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Research Article

PREFORMULATION STUDY OF POLOXAMER 407 GELS: EFFECT OF ADDITIVES

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ABSTRACT

Objective: Present work was aimed to observe effect of additives normally used in thermoreversible gel formulation. As, the formulation is temperature sensitive, it seems gelling is likely be additives dependent. Thermoreversible gels for nasal administration of sumatriptan succinate were prepared to improve bioavailability and patient compliance.

Methods: In this, effect of concentrations of various additives on that is enthalpy of gelation and enthalpy of gel melting were observed. These include poloxamer 407 (thermoreversible polymer), sorbitol (osmotic agent), carbopol 934 P (mucoadhesive agent), benzalkonium chloride (preservative) and sumatriptan succinate. Aqueous gels containing poloxamer 407 (16%, 18%, 20%, 22%, 24% w/w) were prepared. Gels of all above additives were prepared separately by cold method with a concentration of sorbitol (0.5 M, 1M, 1.5M), carbopol 934 P (0.25%, 0.5%, 0.75%, 1% w/w), sodium chloride (0.45%, 0.90 %, 1.5% w/w) benzalkonium chloride (0.02, 0.04, 0.06% w/w) and sumatriptan succinate 25mg/100 g.

Results: For plain poloxamer gels, as T_1 decreases and T_2 increases with increase in poloxamer 407 concentrations, enthalpy of gelation was reduced and enthalpy of gel melting increased. Decrease in T_1 and T_2 was found with sorbitol and extent of decrease in T_2 was significant. Carbopol 934 P and sodium chloride was shown to decrease T_1 and T_2 with increase in their concentration. No effect of benzalkonium chloride and sumatriptan succinate was observed on T_1 and T_2.

Conclusion: There are considerable thermodynamic effects of additives on thermoreversible gelation. It is essential to consider this in formulation development of thermoreversible gel.

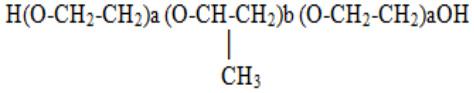
Keywords: Enthalpy, Gelation temperature, Phase transition temperature, Sumatriptan succinate

INTRODUCTION

Much attention is given now days to intranasal administration of drugs due to opportunity provided by nasal route with number of advantages compared to other routes of administration. Chances of metabolism of drug are little as enzyme contents in nasal route are very low. This provides chances of maximum bioavailability of drug. This is similar to intravenous administration. The drug is directed to reach to systemic circulation or to brain or may be limited to local effect. Systemic effect is possible due to high vascularised mucosa and brain targeting due to high permeability of olfactory region. These possibilities indicate great potential in nasal route for drug administration and now days it became route of vaccination. Other benefits include, non-invasiveness, self medication, patient comfort and patient compliance [1]. Drugs are absorbed rapidly by paracellular or transcellular pathways; there is fast onset of action and improved bioavailability. This fact may be utilized for delivery of drugs where quick pharmacological response is essential. Low molecular and high molecular drugs and biologicals such as proteins and peptides are also absorbed well if they are formulated properly. However, rate limiting step in drug absorption is mucocilliary clearances which reflect in small residential time in nasal cavity. This leads to lesser bioavailability of drug and produces inter-subject variability in pharmacological response. Therefore, to avoid this, it is essential to provide longer residential time for delivery system at the site of absorption which will allow absorption for longer time.

Formulation consideration in such delivery system is important. Not only delivery of drug across the mucus membrane but ease of administration at the site is equally important. In situ formation of delivery system is one of the potential approaches in such cases.

Poloxamers are widely used in pharmaceuticals, cosmetics and health care applications. Thermoreversible behaviour is one of the properties which can be utilized in the formation of in situ gels. Poloxamer 407 is ABA type block copolymer contains 70% of polyoxyethylene (PEO) fraction with molecular weight of 12000 and general formula is



The property of poloxamer 407 is depending upon proportion of hydrophilic, lipophilic groups in the chain. Poloxamers are good stabilizers, non toxic in nature and good solubility agent. Therefore, it is suitable for drug delivery system [2].

Thermoreversible behaviour is attributed to temperature dependent solubility. Poloxamer 407 is more soluble in cold water and less in hot water. This property can be utilized effectively in the development of drug delivery system. Poloxamer 407 forms solution at 5 ^{0}C due to excessive hydrogen bonding between water molecule and ethereal oxygen of the polymer. It has been observed that aqueous solutions of 20% to 40% w/w of poloxamer 407 converts into high viscosity gel at human body temperature. Thus, sol-gel is important phenomenon for poloxamer solutions. Conversion of gel to sol at lower temperatures is also possible. Thus, poloxamer 407 shows temperature dependent phase transition. This temperature dependent gelling is micellar in nature which is made up of micellar subunits of cubic orientation. Micellar mode of polymer is useful as drug delivery system[3].

The reverse thermal gelation exhibited by poloxamer 407 (18% to 35%) has been used as drug delivery system for nasal[5] [6] [7] [8].

Sumatriptan succinate is selective 5 hydroxytryptamine receptor subtypes agonist. It is used as antimigraine agent. After oral administration bioavailability is found to be approx. 15% primarily due to presystemic metabolism and partly due to incomplete absorption. Therefore attempts have been made to develop thermorversible nasal gels of sumatriptan succinate with poloxamer 407. This was aimed to improve bioavailability, onset of action, and ease of administration through nasal route. As there is sol gel transition of formulation takes place due to poloxamer 407, it was very interesting to know the thermodynamic changes in formulation. It was thought that excipients can affect phase transition properties

which play significant role in formulation development and performance of drug delivery system.

MATERIALS AND METHODS

Materials

Poloxamer 407 was a gift sample from BASF Corporation, Mumbai, India. Sumatriptan succinate was a gift sample from SMS Pharmaceuticals Ltd, Hyderabad, India. Sorbitol, sodium chloride, benzalkonium chloride were purchased from Loba chemicals, Mumbai. Carbopol 934 P was purchased from Analab fine chemicals, Mumbai. Other chemicals were of research grade and were used without further purification.

Methods

Preparation of poloxamer 407 gels

Poloxamer 407 gels were prepared by cold technique described by Schmolka[9]. A weighed amount of poloxamer 407 (16%, 18%, 20%, 22% and 24% w/w) was slowly added to 8 ml of water at room temperature with continuous magnetic stirring. These mixtures were kept overnight at 4^0C and weight was adjusted to 10 g with distilled water.

Gels with sorbitol (0.5, 1, 1.5 M), carbopol 934 P (0.25%, 0.5%, 0.75%, 1% w/w), sodium chloride (0.45%, 0.90%, 1.5% w/w), benzalkonium chloride (0.02%, 0.04%, 0.06% w/w), and Sumatriptan succinate (25mg/100 g) were prepared separately. All gels were stored at cold temperature and evaluated within 48 hours.

Evaluation of gels

Gelation and gel melting

Gelation temperature (T_1) and gel melting temperature (T_2) were determined by modification of Miller and Doravan technique [10]. A 2 ml aliquot of gel was transferred to test tubes immersed in a water bath at 4^0C and sealed with aluminium foil. The temperature of water circulation bath was increased with increments of 1^0C and left to equilibrate for 5 min. at each new setting. The samples were examined for gelation which was said to have occurred when the meniscus would no longer move upon tilting through 90^0.The gel melting temperature, a critical temperature when the gel starts flowing upon tilting through $90^0$was recorded.

Enthalpy of gelation and gel melting

The enthalpy of gelation (ΔH^0_{gel}) and gel melting (ΔH^0_{mel}) for plain poloxamer 407 gels and for gels with various formulation additives were calculated. Enthalpy of transition was obtained from semi-log plot of poloxamer 407 concentrations versus reciprocal of transition temperature using following equations.

$$\ln C = \frac{\Delta H^0_{gel}}{RT_1} + \text{constant} \quad (1)$$

$$\ln C = \frac{\Delta H^0_{mel}}{RT_2} + \text{constant} \quad (2)$$

Where, T_1 and T_2 represent gelation and gel melting temperature, respectively.

Viscosity determination

Viscosity of plain poloxamer 407 gels and gels containing benzalkonium chloride were measured using Brookfield's DVR II Pro model. The gel sample (about 10 ml) at low temperature was placed in small sample adaptor. The temperature of the sample was raised above 30^0 to 34^0 C using circulation bath. The sample was allowed to cool and viscosity at various temperatures was recorded using suitable spindle. T_1 and T_2 of poloxamer gels containing benzalkonium chloride was measured by the procedure described above.

RESULTS

Effect of additives on gelation temperature and gel melting temperature and enthalpy

Phase transition temperature that is gelation temperature (T_1) and gel melting temperature (T_2) were observed for concentration range of 16% to 24% w/w of poloxamer 407. This range was found suitable to find minimum gelling concentration of poloxamer 407. It was observed that gelation temperature and gel melting temperature were dependent on concentration of poloxamer 407. In this study, T_1 decreased with increase in concentration (%w/w) of poloxamer 407 and T_2 increased significantly. (Fig no.1)

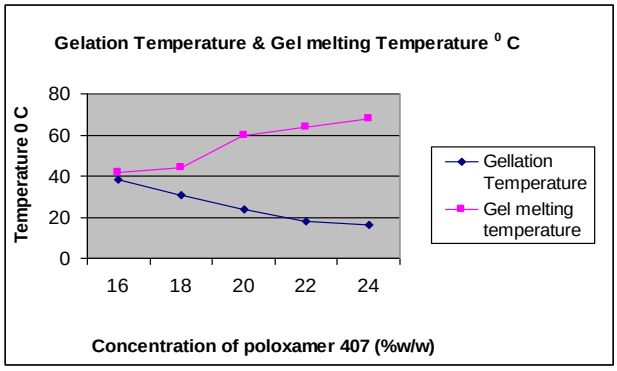


Fig.1: Gelation and gel melting temperature of poloxamer gels

Sorbitol can be used as osmotic agent in the formulation of gel. The effect of sorbitol was observed at three different levels viz 0.5 M, 1.0 M, and 1.5 M. It was observed that at fixed concentration of poloxamer 407 (18% w/w), decrease in gelation (T_1) and gel melting temperature (T_2) was observed with increase in concentration of sorbitol. (Fig No. 2 and Fig No.3)

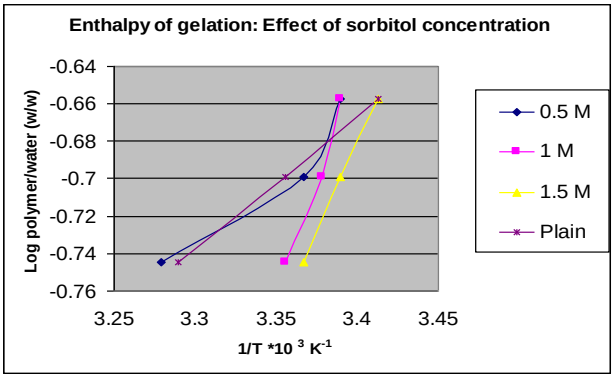


Fig. 2: Enthalpy of gelation: Effect of sorbitol concentration

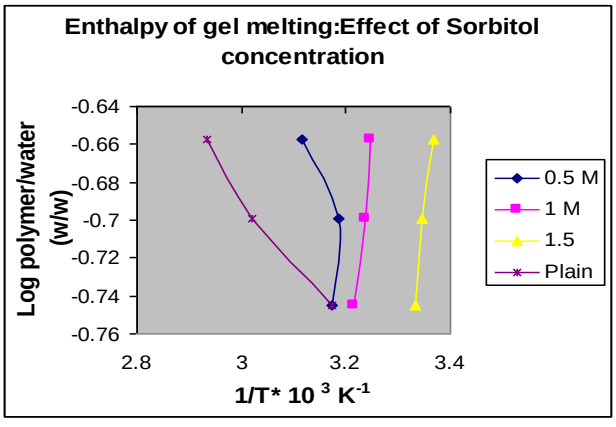


Fig. 3: Enthalpy of gel melting: Effect of sorbitol concentration

At concentration of 2M, only increase in viscosity without gelling was observed. With increase in poloxamer 407 concentrations (20% and 22% w/w), the same pattern was observed for gelation and gel melting. Decrease in gel melting temperature (T_2) was found to be significant as compared to gelation temperature (T_1). (Fig No. 4 and Fig No. 5) The gel melting was observed at room temperature for sorbitol concentration of 1.5M.

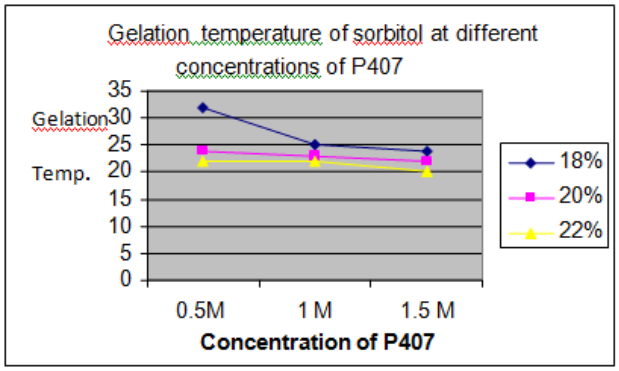


Fig. 4: Gelation temperature of sorbitol gels at different concentrations of Poloxamer 407

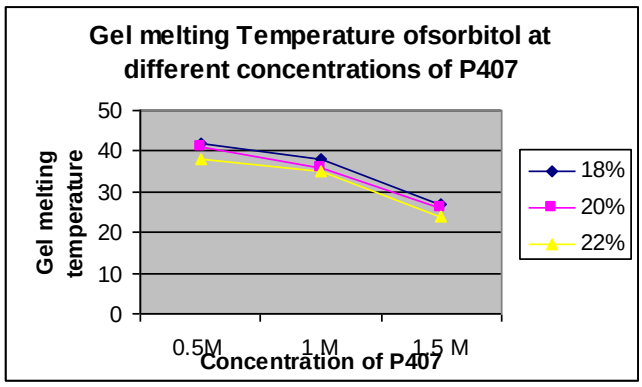


Fig.5: Gel melting temperature of sorbitol gels at different concentrations of Poloxamer 407

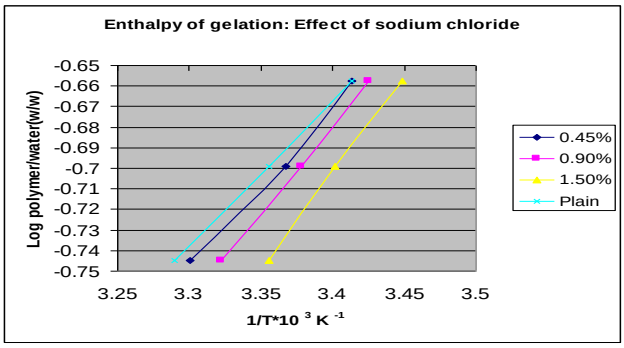


Fig.6: Enthalpy of gelation: Effect of sodium chloride concentration

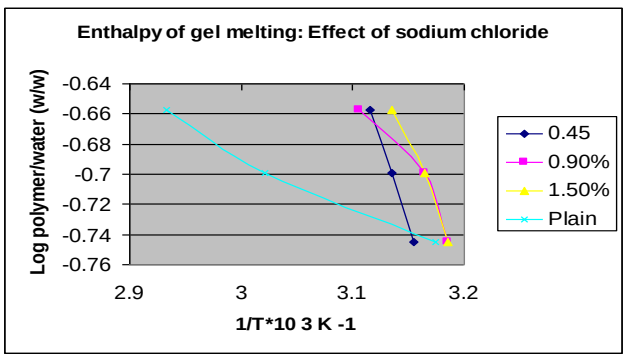


Fig.7: Enthalpy of gel melting: Effect of sodium chloride concentration

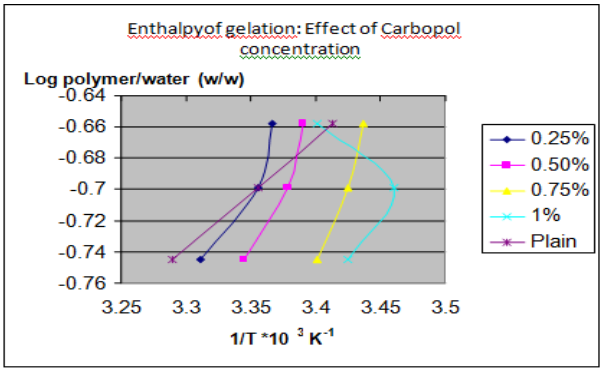


Fig. 8: Enthalpy of gelation: Effect of carbopol concentration

Sodium chloride, an electrolyte, can be used as osmotic agent in gel preparations. It's effect was observed at three levels 0.45%, 0.90% and 1.5% w/w. It was observed that at concentrations of poloxamer 407 (18%, 20% and 22% w/w) there was decrease in gelation temperature with increase in concentration of sodium chloride. The slope of the line decreases with increase in concentration of sodium chloride. This is attributed to interaction of sodium ions with ethereal oxygen of the polymer.

Carbopol 934P is anionic polymer which can be used easily to prepare mucoadhesive gels due to its mucoadhesive nature. It's effect was seen with concentration of poloxamer 407 (18%, 20%, 22%w/w) at four different levels viz 0.25%, 0.5%, 0.75% and 1% w/w. A trend of decrease in gelation temperature was observed with increase in concentration. The onset of gel melting increased.

Sumatriptan succinate was used in concentration of 25 mg/100 g to observe gel transition temperatures. There was no effect on (T_1) and (T_2).

Effect of benzalkonium chloride concentration on viscosity

Benzalkonium chloride, a quaternary ammonium compound is usually used as preservative in nasal formulations. Concentrations 0.02, 0.04, and 0.06% w/w were used to observe concentration-viscosity and temperature viscosity relationships. The said concentrations are likely to be used for preservation of gel. At fixed concentration of poloxamer 407 (18% w/w), no significant effect was found on T_1 as well as T_2. Benzalkonium chloride is a mixture of alkyls with chain length between C8 to C18 and exhibit weak surface tension properties. Effect on viscosity at room temperature and at gelation temperature was observed for a sample volume of 10 g in small sample adaptor of Brookfield viscometer with a suitable spindle number at constant shear rate and varying shear rates. For all concentrations, viscosity was found to be decreased at temperature 25 ^{0}C and found to be increased significantly at gelation temperature of 31 to 34 ^{0}C at constant shear rates. Constant shear rates were used because gels are non Newtonian. The increase in viscosity at gelation range is attributed to formation of close packed micelles and aggregation. The rise in viscosity was dependent on concentration of benzalkonium chloride. It was found that the slope of viscosity-temperature lines increases with increase in benzalkonium chloride concentration. Sumatriptan succinate was used in concentration of 25 mg/100 g to observe gel transition temperatures. There was no effect on (T_1) and (T_2).

DISCUSSION

Effect of additives on gelation temperature and gel melting temperature and enthalpy

As the temperature of aqueous solutions of these concentrations of poloxamer 407 increases, micellar entanglement takes place and which ultimately result in overall increase in bulk viscosity. It has been observed by earlier researchers that gelation of poloxamer 407 takes place due to orientation of body centered cubic packaging of spherical micelles. Temperature plays important role in the micelle formation of poloxamer 407 through the temperature dependent

hydration of ethylene oxide units. At lower temperature, water serves as good solvent for polyoxyethylene and polyoxypropylene units of poloxamer 407. At the lower temperature, hydrogen bonding between polyoxypropylene chains and water keeps hydrophobic portions of poloxamers separate. At higher temperature, hydrogen bonding is disrupted and hydrophobic interactions cause a gel to be formed. Thus, gelling properties of poloxamers are dependent on proportion of hydrophobic portion. With increase in concentration of poloxamer 407, there was decrease in gelation temperature due to increase in hydrophobic portion of poloxamer 407. Thus, at higher temperature the solubility of polyoxypropylene is reduced and micelle formation takes place. Increase in gel melting temperature is associated with high hydrophobic interactions at higher temperature. Therefore, energy required for gel melting was more. Thus, enthalpy of gelation was reduced and enthalpy of gel melting increased with concentration of poloxamer 407 [11].

The decrease in gelation temperature (T_1) due to sorbitol is attributed to the favouring of association between the polymer molecules due to participation of sorbitol in hydrogen bonding with the etheral oxygen of the polymer. Also, decrease in gel melting temperature is attributed to desolvation of polyoxyethylene chains of the polymer by sorbitol. The enthalpy of gelation decreases with increase in sorbitol concentration. As the concentration of sorbitol increases, the difference in the gel melting temperature reduces.

The decrease in gel melting temperature is associated to desolvation of polyethylene oxide chains of polymer. Miller S. C. and Drabik B. R. [12]have reported that poloxamer 407 has tendency to salt out of aqueous solution in the presence of strong electrolyte such as sodium chloride. Waikar S. B. et al. [13] have reported the ability of inorganic salt (sodium chloride) to reduce water activity of system and its salting out effect. Therefore enthalpy of gelation and enthalpy of gel melting progressively decreases. (Fig No.6 and Fig No.7)Thus, the fact studied supports the observations of earlier researchers.

The decrease in gelation temperature is due to contribution of carbopol 934P in the formation of hydrogen bonding with ethereal oxygen of the polymer. (Fig. No.8) A progressive decrease in sol gel transition temperatures with increase in carbopol 934 P concentrations has been reported by Gonjari I.D. and Kasture P. V·[5] This supports the current findings.

Effect of benzalkonium chloride concentration on viscosity

Effect of benzalkonium chloride (0.05, 0.1, 0.125 and 0.250% w/v) on viscosity of gels studied by S. S. Pisal et al., has shown that presence of benzalkonium chloride significantly reduced the gelation onset temperature from 27.94 to 22.2 ^{0} C. The lowering of gelation onset temperature is due to hydrophobic interactions between alkyl chain of benzalkonium chloride and polypropylene oxide chains of poloxamer 407 which lead to squeezing out water at lower temperatures. Further, it is responsible for reduced solubility of polyoxypropylene chain of polymer at the temperature where micelle formation takes place. However, in present study, no significant effect on T_1 and T_2 was noticed. This may be due to lower concentration range studied. If compared, viscosities of gels with benzalkonium chloride and without benzalkonium chloride at 25 ^{0} C, viscosity was found to be decreased with benzalkonium chloride gels and increased at 34 ^{0} C at constant shear rates.

CONCLUSION

This study indicates that thermodynamic properties of poloxamer 407 gels are dependent on concentration of polymer and water soluble additives. The gelation range broadens with polymer concentration. The change in enthalpy during phase transition was significant with gels of sorbitol, carbopol indicating interaction with polymer. In case of gels with sodium chloride, significant effect on enthalpy change indicates salting out effect. The viscosity of gels with benzalkonium chloride is dependent on concentration of benzalkonium chloride. This study is useful for selection of additives and formulation development of mucoadhesive thermoreversible gel.

ACKNOWLEDGEMENT

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