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Sol-gel transitions of carbopol by conductometric investigation: The impact of hydroxypropyl methylcellulose and benzalkonium chloride

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ABSTRACT

The gelation of carbomer occurs due to neutralization process of the polymer solution. The present work describes the changes in the thermophysical parameters such as molar conductance and related energetic as the polymer solution undergoes gelation so to provide more insight on the process of sol-gel transition. Hydroxypropyl methylcellulose (HPMC) as a viscosity enhancer and benzalkonium chloride (BKCl) which is a preservative and penetration enhancer were also added to the solution to study their effects on gelation. For the first time we experimented the sol-gel transitions in minute manner by conductometric titrations. The results are analyzed in terms of polymer solvent interactions with involved energetic.

Key words: Sol – gel transition, molar conductance, limiting molar conductance, activation energy, carbomol

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INTRODUCTION

The ophthalmic drug delivery presents unique challenges to formulation scientists. Eye drops are the most common method of drug delivery uses. Although this method is cheap, easy to manufacture and have good patient compliance, it suffers with many disadvantages. This method is limited to soluble drugs and requires frequent instillation of highly concentrated solution [1]. This problem is further aggravated by the impermeable corneal barrier, high tear turnover rate, nasolacrimal drainage, and many other factors that constitute the ophthalmic defense mechanism [2]. However, recent advances have found that one of the methods to alleviate this problem is to use an *in - situ* forming hydrogel using the environment sensitive polymer. These hydrogels is made of network of hydrophilic polymer that swells in water and can hold large amount of water while maintaining its structure [3]. Furthermore the phenomenon of *in – situ* sol – gel transition can be triggered by temperature, pH and presence of certain electrolyte, making it a more versatile for drug delivery [2].

There have been many researches that demonstrated improved ophthalmic drug delivery of selected drug candidates for different ophthalmic disease condition using pH – triggered *in* – situ gel system [4 - 9]. For a pH triggered system, one of the commonly used hydrogel is carbomer which is made from repeating unit of polyacrylic acid with molecular weight ranging from 2 – 30 $x10^6$ with a pKa of 5. In a dry form, the polymer is strongly coiled in spiral form that can slowly unwind due to electrostatic repulsion when is solvated [10]. When carbomer is dissolved in aqueous media, the solution will become acidic and the polymer will be in a collapsed state due to hydrogen bonding. However with the addition of alkaline compound the pH will increase causing dissociation of the complex leading to an increase in pore size which subsequently increases the hydrogel volume. The addition of alkaline

compound may also causes solvation and salt formation which increases the electrostatic repulsion between the chain and further increases the viscosity [11]. The increase in viscosity is considered an important aspect because it increases the formulation residence time on the ophthalmic membrane due to the mucoadhesive property of carbomer [1]. The mucoadhesion of carbomer is achieved via physical entanglement, chemical interaction or covalent bonds between the carbomer and the mucin layer [12]. The gel formed by carbomer have been found to be resistant to bacterial or fungal degradation due to its cross linked nature, as it can hold a robust structure that resist erosion [13]. Due to its ability to increases its viscosity in alkaline environment; it has been used for buccal, transdermal, rectal and nasal drug delivery aside from ophthalmic drug delivery [14].

To maintain high mechanical strength to withstand high shear rate due to blinking, formulator are forced to use high concentration of polyacrylic acid. These however cause irritation to the ophthalmic membrane [15]. To counter this disadvantage, another polymer has been used to strengthen the carbomer gel. One of the widely used polymers is hydroxypropyl methylcellulose (HPMC) [16]. It is obtained by modifying methylcellulose with small amount of 2-hydroxypropyl group that will attach to the anhydroglucose unit of the cellulose. In ophthalmic field, it have been used an ophthalmic viscosurgical devices during cataract surgery along with its use as a viscosity enhancing agent [17]. Even though it can undergoes gelation with change in temperature [15] it have been found to cause irritation due to its high surface active properties that may interact with the component of the tear film and alter the physicochemical parameter that maintain tear film stability. This will leads to increase blinking rate and reduce the drug residence time on the ophthalmic membrane [18]. Martin et al., 2010 found that the gelation temperature and the gel stiffness depends on the level of the methoxyl and hydroxypropyl substitutes on the cellulose ring and also on the molecular weight of the cellulose ether[19]. Higher number of substituted group will increase the gelation temperature and will cause a reduction in gel stiffness at physiological temperature. However, the gel stiffness can be increased by increasing molecular weight of the cellulose ether used [18].

Another component that is commonly used in a preparation of a pH triggered system is the benzalkonium chloride (BKCl). It acts as a preservative due to its ability to prevent bacterial and fungi contamination on multidose eye drop. It is a cationic surfactant and tensioactive compound that functions as detergent for the lipid layer of the tear film and on the lipids of cell plasma membrane. It has been found to cause fewer side effects and is relatively well tolerated though it might cause irritation such as inflammation or cell death in long term treatment. It might also cause apopotosis and oxidative stress on the ocular surface epithelia and increases the IOP. However, it was deemed negligible for short term treatment [20]. Along with its function as a preservative, BKCl has been used as a penetration enhancer. By acting on the tight junction of the epithelial layer, large molecule or impermeable drug molecule have been able to penetrate into the ocular body [21].

The reported literatures on pH triggered systems concentrated on the feasibility of the *in – situ* gel systems containing a suitable drug candidates and characterized the studied formulations in terms of their spontaneity of gelation, viscosity, stability, *in vitro* drug release and involved kinetics of drug release. However, among the many ways to characterize the formulation, conductometric technique has been one of the valuable tools in characterizing the changes in a solution system. Needless to say for an in situ forming hydrogel, the change that occurs from a solution into a soft gel is a substantial change worthy of a detailed observation. A thorough literature survey revealed a very limited research that has been done in regard to the polymeric solution systems and the subsequent gel formation. Conductometric titrations are the measurement of electrolytic conductivity of a solution system to monitor the progress of a physic-chemical alteration with a perspective of solute – solvent interaction [22]. One of the researches that observe the changes in conductivity of a gel is done by Sekhon et al. whereas the authors hypothesize that as the polymer undergoes gelation, a polymer network is being formed inside the media. This network may either hinder or promote the conductivity of the system. It also highlighted the effect of polymer concentration and different type of electrolyte on the different parameters such as viscosity and conductivity of a gel network [23]. However, a through literature search revealed, no systematic study in regard to the changed physico-chemical character during a sol – gel transitions involving suitable polymers. Hence, we intend to systematically study the pH – triggered sol – gel transition of carbomer, the impact of the polymer HPMC and the preservatives BKCl on the transition phenomena by performing conductometric titration for the first time. The viscosity experiments of the samples during titration shall be carried out for the confirmation of the phenomenon of a pH triggered sol – gel transitions. We expect to elucidate the carbomer – solvent interaction in presence of HPMC and BKCl respectively during the pH – triggered sol – gel transition

EXPERIMENTAL SECTION

2.1. Materials:

The carbomer was obtained from Sigma Aldrich, USA. Its melting point agreed nicely with the literature value and the material was used without further purification. Sodium hydroxide was of analytical grade. Doubly distilled water was used in all preparation. HPMC and BKCl were also purchased from Sigma Aldrich, USA.

2.2. Methods:

2.2.1 Preparation of polymeric solutions:

One liter aqueous solutions of different concentrations (0.3, 0.4, 0.5 and 0.6%) of carbomer were prepared. The polymeric solutions were divided into ten 100ml beakers and denoted as blank, S1, S2, S3, S4, S5, S6, S7, S8 and S9. The base polymeric solutions were considered as blank for the respective concentrations of carbomer for the purpose of comparison. In case of sample S1 to S9, the pH of respective polymeric solutions were changed by adding 0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4 and 2.0 mL of 1M NaOH solutions respectively and mixing the solutions with the help of a glass rod thoroughly instead of using any mechanical mixing device to avoid the entrapment of air. The systems were then subjected to the measurements of pH followed by conductance and viscosity. These experiments we termed as conductometric and viscometric titrations.

2.2.2 Measurement of pH, Viscosity and conductance:

After the solutions were mixed thoroughly the pH of the contents of the different systems were measured using a Eutech instruments pH 700 to determine its pH. The solutions were then transferred to a water-jacketed sample holder with the water temperature heated to 45^{o}C. The conductance for each sample was measured at 298.15, 303.15, 308.15 and 313.15 K using a Eutech instruments (Con 700). This procedure was repeated on all of the polymeric systems.

Fresh polymeric solutions were prepared for each new measurement. The viscosity measurement was done using a Brookfield R/S CP Rheometer. The sample was placed on the stationary plate and the rotating plate was pressed firmly onto the sample. Excess sample was then wiped off to ensure homogeneity in the volume of sample introduced. The measurement was done using a temperature programmed method. At certain intervals the temperature was ramped up to 25, 30, 35 and 40°C and the average was taken for each step. The rpm was maintained at 100 on the basis of the resultant torque of 10 percent. This procedure was used on all of the polymer concentration under study.

RESULTS AND DISCUSSION

The sol-gel transition triggered by a pH change has been investigated extensively with respect to the carbopol based formulation. The formulation contains HPMC as an adjunct polymer so to improve the formulation characteristic, benzalkonium chloride as a preservative. The initial part of the study deals with the effect of HPMC and benzalkonium chloride (BKCl) upon the sol-gel transition behavior of carbopol as the base polymer.

Carbopol are the reticulated polymers of acrylic acid, with molecular weight ranging from 2 to 30 x 10^6, on the basis of the involved resin [24]. This polymer is widely used as a major component of drug delivery gel systems for different applications such as ocular [25], rectal [26], nasal [27], transdermal [28] and buccal [29] etc.

The drug release and other associated physical properties of carbopol gels are highly sensitive to the presence of concentration of additives [30].

Several studies characterize the pH triggered sol-gel transition of carbopol in regard to its rheology, ocular contact time [31], determination of mucoadhesive force [32], in vitro drug release studies, and drug content uniformity [33]. However no literatures were found in regard to the thermo physical characterization during a sol-gel transition. Hence this research envisaged to study systematically the pH triggered sol-gel transition of carbopol with polymer concentration, presence of HPMC and BKCl at different concentrations as variables respectively using conductometric titrations.

3.1 Conductometric titration:

As described in the methodology fixed amount of polymeric solution at different concentration (0.3 – 0.6%) have been exposed to a systematic increment (0.1 – 2 ml) of 1M NaOH solution considering independent solution systems. A perusal of figure 1 shows that in case of carbopol systems, the pH of the solution systems increases from 3.33 (blank) till 6.02 as the amount of NaOH increases. The polymer solutions gel at around the pH of 5.

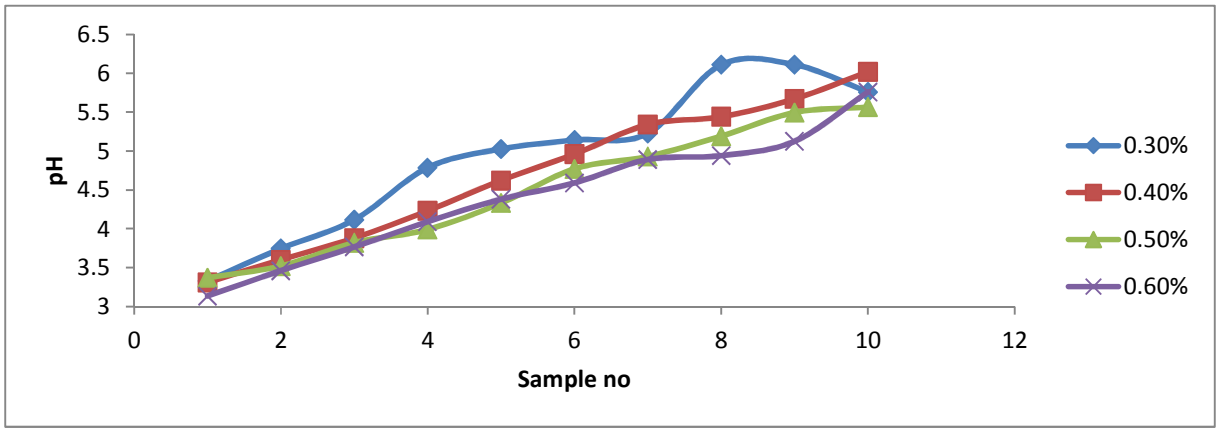

Fig 1. The changes in the pH values in responses to systematic neutralization of the different polymeric samples of different carbomer concentration (% w/v)

The obtained experimental conductance data (κ) in case of different system was converted to the molar conductance (λ_m) using the equation in the form of:

$$\lambda_m = 1000k/c \qquad (1)$$

The molar conductance data at four different temperatures (298.15 – 313.15K) of the different carbopol systems during the titration and those of the blank are listed in table 1. The limiting molar conductance (Λ_m°) of the systems was obtained using the least square fitting of the experimental data to the expression below:

$$\Lambda = \Lambda_m^\circ - A\sqrt{C}/1 + B\sqrt{C} \qquad (2)$$

Where, A and B are fitting parameter, C is the concentration [34]. The obtained limiting molar conductivities of the different systems are summarized in table 1. It can be seen from the table 1 that the values of Λ in blank carbopol polymer solutions shows anomalous behavior with increasing polymer concentration, as represented by an initial decreasing trend from 0.3% to 0.4% followed by an increase at the highest experimental concentration 0.6%w/v at 298.15K.

Polymer gels are special systems where in the polymer network envelops the liquid and prevents it from escaping as a result of which the system possesses the characteristic of both solid and liquids. So herein the network of polymer and its interaction with the contained liquid affect the properties of the gel [22]. Due to the large amount of the trapped solvent, the polymeric networks are highly solvated as a result of which gels got high extent of mobility.

The anomalous behavior (initial decrease followed by increase at higher concentration) in case of carbopol blank solutions with increase in polymer concentration can be explained by the fact that (I) increase in polymer concentration at 0.4 and 0.5% resulted in an increase in viscosity (η), that decreases the mobility of the networks hence decreasing the conductivity [35] (II) furthermore, another school of thought suggests, the polymer network does not take part in the conduction process rather acts as a stiffener increasing its mechanical stability [36 - 39], (iii) in case of 0.6% of polymer concentration. Further addition of polymer might contribute to the macroscopic viscosity but if the network provides a continuous path through the solvent, the macroscopic viscosity may not be related to the ion mobility [14], (IV) the polymer addition may affect the extent of polymer – solvent interaction resulting in a modified polymer network with higher extent of solvation that can otherwise be termed as increasing

the carrier concentration. The former two describes the decrease in conductivity where as the later two explain the increase in conductivity.

Table 1: Conductance and the limiting molar conductance of different carbopol based systems at 4 different temperatures

sample	λ(S)					λ_0 (S)
	T/K	I	II	III	IV	
Blank	298.15	1.05	0.78	1.00	1.36	-1.81
	303.15	1.05	0.77	0.98	1.40	-2.06
	308.15	1.00	0.74	0.94	1.35	-2.00
	313.15	0.95	0.89	0.91	1.33	-1.08
S1	298.15	0.97	1.08	0.92	0.91	1.12
	303.15	0.96	1.07	0.90	0.89	1.13
	308.15	0.93	1.05	0.86	0.85	1.12
	313.15	0.89	1.02	0.83	0.82	1.07
S2	298.15	1.23	1.08	1.02	0.96	1.86
	303.15	1.22	1.07	1.00	0.94	1.88
	308.15	1.24	1.05	0.97	0.91	2.05
	313.15	1.16	1.02	0.95	0.88	1.82
S3	298.15	2.10	1.63	1.23	1.24	5.08
	303.15	2.09	1.62	1.22	1.23	5.07
	308.15	2.05	1.60	1.19	1.20	4.99
	313.15	2.00	1.57	1.16	1.16	3.93
S4	298.15	2.97	2.39	1.45	1.65	6.07
	303.15	3.07	2.38	1.44	1.63	6.40
	308.15	3.02	2.34	1.42	1.61	8.58
	313.15	2.96	2.28	1.39	1.57	6.19
S5	298.15	4.00	2.97	2.15	2.10	10.32
	303.15	3.99	2.96	2.15	2.09	8.32
	308.15	3.93	2.92	2.11	2.05	10.15
	313.15	3.85	2.87	2.07	2.00	9.96
S6	298.15	5.06	3.59	2.68	2.61	13.17
	303.15	5.07	3.65	2.67	2.60	10.62
	308.15	4.99	3.61	2.62	2.57	13.12
	313.15	4.91	3.57	2.57	2.50	12.94
S7	298.15	6.02	5.41	4.93	4.56	9.54
	303.15	6.06	5.45	4.95	4.61	9.57
	308.15	5.99	5.35	4.88	4.55	9.42
	313.15	5.87	5.28	4.75	4.48	9.27

Sample I, II, III and IV contains 0.3%, 0.4%, 0.5% and 0.6% carbopol respectively

The increase in conductivity because of the polymer addition is linked to the phenomenon of increase in carrier concentration is also explained by the case of proton conducting polymers [22] that contain weak carboxylic acid groups, those are not fully dissociated in the system. The increase in their concentration through increase in their viscosity was also associated with dissociating the undissociated acid or ion aggregates hence increasing the net conductivity.

As can be seen in figure 1 the addition of different volume (0.1 – 2 ml) of 1M NaOH to different concentration of carbopol solution resulted in an increase in pH of the system. The neutralization process causes the transformation of the polymer solution towards a viscous gel. However it is interesting to note that the increment of pH with respect to the neutralization process does not follow a specific trend or a smooth pattern. The pH change in case of 0.5% carbopol shows a better pattern compared to those of the other studied concentration.

Further it can be seen in table 1 that the conductivities of systems increase with increase in pH of the system i.e. the more the system is neutralized, more is the extent of gelation and is represented with more conductivity values. These observation can be attributed to the fact that (I) carbopol molecules are strongly coiled into a spiral form in dry powder state, where as they slowly unwind once dispersed in water resulting in a system with increased viscosity (II). Neutralization by sodium hydroxide ionizes the resin with the negative charges along the polymer chain, resulting in repulsion between these chains that leads to the unfolding of the chain structure and subsequently intertwining of the structures yielding a three – dimensional matrix being heavily solvated (III). The nature of networking and extent of the solvation dictates the extent of conductivity.

Table 2: Activation energy of different carbopol based systems at 4 different temperatures

Sample	E_s(S cm^2 mol^{-1})			
	I	II	III	IV
Blank	-5358.41	-5501.99	-5107.62	-1686.59
S1	-4393.55	-3149.19	-5287.57	-5364.15
S2	-2226.45	-3149.19	-3805.83	-4204.02
S3	-2527.01	-2006.29	-3030.5	-3342.54
S4	-237.386	-2440.86	-2211.13	-2519.35
S5	-2006.29	-1892.96	-2134.56	-2565.3
S6	-1587.61	-427.868	-2371.94	-2260.91
S7	-1356.71	-1474.85	-1937.37	-1042.77

Sample I, II, III and IV contains 0.3%, 0.4%, 0.5% and 0.6% carbopol respectively

As observed in table 1, the values of molar conductance are found to decrease with increase in polymer addition in almost all system except for a few deviations. In case of the carbopol based system, the increase in temperature resulted in the decrease in the values of molar conductance excepting few cases where in the reverse is the case. The former can be explained by the fact that increase in thermal energy (due to increase in temperature) resulted in more stiffening of the polymer cross linking there by decrease the mobility of the solvated polymeric chain where in case of the later increasing in thermal energy increases the mobility of the solvated polymeric chain resulting the increase in molar conductance.

The measurement of conductance of a solution system depends upon the mobility of ions in case of an electrolytic solution where as on the mobility of solvated solute units in case of a solution containing polymeric solutes that usually undergoes hydrophobic solvation. Hence it is reasonable to treat the conductance data similar to the one employed for the rate process taking place with the change in temperature [34] i.e.:

$$\Lambda_m^{\circ} = Ae^{-E_s/RT} \qquad (3)$$

Where A is the frequency factor, R is the gas constant and E_s is the Arrhenius activation energy of the transport process. The E_s values have been computed from the slope ($-E_s$ /2.303R) of the plot of log vs. 1/T and are recorded in table 2.

It can be seen that the values of E_s are negative for the different carbopol based system pointing to the fact that the process of sol – gel transition is non – favorable or otherwise can be said as not an activation energy dependent phenomenon. Rather it is linked to the behavior of the polymer as intrinsic characters.

Further with the different carbopol concentrations along the process of sol – gel transition on the basis of the pH triggered neutralization, the activation energy is found to increase except for a few other systems. However in case of 0.5% w/v of carbopol system the trend in regard to the parameter of activation energy is observed to be very regular. These observations support the 0.5% w/v of carbopol concentration to be the optimum concentration for a formulation.

3.2 Presence of HPMC:

In this set of experiment four different concentrations (0.5%, 1%, 1.5% and 2% w/v) of HPMC is blended with a fixed concentration of carbopol (0.5% w/v) in order to study the impact of the adjunct polymer upon its sol gel transitions.

The figure 2 shows that incorporation of different HPMC concentration to a fixed concentration of carbopol rendered the system network more systematic as revealed in the plot (viscosity vs. pH of the systems) indicating the contribution of HPMC in the gel network to be a stiffener. Table 3 (Conductance and the limiting molar conductance of different carbopol based systems in presence of HPMC at 4 different temperatures) shows the molar conductance and limiting molar conductance data at four different temperatures. During the conductometric titration as the pH of the systems increases, the limiting molar conductance of the system increases respectively. Also the temperature effect upon the values of conductance is observed to decrease with increase in temperature. The increase in polymer concentration resulted in a decrease in conductance. Thus a regular trend is observed throughout the experiments with respect to the variables.

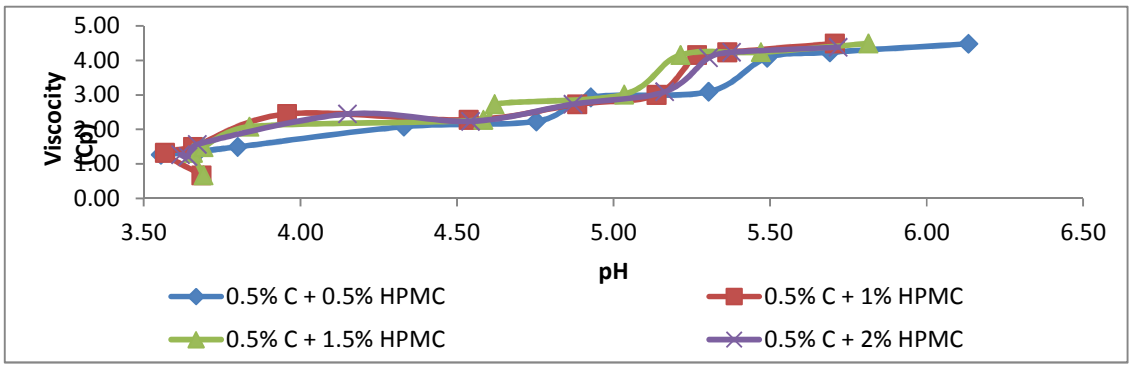

Fig 2. The change in viscosity to the corresponding changes in pH at 0.5% carbomer with different concentrations of HPMC

Table 3: Conductance and the limiting molar conductance of different carbopol based systems in presence of HPMC at 4 different temperatures

sample	λ(S)					λ_0(S)
	T/K	I	II	III	IV	
Blank	298.15	0.64	0.37	0.32	0.26	0.96
	303.15	0.63	0.36	0.31	0.25	0.96
	308.15	0.61	0.34	0.29	0.24	0.92
	313.15	0.59	0.33	0.28	0.24	0.89
S1	298.15	0.66	0.36	0.31	0.26	0.99
	303.15	0.63	0.35	0.30	0.25	0.95
	308.15	0.60	0.33	0.28	0.24	0.91
	313.15	0.58	0.32	0.27	0.24	0.87
S2	298.15	0.73	0.48	0.30	0.29	1.16
	303.15	0.70	0.46	0.30	0.27	1.11
	308.15	0.66	0.44	0.28	0.26	1.06
	313.15	0.64	0.43	0.28	0.25	1.02
S3	298.15	1.32	0.71	0.55	0.45	2.09
	303.15	1.32	0.71	0.55	0.44	2.08
	308.15	1.29	0.69	0.54	0.44	2.04
	313.15	1.27	0.68	0.53	0.44	2.00
S4	298.15	1.88	0.90	0.64	0.54	3.05
	303.15	1.88	0.90	0.65	0.54	3.04
	308.15	1.85	0.89	0.64	0.53	3.00
	313.15	1.83	0.87	0.63	0.52	2.97
S5	298.15	2.25	1.08	0.80	0.63	3.65
	303.15	2.24	1.07	0.81	0.62	3.64
	308.15	2.21	1.06	0.79	0.61	3.59
	313.15	2.18	1.04	0.78	0.60	3.54
S6	298.15	2.74	1.40	0.93	0.70	4.58
	303.15	2.72	1.40	0.93	0.70	4.55
	308.15	2.70	1.38	0.92	0.69	4.51
	313.15	2.65	1.36	0.91	0.68	4.42
S7	298.15	3.32	1.54	1.10	0.78	5.53
	303.15	3.37	1.53	1.10	0.78	5.62
	308.15	3.32	1.54	1.10	0.78	5.54
	313.15	3.26	1.54	1.09	0.77	5.44
S8	298.15	3.69	1.66	1.24	0.90	6.08
	303.15	3.68	1.71	1.23	0.91	6.10
	308.15	3.63	1.69	1.21	0.89	6.02
	313.15	3.58	1.66	1.20	0.88	5.93
S9	298.15	4.41	2.21	1.50	1.06	7.42
	303.15	4.41	2.24	1.49	1.06	7.43
	308.15	4.36	2.23	1.48	1.05	7.36
	313.15	4.28	2.20	1.46	1.03	7.22

Sample I,II, III and IV contains 0.5%, 1%, 1.5% and 2% of HPMC respectively

These observations can be ascribed to the fact that HPMC contributed to the polymer network as a stiffener hence increasing the hydrodynamics volume of the network segments hence decreasing the overall mobility and the values of conductance. The regular decreasing trend with the effect of temperature can be explained by the contribution of

thermal energy in increasing the rigidity of the gel network instead of increasing the mobility and also to the expansion of the hydrodynamic volume thereby decreasing its mobility. As in the case of carbopol systems, the HPMC addition did not alter the activation energy and negative activation energy was observed in all the cases. (Table 4: Activation energy of different carbopol based systems in presence of HPMC at 4 different temperatures).

Table 4: Activation energy of different carbopol based systems in presence of HPMC at 4 different temperatures

Sample	E_s (S cm^2 mol^{-1})			
	I	II	III	IV
Blank	-4428.73	-5912.64	-6100.28	-5813.07
s1	-6462.16	-6255.37	-6316.64	-5623.52
s2	-6663.21	-6025.61	-3758.58	-7004.02
s3	-2110.02	-2121.50	-1809.40	-1678.82
s4	-1261.22	-1842.72	-2538.91	-1991.30
s5	-2393.39	-1570.26	-2690.17	-2081.29
s6	-1802.51	-1365.19	-1421.68	-1460.93
s7	-2569.55	283.76	255.81	-236.08
s8	-1444.84	-1991.30	-1825.11	-2500.62
s9	-2357.01	-1596.87	-1429.53	-2450.83

Sample I,II, III and IV contains 0.5%, 1%, 1.5% and 2% of HPMC respectively

3.3 Presences of Benzalkonium Chloride (BKCl):

BKCl is a cationic surfactant system. At different pH, the carbopol-BKCl interaction would be different as at low pH, the degree of dissociation of the carboxylic acid groups of carbopol is low and the polymer adopts a coil conformation. While at higher pH, the chain expands as a result of intrapolymeric electrostatic repulsions.

When the polymer chains are in a compact conformation, it appears to be more hydrophobic. Hence hydrophobic interaction predominates with the surfactant. Whereas in the coiled conformation, two or three dimensional interaction among the hydrocarbon tails of bound surfactants become possible, which compensate the weaker electrolytic stabilization of the aggregates.

In this study, four different concentrations of BKCl (0.08, 0.12, 0.16 and 0.2%) in presence of 0.5% of carbopol were systematically neutralized using 1M NaOH solutions.

The carbopol-BKCl composition showed a more acidic environment than that of carbopol or carbopol-HPMC composition. Table 5 (Conductance and the limiting molar conductance of different carbopol based systems in presence of BKCl at 4 different temperatures) shows that as the pH of the compositions increased because of the fixed amount of addition of 1M NaOH, the molar conductance increases accordingly. If compared between the tested groups, carbopol-BKCl system exhibited higher conductance value than that of the other systems.

The comparatively high molar conductance values in case of carbopol-BKCl systems may be attributed to the proton released to the medium because of electrostatic interaction between the surfactant and the carboxylic groups of carbopol [14]. Further the chloride ions from BKCl also contributed to the phenomenon of enhanced mobility of the solvated chain networks. Our observations in this regard have been well documented in other literature [22].

The limiting molar conductance of carbopol-BKCl (blank) showed an initial pH value of between 2.7 – 3.07 depending on the concentration of BKCl that is lower than the carbopol and carbopol-HPMC systems. As the system is subjected to the systematic neutralization/ionization, an initial decrease in limiting molar conductance value occurs followed by an increase in limiting molar conductance. This dual behavior can be attributed to the face that (I) with an initial increase of the system pH, BKCl is absorbed on to the hydrophobic and ionic domains of the carbopol and act as a cross linking agent that resulted in interpolymeric aggregates. Once solvated, it will cause an increase in hydrodynamic volumes and thus lowering the network mobility [14]. (II)Whereas at subsequently higher pH, the systems lean toward more ionization, electrostatic interaction along with presence of free chlorine ions enhanced the solvated network mobility [40 - 43].

Table 5: Conductance and the limiting molar conductance of different carbopol based systems in presence of BKC at 4 different temperatures

Sample	λ(S)					λ_0 (S)
	T/K	I	II	III	IV	
Blank	298.15	26.88	25.83	25.97	24.98	29.66
	303.15	26.38	25.46	25.56	24.33	29.82
	308.15	25.06	24.29	24.44	23.33	27.97
	313.15	24.14	23.29	23.50	22.38	27.07
S1	298.15	22.10	20.67	21.50	21.55	23.10
	303.15	22.48	21.42	21.72	21.13	24.75
	308.15	21.65	20.88	20.94	20.33	23.86
	313.15	20.80	20.08	20.19	19.55	22.79
S2	298.15	16.46	17.96	17.66	19.10	12.64
	303.15	19.33	18.21	18.09	18.35	22.24
	308.15	18.79	17.58	17.50	17.73	21.81
	313.15	18.12	16.86	16.75	17.03	21.33
S3	298.15	13.09	13.07	12.60	12.33	15.62
	303.15	14.78	13.50	12.84	12.60	18.37
	308.15	14.47	13.15	12.26	12.25	18.23
	313.15	14.04	12.77	12.14	11.93	17.52
S4	298.15	15.28	10.81	10.19	8.77	25.11
	303.15	14.23	11.28	10.48	9.12	22.29
	308.15	14.17	11.07	10.39	9.03	22.17
	313.15	14.08	10.88	10.22	8.86	22.16
S5	298.15	19.49	13.00	11.15	9.71	34.85
	303.15	19.33	13.09	11.60	9.85	34.04
	308.15	18.45	13.03	11.37	9.67	32.33
	313.15	18.35	12.83	11.06	9.39	32.56
S6	298.15	21.62	14.84	12.59	10.80	38.81
	303.15	22.13	15.03	12.62	10.88	40.04
	308.15	21.81	14.82	12.43	10.68	39.54
	313.15	21.45	14.63	12.23	10.33	39.21
S7	298.15	25.88	17.71	13.75	11.20	49.96
	303.15	25.88	17.63	13.88	11.58	49.20
	308.15	25.31	17.29	13.66	11.45	47.92
	313.15	24.93	17.08	13.56	11.23	47.25
S8	298.15	28.75	19.67	15.97	12.43	55.18
	303.15	28.69	19.50	15.94	11.83	55.92
	308.15	28.31	19.25	15.63	11.68	55.23
	313.15	27.69	18.96	15.41	12.00	53.09
S9	298.15	37.19	25.79	19.56	15.03	73.97
	303.15	37.00	24.42	19.28	14.63	73.22
	308.15	36.38	25.25	19.19	14.33	72.96
	313.15	35.75	24.79	18.91	14.60	70.79

Sample I, II, III and IV contains 0.08%, 0.12%, 0.16% and 0.2% of BKC

It can be seen in table 5 (Conductance and the limiting molar conductance of different carbopol based systems in presence of BKC at 4 different temperatures) that as the concentration of BKCl increases, the value of molar conductance decreases in case of the carbopol BKCl system (blank) and as well as the system with higher pH conditions respectively along the path of neutralizations. These observations can be explained by the cross linking capability of the BKCl at particular pH environment.

The temperature effect upon the different systems can be classified in two way; the blank system and the systems from S4 onwards showed a decreasing trends while for S1 till S3 it exhibit an irregular pattern.

The activation energy in all cases showed a negative results indicating the smart behavior of carbopol being non effected even in presence of BKCl so far as the sol-gel transitions is concerned. Furthermore the system is not driven by the concept of activation energy. (Table 6: Activation energy of different carbopol based systems in presence of BKCl at 4 different temperatures)

Table 6: Activation energy of different carbopol based systems in presence of BKC at 4 different temperatures

sample	E_s (S cm^2 mol^{-1})			
	I	II	III	IV
blank	-5776.69	-5537.35	-5338.22	-5763.29
s1	-6132.83	-5068.25	-5770.95	-5125.69
s2	-5108.46	-6058.16	-6084.96	-5893.49
s3	-4036.22	-4380.87	-1964.50	-4346.40
s4	-870.43	-2851.01	-1949.18	-2301.49
s5	-3536.48	-1594.38	-3720.29	-3768.16
s6	-2466.15	-2150.22	-2479.55	-4089.83
s7	-2075.55	-1964.50	-1801.94	-2418.28
s8	-1947.26	-1898.44	-1970.24	-4771.47
s9	-2092.78	-1979.81	-1664.65	-3645.62

Sample I, II, III and IV contains 0.08%, 0.12%, 0.16% and 0.2% of BKC

CONCLUSION

Carbopol is able to undergo gelation when the pH changes from acidic to alkaline. The gelation process will cause the viscosity of the solution to increase and reduces the mobility of the solvated polymeric networks and reduces the conductivity. However, in certain cases the increase in macroviscosity will not change the microviscosity of the gel thus will not hinder the mobility of the solvated species which in turn will not reduce the conductance of the gel.

The addition of HPMC into the gel solution further increases the viscosity and reduces the conductivity. However the HPMC addition demonstrated a more defined trend during sol-gel transition as compared to carbopol only systems. This suggests that gelation process has become more ordered.

The last system observes the changes in conductivity for carbopol/BKCl based solution. The addition of BKCl into the system causes the formation of weaker gel (lower viscosity compared to other system) with higher conductivity. The increase in conductivity is attributed to increase in proton carrier concentration and the increased in concentration of solvated ions.

In all the system observed, the activation energy (E_s) has a negative value showing that the gelation process of carbopol is not spontaneous and is controlled by the intrinsic property of polymer.

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REFERENCES

[1] CL Bourlais; L Acar; H Zia; PA Sado; T Needham; R Leverge, *Prog. Ret. & Eye Res*., **1998,** 17(1), 33-58.
[2] H Almeida; MH Amaral; P Lobáo; JMSM Lobo, *Drug Disc Today,* **2014,** 19(4), 400-412.
[3] Y Qiu; K Park, *Adv. Drug Del. Rev.,* **2001,** 53, 321-339.
[4] F Ferrari; C Ronchi; C Caramella, *Euro J. Pharm. & Biopharm*., **2006,** 62, 59 – 69.
[5] J Ceulemans; A Ludwig, *Euro J. Pharm. & Biopharm*., **2002,** 54, 41 -50.
[6] SL Esteban; RH Manzo; FL Alovero, *Int. J. Pharm.*, **2009**, 366, 53 – 57.
[7] AM Durrani; NM Davies; M Thomas; IW Kellaway, *Int. J. Pharm*., **1992,** 88, 409 – 415.
[8] AESF Abou el Ela; MME Khatib, *Saudi Pharm. J.*, **2014,** 1-9.
[9] HR Lin; KC Sung, *J. Control Rel.,* **2000**, 69, 379 - 388.
[10] TS Taberner; AM Villodre; JMP Delfina; JVC Herráez, *Int. J. Pharm*., **2002,** 233, 43 – 50.
[11] IH Suhaime; M Tripathy; ABA Majeed, *Int. J. Pharma. & Bio. Sci*., **2012,** 3(1), 586 – 608.
[12] NS Miller; M Chittchang; TP Johnston, *Adv. Drug Del. Rev.,* **2005,** 57, 1666 – 1691.
[13] SP Leggs; SH Neau, *Int. J. Pharm,,* **2008,** 361,169 – 176.
[14] RB Iglesias; CA Lorenzo; A Concheiro, *Int. Control Rel.,* **2001,** 77, 59 – 75.
[15] BK Nanjawade; FV Manvi; AS Manjappa, *J. Control Rel.,* **2007,** 122: 119 – 132.
[16] B Srividya; RM Cardoza; PD Amin, *J. Control Rel.,* **2001,** 73, 205 – 211.
[17] A Fatimi; JF Tassin; R Turczyn; MAV Axelos; P Weiss, *Acta Biomat.,* **2009,** 5, 3423 – 3443.
[18] A Ludwig, *Adv. Drug Del. Rev.*, **2005,** 57, 1595 – 1639.

[19] CP Martin; T Sanz; DW Steringa; A Salvador; SM Fiszman; TV Vliet, *Food Hydro*., **2010,** 24, 702 -708.
[20] FB Baudouin; N Desbenoit; G Hamm; H Liang; JP Both; A Brunelle; L Fournier; V Guerneaus; R Legouffe; J Stauber; D Touboul; M Wisztorski; M Salzet; O Laprevote; C Baudouin, PLoS ONE, **2012**, 7(11), 1 -12.
[21] K Okabe; H Kimura; J Okabe; A Kato; H Shimizu; T Ueda; S Shimada; Y Ogura, *Invest Ophthal & Vis. Sci.*, **2005,** 46(2), 703 - 708.
[22] SM Khopkar. Basic Concept of Analytical Chemistry, 3rd Edition, New Age Science, **2007;** 978-81-224-2092-0
[23] SS Sekhon, *Bull Mater Sci.*, **2003,** 26(3), 321 -328.
[24] BW Barry. Rheology of Dermatological Vehicles in Dermatological Formulations, Percutaneous Absroption. *Marcel Dekker*, **1983**, 351 – 407.
[25] S Kumar, BO Haglund; KJ Himmelstein, *J. Ocul. Pharmacol* **1994,** 10, 47 – 56.
[26] K Morimoto; I Hama; Y Nakamoto; T Takeeda; F Hirano; K Morisak, *J. Pharm. Dyn.*, **1980,** 3: 24 – 32.
[27] JS Chu; R Chandrasekharan; LA Godon; DW Norman; HG Arthur, *Pharm. Res.*, **1991,** 11, 1408 – 1412.
[28] R Ilango; S Kavimani; KS Kumar; KR Deepa; B Jaykar, *East Pharm*., **1998,** 41, 123 – 125.
[29] M Dittgen; M Durrani; K Lehman, *S.T.P Pharm. Sci.*, **1997**, 7: 403 – 437
[30] RB Iglesias; CA Lorenzo; A Concheiro, *J. Control Rel*., **2003,** 93, 319 - 330.
[31] K Edsman; J Carlfors; K Harju, *Int. J. Pharma*. **1996,** 137, 233 – 241.
[32] H Takeuchi; Y Matsui; H Yamamoto; Y Kawashima, *J. Control Rel.*, **2002,** 86, 235 - 242.
[33] Ç Tas; Y Ozkan; A Savaser; T Baykara, *Il Farmaco*, **2003,** 58, 605 – 611.
[34] M Mohamed; M Tripathy; ABA Majeed, *K. Arab J. Chem.*, **2013,** 1-5.
[35]O Bohnke; G Frand; M Resrazi; C Rousselet; C Truche, *Sol State Ion* **1993,** 66, 97 – 104.
[36] A Weber, *J. Electrochem. Soc*., **1991,** 138(9): 2586 – 2590.
[37] R Koksbang; II Oslen; D Shackle, *Solid State Ionics*, **1994,** 69, 320-335.
[38] SA Agnihotry; S Nidhi; P Pradeep; SS Sekhon, *Solid State Ionics* **2000,** 136 – 137, 573 – 576.
[39] N Arora; SS Sekhon, *Solid State Ionics*, **2000,** 10, 9789812791979_0063.
[40] SC Joshi, Materials 4, **2011,** 1861 – 1905.
[41] T Shimizu, *Colloid Surf A*, **1994,** 84, 239 – 248.
[42] C Coquelet; N Lakhchaf; B Pages; M Persin; LS Rao; J Sarrazin; G Tarrago, *J. Membr. Sci.*, **1996,** 120, 287 – 293.
[43] RB Iglesias; CA Lorenzo; A Concheiro, *J. Control Rel*., **2003,** 93, 319 - 330.