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Effects of Viscoelastic Properties and Hydration Kinetic on Drug Release from the Tablet of Diclofenac Sodium Based on Poly (Sodium Acrylate)-Grafted-Gellan Matrix

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ABSTRACT

Investigation of the effects of viscoelasticity and hydration kinetic on the drug release behavior from the poly (sodium acrylate)-grafted-gellan matrix (PSAc-g-GG) was the main objective of this study. At first, poly (acrylic acid)-grafted-gellan was treated with 0.05M NaOH to obtain poly (sodium acrylate)-grafted-gellan followed by its purification and subsequent lyophilicity study and viscoelastic study on PSAc-g-GG with different degree of grafting. The study revealed that the degree of grafting greatly affects the viscoelastic and rheologic characteristics of the copolymer, which further affect the drug release profile from the polymeric matrix. The copolymer with highest grafting (626.3%) exhibited much higher starting % strain (17.79%), stress (53.7 Pa) for structural breakdown at $G' = G''$ (214.4 Pa), higher storage modulus (G'), much greater values of complex viscosity (11.5 Pa.s) and cross-over point ($G' = G''$ =271.65 Pa) compared to that of the batch of copolymer with lower grafting. The water uptake index ($\%W_E$) was found to be directly proportional to the percentage grafting (%G), whereas the batches with higher grafting revealed lower initial swelling rate representing its inversely proportional relation to %grafting in case of 0.1N HCl acid. Equilibrium swelling and hydration were also found to be proportional to % grafting. The similar effect was observed in phosphate buffer solution (pH 6.8) with an exception that the degree of the swelling parameters obtained from phosphate buffer was very much greater compared to that found in 0.1N HCl. PSAc-g-GG exhibited extended drug release over a period of 10 hours with the drug release mechanism based on Case-1 Fickian diffusion or square root of time kinetic. The study also exhibited the usefulness of viscoelastic and swelling study in order to identify the effects of the degree of grafting on the drug release.

Keywords: Viscoelasticity, hydration kinetic, Poly (sodium acrylate)-grafted-gellan, diclofenac sodium.

1. INTRODUCTION

Exploration of apposite pharmaceutical additives especially extended-release drug carrier from natural resources and their development to make them elegant tailor-made drug carriers have been current trends in drug-delivery-additive science [1]. Natural carbohydrate-polymers such as xanthan gum, sodium alginate, gum tragacanth, gum acacia, guar gum, locust bean gum, gellan gum, etc. have been reported as drug delivery matrix in various types of drug delivery devices and especially in peroral extended-release formulations as release controller due to their capacity along with some benefits such as abundance, easy availability, environment-friendliness, physio-compatibility and low cost [2]. Chemical exploitations of these natural carbohydrate polymers have been deemed in order to eliminate their innate drawbacks such as change in rheological cum viscoelastic nature upon aging, hysterical hydration rate, advance enzymatic biodegradation in gastro-intestinal tract and subsequent matrix erosion, etc. [3]. Different techniques for chemical amendment of the natural carbohydrate polymers include graft-copolymerization, carboxyethylation, carboxymethylation, cyanoethylation, chemical and ionic-crosslinking, etc. [4]. Graft-copolymerization especially employing free radical initiation method with redox-initiators such as ceric ammonium nitrate or ammonium persulphate has gained popularity due to certain features such as simplicity and promptness [5]. In our previous investigation, a graft-copolymer of poly (acrylic acid) and gellan gum was synthesized, characterized with FTIR, elemental analysis (carbon, hydrogen and oxygen), DSC,

TGA, solid state ^{13}C NMR, acute oral toxicity study, histological and ex-vivo mucoadhesion studies and reported [6].

Copolymerization by grafting technique mainly introduces steric bulkiness to the polymeric matrix through addition of numerous side-branches to the main molecular backbone of the native polymer. Formation of a three-dimensional (3-D) gel matrix is found after absorption of water when the drug-loaded matrix composed of this graft-copolymer is placed in gastrointestinal fluid. This hydrated polymeric gel posses certain viscoelastic properties which govern the drug release rate and pattern greatly from the 3-D gel matrix. Furthermore, viscoelastic properties of a polymeric gel matrix with 3-D network depend on the microstructures of the matrix which also influence the release of the drug [7]. On the other hand, kinetic of the water absorption (hydration) also governs greatly both the viscoelastic behavior and drug release kinetics [1].

In the present study, the developed copolymer of poly (acrylic acid) and gellan in our previous report, has been treated with 0.05M NaOH solution to obtain the sodium salt of the copolymer, poly (sodium acrylate)-grafted-gellan (PSAc-g-GG). The main objective of this present study was to investigate the effect of the viscoelastic natures and hydration kinetics of the salt form of the copolymer on the drug release from the tablets composed of the same salt form of the copolymer. The effects of the viscoelastic nature and hydration kinetic behaviors on the drug release were investigated in both 0.1N HCl and phosphate buffer solution of pH 6.8 (PBS). The viscoelastic study and dynamic water uptake study of the salt forms of the copolymer obtained from different synthetic batches of poly (acrylic acid)-grafted-gellan (PAAc-g-GG) were carried out. Finally, extended release monolithic matrix tablets of a water soluble model drug diclofenac sodium were formulated with various batches of the copolymer, PSAc-g-GG, prepared and evaluated for *in vitro* drug release study.

2. MATERIALS AND METHODS

2.1. Materials

Gellan gum and ceric ammonium nitrate were bought from HiMedia Laboratories Private Limited, Mumbai, India and Qualigens Fine chemicals, Mumbai, India, respectively. Diclofenac sodium was obtained as gift sample from La Chemico, Barasat, Kolkata, India. Acrylic acid, sodium hydroxide, potassium dihydrogen phosphate and polyvinylpyrrolidone K-30 were procured from Merck India Pvt. Ltd., Mumbai, India. Other reagents and chemicals were of laboratory grade and used as received. In all experiments triple-distilled water was used.

2.2. Synthesis of PAAc-g-GG and preparation of PSAc-g-GG

The synthesis of copolymer PAAc-g-GG was carried out employing the procedure reported earlier [6] and the products obtained from different batches were used to prepare the salt form of the respective batches. Different parameters of grafting in different batches of the grafted copolymer were represented in Table 1, which have been published elsewhere [6]. For the preparation of the salt form of the copolymer, the copolymer was first powdered, 10 g of the powder dispersed in 100 ml of 0.05N NaOH solution and stirred magnetically until dissolved. The solution obtained was allowed to stand for 1 hour and then double amount of acetone was added to it for precipitation of the sodium salt of the copolymer, poly (sodium acrylate)-grafted-gellan (PSAc-g-GG). The precipitate was collected, washed thoroughly with distilled water, dried in a hot air oven at 60°C temperature until constant weight and finally powdered. The powder was sieved through a 100 mesh and kept in a dessicator for use in experiments. The salt form of the each batch of the copolymer was designated as MSS1, MSS2, etc.

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])

2.3. Characterization of PSAC-G-GG

2.3.1. Lyophilicity study

An approximate idea about the affinity of the salt copolymer towards various solvents was investigated in this study. Firstly, 100 mg powder of PSAc-g-GG (MSS2) was dispersed in 10 ml of distilled water, 0.1 N HCl, phosphate buffer solution (PBS) of pH 6.8, 7.4, 8.0, Dimethyl sulfoxide, acetone, methanol and ethanol separately, stirred magnetically over a period of 24 hours at 30^{0}C temperature and the dispersibility or solubility was observed visually.

2.3.2. Viscoelastic study

The PSAc-g-GG copolymer was found to form a clear transparent hydrogel in water when added. The rheological behaviors especially such as viscoelasticity, which is a dependent factor of the microstructures of the 3-D polymeric hydrogel, macromolecular conformation and steric bulkiness, significantly affects the rate of drug release from the drug loaded matrix. Viscoelastic properties are obtained usually by dynamic mechanical tests which assess the structural breakdown or rearrangement and the small periodic deformations [7]. The dynamic mechanical "strain sweep" test reveals the microstructural natures of the

hydrogel under increasing strain condition. It evaluates the storage modulus, G', which designates the elastic patterns and articulates the capacity of the copolymer matrix to collect the elastic energy related to the recoverable elastic deformation, whereas, the loss modulus, G'', is a pointer of the dynamic viscous natures which is related to the dissipation of the energy coupled with unrecoverable viscous loss. Two 1%, w/v, aqueous gels (solvent: distilled water) with MSS2 and MSS7 batch were prepared for viscoelastic study and covered with a thin layer of light liquid paraffin to prevent water loss. The study was performed using a Rheometer (MCR-102, Anton Paar, Austria) with the plate geometry CP40-1 (Diameter 40mm and measuring gap of 0.08 mm). The temperature was maintained at 25 °C automatically by the Rheometer. Loss modulus (G''), storage modulus (G') and shear stress (τ) were determined at various levels of % strain (γ) and angular frequency (ω) separately. In strain-sweep, angular frequency was maintained constant at 10 rad/s and in case of frequency sweep, the % strain was kept constant at 0.05% at 25°C.

2.3.3. Hydration kinetic study

A dry sheet of the xerogel (1cm×1cm×1mm) of each batch (MSS1 to MSS8) of PSAc-g-GG was prepared by formation of a gel in a petridish, subsequent drying and cutting with knife dimensionally. Each sheet was weighed, taken in wire basket and immersed in 100 ml 0.1N HCl (pH 1.2) and PBS (pH 6.8) at 37^{0}C for 24 h, seperately. The basket was taken out from the buffer at the end of each predetermined interval and reweighed using an electronic balance (Electronic Balance, model TP313, Denver Instrument, India) after soaking of the surface water with tissue paper. Equilibrium water uptake by PSAc-g-GG was determined using the following formula:

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

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

The hydration-kinetic of PSAc-g-GG was determined by measuring the increment in weight of sheet after immersion in buffer in different time points [8]. A curve of the weight of absorbed water (W, g) per gram of the xerogel (dry sheet) of PSAc-g-GG against time (t in minutes), is known as hydration-isotherm. The horizontal portion of the isotherm indicates the equilibrium swelling. A linear expression can be obtained by plotting t/W against t according to the Eq.2:

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

Rearrangement and subsequent differentiation of the Eq.2 yields the following expression (Eq. 3):

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

Where, if $t \rightarrow 0$, the above equation corresponds the *initial swelling rate*, dW/dt = 1/A, which is the reciprocal of the intercept of the curve, t/W versus t, whereas, the reciprocal of the slope, $1/B$ = W_∞ corresponds to the equilibrium swelling which also designates the theoretical maximum water uptake at t_∞. The *Matrix Hydration*, H, was determined using the following formula (Eq.4):

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

Where, w_s, indicates the weight of the gel after absorbing water at equilibrium and w_0 indicates the weight of dry sheet (xerogel).

2.4. Preparation of extended release monolithic matrix tablet of diclofenac sodium

Extended release diclofenac sodium loaded tablets based on PSAc-g-GG were formulated and prepared by wet granulation technique. For the purpose of formulation, gellan gum (GG) and five batches of PSAc-g-GG copolymer were selected (MSS1, MSS2, MSS3, MSS5 and MSS7). Each batch of 100 tablets (each containing 100 mg of diclofenac sodium, 100 mg of GG/PSAc-g-GG and 30 mg polyvinyl pyrrolidone K30, 2.5 mg purified talc and 2.5 mg magnesium stearate) was prepared. At first, gellan gum or PSAc-g-GG copolymer and diclofenac sodium were mixed together intimately using a pestle-morter and then it was moistened with a minimum amount of aqueous solution of polyvinyl pyrrolidone K30 in a large petridish. The moistened mass was then passed through a sieve no #18 in order to obtain granules. The granules were then dried at 60^{0}C for 30 mins and again passed through # 18 mesh. The granules passed through the sieve no. 18 were collected and lubricated with purified talc (2.5 mg / tablet) and magnesium stearate (2.5 mg/tablet). The lubricated granules were compressed using 10 mm single punch diameter in a rotary tablet machine (Labpress, 10 stations, Remi, Mumbai, India). Hardness was measured and maintained within the range from 4.0 to 5.0 kg/m^2.

2.4.1. Evaluation of tablet

The prepared tablets were evaluated for hardness, friability, diameter, thickness, weight variation, content uniformity and disintegration as per Indian Pharmacopoeia, 2007.

2.4.2. In vitro drug release test

In vitro drug release test was carried out in 900 ml 0.1N HCl (pH 1.2) and phosphate buffer solution (pH 6.8) using USP dissolution test apparatus type-II (DS-800; 6+2; SC/TR, Lab India, Mumbai, India), separately. The temperature of the drug release medium was maintained at 37^{0}C and the speed of the stirring shaft was maintained at 50 rpm. At different predetermined time points, 5 ml of aliquot from the drug-release medium was taken out and same volume of buffer was replaced each time. Drug released from the tablet in the dissolution medium was measured using a spectrophotometer (UV-vis double beam spectrophotometer, Pharmaspec-1700, Shimazdu, Japan) at the λ_{max} value = 275nm. The release study was repeated in triplicate for all formulations.

2.4.3. Drug release kinetic

At first, cumulative percent drug release (CPR) at different time points were calculated from the absorbance measured by spectrophotometer and then the data were analyzed by following different mathematical release kinetic models suggested by various researchers such as zero order, first order, Higuchi-kinetic, Hixson-Crowell and Peppas-Korsmeyer models in order to recognize the drug release mechanism [9].

Zero order: $Q_t = K_0 t$ (Q_t is the weight of drug dissolved at time, t, K_0 is zero order drug release constant) [10].

First order: $log\ Q_t = log\ Q_0 + K_1 t/2.303$ (Q_0 is the initial weight of drug dissolved in medium) [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 dissolved at time, t) [13].

Korsmeyer-Peppas: $f_t = at^n$ (a is a drug-release-rate-constant corresponding the structural and geometrical characters of the drug delivery device, n is the release-exponent which describes the drug-release-mechanism) [14].

Higuchi model indicates drug-release as a diffusion process based on the Fick's law of diffusion and dependent on square root of time. This model could be used to describe the drug release from different types of extended release pharmaceutical dosage forms such as matrix tablets with water soluble drugs [15, 16].

The release exponent (n) obtained from Korsmeyer-Peppas model characterizes different mechanism of drug release: $n = 0.5$, $0.5 < n < 1$, $n = 1$ and $n > 1$ corresponds to Case-I (Fickian) diffusion or Higuchi model, non-Fickian anomalous diffusion, Case-II transport and super Case-II transport, respectively [9]. The time to 90% drug release (T$_{90\%}$) was also calculated from the equation of best fitting model.

3. RESULT AND DISCUSSION

3.1. Preparation of PSAc-g-GG

When poly (acrylic acid)-grafted-gellan was treated with sodium hydroxide, -COOH groups present in the poly (acrylic acid) side chain of the copolymer, react with NaOH and –COONa groups are formed, which results in the formation of poly (sodium acrylate)-grafted- gellan (PSAc-g-GG).

3.2. Lyophilicity study

PSAc-g-GG was found to show significant miscibility with distilled water and phosphate buffer solutions (pH 6.8, 7.4 and 8.0) but poor miscibility in 0.1N HCl. It may be due to the fact that PSAc-g-GG contains numerous –COONa groups which get ionized in neutral and alkaline media into –COO$^-$ and Na$^+$ resulting good affinity with water in neutral and alkaline pH. But due to acidic nature of –COO$^-$ ions it shows poor miscibility in acidic pH as acids are less soluble in acidic pH. Furthermore, PSAc-g-GG was found to increase in volume in PBS which may be due to initiation of partial ionization of –COONa groups present at surface resulting in more hydration and subsequent swelling. The probable mechanism has been shown in Fig.1. The copolymer exhibits no significant miscibility in dimethyl sulfoxide, acetone, methanol and ethanol. The study exhibits the pH dependent water miscibility of the copolymer.
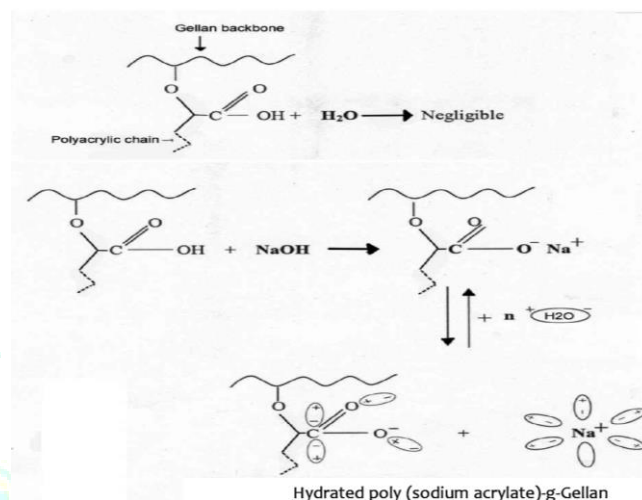
Fig. 1: Proposed mechanism of the hydration of PSAc-g-GG in water and phosphate buffer solution.

Table 2: Rheological and viscoelastic comparision between batch MSS2 and MSS7of PSAc-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)
MSS2	17.79	53.7	214.4	71.67	11.50	271.65
MSS7	4.44	0.0031	0.0469	98.37	0.0019	0.079

3.3. Viscoelastic study

Various viscoelastic parameters are represented in Table 2. Fig.2 depicts the strain sweep plots and frequency sweep plots obtained from MSS2 and MSS7 batches of PSAc-g-GG. MSS2 exhibited much greater starting % strain (17.79%), stress (53.7 Pa) corresponding structural breakdown at $G' = G''$ (214.4 Pa), which designates the stronger micro-structure and higher stringency of the gel-matrix indicating to longer molecular chain of PSAc-g-GG copolymer (obtained from MS2: highest % grafting of 626.3%) with higher steric bulkiness due to originating of several side chains from various points of main polymeric-backbone of gellan gum. Greater values of the storage modulus (G') exhibited by MSS2 batch compared to that in MSS7, points to the stronger and thickened nature of the polymeric-gel-matrix. This is also corroborated by the much greater values of the complex viscosity (11.50 Pa.s) and cross-over point ($G' = G'' = 271.65$ Pa) obtained from MSS2 in the frequency-sweep study [17].
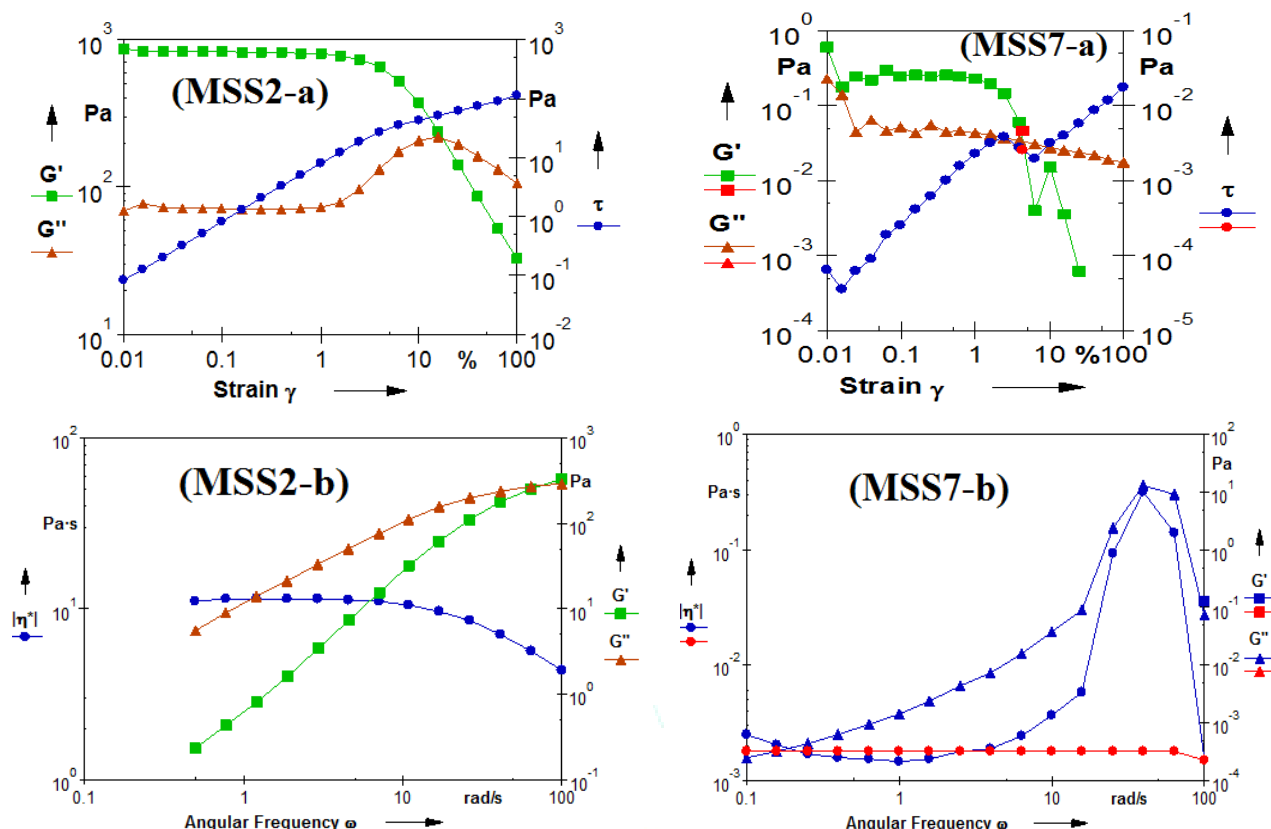
Fig.2: Various viscoelastic parameters against % strain and angular frequency plots exhibited by MSS2 and MSS7 batches.

Table 3: Hydration parameters shown by different batches of PSAc-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)
MSS1	133.44	1.21	1.289	0.61	892.26	1.75	15.87	0.88
MSS2	141.62	1.94	1.148	0.57	908.33	1.49	13.41	0.91
MSS3	56.33	13.99	0.437	0.34	305.41	1.44	6.72	0.77
MSS4	59.77	7.92	0.592	0.38	434.90	1.20	3.98	0.82
MSS5	88.24	2.56	0.87	0.48	675.00	1.12	9.03	0.86
MSS6	85.02	13.02	1.019	0.45	694.22	1.55	7.38	0.86
MSS7	55.44	39.29	0.667	0.36	374.88	5.25	3.83	0.80
MSS8	90.91	84.51	0.695	0.46	382.30	6.08	3.74	0.79

3.3. Swelling kinetic

Fig.3 (a) and (b) represent the kinetic of hydration behavior of various batches of PSAc-g-GG in 0.1N HCl with pH 1.2 and phosphate buffer solution with pH 6.8, respectively. Equilibrium water uptake (%W_E), initial swelling rate, equilibrium swelling and matrix hydration are represented in Table 3. In 0.1N HCl, %W_E was found to be directly proportional to %grafting (Eq. 5). It may attribute to the physical entrapment of more water by more branched and large network-matrix of the batches such as MSS1 and MSS2 with greater % grafting. MSS1 and MSS2 demonstrated lower initial swelling rate, which exhibits the inversely proportionality to % grafting. This may attribute to the fact that greater grafting includes numerous –COOH groups (subsequently –COONa upon treating with NaOH) in side chains of the copolymer, which initially, due to presence of

HCl acid, restricts entry of water molecules in the matrix. Equilibrium swelling as well as hydration was also found to be proportional to % grafting, which may attribute to slower imbibition of water in the matrix. The similar effect has been exhibited in phosphate buffer solution with an exception that the magnitude of various parameters observed in phosphate buffer is very much greater compared to that observed in 0.1N HCl. It may attribute to the greater ionization of –COONa groups in phosphate buffer, which results in much more hydration. Hydration isotherms (t/W versus t) were depicted in Fig.3. The equations relating % Equilibrium water uptake and % grafting in both 0.1N HCl and phosphate buffer were presented in Eq. 5 and 6.

$$\%W_E \text{ (HCl)} = 0.171(\%G) + 39.02 \ (R^2 = 0.874) \quad (5)$$

$$\%W_E \text{ (PB)} = 2.005(\%G) + 234.7 \ (R^2 = 0.844) \quad (6)$$
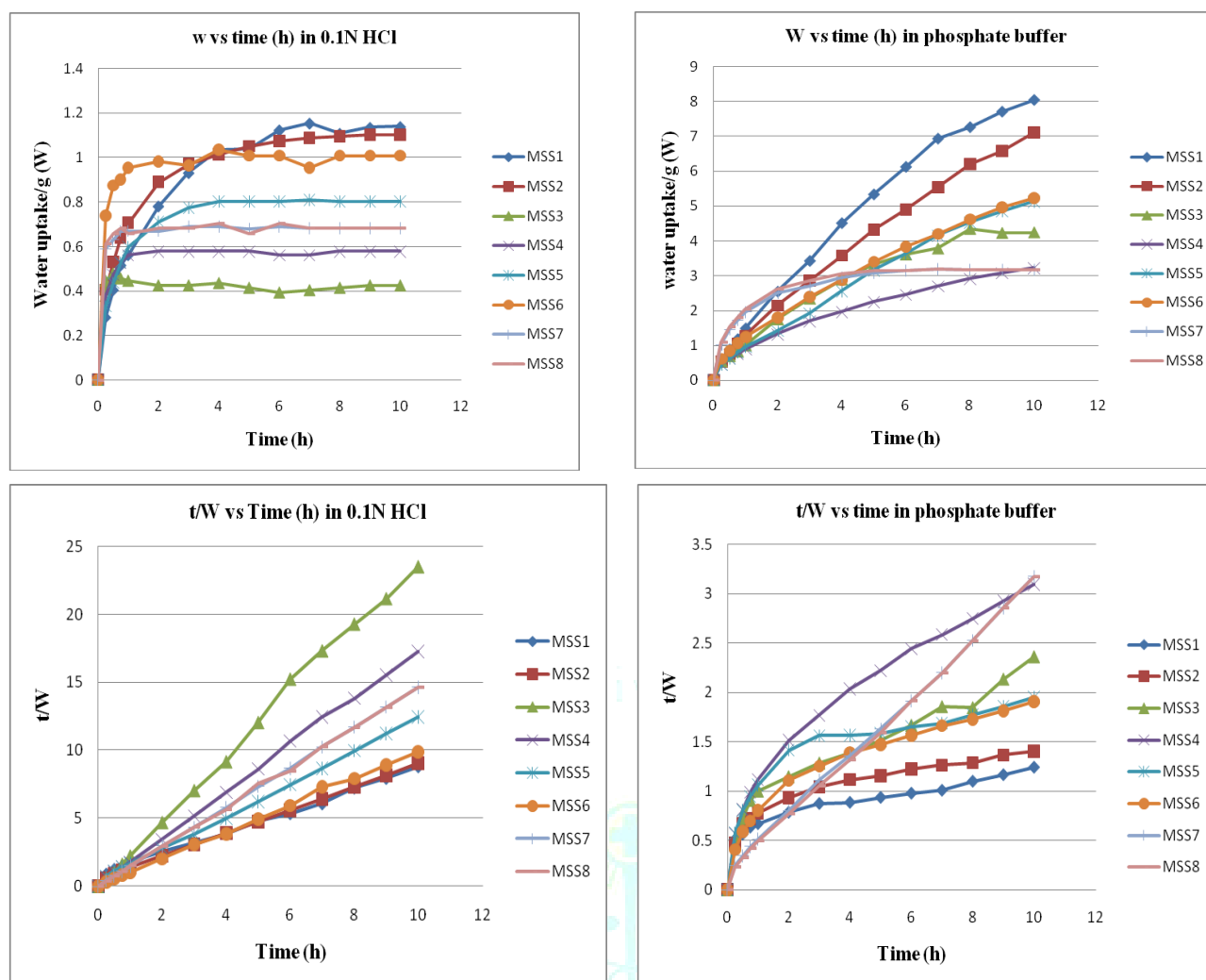
Fig. 3. Various hydration isotherms in 0.1N HCl and phosphate buffer solution

3.5. Evaluation of tablets

Various evaluations of the prepared tablets were carried out to assess the formulation and potential of PSAc-g-GG as tablet excipient. The tablets showed to possess a sufficient hardness ranging from 4.0 to 5.0 kg/m^2. The results of the weight and content uniformity tests were found to be within the limits prescribed by Indian Pharmacopoeia, 2007. Variations in diameter and thickness were also found to be within the permissible range. % friability was found to be well less than 1% in all batches. The tablets were also not found to disintegrate in buffer in disintegration 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	0.748	0.699	0.879	0.872	0.912	0.567	0.792	0.94
MSS1	0.974	0.787	0.995	0.991	0.992	0.625	0.266	13.12*
MSS2	0.979	0.769	0.997	0.987	0.989	0.732	0.258	14.64*
MSS3	0.948	0.789	0.998	0.990	0.993	0.537	0.313	8.88
MSS5	0.944	0.765	0.994	0.985	0.991	0.571	0.293	9.81
MSS7	0.957	0.805	0.999	0.987	0.996	0.515	0.319	8.52

*extrapolated from best fitting kinetic model

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		
MSS1	0.945	0.849	0.995	0.837	0.996	0.435	0.319	6.02
MSS2	0.957	0.824	0.999	0.849	0.995	0.431	0.317	6.95
MSS3	0.939	0.810	0.988	0.930	0.985	0.495	0.462	3.55
MSS5	0.944	0.835	0.994	0.927	0.993	0.438	0.392	4.30
MSS7	0.949	0.853	0.998	0.883	0.991	0.488	0.499	3.24

3.6. Drug release

The cumulative % drug release (CPR) versus time curve for 0.1N HCl and phosphate buffer were depicted in Fig. 4. The curves for 0.1N HCl represent that about 96% drug release takes place within the period of less than 1hour in case of unmodified pristine gellan, whereas extended-release profile was observed in case of MSS1 and MSS2 to a higher degree and in MSS3, MSS5 and MSS7 to relatively lesser degree. This may attribute to the fact that the tablets of MSS3, MSS5 and MSS7 were composed of PSAc-g-GG possessing lower degree of grafting, and the rapid hydration and premature network-relaxation associated with these less-branched polymeric-networks are liable for faster drug-release. The tablet-matrices composed of MSS1 and MSS2 with relatively denser networks result in extended-drug-release over a longer period of 10 hours due to slower rate of hydration and network-relaxation. The drug-release-rate revealed by the same batches in phosphate buffer were found to be quicker compared to that observed in HCl, which may attribute to the degree of ionization of –COONa groups resulting in faster hydration and subsequent erosion of tablet-matrix. The regression coefficients (R^2) , rate constant (k), diffusion exponent (n) and $T_{90\%}$ obtained from both HCl and phosphate buffer were presented in Table 4 and 5. Most of the tablet formulations were found to follow Higuchi and

Peppas-Korsemeyer (PK) release kinetic model. The diffusion exponent (n) values obtained from PK modelling for all the tablet-formulations were found to be within the range from 0.515- 0.732 (HCl) and 0.431 – 0.495 (phosphate buffer) which designates the release mechanism based on Case-1 Fickian diffusion or square root of time kinetic. The lowest values of rate constant (k) observed in MSS1 and MSS2 substantiate their capacity to extend the drug release, which is also further corroborated by the greater magnitude of $T_{90\%}$ observed in these two tablet-formulations. Fig. 5 portrays the changes in drug-release-rate constants and T90% with the variation in % grafting. The release-rate-constants and $T_{90\%}$ were shown to be inversely proportional and directly proportional to % grafting, respectively, that exhibits the positive effects of % grafting on extended-release potential of PSAc-g-GG. This is also ratified by the following equations of the corresponding drug release parameters (k, T90%) versus % grafting curves.
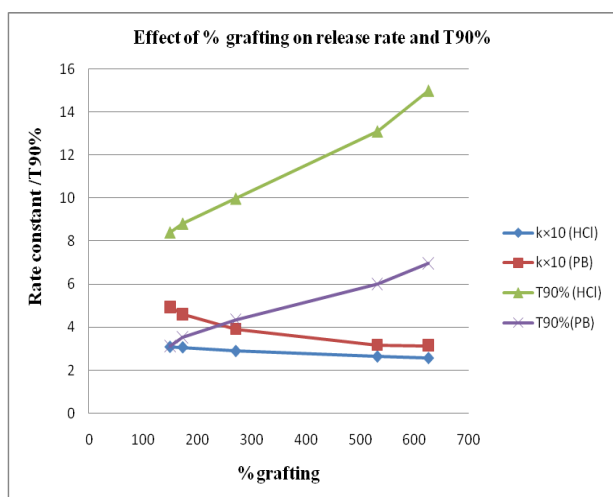
$K \times 10$ (HCl) = -0.0009(%G) + 3.229 (R^2 = 0.987)   (7)

$K \times 10$ (PBS) = -0.0031(%G) + 5.210 (R^2 = 0.914)   (8)

$T_{90\%}$ (HCl) = 0.0132(%G) + 6.445 (R^2 = 0.992) (9)

$T_{90\%}$ (PBS) = 0.0068(%G) + 2.153 (R^2 = 0.989) (10)
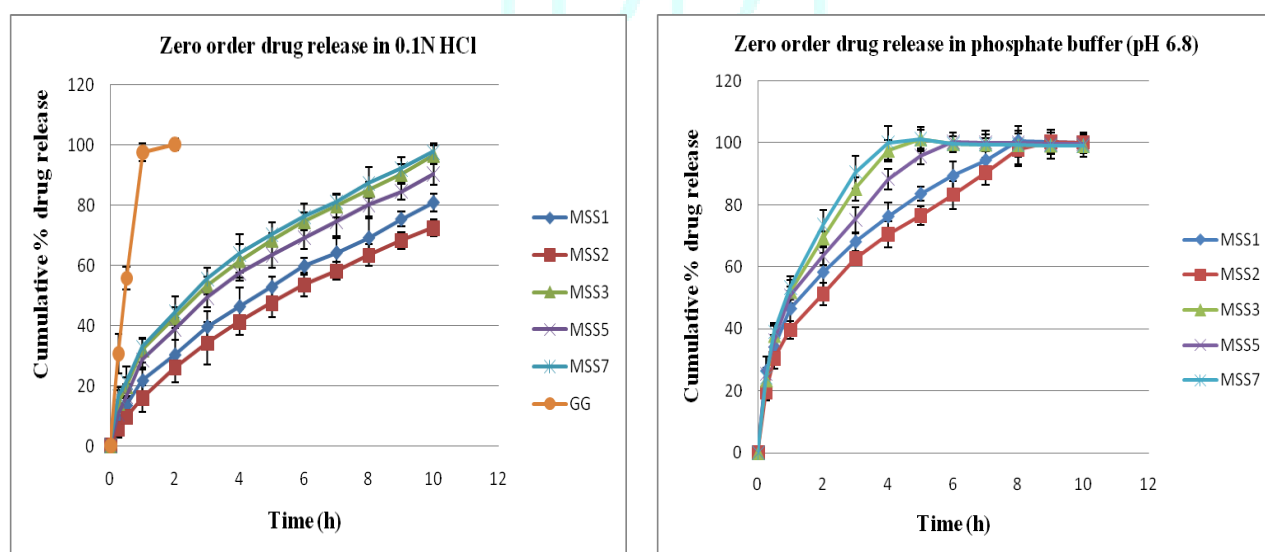
Fig. 4. Zero order drug release curve in 0.1N HCl and phosphate buffer solution.

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

4. CONCLUSION

Poly (acrylic acid)-grafted-gellan (PAAc-g-GG) has been reported as brilliant mucoadhesive and extended release copolymer especially apposite for gastroretentive stomach specific drug delivery in our previous attempt. In the present investigation, it has been observed that the sodium salt of the copolymer, PAAc-g-GG (PSAc-g-GG) is significantly soluble in distilled water and in phosphate buffer but is very less soluble in acidic pH. This salt form of the copolymer might be fabricated as various pH responsive drug delivery matrix such as delayed release or lower-gastro-intestinal-targeted drug delivery due to its pH dependent aqueous-solubility. Viscoelastic study exhibits that gel-matrix composed of this copolymer obtained from the batch with greater grafting exhibited greater network-rigidity and stronger-microstructure which might also be considered as a release-controlling factor. The drug-release study revealed the pH dependent drug release pattern and brilliant extended release capability over a longer period of time in acidic pH. Thus, it may be concluded that PSAc-g-GG could be fabricated as pH sensitive extended-release polymer in a preferred site-specific controlled-release peroral dosage forms.

5. CONFLICT OF INTEREST

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

6. ACKNOWLEDGEMENTS

7. REFERENCES

1. Rokhade AP, Patil SA, Aminabhavi TM, Synthesis and characterization of semi-interpenetrating polymer network microspheres of acrylamide grafted dextran and chitosan for controlled release of acyclovir. Carbohydrate Polymers, 2007; 67:605-613.
2. Prajapati VD, Jani GK, Moradiya NG, Randeria NP, Pharmaceutical application of various natural gums, mucilage and their modified forms, Carbohydrate Polymers, 2013; 92:1685- 1699.
3. Singh B, Sharma N, Development of novel hydrogels by functionalization of sterculia gum for use in anti-ulcer drug delivery, Carbohydrate polymers, 2008;74:489-497.
4. Nandi G, Patra P, Priyadarshini R, Kaity S, Synthesis, characterization and evaluation of methacrylamide grafted gellan as sustained release tablet matrix, International Journal of Biological macromolecules, 2015;72:965-974.
5. Singh AV, Nath LK, Evaluation of microwave assisted grafted sago starch as controlled release polymeric carrier, International Journal of Biological Macromolecules, 2013;60:62-68.
6. Sarkar D, Nandi G, Changder A, Hudati P, Sarkar S, Ghosh LK, Sustained release gastroretentive tablet of metformin hydrochloride based on poly (acrylic acid)-grafted-gellan, International Journal of Biological Macromolecules, 2017;96:137-148.
7. Adeyeye MC, Jain AC, Ghorab MKM, Reilly WJ, Viscoelastic evaluation of topical creams containing microcrystalline cellulose/sodium carboxymethyl cellulose as stabilizer, AAPS PharmSciTech, 2002:3(2): article 8.
8. Ofner CM III, Schott H, Swelling studies of gelatin I: gelatin without additives, Journal of Pharmaceutical Sciences, 1986;75:790.
9. Costa P, Lobo JMS, Modeling and comparison of dissolution profiles, European Journal of Pharmaceutical Sciences, 2001;13:123-133.
10. Varelas CG, Dixon DG, Steiner C, Zero order release from biphasic polymer hydrogels. Journal of Controlled Release, 1995;34:185-192.
11. Gibaldi M, Feldman S, Establishment of sink conditions in dissolution rate determinations – theoretical considerations and application to nondisintegrating dosage forms, Journal of Pharmaceutical Sciences, 1967;56:1238-1242.
12. Higuchi T, Mechanism of sustained-action medication, Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, Journal of Pharmaceutical Sciences, 1963;52:1145-1149.
13. Niebergall PJ, Milosovich G, Goyan JE, Dissolution rate studies. II. Dissolution of particles under conditions of rapid agitation. Journal of Pharmaceutical sciences, 1963;52: 236-241.
14. Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA, Mechanism of solute release from porous hydrophilic polymers, International Journal of Pharmaceutics, 1983;15:25-35.
15. Desai SJ, Singh P, Simonelli AP, Higuchi WI, Investigation of factors influencing release of solid drug dispersed in inert matrices. III. Quantitative studies involving the polyethylene plastic matrix, Journal of Pharmaceutical Sciences, 1966a; 55:1230-1234.
16. Desai SJ, Singh P, Simonelli AP, Higuchi WI, Investigation of factors influencing release of solid drug dispersed in inert matrices, IV. Some studies involving the polyvinyl chloride matrix, Journal of Pharmaceutical Sciences, 1966b;55:1235-1239.
17. Rohn CL, The rheology of coatings and dispersions, Journal of Water-borne Coatings, 1987;10(3):9:12-17.