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VISCOELASTIC, SWELLING KINETIC AND DRUG RELEASE CHARACTERIZATION OF POLY (ACRYLIC ACID)-GRAFTED-GELLAN

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ABSTRACT

Lyophilic, viscoelastic, swelling kinetic and drug release characterizations of poly (acrylic acid) –grafted-gellan (PAAc-g-GG) were the main objective of this study. At first, a suitable solvent for PAA-*g*-GG was found out by lyophilicity study followed by viscoelastic study on PAAc-g-GG with different degree of grafting. The study showed that the degree of grafting greatly influences the viscoelastic nature of copolymer, which further governs the drug release pattern from the polymer matrix. The copolymer with highest grafting showed much higher starting % strain (17.73%), stress (53.3 Pa) for structural breakdown at $G' = G''$ (213.5 Pa), higher storage modulus (G'), much higher values of complex viscosity (11.46 Pa.s) and cross-over point ($G' = G''$ =271.86 Pa) compared to that of low-grafted copolymer. In 0.1N HCl, swelling index ($\%W_E$) is found to be directly proportional to percentage grafting (%G) and batches with higher grafting exhibited lowest initial swelling rate demonstrating its inversely proportional relation to %G. Equilibrium swelling and hydration are also found to be proportional to %G. The same effect has been observed in PBS with exception that the magnitude of the parameters obtained in PBS is very much higher compared to that in 0.1N HCl. The copolymer showed sustained drug release over 10 hours period and the study revealed Case-1 Fickian diffusion or square root of time kinetic based release mechanism. The study reveales that viscoelastic and swelling study might be useful to understand how the degree of grafting governs the drug release.

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INTRODUCTION

Exploration of suitable pharmaceutical excipients preferably sustained release drug carriers from natural sources and their exploitation to make them smart tailormade drug carriers have been recent trend in drug-delivery-excipient science [1]. Natural polysaccharides such as gum acacia, gum tragacanth, xanthan gum, sodium alginate, locust bean gum, guar gum, gellan gum, etc. have been used in different types of dosage forms and even in oral controlled release formulations as release modulator due to their potential as well as certain advantages such as low cost, easy availability, biodegradability and biocompatibility [2]. Chemical modifications of these natural polysaccharides have been considered in order to overcome their certain inherent drawbacks such as uncontrolled hydration kinetic, premature enzymatic degradation and matrix erosion, change in rheological behavior due to aging, etc. [3]. Various approaches for chemical modification include carboxymethylation, cyanoethylation, graft-copolymerization, crosslinking, etc. [4]. Graft-copolymerization especially free radical initiation method became popular because of its simplicity [5]. In our previous attempt, synthesis and characterization of a graft-copolymer of acrylic acid onto gellan gum has been reported, in which various characterization such as FTIR, elemental analysis, solid state ^{13}C NMR, DSC-TGA, acute oral toxicity study and ex-vivo mucoadhesion were done [6].

Graft copolymerization mainly imparts steric bulkiness incorporating numerous branches to the main polymeric backbone. When the drug loaded matrix composed of this copolymer is placed in gastrointestinal fluid, uptake water and a three dimensional gel matrix is formed. The polymeric gel has a viscoelastic property which plays an important role in drug release process through this gel network. Furthermore, viscoelastic nature of a gel matrix having 3-D polymeric network is a function of its microstructure that also governs the drug release from the matrix [7]. On the other hand the water uptake (swelling) kinetic also influences the viscoelastic behavior as well as drug release rate [1].

The main objective of this work was to carry out some additional characterizations of the developed copolymer such as viscoelastic nature and swelling kinetic behavior along with drug release in both 0.1N HCl and phosphate buffer solution (PBS, pH 6.8). In the present study, viscoelastic and swelling kinetic behavior of different synthetic batches of PAAc-g-GG were performed. Finally, sustained release monolithic matrix tablets of a water soluble drug ranitidine hydrochloride were prepared using different synthetic batches of the copolymer and *in vitro* drug release study was performed.

MATERIALS AND METHODS

Materials

Gellan gum was procured from HiMedia Laboratories Private Limited, Mumbai, India. Ceric Ammonium Nitrate was bought from Qualigens Fine chemicals, Mumbai, India. Ranitidine hydrochloride (99.31% purity) was obtained as gift sample from La Chemico, Kolkata, India. Acrylic acid and Polyvinylpyrrolidone K-30 were purchased from Merck India Pvt. Ltd., Mumbai, India. All other chemicals and reagents used were of laboratory reagent grade and used as received. In all experiment triple-distilled water was used.

Synthesis of PAAc-g-GG

The products obtained from the synthesis of copolymer PAAc-g-GG reported earlier [6] were used in all the experiments throughout the study. Different grafting parameters of the grafted copolymer were presented in Table 1 which has been published elsewhere [6].

Table 1: Different grafting parameters of poly (acrylic acid) grafted gellan.

Batch No.	%G	%GE	%C	Viscosity (cP) @ 1.0 rpm
GG	-	-	-	535.2
MS1	532.2	50.71	60.24	1065.4
MS2	626.3	59.70	69.23	1072.2
MS3	173.0	16.49	26.02	877.5
MS4	164.3	15.66	25.19	889.3
MS5	270.9	51.64	70.71	945.8
MS6	257.4	49.07	68.14	941.1
MS7	149.6	28.52	47.58	903.9
MS8	156.5	29.83	48.90	911.4

GG, gellan; %G, % grafting; %GE, % grafting efficiency; %C, % conversion.
(from reference [6])

Characterization of PAAc-g-GG

Lyophilicity study

100 mg of PAAc-g-GG (MS2) was added to 10 ml of distilled water, 0.1 N HCl, Phosphate buffer solution (PBS) of pH 6.8, 7.4, 8.0, NaOH solution (0.05M, 0.1M, 0.2M, 0.3M, 0.4M, 0.5M), DMSO, acetone, ethanol and methanol separately, magnetically stirred over 24 hours at 30^{0}C and observed visually.

Viscoelastic study

The PAAc-g-GG copolymer is found to form a hydrogel in 0.1M NaOH. The rheological behavior especially viscoelastic nature which is a function of microstructure of the hydrogel, macromolecular bulkiness and conformation, that greatly influence the pattern of drug release from the copolymer matrix. Viscoelastic properties are measured mainly by dynamic mechanical tests which evaluate small periodic deformations, structural breakdown or rearrangement [7]. The dynamic mechanical "strain sweep" test analyses the microstructural properties of the hydrogel under increased strain. It measures the storage modulus, G', which indicates elastic manners and express the ability of the polymer system to accumulate elastic energy related to recoverable elastic deformation. The loss modulus, G'', is an indicator of the dynamic viscous behavior that is related to the dissipation of energy associated with unrecoverable viscous loss. Viscoelastic study was done on 1%, w/v, aqueous gel (solvent: 0.1M NaOH) prepared with MS2 and MS7 batch using Rheometer, Anton Paar, Austria. Storage modulus (G'), loss modulus (G''), and τ (shear stress) were measured at different levels of % strain (γ) and angular frequency, separately, and plotted. In strain-sweep, angular frequency was kept constant at 10 rad/s.

Swelling-kinetic study

A dry sheet (1cm×1cm×1mm) of each batch (MS1 to MS8) of PAAc-g-GG was weighed and placed in wire basket and immersed in 200 ml 0.1N HCl (pH 1.2) at 37^{o}C for 24 h. The basket was removed from the solution at the end of the period and weighed after removing the surface water with tissue paper in an electronic balance (Electronic Balance, model TP313, Denver Instrument, India). Equilibrium water uptake by PAAc-g-GG was calculated from the following relationship:

$$W_E = \frac{(w_1 - w_0) \times 100}{w_0} \qquad (1)$$

Where, W_E is the equilibrium water uptake (%), w_0 is the dry weight of sheet plus basket and w_1 is the weight of sheet plus basket after removal from the solution.

The swelling-kinetic of PAAc-g-GG was studied by measuring the increment in weight of sheet after immersion in 0.1N HCl (pH 1.2) as a function of time, t [8]. A plot of the weight, W, in grams of the water absorbed per gram of the dry sheet of PAAc-g-GG against time, t in minutes, gives the swelling isotherm. The horizontal portion of the isotherm corresponds to equilibrium swelling. To obtain a linear expression, t/W is plotted against t according to the Eq.2:

$$\frac{t}{W} = A + Bt \qquad (2)$$

Rearranging and differentiate the Eq.5, the following expression (Eq. 3) can be obtained:

$$\frac{dW}{dt} = \frac{A}{(A+Bt)^2} \qquad (3)$$

as $t \rightarrow 0$, the above equation gives the *initial swelling rate*, $dW/dt = 1/A$, which is the reciprocal of the intercept of t/W versus t plot. The reciprocal of the slope, $1/B = W_\infty$ is the equilibrium swelling which also indicates the theoretical maximum uptake of buffer solution at t_∞. The *Matrix Hydration*, H, is calculated using the following formula (Eq.4):

$$H = \frac{(w_s - w_0)}{w_s} \qquad (4)$$

Where, w_s, is the weight of swollen gel at equilibrium and w_0 is the weight of xerogel. This study is repeated with PBS (pH 6.8).

Preparation of extended release monolithic matrix tablet of ranitidine HCl

Extended release ranitidine hydrochloride loaded tablet based on PAAc-g-GG were prepared employing wet granulation method. For this purpose, five synthetic batches of PAAc-g-GG copolymer were selected. A batch of 100 tablets (each containing 300 mg ranitidine HCl, 300 mg gellan / PAAc-g-GG copolymer and 50 mg polyvinyl pyrrolidone K30) was prepared in every formulation at a time. At first, gellan gum or grafted copolymer and drug were mixed intimately in a pestle-morter and it was then moistened with minimum amount of hot water (50^{o}C) containing polyvinyl pyrrolidone K30. The granules obtained by passing the moistened mass through sieve no #18, were dried at 60^{o}C for 20 mins and passed through # 18 mesh. The granules were lubricated with purified talc (6 mg / tablet) and magnesium stearate (6 mg/tablet) and compressed in a rotary tablet machine with 10 mm single punch diameter (Labpress, 10 stations, Remi, Mumbai, India). Hardness was within the range of 4.5 – 5.5 kg/m^2.

Evaluation of tablet

Weight variation, content uniformity, hardness, diameter, thickness, % friability and disintegration tests were done as per Indian Pharmacopoeia, 2007.

In vitro dissolution test and drug release kinetic

In vitro dissolution test was performed using USP dissolution test apparatus type-II (DS-800; 6+2; SC/TR, Lab India, Mumbai, India) in 900 ml 0.1N HCl (pH 1.2) and phosphate buffer solution (pH 6.8) separately maintained at 37^0C with a stirrer rotation speed of 50 rpm. Each time, 5 ml of aliquot from release medium was withdrawn at preset time intervals and replaced with same volume fluid each time. Drug released from the tablet was measured spectrophotometrically (UV-vis double beam spectrophotometer, Pharmaspec-1700, Shimazdu, Japan) at the λ_{max} value at 314 nm. The in vitro drug dissolution data were analysed following various release kinetic mathematical models viz. zero order release kinetic, first order release kinetic, Higuchi release kinetic, Hixson-Crowell kinetic and Korsmeyer-Peppas kinetic models in order to understand the drug release mechanism [9].

Zero order kinetic: $Q_t = K_0 t$ (Q_t is the mass of drug released in time, t, K_0 is zero order release constant) [10].

First order kinetic: $log\ Q_t = log\ Q_0 + K_1 t/2.303$ (Q_0 is the initial quantity of drug in solution) [11].

Higuchi kinetic: $Q_t = K_H t^{1/2}$ [12].

Hixson-Crowell kinetic: $(1-f_t)^{1/3} = 1 - K_\beta t$ (f_t is the fraction of drug released at time, t) [13].

Korsmeyer-Peppas kinetic: $f_t = at^n$ (a is a release rate constant incorporating structural and geometric characteristics of the dosage form, n is the release exponent which indicates the drug release mechanism) [14].

Higuchi kinetic model describes drug release as a diffusion phenomenon based on the Fick's law and square root time dependent. This relation can be used to explain the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some matrix tablets with water soluble drugs [15, 16].

Korsmeyer-Peppas model describes the n value in order to characterize different mechanism of drug release, when n = 0.5, $0.5 < n < 1$, n = 1 and $n > 1$ corresponds to Case-I (Fickian) diffusion or Higuchi kinetic, anomalous (non-Fickian) diffusion, Case-II transport and super Case-II transport respectively [9]. The study was repeated in triplicate for each formulation. Finally, $T_{90\%}$ was calculated from the best fitting kinetic model equation.

RESULT AND DISCUSSION

Lyophilicity study

PAAc-g-GG is not found to show miscibility in distilled water, 0.1N HCl and phosphate buffer solutions (PBS; pH 6.8, 7.4 and 8.0) except higher swelling in PBS compared to that in 0.1N HCl. It may be due to the fact that PAAc-g-GG contains numerous –COOH groups which do not get ionized in acidic media resulting nonaffinity with water. PBS might initiate partial ionization of –COOH groups at surface that results more hydration and subsequent swelling. The copolymer exhibits good miscibility in NaOH solutions showing proportionality to the conc. of NaOH and found to form a smooth gel. It may be due to the formation of Na-salt with –COOH groups of grafted poly (acrylic) chains as well as main backbone of PAAc-g-GG. The probable mechanism is shown in Fig.1. The copolymer exhibits no miscibility in DMSO, acetone, ethanol and methanol. The study reveals pH dependent aqueous solubility of the copolymer.

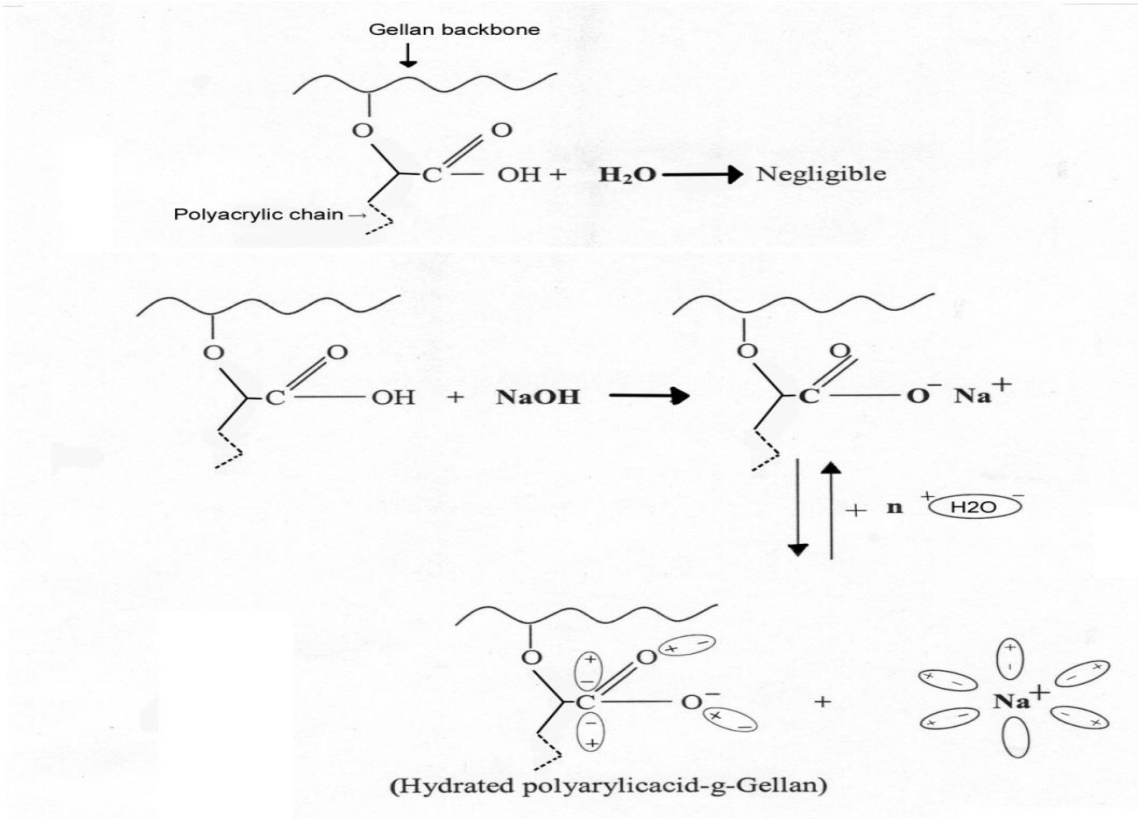


Fig. 1. Proposed hydration behaviour of Paa-g-GG in water and in NaOH solution.

Table 2: Rheological and viscoelastic comparision between batch MS2 and MS7of PAAc-g-GG.

Batch no	Cross over point					
	Strain sweep			Frequency sweep		
	Strain (γ), %	Shear stress (τ), Pa	G' = G" (Pa)	Angular frequency (ω), rad/s	Complex viscosity (η^*), Pa.s	G' = G" (Pa)
MS2	17.73	53.3	213.5	72.56	11.46	271.86
MS7	4.39	0.0025	0.0461	99.62	0.0018	0.077

Viscoelastic study

Different viscoelastic parameters are presented in Table 2. Fig.2 portrays strain sweep curve and frequency sweep curve exhibited by MS2 and MS7 batch. MS2 showed much higher starting % strain (17.73%), stress (53.3 Pa) for structural breakdown at $G' = G''$ (213.5 Pa), which indicates stronger microstructure and high rigidity of the gel matrix attributing to large molecular size of PAAc-g-GG copolymer (MS2: highest % grafting) with high steric bulkiness due to emanating of numerous side chains from different points of main polymeric backbone of gellan. Higher values of storage modulus (G') observed in MS2 compared to that in MS7, indicates stronger thickened property of the gel matrix. This is also substantiated by the much higher values of complex viscosity (11.46 Pa.s) and cross-over point ($G' = G''$ =271.86 Pa) exhibited by MS2 in frequency-sweep [17].

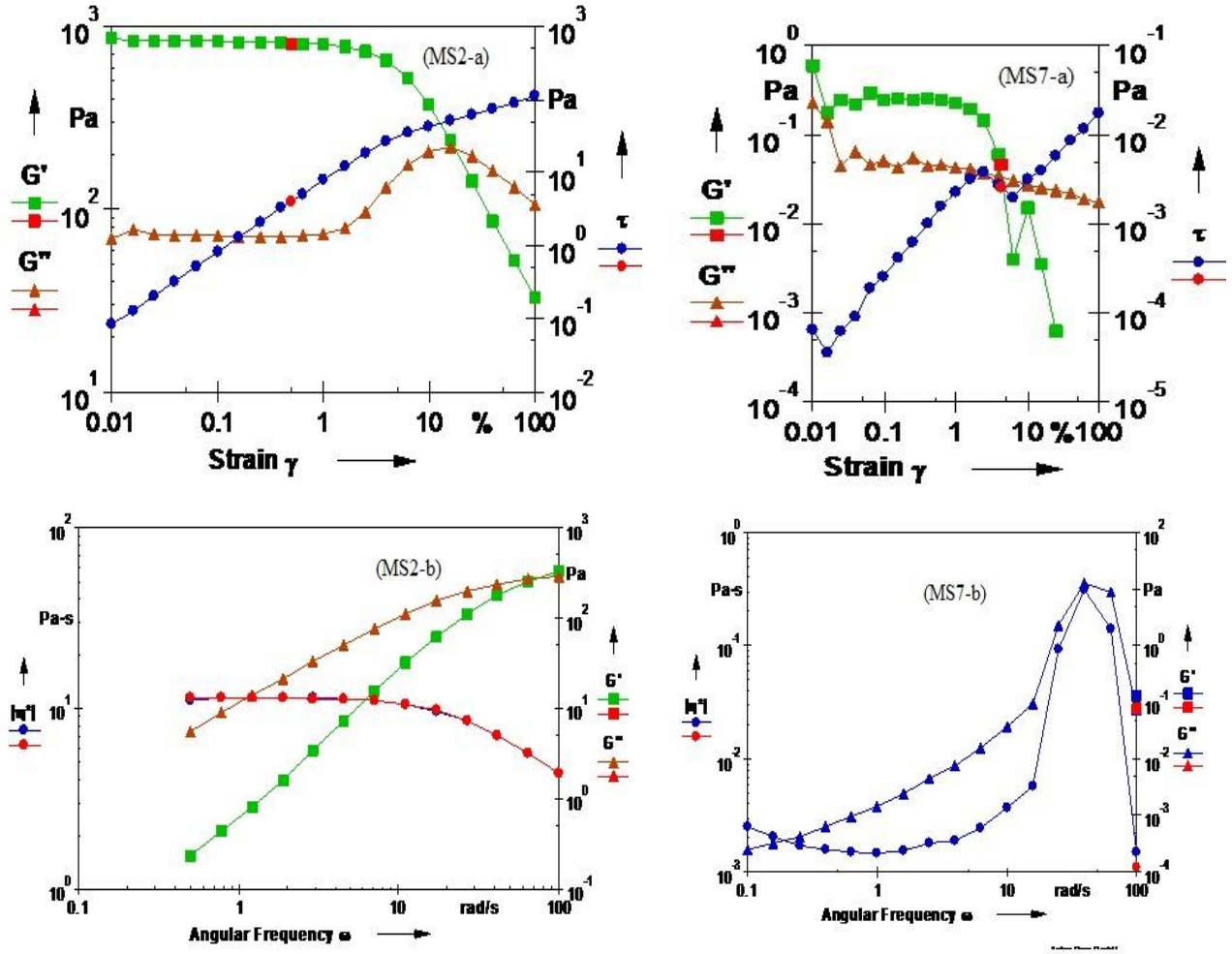


Fig.2. Different rheological parameters against % strain and angular frequency plots exhibited by MS2 and MS7 batches.

Table 3: Swelling parameters shown by different batches of PAAc-g-GG.

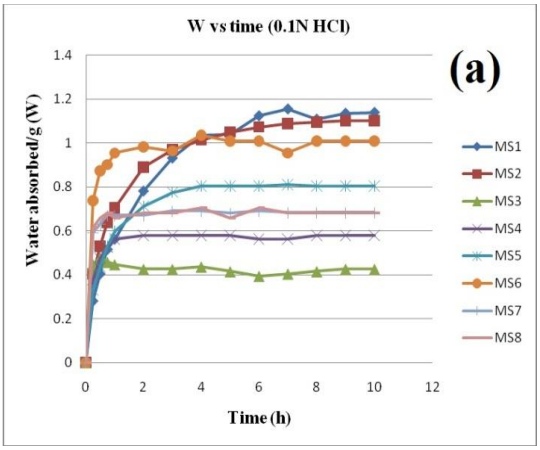
Batch code	0.1 N HCl acid				Phosphate buffer (pH 6.8)			
	Equilibrium water uptake (%) W_E	Initial swelling rate (dW/dt), h^{-1}	Equilibrium swelling (W_α), g/g	Matrix hydration, H, (g/g)	Equilibrium water uptake (%) W_E	Initial swelling rate (dW/dt), h^{-1}	Equilibrium swelling (W_α), g/g	Matrix hydration, H, (g/g)
MS1	132.59	1.19	1.279	0.57	898.28	1.72	14.92	0.89
MS2	139.51	1.96	1.175	0.58	905.75	1.47	12.34	0.90
MS3	54.45	14.28	0.416	0.35	302.88	1.41	6.25	0.75
MS4	57.86	8.00	0.58	0.37	432.65	1.17	4.11	0.81
MS5	87.26	2.35	0.84	0.47	677.55	1.08	8.77	0.87
MS6	85.96	13.69	1.012	0.46	696.11	1.52	7.19	0.87
MS7	54.77	40.00	0.685	0.35	372.02	5.05	3.42	0.79
MS8	89.90	83.33	0.684	0.47	378.0	5.99	3.39	0.79

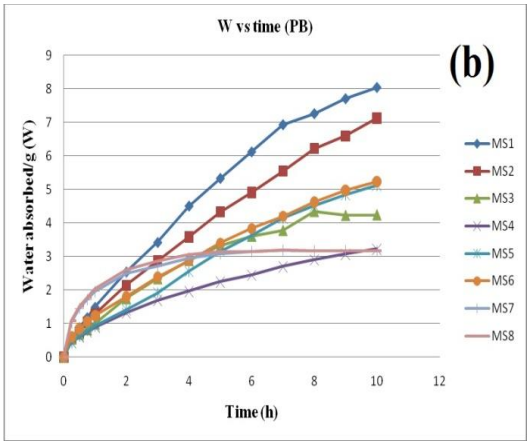
Swelling kinetic

Fig.3 (a) and (b) depicts the kinetic of swelling behavior of different batches of PAAc-g-GG in 0.1N HCl (pH 1.2) and phosphate buffer solution (pH 6.8), respectively. $\%W_E$, initial swelling rate, equilibrium swelling and matrix hydration are presented in Table 3. In 0.1N HCl, $\%W_E$ is found to be directly proportional to %G (Eq. 14). It may be due to physical entrapment of more water by more branched and bulky network matrix of batches like MS1 and MS2 having higher %G. MS1 and MS2 exhibited lowest initial swelling rate, which demonstrates its inversely proportional relation to %G. This may be attributed to the fact that higher grafting introduces large number of –COOH groups in side chains, which initially, due to presence of HCl, prevent entry of water molecules in the copolymer matrix. Equilibrium swelling and hydration are also found to be proportional to %G, which may be due to slow imbibitions of water in the matrix. The same effect has been observed in PBS with exception that the magnitude of the parameters obtained in PBS is very much higher compared to that in 0.1N HCl. It may be due to partial ionization of –COOH groups in PBS, which leads to more hydration. Swelling isotherms (t/W versus t) are shown in Fig.3 (c) and (d). The relation between % Equilibrium water uptake and % grafting in both acidic and alkaline environment were given below.

$$\%W_E \text{ (HCl)} = 0.168(\%G) + 38.87 \ (R^2 = 0.869) \quad (5)$$

$$\%W_E \text{ (PB)} = 1.199(\%G) + 233.5 \ (R^2 = 0.836) \quad (6)$$





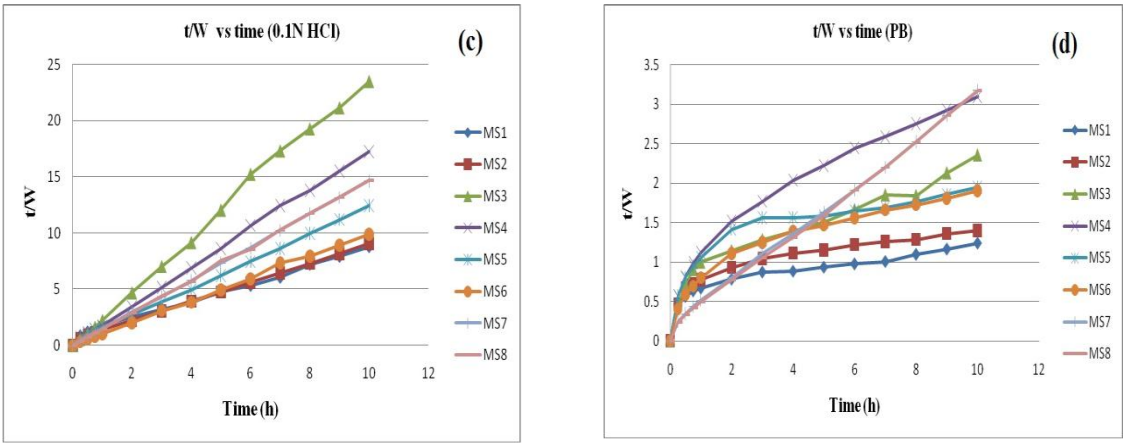


Fig. 3. (a) Swelling isotherm in 0.1N HCl, (b) Swelling isotherm in PBS, (c) t/W vs time in 0.1 N HCl (d) t/W vs time in PBS.

Evaluation of tablets

The tablets were found to pass the weight and content uniformity tests as per Indian Pharmacopoeia, 2007. The hardness shown by the tablets was within the range from 4.5 to 5.5 kg/m^2. Variations in diameter and thickness were within the permissible range. % friability was found to be less than 1% in all batches. The tablets were also found to remain intact in disintegration test and dissolution test.

Table 4: Kinetic modeling of drug release data, release rate constant and $T_{90\%}$ in 0.1N HCl acid.

Batch	R^2 value						Rate constant (K_H)	$T_{90\%}$ (h)
	Zero order	First order	Higuchi kinetic	Hixson-Crowell	Korsemeyer-Peppas			
					R^2	n		
GG	0.734	0.688	0.837	0.876	0.904	0.562	0.789	0.95
MS1	0.970	0.794	0.998	0.996	0.994	0.623	0.264	13.09
MS2	0.972	0.762	0.999	0.996	0.988	0.74	0.257	14.98
MS3	0.948	0.787	0.998	0.993	0.995	0.533	0.306	8.82
MS5	0.947	0.763	0.993	0.987	0.992	0.569	0.289	9.98
MS7	0.947	0.798	0.998	0.988	0.997	0.511	0.308	8.41

Table 5: Kinetic modeling of release data, release rate constant and $T_{90\%}$ in PBS (pH 6.8).

Batch	R^2 value						Rate constant (K_H)	$T_{90\%}$ (h)
	Zero order	First order	Higuchi kinetic	Hixson-Crowell	Korsemeyer-Peppas R^2			
					0.998	n		
MS1	0.947	0.84	0.997	0.833	0.996	0.432	0.316	6.0
MS2	0.955	0.831	0.998	0.848	0.987	0.429	0.314	6.97
MS3	0.933	0.814	0.987	0.931	0.994	0.493	0.46	3.53
MS5	0.945	0.837	0.992	0.907	0.996	0.436	0.391	4.35
MS7	0.959	0.859	0.997	0.891			0.493	3.13

Drug release

The % drug release versus time curves is shown in Fig. 4 (a) and (b). The curves for 0.1N HCl portray that about 97% drug release occurs in the period of less than 1h in case of native gellan whereas sustained release is shown in case of MS_1, MS_2 to a greater extent and in MS3, MS5 and MS_7 to comparatively lesser extent. This may be due to the fact that the tablet-matrix (MS3, MS5 and MS7) is composed of graft-copolymer of gellan having lower degree of grafting, and the faster swelling and advance network relaxation associated with this less-branched polymeric-network are responsible for rapid drug-release. The matrices of MS_1 and MS_2 composed of comparatively denser network result in sustained drug release over a period of 10h due to slower water uptake and network relaxation. The release rate exhibited by the same batches in PBS are found to be faster compared to that in HCl, which may be due to ionization of –COOH groups leading to rapid hydration and subsequent erosion of matrix. The regression coefficients, rate constant (k), diffusion exponent (n) and $T_{90\%}$ are shown in Table 4 and 5. Most of the formulations showed to follow Higuchi and Korsemeyer-Peppas release kinetic.

The diffusion exponent (*n*) values for all the formulations are within the range of 0.511- 0.740 (HCl) and 0.429 – 0.493 (PBS) which indicates Case-1 Fickian diffusion or square root of time kinetic based release mechanism. The lowest values of rate constant (*k*) exhibited by MS_1 and MS_2 confirm their capability to sustain drug release, which is also further established by the higher magnitude of $T_{90\%}$ exhibited by these two formulations. Fig. 5 depicts the changes in rate constant and T90% with the changes in %G. The rate constant and $T_{90\%}$ are shown to be inversely proportional and directly proportional to %G, respectively, that demonstrates the positive effect of %G on sustained-release potential. This is also established by the following equations of the corresponding release parameters versus %G curves.

$$K\times10\ (HCl) = -0.001(\%G) + 3.226\ (R^2 = 0.985) \quad (7)$$
$$K\times10\ (PBS) = -0.003(\%G) + 5.212\ \ (R^2 = 0.915) \quad (8)$$
$$T_{90\%}\ (HCl) = 0.013(\%G) + 6.441\ (R^2 = 0.993) \quad (9)$$
$$T_{90\%}\ (PBS) = 0.007(\%G) + 2.151\ (R^2 = 0.991) \quad (10)$$

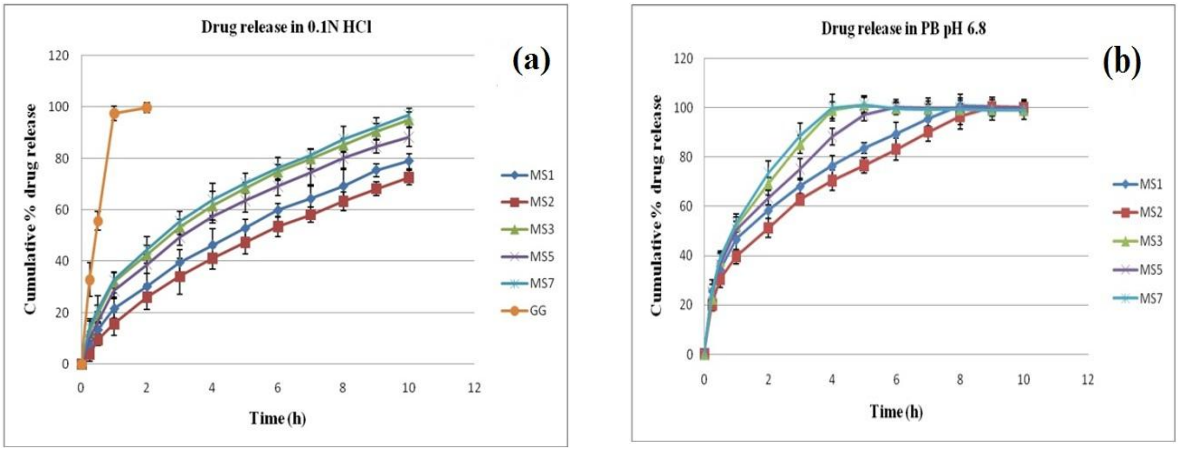


Fig. 4. Zero order drug release curve in 0.1N HCl (a) and phosphate buffer solution (b).

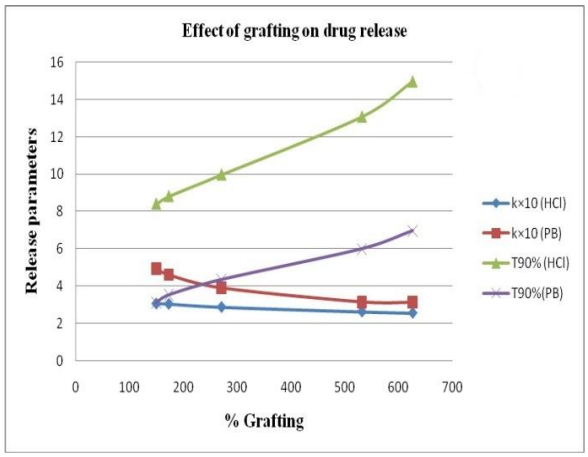


Fig. 5. Effect of % grafting on drug release rate constant and $T_{90\%}$.

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	Equilibrium water uptake (%) W_E	Initial swelling rate (dW/dt), h^{-1}	Equilibrium swelling (W_a), g/g	Matrix hydration, H, (g/g)	Equilibrium water uptake (%) W_E	Initial swelling rate (dW/dt), h^{-1}	Equilibrium swelling (W_a), g/g	Matrix hydration, H, (g/g)
MS1	132.59	1.19	1.279	0.57	898.28	1.72	14.92	0.89
MS2	139.51	1.96	1.175	0.58	905.75	1.47	12.34	0.90
MS3	54.45	14.28	0.416	0.35	302.88	1.41	6.25	0.75
MS4	57.86	8.00	0.58	0.37	432.65	1.17	4.11	0.81
MS5	87.26	2.35	0.84	0.47	677.55	1.08	8.77	0.87
MS6	85.96	13.69	1.012	0.46	696.11	1.52	7.19	0.87
MS7	54.77	40.00	0.685	0.35	372.02	5.05	3.42	0.79
MS8	89.90	83.33	0.684	0.47	378.0	5.99	3.39	0.79

Table 4: Kinetic modeling of drug release data, release rate constant and $T_{90\%}$ in 0.1N HCl acid.

Batch	R^2 value						Rate constant (K_H)	$T_{90\%}$ (h)
	Zero order	First order	Higuchi kinetic	Hixson-Crowell	Korsemeyer-Peppas			
					R^2	n		
GG	0.734	0.688	0.837	0.876	0.904	0.562	0.789	0.95
MS1	0.970	0.794	0.998	0.996	0.994	0.623	0.264	13.09
MS2	0.972	0.762	0.999	0.996	0.988	0.74	0.257	14.98
MS3	0.948	0.787	0.998	0.993	0.995	0.533	0.306	8.82
MS5	0.947	0.763	0.993	0.987	0.992	0.569	0.289	9.98
MS7	0.947	0.798	0.998	0.988	0.997	0.511	0.308	8.41

Table 5: Kinetic modeling of release data, release rate constant and $T_{90\%}$ in PBS (pH 6.8).

Batch	R^2 value						Rate constant (K_H)	$T_{90\%}$ (h)
	Zero order	First order	Higuchi kinetic	Hixson-Crowell	Korsemeyer-Peppas			
					R^2	n		
MS1	0.947	0.84	0.997	0.833	0.998	0.432	0.316	6.0
MS2	0.955	0.831	0.998	0.848	0.996	0.429	0.314	6.97
MS3	0.933	0.814	0.987	0.931	0.987	0.493	0.46	3.53
MS5	0.945	0.837	0.992	0.907	0.994	0.436	0.391	4.35
MS7	0.959	0.859	0.997	0.891	0.996	0.486	0.493	3.13

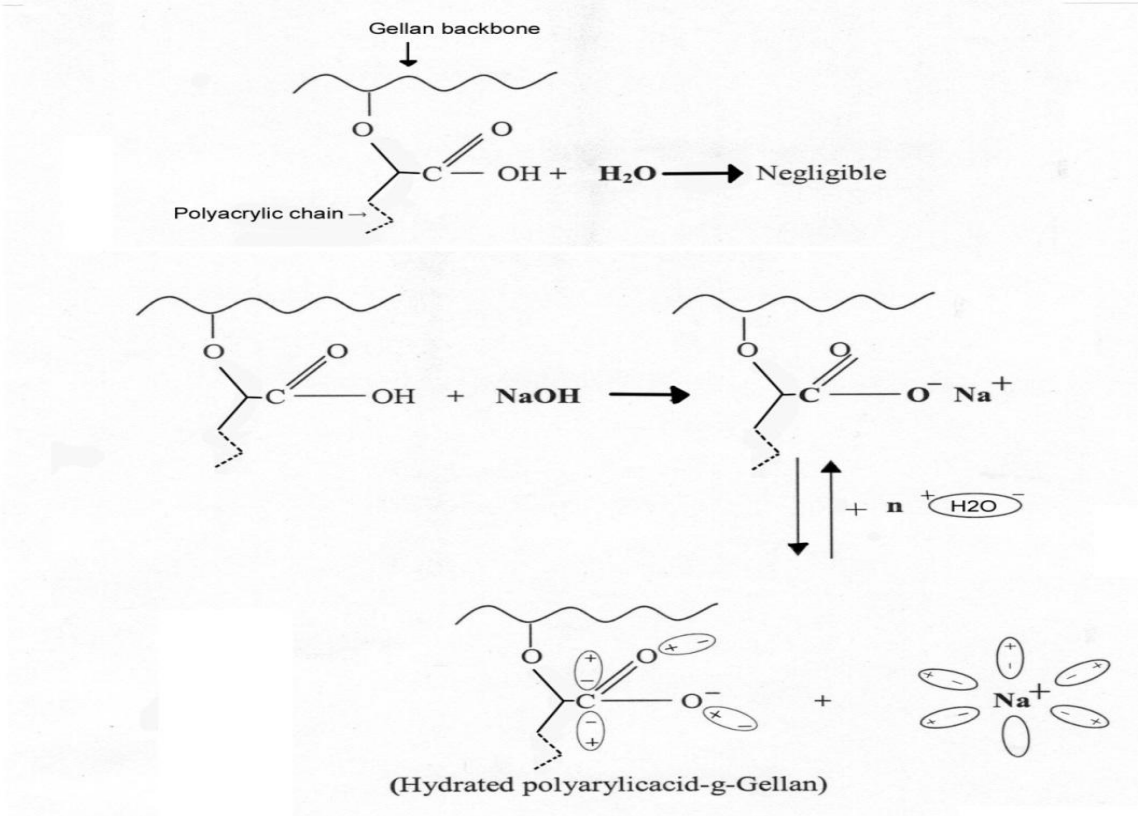
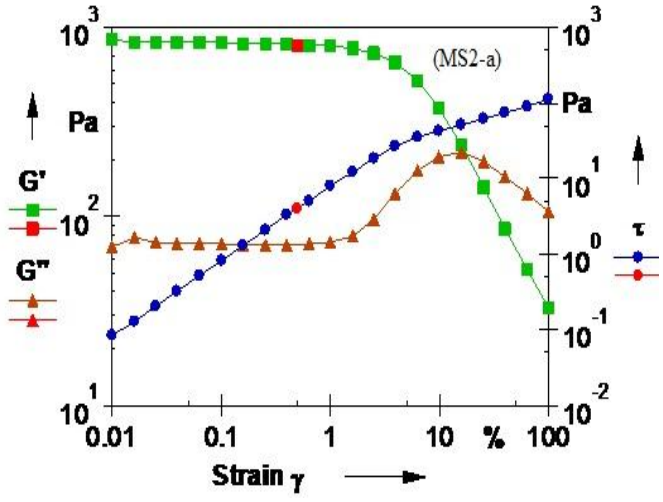
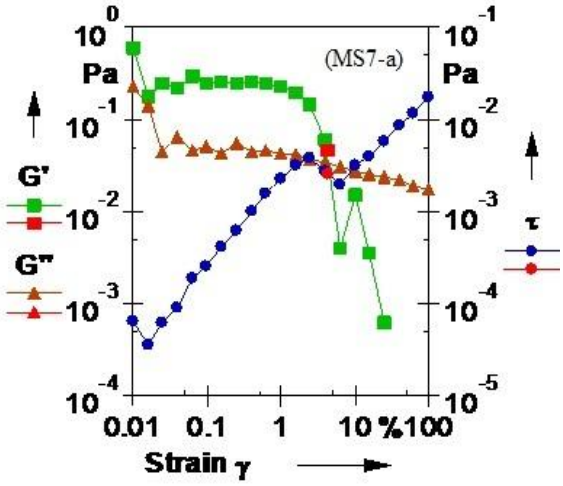


Fig. 1. Proposed hydration behaviour of Paa-g-GG in water and in NaOH solution.





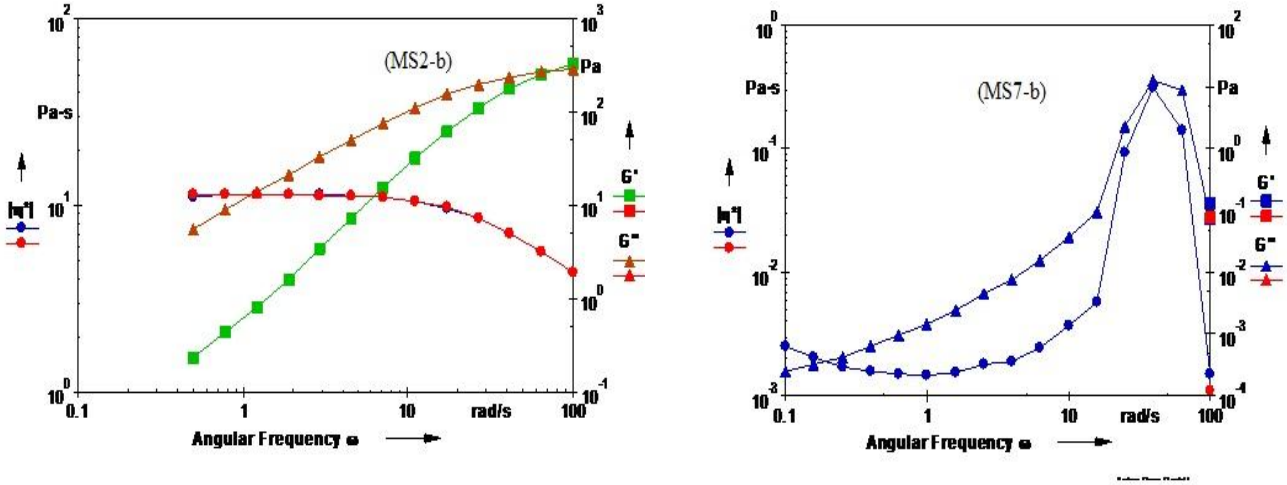


Fig.2. Different rheological parameters against % strain and angular frequency plots exhibited by MS2 and MS7 batches.

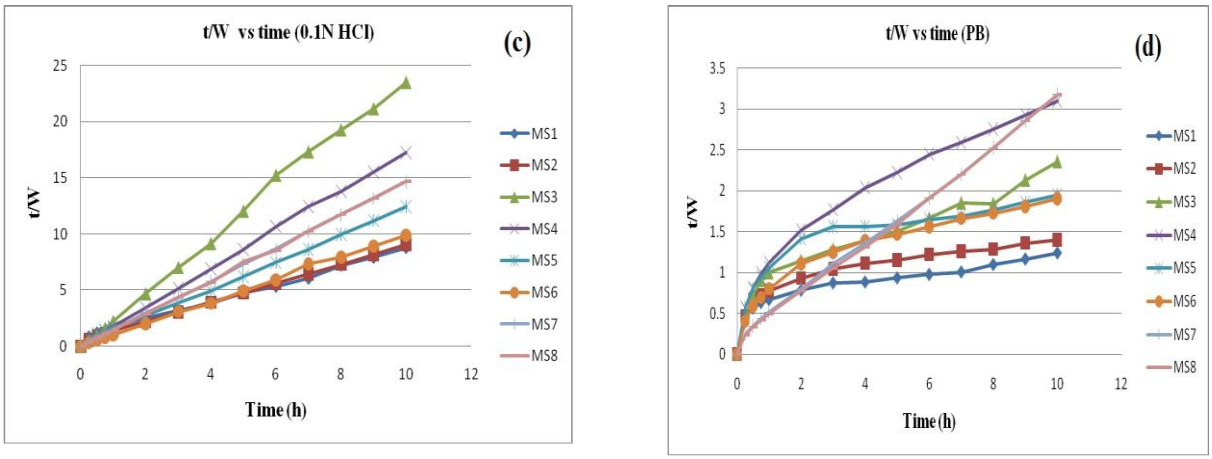


Fig. 3. (a) Swelling isotherm in 0.1N HCl, (b) Swelling isotherm in PBS, (c) t/W vs time in 0.1 N HCl (d) t/W vs time in PBS.

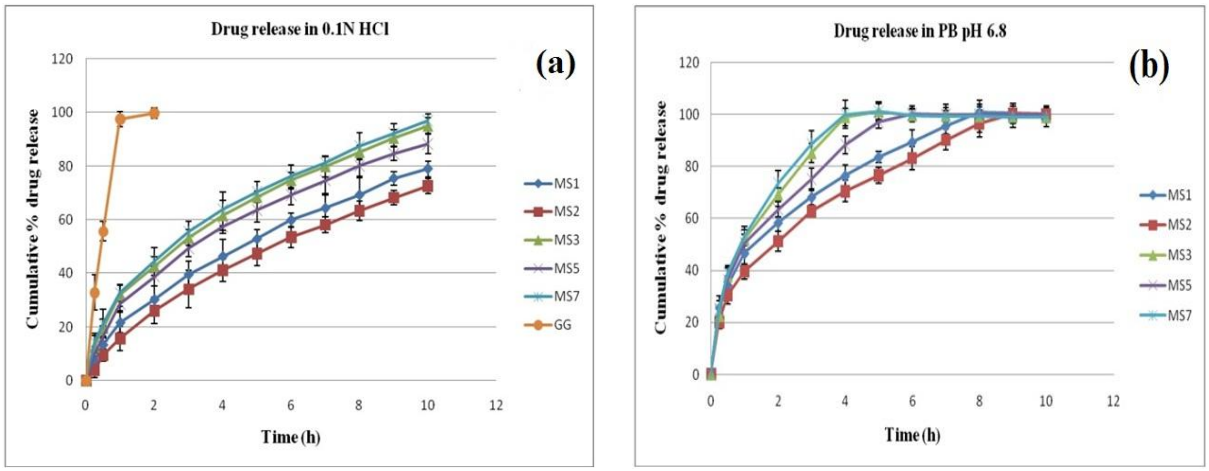


Fig. 4. Zero order drug release curve in 0.1N HCl (a) and phosphate buffer solution (b).

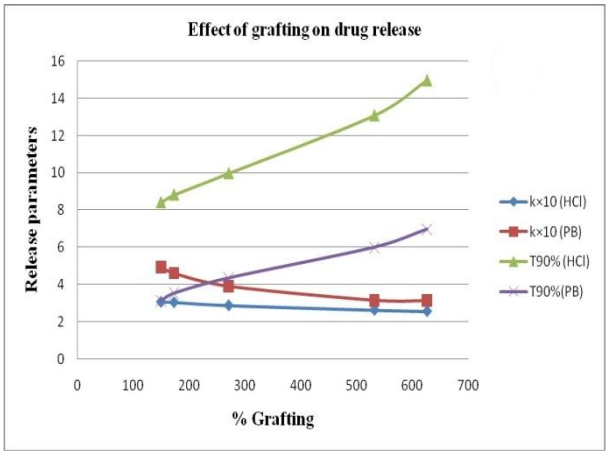


Fig. 5. Effect of % grafting on drug release rate constant and $T_{90\%}$.

CONCLUSION

Poly (acrylic acid)-grafted-gellan has been reported as excellent mucoadhesive and sustained release copolymer especially suitable for gastroretentive drug delivery in our previous effort. In this study, it has been found that the copolymer is practically insoluble in distilled water and in acidic media but is soluble in alkaline pH. This copolymer could be fabricated as pH responsive drug delivery matrix due to its pH dependent solubility. Viscoelastic study reveals that gel matrix composed of copolymer with higher grafting showed higher network rigidity and stronger microstructure which could also be considered as a controlling factor of drug release. The release study exhibited its nature of pH dependent drug release and excellent sustained release potential over a period of 10h in acidic pH. Thus, it can be concluded that PAAc-g-GG can be fabricated as pH sensitive sustained release smart polymer in a desired site-specific sustained-release oral drug delivery devices. Pharmacokinetic study should be carried out to establish its equivalency. Future study may be conducted to find out the scope of its application in interpenetrating polymeric network based drug delivery.

List of abbreviation

GG, gellan; RNH,
ranitidine hydrocholride; PAAc-g-GG,
poly(acrylic acid)-grafted-gellan; UV-Vis,
ultraviolet-visible; K_H,
drug release rate constant (Higuchi kinetic); $T_{90\%}$,
time at which 90% drug was released respectively,
%G, percentage grafting; %GE,
percent grafting efficiency; %C,
percent conversion.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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