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Synthesis of pH Responsive Hydrogel Matrices from Guar gum and Poly(acrylamide-co-acrylamidoglycolicacid) for Anti-Cancer Drug Delivery

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ABSTRACT

Guar gum (GG) is one of the widely available and naturally occurring polymers; it has a wide range of applications in medicine, pharmacy, food, textile and scores of other industrial and commercial sectors due to its rheological adjusting properties. In this paper a pH-responsive GG/poly(acrylamide-co-acrylamidoglycolicacid) (PGAGA) hydrogel matrices were successfully synthesized via simple redox polymerization and *N,N*-methylene-bis-acrylamide used as cross-linker. 5-fluorouracil (5-FU) is an anticancer drug and it has been loaded into the PGAGA hydrogel matrices via the *in-situ* method. Pristine as well as 5-FU loaded PGAGA hydrogel matrices have been characterized by Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC). FTIR and DSC studies have demonstrated that 5-FU is distributed in molecular level throughout the PGAGA hydrogel matrices during *in situ* loading. Morphology of PGAGA hydrogel matrices was measured by scanning electron microscopic (SEM) analysis. The swelling kinetics of hydrogel matrices were performed in double distilled water and the equilibrium selling is performed at various pH solutions. *In vitro* release of 5-FU from the PGAGA hydrogel matrices were studied at pH 1.2 and 7.4.

INTRODUCTION

In recent years, hydrogels have received a prominent attention due to their well-known three-dimensional physicochemical structure, chemical tunability, high water absorbability, and biocompatibility (Oh *et al.*, 2008). Several natural polymers based physically or chemically cross-linked hydrogel matrices are developed with a high degree of available functional groups (Ho *et al.*, 2009; Chacko *et al.*, 2012; Hoare *et al.*, 2008). It has been a potential interest to utilize natural polymers in the area of targeted and sustained drug release devises, due to their ease of preparation, diversity of drugs that can be encapsulated with high drug encapsulation capacity, with excellent biocompatibility, biodegradability besides non-toxicity, non-immunogenicity, and responsiveness to external stimuli (Oh *et al.*, 2008; Chacko *et al.*, 2012; Ahmed *et al.*, 2015; Li *et al.*, 2011; Huang *et al.*, 2006; Mousa *et al.*, 2009). Natural polymer-based hydrogel matrices can be prepared from polysaccharides such as chitosan, pectin, heparin, hyaluronic acid and alginate (Mallikarjuna *et al.*, 2013; Neufeld *et al.*, 2017; Veerapratap *et al.*, 2015; Mihye *et al.*, 2010; Lakshmi Narayana Reddy *et al.*, 2014), protein polymers, such as collagen, albumin, brin, and gelatine (Hoare *et al.*, 2008; Ahmed *et al.*, 2015; Chandra Sekhar *et al.*, 2014).

5-Fluorouracil (5-FU) is a pyrimidine analogue, acts as a chemotherapeutic agent, commonly used for the cure of various types of tumors like colon cancer, breast cancer, brain cancer, ovary cancer, and the cancers of liver and pancreas (Arias *et al.*, 2008; Li *et al.*, 2012). Due to its potent curative effect, most of the times it is used alone and sometimes in combination with other chemotherapeutic drugs like leucovorin (Arkenau *et al.*, 2003). It exerts its activity because of its structural similarity with the nucleotides and can be misincorporated into DNA

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and RNA by transcription process and it inhibits the activity of thymidylate synthase (TS), a thymidine nucleotide synthesizing enzyme which leads to improper nucleotide metabolism and finally causes cytotoxicity and cell death (Depani *et al.*, 2013). TS catalyses the conversion of deoxyuridine monophosphate (dUMP) to dTMP by methylation on the uridine ring through a ternary complex of TS–dUMP–methylated tetrahydrofolate, but the 5-FU inhibits the TS ternary complex of TS–5F-dUMP–methylated tetrahydrofolate by which the formation of products halted, as the fluorine substituent fails to dissociate from the pyrimidine ring (Santi *et al.*, 1987). However, similar to general chemotherapeutic drugs, 5-FU also has some shortcomings like low bioavailability and shorter half-life due to fast catabolism. Additionally, there are some negative effects observed at higher dosages of drug substance, such as loss of hair, fatigue, liver disease and abnormal functions of bone marrow. In order to overcome these shortcomings, the clinical researchers have been moved towards advanced drug delivery systems, where 5FU is entrapped into the polymer matrix (Reddy *et al.*, 2016).

Guar gum (GG) is natural polymer isolated from the seeds of *Cyamopsis tetragonolobus*. Chemical structure of GG belongs to the galactomannan family. GG is insoluble in most of the organic solvents such as hydrocarbons, fatty acids, alcohols, esters, ketones, however, in fact, it is soluble in dimethylformamide. Chemically GG has a linear chain of (1→4)-linked β-D-mannopyranosyl units, along with the branches of α-D-galactopyranosyl residues aroused by (1→6)-linkages (Reddy *et al.*, 2016; Prabhanjan *et al.*, 1989). The most prominent characteristic of GG is its ability to hydrate promptly in cold water to attain uniform and very high viscosity even at lower concentrations. Apart from being the most cost-effective stabilizer and emulsifier, it provides texture improvement and water binding, enhances mouthfeel and controls crystal formation in addition to the biocompatibility and biodegradability GG has offered huge industrial and biomedical applications (Wang *et al.*, 2003; Dürig *et al.*, 2002; Minekus *et al.*, 2005; Naoi *et al.*, 2002; Krishnaiah *et al.*, 1998; Bayliss *et al.*, 1986; Najaf Iqbal *et al.*, 2010). Recently, Siva Prasad *et al.,* achieved functional modification GG by grafting of acrylamidoglycolic acid on the GG and other GG based materials are used for biomedical application (Siva Prasad *et al.*, 2012; Mudgil *et al.*, 2014).

In this paper, we nowhere reporting the development of pH-responsive GG/poly(acrylamide-co-acrylamidoglycolicacid) (PGAGA) hydrogel matrices for the controlled delivery of a model chemotherapeutic drug, 5-FU. The natural polymer-based pH sensitive PGAGA hydrogel matrices were synthesized and characterized by using FTIR, DSC, SEM and swelling properties to understand the water diffusion properties of the gels. Finally, the fabricated hydrogel matrices were tested for drug release studies to understand the release kinetics. Furthermore, the release data were fitted with different semi-empirical and empirical mathematical models such as Korsemeyer-Peppas, first-order, and Higuchi equations.

EXPERIMENTAL

Materials

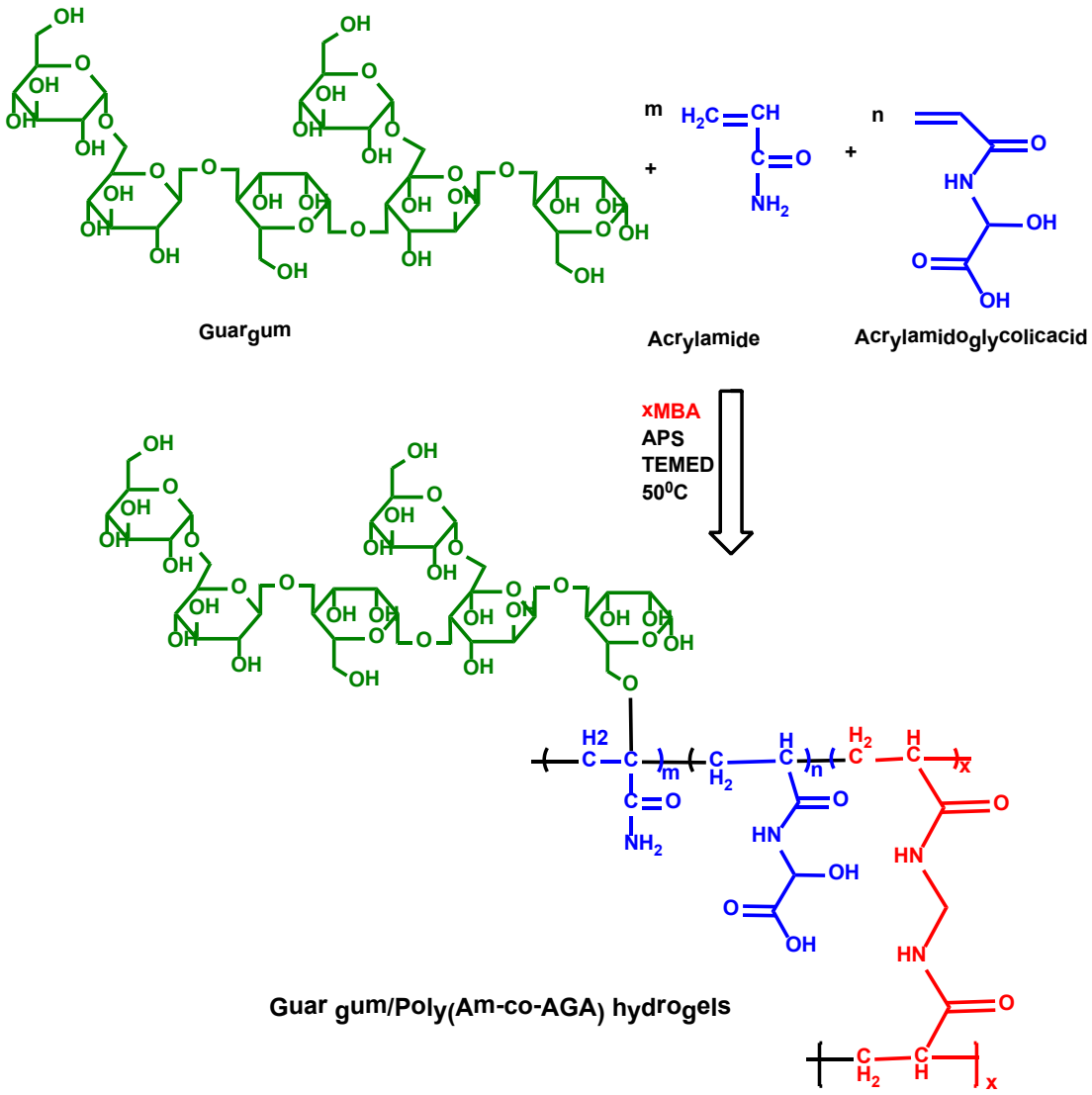
Analytical reagent grade samples of acrylamide (Am), N,N,N',N'-tetramethylethylenediamine (TEMED), guar gum (GG), N,N-methylenebisacrylamide (MBA) and potassium persulphate (KPS), were purchased from sd fine chemicals Mumbai, India. Acrylamidoglycolic acid (AGA) and 5-fluorouracil (5-FU) drug were purchased from Aldrich Chemicals, USA. All other reagents were used as received with the analytical grade. All the experiments were performed using double distilled (DD) water.

Synthesis of PGAGA hydrogel matrices.

PGAGA hydrogel matrices were synthesized by redox polymerization method. A known quantity of monomers was dissolved in 2 mL of distilled water, to this solution 1.0 mL of crosslinking agent (MBA, 2 wt% aqueous solution), 1.0 mL of KPS solution (5 wt% aqueous solution), and 2.0 ml of 2 wt% GG solution. The free-radical cross-linking polymerization was initiated with TEMED (50 µL of 25% solution) in a 50 mL beaker maintained at a 50°C temperature in order to complete the polymerization reaction. Reaction mechanism of synthesis of hydrogel matrix has given in Scheme 1**.** The synthesized PGAGA hydrogel matrices were taken out from the beakers and immersed in distilled water for 48 h by changing the double distilled water every 12 h in such a way to avoid the presence of the unreacted species. The resulting PGAGA hydrogel matrices were dried in air for 4 days and then in a vacuum oven until to attain constant weight at 35°C. The PGAGA hydrogel matrices were formulated by various amounts of monomers and crosslinking agent as shown in Table 1. The Digital Photographs of hydrogels in dry and swollen state are presented in Figure 1.

Table 1. Formulation compositions, % encapsulation efficiency (% EC) and kinetic parameters of PGAGA hydrogels.

Sample	GG (ml) 4%	Am (gm)	AGA (gm)	MBA (ml) 2%	% EC	n	k	r2
PGAGA-A	2	1	0.50	1	69 ± 2.1	1.02	5.75	0.9497
PGAGA-B	2	1	0.25	1	63 ± 0.9	1.12	12.51	0.9620
PGAGA-C	2	1	0.00	1	57 ± 1.2	1.28	49.14	0.9922
PGAGA-D	2	1	0.50	2	66 ± 1.6	1.42	72.58	0.9404
PGAGA-E	2	1	0.50	3	61 ± 1.7	1.37	64.08	0.9652



Scheme 1: Schematic representation of PGAGA hydrogels

Swelling studies

The degree of swelling could be described as water absorptive of the hydrogel matrices. The pre-weighted PGAGA hydrogel matrices were placed in 100 ml beakers and added 50 mL of DD water and allowed the same for about 48 hrs at room temperature to attain the equilibrium state of swelling. Finally, the hydrogel matrices were taken out and surplus surface water of the swollen gel was removed and wiped with a filter paper, and immediately weighed. The percentage of water uptake can be calculated by following eq. (1):

$$\text{Swelling ratio (\%)} = (W_s - W_d)/W_d \times 100, \quad (1)$$

where W_s and W_d are the weight of the swollen PGAGA gel and the weight of dried PGAGA gel, respectively

Swelling nature of macromolecular hydrogels in pH media is of great importance since a small change in pH of swelling media results in fluctuation of free volumes of polymer matrix penetrated water molecules. Hence, it significantly affects the swelling properties of the hydrogel matrix. In the present work, equilibrium swelling behavior of PGAGA cross-linked hydrogel matrices was studied in various pH solutions (pH 2-10) at 25°C. Figure 5 illustrates the swelling behavior of different composition of PGAGA hydrogel matrices at various pH swelling of hydrogel matrices was found to increase with pH for all compositions of PGAGA hydrogel matrices, and the maximum amount of it was at pH = 10.

Encapsulation efficiency of PGAGA hydrogel matrices

5-FU was loaded into hydrogel matrices using an equilibrium swelling method. The PGAGA hydrogel matrices immersed in aqueous solution of 5-FU for 24 h at room temperature. As per the literature the solubility of 5-FU is13 mg/ml in water, but in basic media (NaOH) it increases to 65 mg/ml (Garcia *et al.*, 1994). Hence, to improve the efficiency of 5-FU loading into the PGAGA hydrogel matrices, encapsulation study of 5-FU was performed in aqueous NaOH solution. In order to load the maximum amount of drug into the natural polymer-based

hydrogel matrix, the disks of gel were immersed in an aqueous solution of 5-FU, which was alkalined with NaOH. During this process, the drug present in the aqueous medium will be absorbed into the hydrogel matrices. The 5-FU encapsulated hydrogel matrix (10 mg) was placed in 20 ml of distilled water and allowed for 48 h under vigorous stirring to extract the 5-FU form the hydrogel matrix. The extracted 5-FU solution was analyzed with UV-Vis spectrophotometer (LABINDIA, Model: UV-3092) at λ_{max} 271 nm. The % 5-FU loading and encapsulation efficiency of hydrogel matrices were calculated using eqs. (2) and (3), respectively. These data are compiled in Table 1.

$$\%\,5\text{-}FU\ \text{loading} = \left(\frac{\text{Amount of drug in the PGAGA hydrogel}}{\text{Amount of PGAGA hydrogel}}\right)\times 100 \quad (2)$$

$$\%\,5\text{-}FU\ \text{loading} = \left(\frac{\text{Amount of drug in the PGAGA hydrogel}}{\text{Amount of PGAGA hydrogel}}\right)\times 100 \quad (3)$$

In vitro release study

In vitro release performance of PGAGA hydrogel matrices were evaluated at 37°C under 100 rpm speed by using tablet dissolution system (LABINDIA DS 8000) equipped with eight baskets. The release data were analyzed by the graph plotting between cumulative release (M_t/M_∞) and time. Drug release from PGAGA hydrogel matrices was studied in pH 7.4 and 1.2. Aliquot samples were withdrawn at regular time intervals and analyzed at λ_{max} 271 nm by UV-Vis spectrophotometer.

Characterization

Differential scanning calorimetric analysis

Differential scanning calorimetry (DSC) curves were recorded on a Rheometric scientific differential (Model-DSC SP, UK.) The instrument was calibrated using indium as the standard. Samples were heated in sealed aluminum pans between 30-400°C at the heating rate of 10°C/min under inert nitrogen purge gas at the rate of 20 ml/min.

Scanning electron microscopy (SEM)

SEM is one of the most important studies that can help for a better understanding of hydrogel microstructure morphologies. Surface morphology of the PGAGA hydrogel matrix was recorded using a scanning electron microscope (MERA\\TESCAN).

RESULTS AND DISCUSSION

FTIR studies

A series of FTIR spectra pristine PGAGA hydrogels, drug-loaded hydrogels (5-FU) and pure drug (5-FU) were presented in Figure 2. For plain PGAGA gels, the general absorption band at 3383 cm^{-1} and 2925 cm^{-1} due to O-H stretching vibrations of the polymer associated with C-H stretching vibrations along with the characteristic vibration bands observed at 1731 and 1655 cm^{-1}, indicates C=O stretching vibration of the carboxylic acid group and C=O stretching vibration of the amide group. Additional information from the characteristic absorption bands of PGAGA appears at 1401 cm^{-1} and 1025 cm^{-1} due to C-H bending and O-H bending vibrations. Pure 5-FU is showing characteristic peaks at 1246 cm^{-1} and 805 cm^{-1} which, are due to C-F stretching and bending vibrations, respectively. Same characteristic peaks of 5-FU are newly found in the drug-loaded PGAGA gels with a small change in frequency (1248, 815 cm^{-1}) along with the regular peaks that are present in the pure PGAGA gels conforms the entrapment of 5-FU into the gels by means of physical interactions.

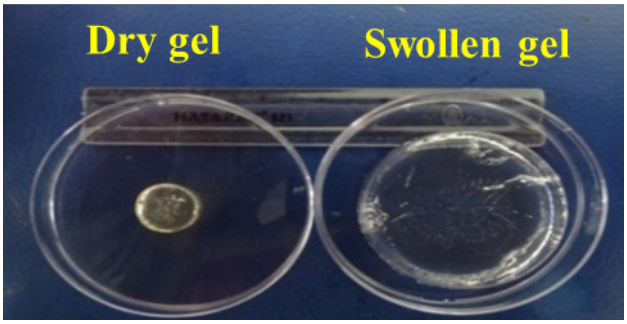


Fig. 1: Digital photograph of PGAGA hydrogel at dry and swollen state.

DSC analysis

Differential scanning calorimetric studies were performed to conform the entrapment drug into the natural polymer-based hydrogel matrix by comparing the thermal properties of plain PGAGA gels, pain drug and drug-loaded PGAGA gels, whose thermograms were presented in Figure 3. The DSC curve of plain PGAGA gels displays two peaks in thermograms, out which the first one is endothermic at 180°C and the second one is at 230°C with exothermic in nature, (which attribute water retention involving −COOH group and −OH group of natural polymer-based hydrogel matrix) while the pure drug (5-FU) exhibits single characteristic endothermic peak at 290°C. The drug-loaded gels display two exothermic peaks at 180°C, 310°C and one endothermic peak at 230°C. by comparing thermograms of pure PGAGA gels and drug-loaded PGAGA gels we can observe that the endothermic peak at 180°C becomes exothermic in drug-loaded gels similarly, the exothermic peak at 230°C becomes endothermic in drug-loaded gels. This contrast thermal behavior of drug-loaded hydrogel matrices may be due to the interaction of entrapped drug and functional groups that are present in the hydrogel matrix.

SEM

SEM image of hydrogel was taken at 6 KX magnification was presented in Figure 4. As shown in the figure, the formed hydrogels are with the rough surface. The intermolecular association and cross-linking reaction involved between the polymer chains of the hydrogels led to the formation of a three-dimensional hydrogel matrix is responsible for the surface and internal morphology of the PGAGA gels.

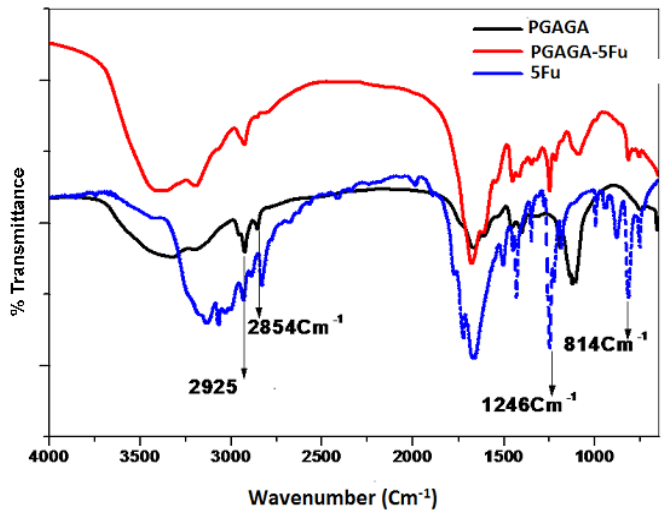


Fig. 2: FTIR spectra of the pristine PGAGA hydrogels, 5-Fu loaded PGAGA hydrogels and 5-Fu drug.

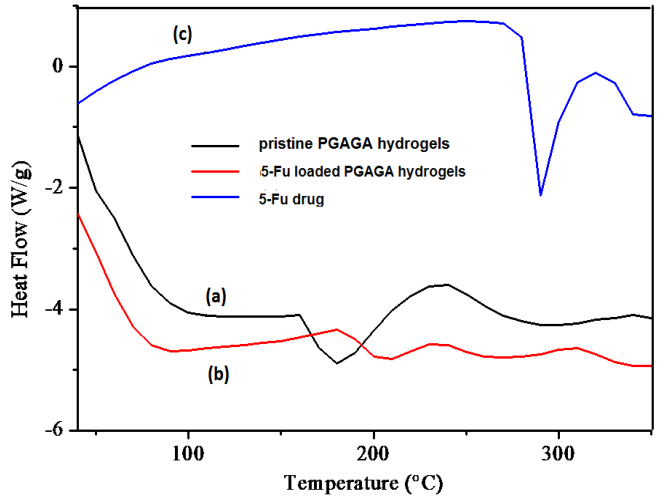


Fig. 3: DSC thermograms of the pristine PGAGA hydrogels, 5-Fu loaded PGAGA hydrogels and 5-Fu drug.

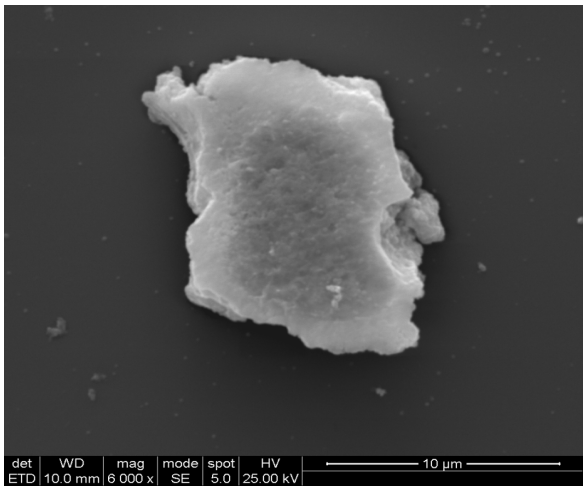


Fig. 4: SEM of the pristine PGAGA hydrogels.

Swelling characteristics

Swelling dynamics data of PGAGA hydrogels were displayed in Figure 5. Figure 5 shows that the maximum water uptake was obtained at 95 hrs, the equilibrium-swelling ratio of all the formulations also shown in Table 1. The % of equilibrium swelling ratios of PGAGA hydrogels were 1290, 1024, 935, 898, and 837 in DD water for the formulations A to E, and it can be observed that the equilibrium-swelling ratio is maximum for formulation A and minimum for formulation E. From the above observation, we can say that the water uptake capacity of PGAGA hydrogel depends on both AGA and MBA. Here as we increase the AGA amount, increases the equilibrium swelling ratio, however when we increase the crosslinking agent the same will be decreased. Increasing swelling ratio with the increase of AGA may be due to increase in the hydrophilic character of semi-IPN hydrogels as an increase in the hydroxyl and carboxylic acid groups.

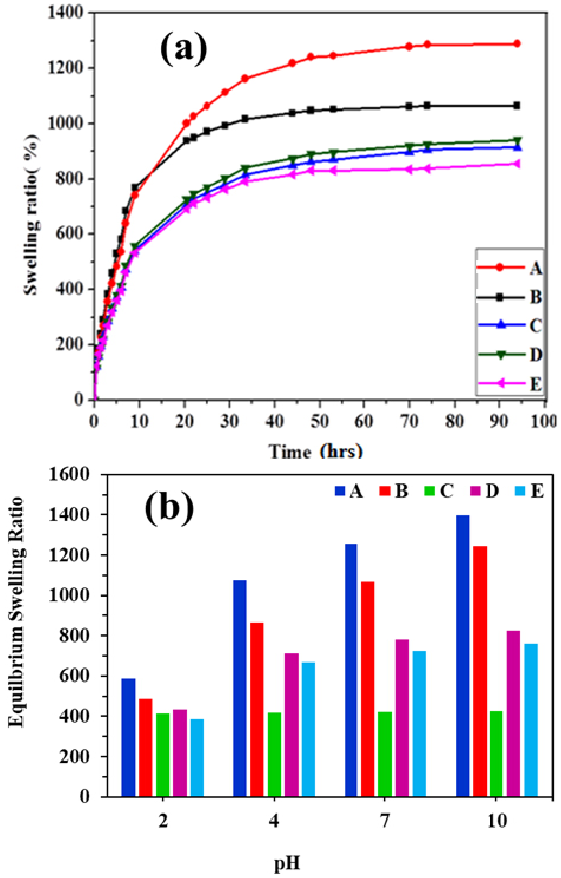


Fig. 5: (a) % Swelling ratio, (b) % equilibrium swelling ratio of PGAGA hydrogels at various pH (2, 4, 7, 10) solutions.

The effect of pH on the Equilibrium swelling was evaluated by measuring the water uptake of the gels at different pH (2-10) solutions, and the data was presented in Figure 5. Here as pH of the medium raised from 2 to 10, the equilibrium swelling of hydrogels was also increased due to interelectronic repulsions between the COO^- ions produced in the network by the dissociation of −COOH group (Pulat *et al.*, 2006). The trend

of equilibrium swelling ratio of different formulations represents the amounts of AGA monomer and cross-linking ratio in the hydrogels.

Encapsulation efficiency and *in vitro* drug release kinetics

Table 1 shows the encapsulation efficiencies of various formulations of the PGAGA hydrogels. The percentage of encapsulation efficiency (% EE) ranged between 57 ± 1.2 to 69 ± 2.1 for different formulations, which is dependent on the composition of the formulation, and the extent of degree of crosslinking. The formulations PGAGA-A, PGAGA-B and PGAGA-C, by the increase the amount of AGA present in the formulation, increased the % EE of 5-FU (57 ± 0.9, 63 ± 1.2 and 69 ± 2.1) due to the increase in the equilibrium swelling of the respective gels. However, as the cross-linking density of the formulations increased (2% MBA volume 1 mL to 3 mL) for the formulations PGAGA-C, PGAGA-D and PGAGA-E, decreased the EE% (69 ± 2.1, 66 ± 1.6, 61 ± 1.7). This trend of EE% will be attributed to the cross-linking density of the hydrogel matrix, as higher the amounts of cross-linking agent greatly influences the swelling ratio of the gels by forming rigid hydrogel matrix, consequently, the encapsulation of drug molecules occurs to a smaller amount.

Finally, the 5-FU loaded PGAGA hydrogels were tested for drug release efficacy of different formulations made. The *in vitro* drug release experiments were studied in phosphate buffer media (pH 1.2 and 7.4) at both 37 ºC. The 5-FU release profiles of PGAGA hydrogels were shown in Figure 6. The release behavior of 5-FU was systematically increased with increasing AGA content in the hydrogel feed ratio, however, for BPEM a cross-linker, 5-FU release is decreased with the amount of BPEM in feed ratio. The influence of pH on the controlled release of 5-FU was studied for the fabricated PGAGA-1 hydrogel.

As the pH of the medium increases, the swelling of hydrogels also increased due to the ionization of −COOH groups. At a completely ionized condition, the polymer chains of gel experiences maximum repulsions. So the gels show the highest swelling. At this condition, large pores of the gels facilitate the diffusion of 5-FU drug easily, so increases the drug release whereas at lower pH smaller pore size of the network disfavor the release. Similarly, as an increase in the cross-linker amount, decreased the pore size of the network finally slower release rate of 5-FU can be obtained. In case of the effect of AGA monomer on the drug release, as an increase in AGA monomer increases the carboxylate functional groups which are responsible for higher swelling of PGAGA hydrogels.

Numerous mathematical models used to describe the discharge of drug molecules from the developed PGAGA formulations. The most important aspect in developing new pharmaceutical products or evaluating drug release mechanisms gives suitable predictability and accuracy of the model. In many cases, the use of simple empirical or semi-empirical models such as classical Higuchi equation and the so-called power law is just sufficient, in which drug release kinetics was analysed by plotting the cumulative release data, (M_t/M_∞) versus time by fitting the data to a simple exponential equation (Ritger *et al.*, 1987; Siepmann *et al.*, 2001).

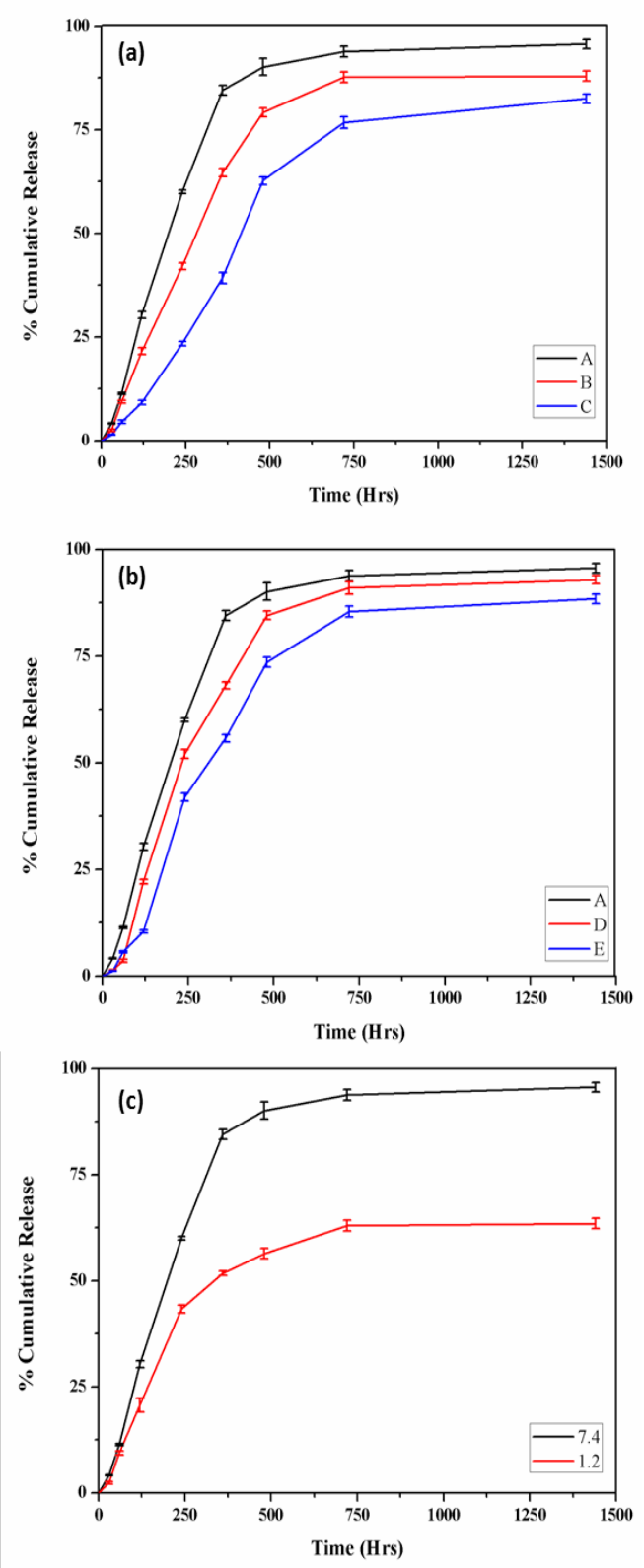


Fig. 6: Cumulative release of 5-Fluorouracil from of poly (Am-co-AGA)/GG hydrogels (a) effect of monomer (b) effect of cross-linker at pH = 7.4 and (c) effect pH on the drug release for formulation A.

$$\frac{M_t}{M_\infty} = kt^n \quad (4)$$

"where M_t corresponds to the amount of drug released in time t, M_∞ is the total amount of drug that must be released at infinite time, k is a constant and n is the release exponent indicating the type of drug release mechanism" (Ritger *et al.*, 1987; Siepmann *et al.*, 2001). For example, if n equals to 0.49, this situation is said to be the case I or Fickian diffusion, which is characterized by a dependence on the square root of time in both the amount diffused and the penetrating diffusion front position. Whereas n equals 0.89, this condition is described as case II transport. In general case II type transport completely obey the relaxation rate of polymer chains, and it exhibits a linear time dependence in both the amount diffused and penetrating swelling front position. However, $0.49 \leq n < 0.89$, this condition can be described as for anomalous behavior or non-Fickian transport, which is exhibited whenever the rates of Fickian diffusion and polymer relaxation are comparable (Ritger *et al.*, 1987; Siepmann *et al.*, 2001).

CONCLUSION

The polysaccharide-based controlled drug release studies are comparatively easy due to the presence of various derivatizable groups, a wide range of molecular weights, varying chemical compositions, low toxicity, and high stability. The selection of a proper polysaccharide is a crucial parameter in the construction of 5-FU delivery system. pH-responsive PGAGA hydrogel matrices having different compositions of monomer AGA and crosslinker MBA were fabricated by free-radical polymerization. The produced hydrogel matrices were characterized with the parameters like equilibrium swelling, FTIR, and DSC. It was seen that the swelling and 5-FU release of the PGAGA gel matrices were increased with the increase of AGA amount, but declined with the crosslinker amount present in the formulations. As the PGAGA hydrogel matrices contained ionizable functional groups, their swelling behavior was significantly dependent on pH. Subsequently, the anionic hydrogel matrices behave in a typical pH-sensitive swelling, i.e., at low pH, the lower swelling ratios leads to the slow release of 5-FU and at higher pH, the high swelling ratios leads to faster rate of 5-FU release.

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