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pH responsive gels of Gellan Gum and Carboxymethyl cellulose: Matrix for Ketoprofen Delivery

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Abstract : Hydrogels of GellanGum and Carboxymethylcellulose are made with two different crosslinkers, namely, N,N'-methylene-bis-acrylamide and diallylphthalate. The gels have been characterized by TGA, SEM and FTIR. The influence of preparation conditions, pH and ionic strength on the swelling has been investigated. The results reveal the influence of the nature of the crosslinker on the gel characteristics. The gels crosslinked with diallylphthalate showed higher sensitivity to the concentration of crosslinker and the ionic strength of the swelling medium. Reasonable pH responsiveness was observed in both type of gels which make them good candidates as matrix materials for slow release drug formulations. The pH dependence of release was studied by loading the gels with ketoprofen. About 10% of the drug was released at pH 1.2, and 80-90% at pH 7.4. The diallylphthalate crosslinked gels exhibited complete release of the entrapped drug at a faster rate compared to the other type of gel.
Key words: Gellan Gum, Sodium carboxymethylcellulose, N,N'-methylene-bis-acrylamide , Diallylpthalate, Swelling, Ketoprofen , pH responsive release.

1. INTRODUCTION

Crosslinked hydrogel networks are widely investigated as therapeutic devices, scaffolds for tissue engineering and controlled/sustained drug release carriers, taking advantage of their special properties, such as high sorption capacity, hydrophilic surface and low interfacial tension in contact with body fluids, minimal irritation of the surrounding tissue [1-3], good biocompatibility and carrier properties, and high permeability for nutrients and metabolites [4-6].

Gellan gum (GG) is a high molecular weight anionic deacetylated exocellular polysaccharide gum, produced as a fermentation product by pure culture of *pseudomonas elodea* (aerobic, gram negative, non pathogenic bacterium). It has tetrasaccharide repeating units consisting of one α-L-rhamnose,one β-D-glucouronic acid and two β-D-glucose residues [7]. Due to its good rheological characteristics, gellan gum has a great commercial potential for food and pharmaceutical applications.

Sodium Carboxymethyl cellulose (NaCMC) is a derivative of cellulose and formed by its reaction with sodium hydroxide and chloroacetic acid. It has a number of sodium carboxymethyl groups (-CH_2COONa), introduced into the cellulose molecule, which promote water solubility.

Compounds with chemically modified CMC and Gellan Gum with improved properties are gaining increasing interest in many fields because of their low cost, biocompability and biodegradability. Many reports are available about drug delivery using gellan based systems [8-11].

Ketoprofen is a widely used non-steroidal anti-inflammatory drug (NSAID) in the treatment of musculoskeletal and joint disorders. It is readily absorbed from the gastro-intestinal tract and exhibits a short biological half life of 2 h. When administered orally, it causes certain gastric side effects like gastric irritation, ulceration, haemorrhage etc. The shorter biological half life and associated side effects make the ketoprofen a suitable candidate for controlled release formulations [12]. Very few reports are available about Ketoprofen drug delivery in gellan based systems [13].

Hence in the present investigation, hydrogels of GG and NaCMC have been made with two different crosslinkers. The swelling of these gels in response to external stimuli such as pH and salt concentration has been studied and compared. The suitability of the gels as matrix materials for sustained release formulation of the drug, ketoprofen has been explored.

2. EXPERIMENTAL

2.1. Materials:

GG, N,N^1-methylenebis-acrylamide (MBA) , Diallyl phthalate(DP) and Ketoprofen were obtained from Aldrich Chemical Company Inc. NaCMC, ammonium persulphate (APS) were obtained from Merck India. All the chemicals and reagents were used as received. Double distilled water was used for polymerizations and swelling experiments.

Stock solutions of MBA (1.5% w/v in distilled water) DP (1% w/v in methanol), APS (1.5% w/v in distilled water) were used for the polymerization reactions.

2.2. Preparation of Buffer solutions:

A solution containing 0.05M KCl and 0.085M HCl was made to obtain a buffer solution of pH-1.2; 28.8g disodium hydrogen phosphate and 11.45g potassium dihydrogen phosphate were dissolved in 1 litre water to make buffer pH-6.8; 2.38g of disodium hydrogen phosphste, 0.19g potassium dihydrogen phosphate and 8.0g sodium chloride were dissolved in 1 litre to obtain buffer of pH-7.4.

2.3. Synthesis of hydrogels of GG and NaCMC (GG-NaCMC gels):

GG (0.2g) and NaCMC (0.05-0.2g) were stirred in 20mL distilled water at 70^0C to achieve a homogenous solution. 1ml of APS solution (1.5%) was added to the above mixture and stirred for 15 min. This was followed by the addition of MBA (1.5% solution) while stirring. The reaction mixture was allowed to cool to ambient temperature. Gelation was observed after 15-20 min. The gel was removed and washed repeatedly with methanol. It was dried at 50^0C to constant weight.

Similarly, other set of gels were made with DP as crosslinker instead of MBA and purified as above. The composition of reaction mixture for the preparation and the designation of the gels obtained have been summarised in Table 1.

Table 1.Details of preparation and designation of GG-NaCMC gels.

a) 'A' Series

GG-NaCMC gel Formulation code	GG(g)	NaCMC(g)	APS(mmol)	MBA(mmol)
A1	0.2	0.2	0.066	0.096
A2	0.2	0.1	0.066	0.096
A3	0.2	0.05	0.066	0.096
A4	0.2	0.05	0.066	0.064
A5	0.2	0.05	0.066	0.128
A6	0.2	0.05	0.066	0.160
A7	0.2	0.05	0.022	0.096
A8	0.2	0.05	0.043	0.096
A9	0.2	0.05	0.109	0.096

b) 'B' Series

GG-NaCMC gel Formulation code	GG(g)	NaCMC(g)	APS(mmol)	DP (mmol)
B1	0.2	0.2	0.066	0.040
B2	0.2	0.1	0.066	0.040
B3	0.2	0.05	0.066	0.040
B4	0.2	0.05	0.066	0.060
B5	0.2	0.05	0.066	0.081
B6	0.2	0.05	0.066	0.101
B7	0.2	0.05	0.022	0.040
B8	0.2	0.05	0.043	0.040
B9	0.2	0.05	0.109	0.040

2.4. Preparation of Ketoprofen loaded GG-NaCMC gels:

To make gels containing the drug, ketoprofen was added to the reaction mixture prior to gelation. In the general method, GG (0.2g) and NaCMC (0.2g) were dissolved in 20ml distilled water at 70^0C. 1ml of APS solution was added and the mixture was continuously stirred for 15 min. 20mg of ketoprofen was then added to the mixture and stirred for about 1hr. Then 1ml of DP was added to the solution. Finally 1mLof MBA/DP solution was added. The reaction mixture was allowed to cool to ambient temperature. Gelation occurred after 15-20 min. The gel containing ketoprofen was dried at 50^0C and stored for further study.

2.5. IR characterization:

The IR spectra of representative GG-NaCMC gels namely GG-NaCMC-A3 & GG-NaCMC-B3 were recorded in KBr pellet form using FTIR spectrophotometer (Perkin-Elmer, USA). IR spectra of Pure GG & NaCMC samples were also recorded for comparison.

2.6. Thermogravimetric analysis:

Thermograms of GG, GG-NaCMC-A3 & GG-NaCMC-B3 samples were recorded on SDT Q600 V20.9 (Japan) thermogravimetric analyser. The samples were heated from room temperature to 800^0C, under nitrogen atmosphere, at a rate of 5^0C/min.

2.7. Scanning Electron Microscopic (SEM) analysis:

The micrographs of GG, GG-NaCMC-A3 & GG-NaCMC-B3 samples were recorded on a JEOL-JSM5800LV scanning electron microscope. The micrographs were recorded with a magnification of 1000 under the voltage of 20 KV.

2.8. Swelling studies:

The swelling behaviour of the GG-NaCMC gels was studied in distilled water and in aqueous buffer media of pH-1.2 and 7.4 using standard buffer solutions, at 30^0C. The weight measurements were made using an electronic balance (Shimadzu AUX120, Japan) with an accuracy of ±0.1mg. Pre-weighed dry gels were immersed in either distilled water or in excess of the buffer solution, maintained at 30℃ . After specific intervals of the time, the gels were removed from the medium, the surface adhered liquid drops were wiped with blotting paper and the increase in weight was measured. The measurements were continued till the weights of the swollen gels attained constant values. The swelling ratio (SR) and the amount of water the gel can hold at equilibrium (percent equilibrium water content) (%EWC) were calculated [14], using the following expressions,

$$SR(g/g) = \frac{W_t - W_o}{W_o} \quad (1)$$

$$Seq(g/g) = \frac{W_{eq} - W_o}{W_o} \quad (2)$$

$$EWC\,(\%) = \frac{W_{eq} - W_o}{Weq} \times 100 \quad (3)$$

Where W_o, W_t and W_{eq} are the weights of the sample in the dry state, the swollen state at time t and in the completely swollen state (equilibrium), respectively.

2.9. Evaluation of Swelling and diffusion characteristics of GG-NaCMC gels:

The swelling/diffusion kinetic parameters, i.e., initial swelling rat 'r_i' swelling rate constant (k_s),maximum equilibrium swelling ratio (S_{max}); diffusion constant (n) and the diffusion coefficient (D) were evaluated by employing various equations reported elsewhere [15]. All these parameters were calculated using the dynamic swelling data.

2.10. Estimation of drug entrapment efficiency:

To determine the amount of drug loaded in the GG-NaCMC gel samples, accurately weighed gels were crushed with a mortar-pestle and were transferred into 50mL of phosphate buffer solution of pH 7.4 After 12 h of stirring, the suspension was filtered and the absorbance of supernatant solution was recorded using a UV Spectrophotometer at 260 nm. The drug entrapment efficiency (%) was calculated using the equation:

$$\text{Entrapment efficiency (\%)} = \left[\frac{\text{Calculated drug content}}{\text{Theoretical drug content}}\right] \times 100 \quad (4)$$

2.11. In vitro drug release study:

To obtain information about the possible mode of action of the proposed drug delivery system in the human body, it is often convenient to perform the studies in an environment similar to that in the body. Hence, for carrying out the drug release study in an in vitro manner, buffer solutions of pH 1.2, 6.8 and pH7.4 were prepared and the drug release studies were carried out in these media using USP-1 basket type apparatus (Electrolab TDT-08L Dissolution Tester). 20mg of drug-loaded hydrogels were taken in the basket and immersed into the dissolution tank containing 500 ml of the buffer. The basket was maintained at 100 rpm at 37℃. 5mL of the sample was withdrawn at predetermined time intervals and replaced with equal volumes of fresh dissolution medium. The samples were analyzed using UV-visible spectrophotometer at the wavelength of 260 nm with suitable dilutions. The percentage cumulative drug release (CDR) was calculated using the following equation:

$$\%CDR = \left[\frac{\text{amount of drug released}}{\text{amount of drug loaded}}\right] \times 100 \quad (5)$$

2.12. Determination of mechanism of drug release:

To determine the mechanism of drug release from the formulations, the data were fitted to the zero-order , first order and Higuchi kinetic models given by equations (6),(7) and (8) respectively.

$M_t = M_0 + K_0t$ …… (6)

$\ln M_t = \ln M_0 + K_1t$ …….…….. (7)

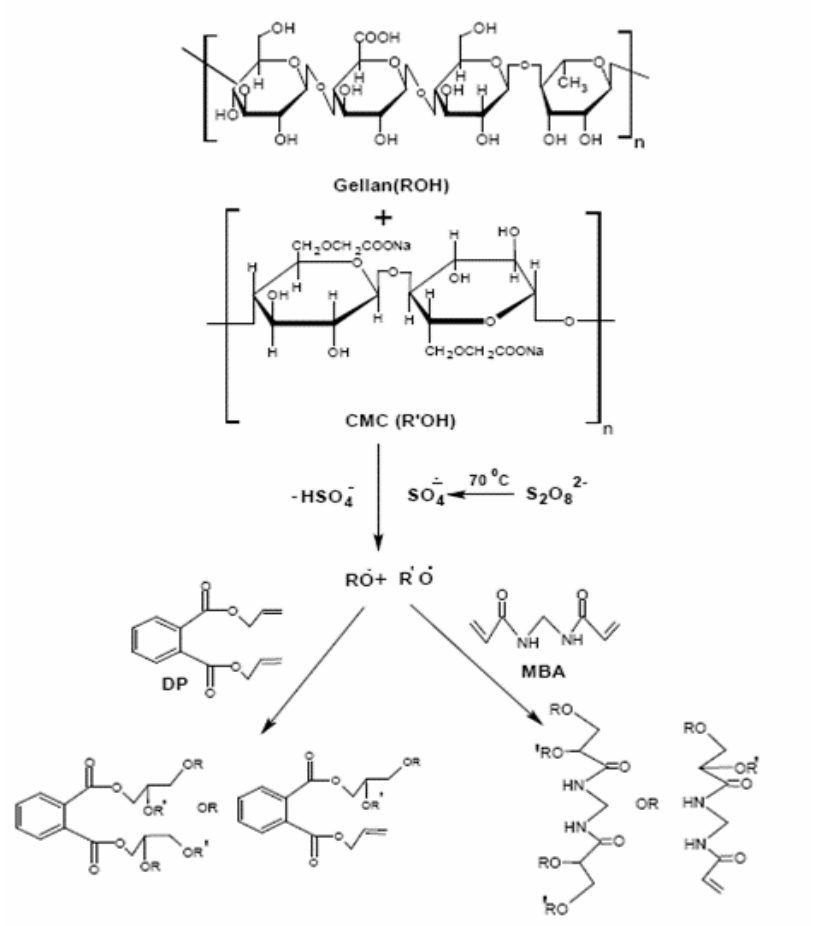
$M_t = M_0 + K_Ht^{1/2}$ …….…….... (8)

where M_t is the cumulative amount of drug released at any time, t, and M_0 is the amount of the drug incorporated in the delivery system. K_0, K_1 and K_H are rate constants for zero-order, first order and Higuchi models, respectively. The first 60% dissolution data were also fitted according to the well-known exponential equation of Peppas [16, 17] given by Eq 9, which is often used to describe drug release behaviour from polymeric systems.

$M_t/M_\infty = Kt^n$ …….……..(9)

Where, M_t/M_∞ is the fraction of drug released at time, t, K is the kinetic constant, and 'n' is the diffusional exponent for drug release. The diffusional exponent, 'n' is dependent on the geometry of the device as well as the physical mechanism of release. Zero order release describes a release rate independent of drug concentration while the Higuchi square root kinetic model describes a time dependent release process. The value of n indicates drug release mechanism; $n \leq 0.45$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxational) transport, and $n > 0.89$ to super case II transport [18].

3. RESULTS AND DISCUSSION



Scheme 1. General mechanism of radical crosslinking of GG-NaCMC chains in the presence of MBA and DP.

GG and NaCMC were simultaneously crosslinked in a homogeneous medium using APS as a free radical initiator and MBA/DP as the crosslinking agent. Scheme 1. shows the mechanism of crosslinking. The sulfate anion radical produced due to thermal decomposition of APS abstracts hydrogen from the hydroxyl groups of the polysaccharide substrates to form corresponding alkoxy radicals on the substrates. The hydrogel formation occurs in two ways: (a) the alkoxy radicals on the GG and NaCMC act as active centres capable of initiating free radical reactions with MBA or DP to form the gel. (b) self-crosslinking of the free radicals occurs on polysaccharides resulting in the formation of the gel [19].

3.1. IR Spectroscopy:

The IR spectra provide conclusive evidence for the formation of gels. The IR spectrum of GG (Fig. 1(a)), shows a broad absorption band at 3417 cm^{-1}, attributed to the stretching of the –OH groups. The band at 2924 cm^{-1} is due to C–H stretching. Two strong peaks are observed at 1619 and 1420 cm^{-1} due to the asymmetrical and symmetrical stretching of $–COO^-$ groups respectively. The IR spectrum of NaCMC (Fig. 1(b)), shows a broad absorption band at 3432 cm^{-1}, due to the stretching of the –OH group. The band at 2909 cm^{-1} is due to C–H stretching. The presence of a strong absorption band at 1603 cm^{-1} indicates the presence of COO^- group. The bands around 1423 and 1325 cm^{-1} are assigned to CH_2 scissoring and –OH bending vibration, respectively. The band at 1061 cm^{-1} is due to CH–O–CH_2 stretching. In the gel B3, (Fig. 1(c)), a new peak appeared at 1728 cm^{-1}attributed to the carbonyl group of DP in the hydrogel. The spectra of A3 (Fig. 1(d)), shows a weak peak at 1649 cm^{-1} attributed to the presence of amide group of MBA in the gel. Most of the peaks corresponding to GG and NaCMC are observed in the IR spectra of hydrogels but they cannot be differentiated due to overlapping.

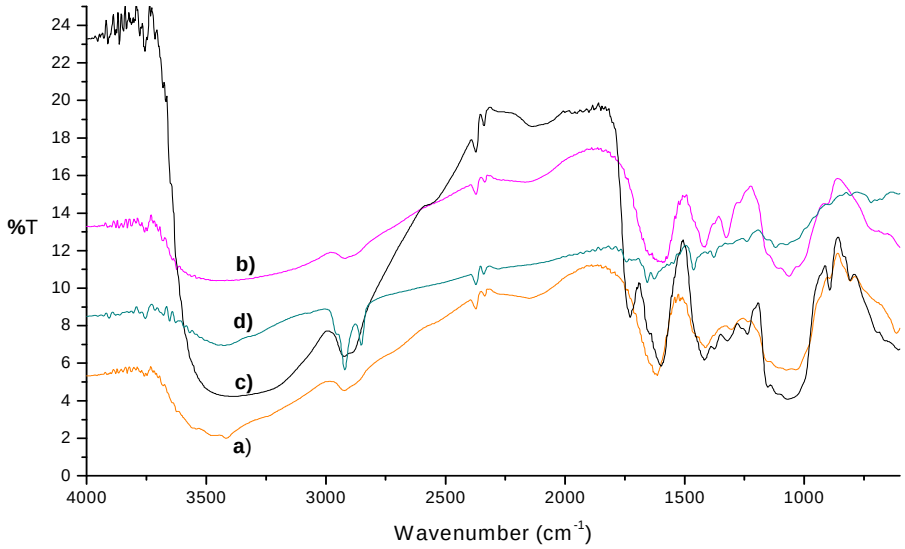


Fig. 1. IR Spectra of a) GG; b) NaCMC; c) B3 and d) A3 samples.

3.2. Thermogravimetric analysis:

The presence of NaCMC, DP and MBA in the gel samples causes significant changes in the thermal behaviour of pure GG. The thermogram of (a)) GG (b)) B3 (c)) A3 are depicted in Fig.2. GG shows a three-step characteristic thermogram, wherein the first stage of weight loss of about 10% occurs in the temperature range of 50-100°C which is attributed to loss of moisture in the sample. The major weight loss (57 %) takes place in the second step within the temperature range of 236–540°C. Finally 10% weight loss occurs around 600°C. The thermal stability of the GG-NaCMC gels (b & c) is improved as is obvious from the TGA curve. In the TGA curve of GG about 57% weight loss takes place in the temperature range of 236–540°C., while it was 40-42 % in GG-NaCMC gels (b & c).Moreover, the high char yield, up to 28-34 wt%, at 600°C observed in thermogram indicates that the GG-NaCMC gels have significantly higher thermal stability than that of the GG (char yield = 18%).

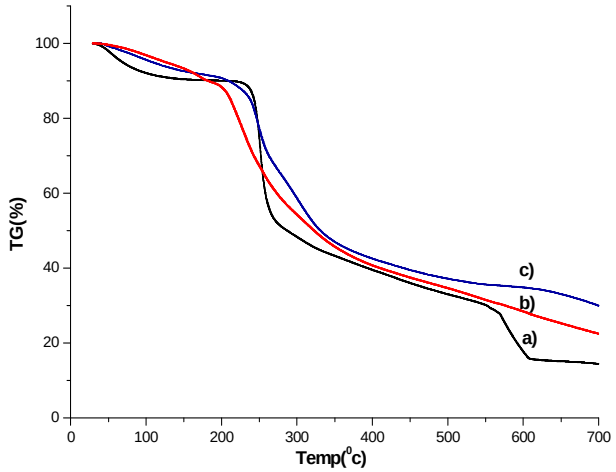


Fig. 2. Thermogram of **a)** GG b**)** B3 and c**)** A3 gel samples.

3.3. SEM analysis:

Fig. 3 shows scanning electron micrographs of GG and GG-NaCMC gel samples of A and B Series. The porous and rough structure of GG appears to be retained in A series of gel samples, crosslinked in the presence of MBA. But the surface morphology drastically changes in DP crosslinked, B series, gel sample. Air trapped bubble like structures are observed to be uniformly distributed on a relatively smooth surface. The SEM micrographs reveal that the nature of crosslinker has an appreciable effect on the surface morphology of the gel samples.

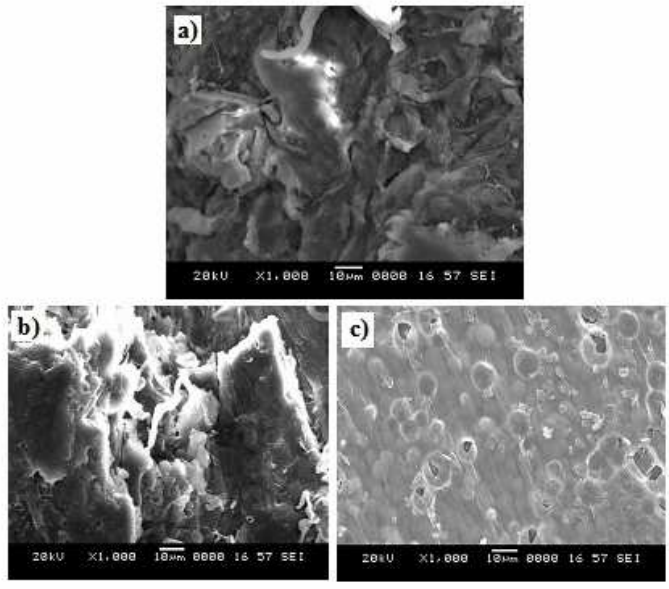


Fig 3. SEM of a**)** GG b**)** A3 and **c)** B3 samples.

3.4. Swelling behaviour of hydrogels:

Swelling behaviour of hydrogel depends on the nature of polymer network involving the presence of hydrophilic groups, crosslinking density, elasticity of network, etc [20]. Therefore, variation in structure of GG-NaCMC gels directly influences their swelling capacity. In the present investigation, different networks of GG-NaCMC were achieved by varying the reaction composition and the type and amount of crosslinker.

3.4.1.Effect of crosslinker on swelling behaviour:

Swelling behaviour of A & B series of samples made with different amounts of MBA and DP is shown in Fig 4. Considerably low amount of DP was sufficient to crosslink the gels compared to MBA and the effect of crosslinker concentration on swelling was more predominant in B series. Swelling ratio decreased from 20.0 to 8.0 with increase in DP in the range 0.04-0.1M. The minimum concentration of MBA required to observe gelation was 0.06 mmol. and the increase in the concentration of MBA does not seem to affect the swelling ratio much. DP appears to be a better choice over MBA for controlling the network structure.

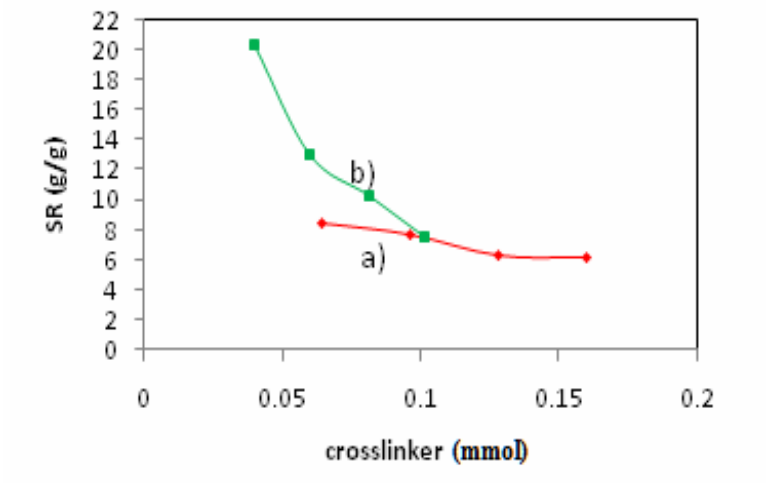


Fig. 4. Effect of crosslinking on swelling of a) 'A' series & b) 'B' series of GG- NaCMC gels (at 90 min).

3.4.2.Effect of salt on swelling behaviour:

Fig.5 illustrates the changes in the swelling behaviour of the gels, A3 and B3 in solutions with different concentrations of NaCl. The swelling decreases in both cases with increase in sodium chloride concentration which is due to the contraction of the gel networks, resulting from screening of charges on polymer network. The osmotic pressure difference between the gel networks and the external solution decreases with increase in the ionic strength of the saline medium [21], resulting in decrease of swelling. The effect of salt was appreciable in the case of B3 gel, especially at low NaCl concentration and levels off with high concentration. In case of A3 gel, the effect is gradual and is comparably very small at low concentration of NaCl when compared to B3 sample. With regard to the effect of ionic strength of the medium on swelling, the DP crosslinked gels appear to be more sensitive than the MBA containing gels.

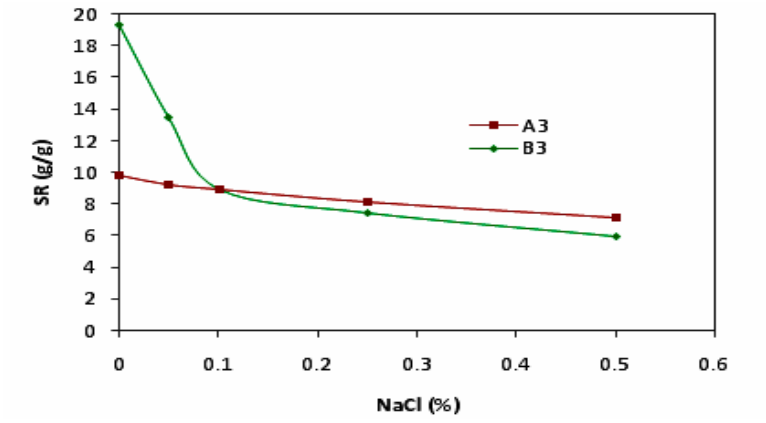


Fig. 5. Effect of sodium chloride content on swelling behaviour of A3 and B3 gel samples.

3.4.3. Effect of pH on swelling behaviour:

Fig.6 displays the swelling behaviour of A3 and B3 gel samples under different pH conditions. Both the gels show good pH responsiveness and the order of swelling is pH7.4> 6.8 > 1.2. The swelling at pH7.4 is 3 times higher than at pH1.2. At pH6.8, 'B3' gel shows higher swelling almost equal to that of pH7.4 but the gel sample 'A3' exhibits very low swelling equal to that of pH1.2. At higher pH values carboxylate groups are ionized and the electrostatic repulsion between COO^- groups causes an enhancement in the swelling. Under acidic pH, the carboxylated anions get protonated and consequently swelling is lowered.

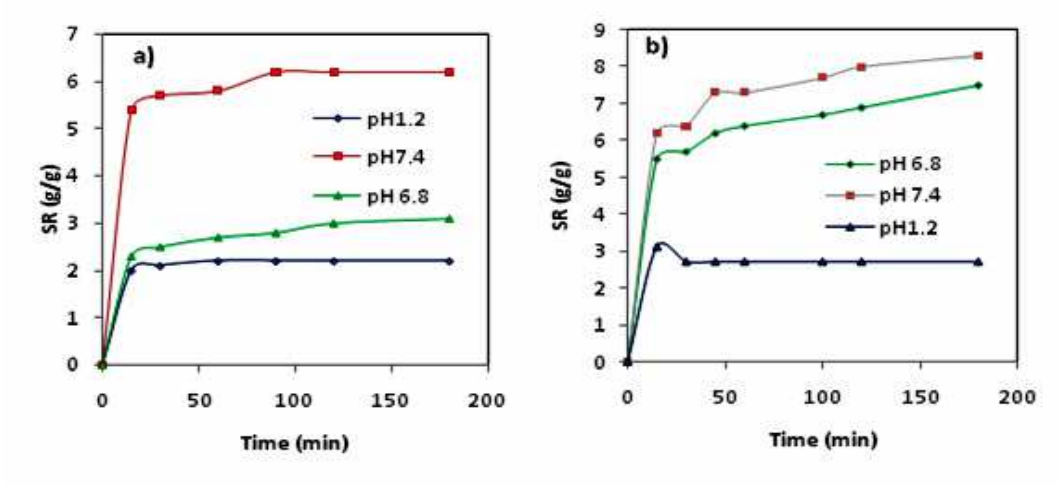


Fig. 6. Effect of pH on swelling behaviour of (**a)** A3 and (**b)**) B3 samples.

3.4.5. Swelling and Diffusion characteristics of gels:

The swelling data with time for 'A' and 'B' series of gels, shown in Fig. 7a and 8a, were analysed to understand the nature of swelling and diffusion of water into the gel network. The various plots for the 2 series of samples are shown in Fig. 7 & 8. The swelling and diffusion parameter obtained using standard methods is listed in Table 2.

Table2. Swelling and diffusion parameters for 'A' and 'B' series of GG-NaCMC gel.

Code of GG-NaCMC gels	EWC (%)	S_{eq}(g/g)	Calculated S_{eq}(g/g)	R_i(g/g)/ min	K_s(g/g) /min (10^{-2})	Swelling Exponent (n)	D(cm^2/ sec)
A1	86.8	6.2	5.9	0.50	1.3	0.407	0.687
A2	85.7	6.6	6.1	0.80	1.9	0.431	0.724
A3	91.3	10.5	10.7	2.85	2.5	0.580	1.269
B1	92.7	12.7	13.1	2.10	1.2	0.656	1.694
B2	93.5	15.8	15.1	2.80	2.6	0.452	2.103
B3	95.3	20.4	21.2	4.97	4.7	0.414	3.041

The linearity of the plot 't/s' vs 't' (Fig. 7b and 8b) indicates that the swelling process follows second-order kinetics. It is confirmed that the S_{eq} calculated from the slopes are in good agreement with the ratio determined experimentally by swelling measurements. The initial swelling rate 'R_i' and swelling rate constant 'K_s' are observed to be dependent on the gel structure. Swelling exponents 'n' was calculated from the slopes and intercepts of the lines of 'ln F' vs. 'ln t' plots (Fig.7c & Fig.8c) were in the range 0.40–0.65, indicating the transport mechanism changes from Fickian to anomalous diffusion, with change in the network structure of the gel. The diffusion coefficients 'D' were calculated from the slope of the lines displayed in Fig. 7d & 8d. The results indicate that 'B' series samples exhibit higher swelling capacity, higher rate of swelling and higher value for 'D' compared to 'A' series. Lowering the amount of NaCMC in the gel formulations during preparation appears to enhance the swelling characteristics.

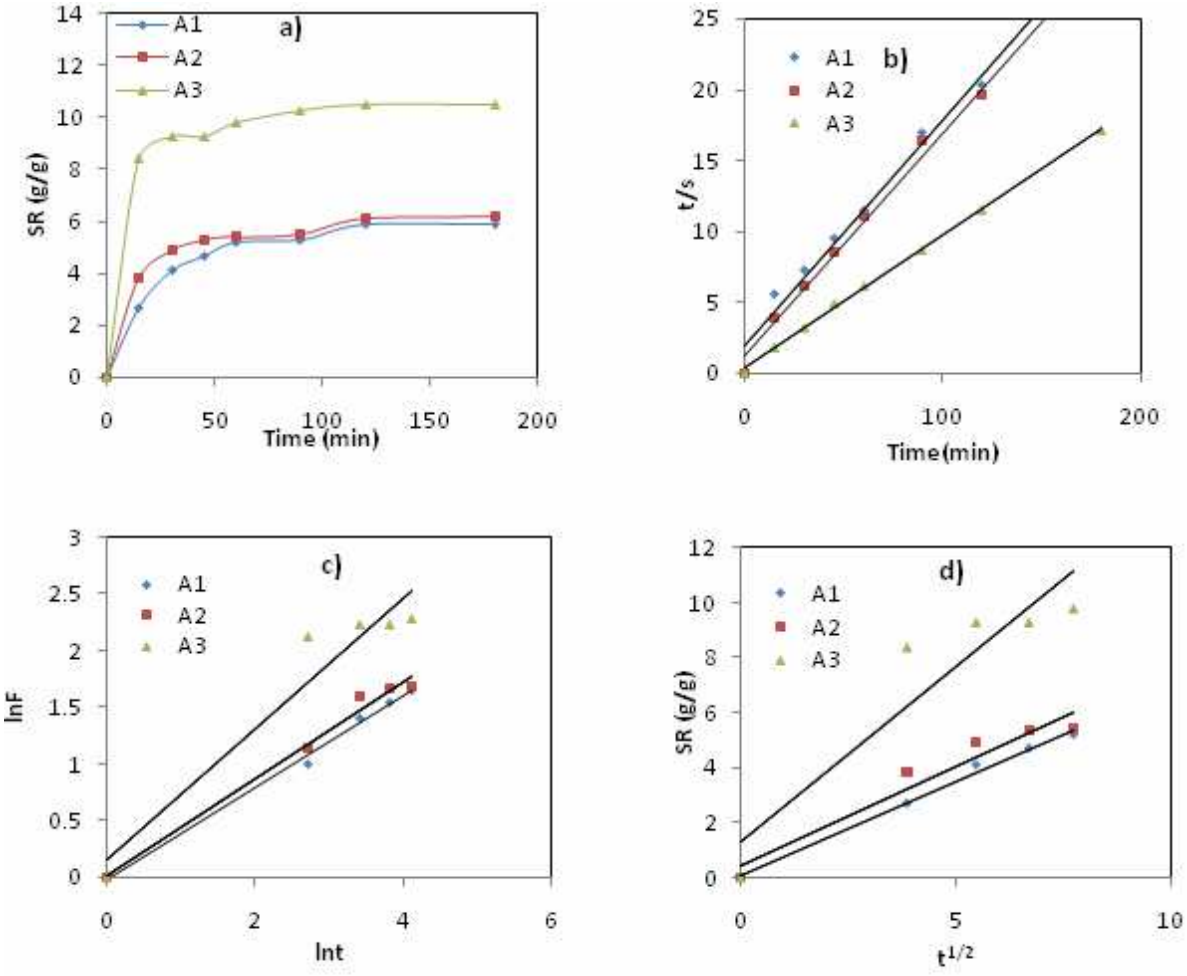


Fig. 7. Swelling curves for 'A' series of GG-NaCMC gels.

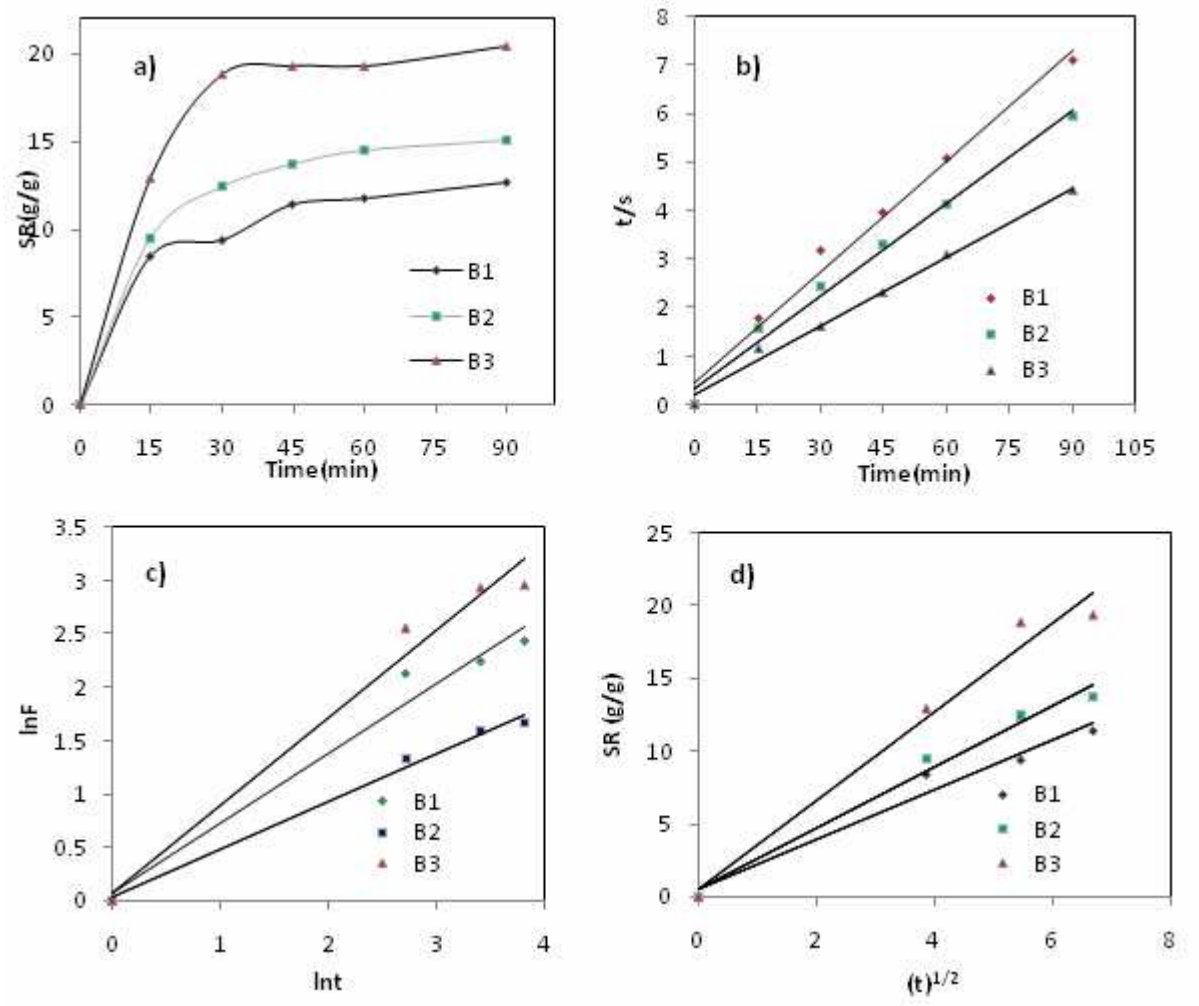


Fig.8. Swelling curves for 'B' series of GG-NaCMC gels.

3.5.Drug entrapment efficiency:

The capacity of A & B series of gels to entrap the chosen drug 'ketoprofen' determined using eqn. (4) is found to be 97.5%.

3.6. In vitro drug release behaviour:

When the drug-loaded dry gels come in contact with a solvent, the gel swells and entrapped drug passes into the external receiving medium, crossing the swollen polymeric matrix [22]. In the present study, the release of ketoprofen from the hydrogels was studied at pH 1.2, 6.8 and 7.4 at the physiological temperature of 37°C. The results depicted in Fig.9 indicate that the samples release a higher amount of ketoprofen in the media of pH7.4 and 6.8 and a comparatively low amount of the drug is found to be released at pH 1.2. The quantity of the total drug released by A1& B1 at the pH 7.4 and pH6.8 are in the range of 80-97%, 95-96%, respectively. At pH1.2, the release was very slow and less than 10% was released for all formulations. The results indicate that the release of the drug from these gels depends on swelling. An initial phase of rapid release (burst effect) was observed in A1 and B1 at pH7.4 & 6.8 possibly due to the release of drug entrapment on the surface of the polymer matrix during preparation process. Such observations are reported earlier, [23, 24] especially in the case of high drug loading where the release occurs immediately upon activation in the release medium.

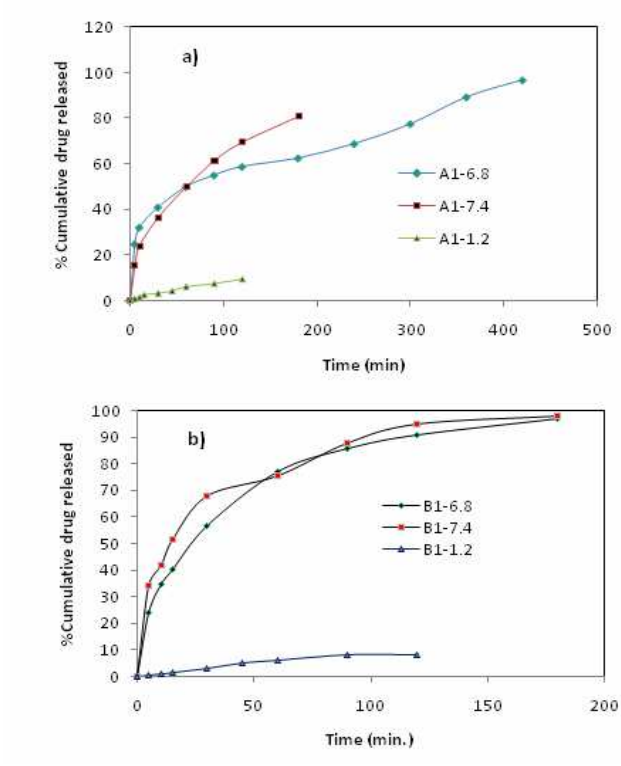


Fig. 9. % CDR from **a)** A1 samples **b)** B1 samples of gels.

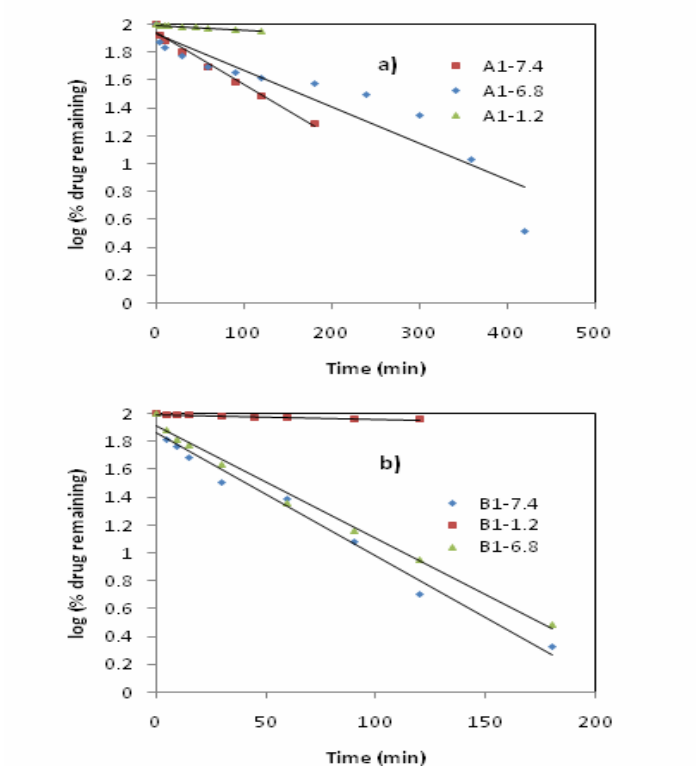


Fig. 10. Drug release data plotted in accordance with first-order equation for **a)** A1 and **b)** B1 samples

3.7. Drug release mechanism:

The drug release data obtained at pH 1.2, 6.8 and pH 7.4 at 37°C for A1 and B1 samples were plotted in accordance with the zero-order equation and displayed in Fig.9. The plots are curvilinear, suggesting that the release process is not zero-order [25-27]. When the dissolution data were plotted in accordance with the first-order equation (log (% drug remaining) vs. time) as displayed in Fig.10, a linear relationship is observed. The correlation coefficient (R^2) values obtained for first-order fit were in the range 0.88–0.99 compared to the low values for zero-order fit (0.71–0.93), indicating that the release is an apparent first-order process. This indicates that the amount of drug released is dependent on the matrix drug load.

To evaluate the mechanism of drug release from the gels, plots of ‘‘percent drug released’’ vs. ‘‘$(t)^{1/2}$’’ as per Higuchi’s equation were constructed and displayed in Fig. 11. These plots were found to be linear with the correlation coefficient values in the range 0.91–0.99 indicating that the drug release from the matrix is diffusion controlled.

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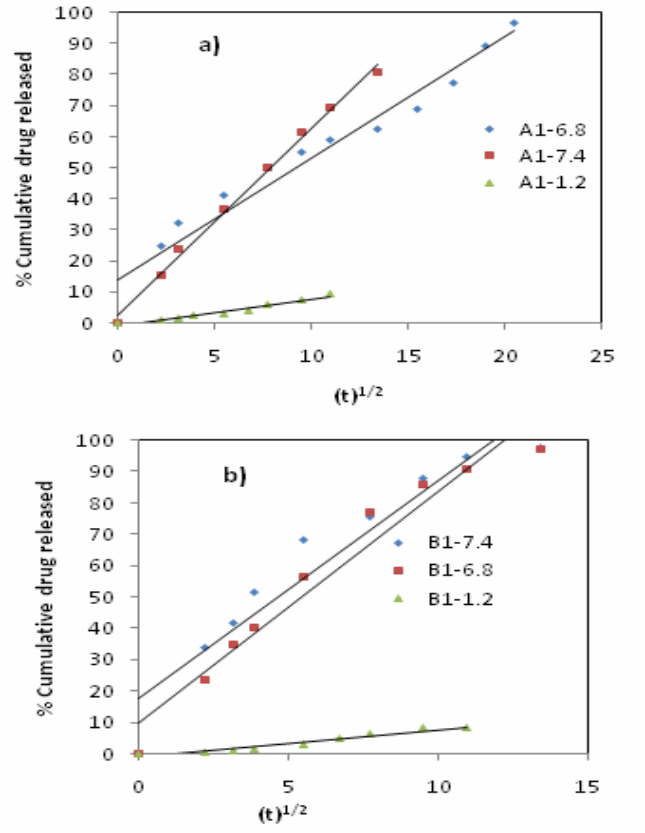

Fig. 11. Drug release data plotted in accordance with Higuchi square root equation for **a)** A1 and **b)** B1 samples.

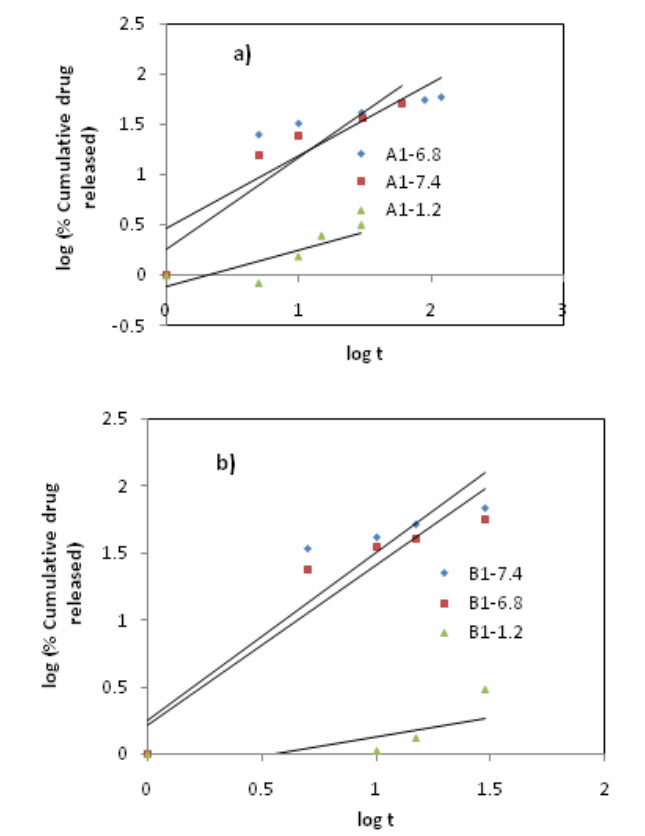

Fig 12. Drug release data plotted in accordance with Korsmeyer equation for **a)** A1 and **b)** B1 Samples.

When the release data were analyzed as per the Korsemeyer and Peppas equation, displayed in Fig. 12, the release exponent ‘‘n’’ was >0.89 for the gels A1-(pH 6.8), B1-(pH 7.4), B1-(pH 6.8) and B1-(pH 1.2) at 37°C (Table 3) indicating that the transport mechanism follows Super case II mechanism.

This suggests that more than one mechanism may be an involved in the release i.e., drug release by diffusion, erosion and polymer chain relaxation [28]. Super Case II transport is reported to be exhibited when diffusion and relaxation rates are comparable. In general, the relaxational contribution was coupled with swelling and erosion attributed to hydrophilic nature of polysaccharide components, leading to super Case II transport.

Table 3. Fit of release data with different kinetic models.

Code (pH)	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	<.....Correlation coefficient (R^2).....>				
					n
A1-(6.8)	0.891	0.882	0.953	0.759	0.722
A1-(7.4)	0.891	0.986	0.995	0.876	0.916
A1-(1.2)	0.975	0.979	0.969	0.777	0.413
B1-(6.8)	0.779	0.992	0.952	0.891	1.200
B1-(7.4)	0.713	0.981	0.913	0.863	1.250
B1-(1.2)	0.931	0.925	0.968	0.970	1.060

4. CONCLUSION

Hydrogels containing different amounts of GG and NaCMC were prepared by the chemical crosslinking using two different crosslinkers. The composition of the gel and nature of the crosslinking agents influence the surface morphology, thermal behaviour, swelling characteristics and drug release behaviour. 'DP' crosslinked gels are observed to have higher swelling capacity and higher rate of swelling compared to 'MBA' crosslinked samples. Both type of gels exhibit a good pH responsive behaviour with 3 times higher swelling in pH 7.4 compared to pH1.2. The extent of drug release significantly increased when pH of the medium was changed from acidic to alkaline. The results indicate that presently studied system may find useful as a matrix for slow release tablet formulations of the drug 'ketoprofen'.

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REFERENCES

1. Park H and Park K., Biocompatibility issues of implantable drug delivery systems, Pharm. Res., 1996, 13, 1770-1776.
2. Smetana K.Jr., Cell biology of hydrogels, Biomaterials., 1993, 14, 1046-1050.
3. Anderson J. M., In vivo biocompatibility of implantable delivery systems and biomaterials, Eur. J. Pharm. Biopharm., 1994, 40, 1-8.
4. Anderson J. M and Langone J. J., Issues and perspectives on the biocompatibility and immunotoxicity evaluation of implanted controlled release systems, J. Control. Release, 1999, 57, 107-113.
5. Katime I.,Novoa R and Zuluaga F., Swelling kinetics and release studies of theophylline and aminophylline from acrylic acid/N-alkyl methacrylate hydrogels, Eur. Polym. J., 2001, 37, 1465-1471.
6. Bae K. H., Yoon J. J and Park T. G., Fabrication of hyaluronic acid hydrogel beads for cell encapsulation, Biotechnol. Progr., 2006, 22, 297-302.
7. Jansson P., Lindberg B and Sandford P. A., Structural studies of gellan gum. an extracellular polysaccharide elaborated by Pseudomonas elodea, Carbohydr. Res., 1983, 124, 135- 139.
8. Emeje M.O., Franklin-Ude P.I and Ofoefule, S.I., Evaluation of gellan gum as a mini-matrix for sustained release ephedrine hydrochloride granules, J. Pharmacol. Toxicol., 2007, 2, 646–652.
9. Carlfors J., Edsman K., Petersson R and Jornving K., Rheological evaluation of Gelrite in situ gels for ophthalmic use, Eur. J. Pharm. Sci., 1998,6, 113–119.
10. Miyazaki S., Aoyama H., Kawasaki N., Kubo W and Attwood, D.J., In situ-gelling gellan formulations as vehicles for oral drug delivery, Control. Release., 1999, 60 ,287– 295.
11. Babu R.J., Sathigari S., Kumar M.T and Pandit J.K., Formulation of controlled release gellan gum macro beads of amoxicillin, Curr. Drug Deliv., 2010, 7, 1, 36–43.
12. Palmieri G.F., Bonacucina G., Di Martino P and Martelli S., Gastro-resistant microspheres containing ketoprofen, J.Microencapsul., 2002, 19, 111-119.
13. Mangond B.S., Sreedar V., Baraskar V.V and Kulkarni R.V., Development and Evaluation of Gellan Gum Based Hydrogel Microbeads for Controlled Release of Ketoprofen, Ind. J. Novel Drug deliv., 2009, 1, 32-35.
14. Murali Mohan Y., Keshava Murthy P.S., Sreeramulu J and Mohana Raju K., Swelling behavior of semi-interpenetrating polymer network hydrogels composed of poly (vinyl alcohol) and poly (acrylamide-co-sodium methacrylate), J. Appl. Polym. Sci., 2005, 98, 302-314.
15. Karadag E and Saraydin D., Swelling studies of super water retainer acrylamide/crotonic acid hydrogels crosslinked by trimethylolpropane triacrylate and 1,4– butanediol dimethacrylate, Polym. Bull., 2002, 48, 299-307.

16. Ritger P.L and Peppas N.A., A Simple Equation for Description of Solute Release. I. Fickian and non-Fickian Release from Non-Swellable Devices in the Form of Slabs, Spheres, Cylinders or Discs, J. Control. Release, 1987, 5, 1, 37-42.
17. Korsmeyer R., Gurny R and Peppas N.A., Mechanisms of solute release from porous hydrophilic polymers, Int. J. Pham.,1983, 15, 25-35.
18. Peppas N.A., Analysis of Fickian and non-Fickian drug release from polymers Pharm, Acta. Helv., 1985, 60, 110-111.
19. Chen J and Zhao Y., Relationship between water absorbency and reaction conditions in aqueous solution polymerization of polyacrylate superabsorbents, J. Appl. Polym. Sci., 2000, 75, 808–814.
20. Pourjavadi A., Harzandi A.M and Hosseinzadeh H., Modified Carragenan. Synthesis of novel polysaccharide based superabsorbent hydrogel via graft copolymerization of acrylic acid onto kappa-carragenan in air, Eur. Polym. J., 2004, 40, 1363-1370.
21. Keshava Murthy P.S., Murali Mohan Y., Sreeramulu J and Mohana Raju K., Semi-IPNs of starch and poly (acrylamide-co-sodium methacrylate): Preparation, swelling and diffusion characteristic evaluation, React.Funct.Polym., 2006, 66, 1482-1493.
22. Peppas N. A and Khare A. R., Preparation, structure and diffusional behavior of hydrogels in controlled release, Adv. Drug Deliv. Rev., 1993, 11, 1-35.
23. Verma A and Pandit J.K.,Rifabutin-loaded Floating Gellan Gum Beads: Effect of Calcium and Polymer Concentration on Incorporation Efficiency and Drug Release,Trop J.Pharm. es.,2011,10,1,61-67.
24. Xiao H and Brazel C. S., On the importance and mechanisms of burst release in matrix-controlled drug delivery systems, J. Control. Release., 2001, 73, 121- 136.
25. Chowdary K. P. R., Mohapatra P. M and Muralikrishna, N., Evaluation of olibanum and its resin as rate controlling matrix for controlled release of diclofenac, Indian J. Pharm. Sci., 2006, 68, 497-500.
26. Reddy K. R., Mutalik S and Reddy S., Once daily sustained release matrix tablets of Nicorandil formulation and in vitro evaluation, AAPS Pharma. Sci. Tech., 2003, 4, 480- 488.
27. Mohanan A., Vishalakshi B., Charyulu R. N., Harish N. M and Ganesh S., Sustained Release of Atorvastatin from Radiation-Synthesized Stimuli-Responsive Hydrogels, Int. J. Polym. Mater, 2011, 62, 5–9.
28. Dash S., Murthy P.N., Nath L and Chowdhury, P., Kinetic modeling on drug release from controlled drug delivery systems, Acta Pol. Pharm., 2010, 67, 3, 217- 223.

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