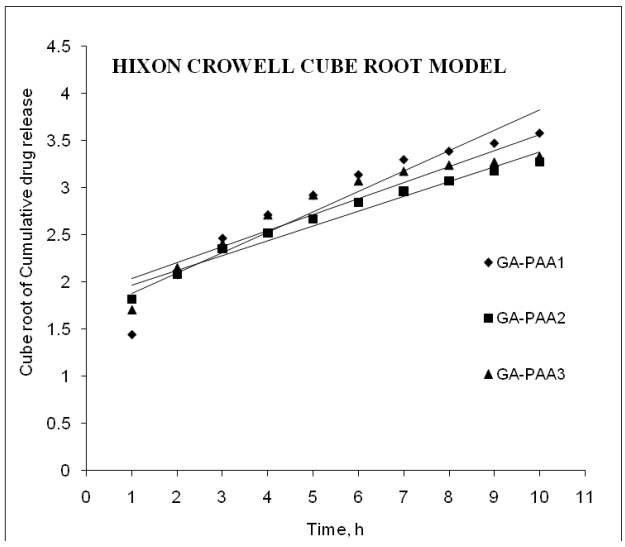

Figure 8 Hixon Crowell release of GA-PAA at pH 1.2

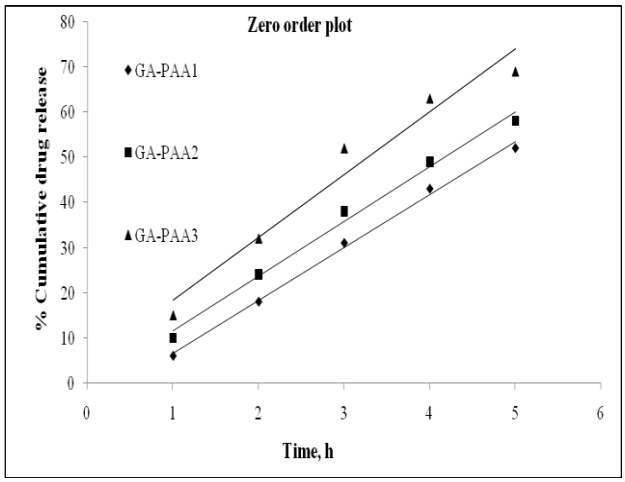

Figure 9 Zero order release of GA-PAA at pH 7.4

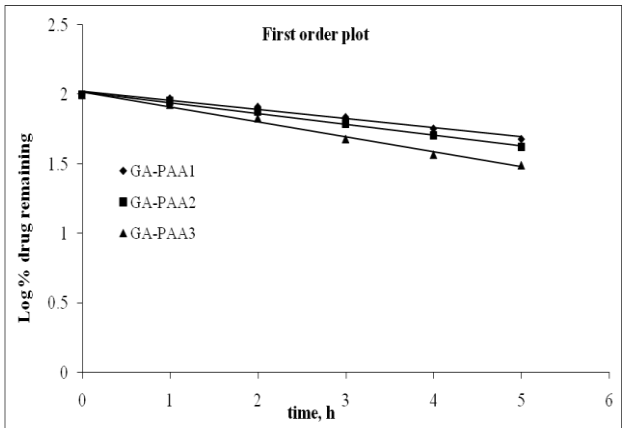

Figure 10 First order release of GA-PAA at pH 7.4

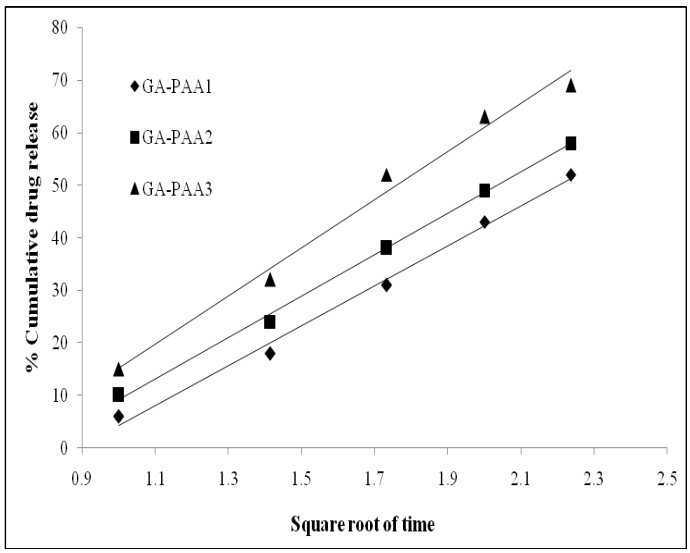

Figure 11 Higuchi release of GA-PAA at pH 7.4

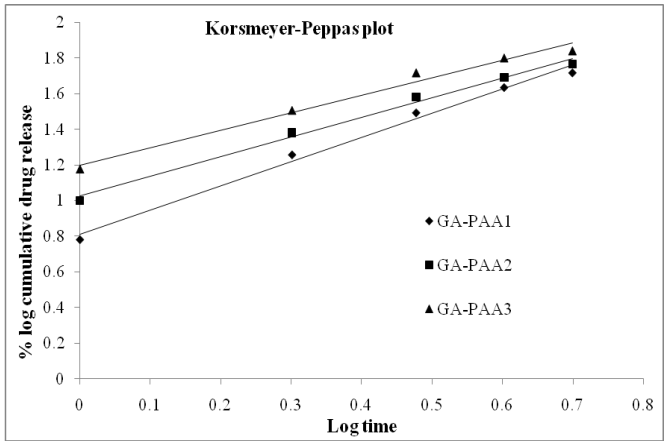

Figure 12 Korsemeyer– Peppas release of GA-PAA at pH 7.4

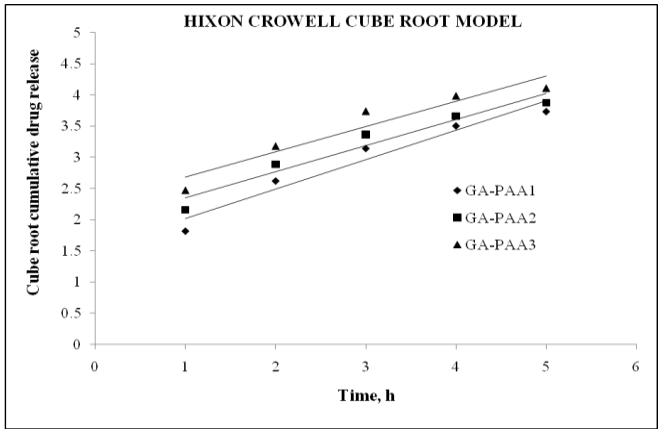

Figure 13 Hixon Crowell release of GA-PAA at pH 1.2

IV. Conclusion

The hydrogels GA-PAA1, GA-PAA2 and GA-PAA3 provided a pH sensitive matrix system for site-specific drug delivery. In vitro release profiles of paracetamol showed that as the % amount of crosslinker increases the drug release rate decreases, which may be attributed to the matrix stabilization due to the hydrogen bonding resulting in slower release of the loaded drug. Thus, it may be concluded that hydrogels may be useful tool to overcome the harsh environment of the stomach and can possibly be used in future as excipient for the colon-targeted drug delivery.

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