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Effect of Flavors on the Viscosity and Gelling Point of Aqueous Poloxamer Solution

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This study examined the effects of flavors, which are usually added to improve the appeal of pharmaceutical agents, on the viscosity and gelling point of 18% (w/w) aqueous poloxamer 407 solutions. Monoterpenes, esters, alcohols, aldehyde·ketones and lactone type flavors were examined. The concentrations of flavor ranged from 0.1 to 1.0%(w/w). After adding a flavor to the aqueous poloxamer 407 solution, the viscosity of the solution was measured using a Brookfield viscometer, and the gelling point was determined from the viscosity vs. temperature plot. The gelling point of the aqueous poloxamer 407 solution decreased with increasing concentration of flavors except for coumarin, vanillin and ethylvanillin. Thermal analysis with DSC showed an interaction between the flavors and poloxamer 407. These results suggest that the flavors bind to the hydrophilic end chains of poloxamer 407, which increases the viscosity, causing gelation at lower temperatures.

Key words: Poloxamer, Flavors, Viscosity, Gelling point, Thermal analysis

INTRODUCTION

Poloxamers are poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) triblock copolymers and non-ionic surfactants that are compatible with various drugs and are excellent solubilizing agents for water insoluble drugs. Therefore, poloxamers have been widely used in the pharmaceutical and cosmetic industry as gelling agents, wetting agents, emulsifying agents and ointments bases.

A poloxamer solution of approximately 20% (w/w) shows a Newtonian behavior in the sol state but becomes pseudoplastic around the gelling point. Upon heating from a low temperature, the viscosity of the polymer solution initially decreases slightly and then, increased gradually. As the temperature approaches the gelling point, the viscosity of the poloxamer solution increases steeply. This sudden change in viscosity in the poloxamer solution is caused by a tighter network, known as gels. Ruel-Gariépy *et al.* (2004) proposed the process for the gelation of an aqueous poloxamer solution. Micelle formation occurs at the critical micellization temperature as a result of poly (propylene oxide) block dehydration (Zhou and Chu, 1988; Bohorquez *et al.*, 1999). With increasing temperature, micellization becomes more important, and at a certain point, the micelles come into contact and can no longer move. In addition, the formation of highly ordered structures, such as a cubic crystalline phase, has been proposed as the driving force for gel formation (Mortensen and Pederson, 1993; Wanka *et al.*, 1990; Mortensen, 1993; Schillén *et al.*, 1993). Therefore, the packing of micelles and micelle entanglements may be the mechanism for poloxamer solution gelation with increasing temperature (Cabana *et al.*, 1997).

Poloxamer gels have shown promising results in the area of controlled or improved drug delivery systems (Miyazaki *et al.*, 1984; Johnston and Miller, 1989; Kim *et al.*, 2002; Yong *et al.*, 2004; Fawaz *et al.*, 2004; Pisal *et al.*, 2004; Abdel-Hamid *et al.*, 2006). In order to develop such controlled delivery systems, it is essential to characterize the gelation process as well as the effect of additives on gel formation. This is because an alteration of gelling point in a poloxamer solution affects the diffusion of drugs from the gels leading to a change in the release rate. Thus far, it has become clear that several compounds exert an influence on the gel formation of poloxamer. Gilbert *et al.* (1987) reported that the viscosity of an aqueous poloxamer solution increased with the addition of glycerin or propylene glycol. Bahadur (1993) showed that

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inorganic salts decreased the gelling point of an aqueous poloxamer solution and that the effects could be viewed in terms of a reduction in the water activity leading to an increase in the active concentration of the polymer in the system. Sodium dodecyl sulfate is known to increase the gelling point due to micellar solubilization, and alcohol also increases the gelling point due to a disruption of the hydration sphere presumably around the hydrophobic portion of the poloxamer. Pisal *et al.* (2004) reported that the presence of vitamin B_{12} reduced the gelation temperature of a poloxamer gel and presence of sorbitol narrowed and shifted the gelation range significantly to lower temperatures. In addition, a linear increase in gelation temperature was observed with the PEG 15000 concentration. Yong *et al.* (2004) reported that ibuprofen increased the gelation temperature, whereas menthol decreased the gelation temperature of poloxamer gel (liquid suppository).

The physicochemical properties of aqueous poloxamer 407 solutions have already been studied (Alexandridis and Hatton, 1995; Cabana *et al.*, 1997; Ruel-Gariépy and Leroux, 2004). However, there are few reports on the effects of additives on both the gelling point and viscosity. This study examined the effect of flavors on the gelling point and viscosity of aqueous poloxamer 407 solutions and investigated the mechanism for the change in the viscosity of aqueous poloxamer 407 solutions in which flavors had been added.

MATERIALS AND METHODS

Materials

All solutions were prepared with deionized water. The following materials were used as received without further purification: poloxamer 407 (BASF Wyandotte Co., Germany), benzyl acetate, cinnamaldehyde, cinnamyl alcohol, ethyl-trans-cinnamate, ethyl 3-phenyl glycidate, ethylvanillin, linalyl acetate and (lR)-(-)-menthyl acetate (Aldrich Chemical Co., U.S.A.), *dl*-citronellol, coumarin, n-decyl aldehyde, eugenol, geraniol, β-ionone, 4-methyl acetophenone, (R)-(+)-sec-phenyl ethyl alcohol, terpineol and vanillin (Sigma Chemical Co., U.S.A.), 2-phenyl ethyl acetate and (±)-α-terpinyl acetate (Fluka Chemical Co., Switzerland), cineole and limonene, (Wako Chemical Co., Japan), menthol (Jassen Chemical Co., Japan), *dl*-camphor (Junsei Chemical Co., Japan), thymol (Beizan Chemical Co., Japan) and ethanol (J.T Baker Chemical Co., U.S.A.).

Preparation of aqueous poloxamer 407 solution

The aqueous poloxamer 407 solutions were prepared using the 'cold method' (Schmolka, 1972). A weighed amount of poloxamer 407 was added slowly to cold water with gentle mixing and stored overnight at 4°C.

Preparation of aqueous poloxamer 407 solution containing flavors

Since most of the flavors used in this study are insoluble in water but soluble in ethanol, ethanol was added to a concentration of 10% (w/w) in the formulation to obtain a homogeneous mixture of flavor. After the flavors had been dissolved in ethanol, the solutions were mixed with a 20% poloxamer solution. The concentrations of flavors were fixed to 0.1, 0.2, 0.5 and 1.0% (w/w), respectively. As a control solution, an 18% poloxamer 407 solution containing 10% ethanol (20% poloxamer solution 90 mL + ethanol 10 mL) was used. Table I shows the flavors used for the experiments. All the solutions were stored at 4°C immediately before the viscosity measurements.

Measurement of apparent viscosity and gelling point

The apparent viscosity of the poloxamer solution was measured using a viscometer (Brookfield Engineering Laboratories, Model DVII+). The viscometer was connected to a water bath (Jeio Tech., Model MC-31) in order to observe a change in the viscosity as a function of temperature. The heating rate was fixed to 1.8°C/min and the viscosity was recorded every 0.5°C. The viscosity was measured three times for each sample. In order to validate the experimental methodology, the viscosity of 20, 25 and 30% (w/w) aqueous poloxamer solutions as well as that of the aqueous poloxamer solutions containing the flavors were measured. The gelling point was determined from the viscosity vs. temperature curve. The linear portion of the curve at high temperature was extrapolated to the temperature axis. The intersection was determined to be the gelling point.

Thermal analysis

Thermal analysis was carried out on a differential scanning calorimeter (Pyris 1, Perkin-Elmer, U.S.A.) to

Table I. Flavors employed for the evaluation of the effect on the viscosity and gelling point of 18%(w/w) aqueous poloxamer 407 solution

Group	Ingredients
Monoterpenes	Menthol, Cineole, Limonene, Thymol, Camphor, Geraniol
Alcohols	Cinnamyl alcohol, Phenethyl alcohol, Terpineole, Eugenol, Citronellol
Esters	Benzyl acetate, Linalyl acetate, Ethyl cinnamate Menthyl acetate, Ethyl phenyl glycidate Terpinyl acetate, 2-Phenyl ethyl acetate
Aldehyde·Ketones	Cinnamaldehyde, Vanillin, Ethylvanillin Methyl acetophenone, n-Decyl aldehyde, Ionone
Lactones	Coumarin

examine the interaction between the flavors and poloxamer 407. The thermograms of the poloxamer, flavors and their physical mixture were determined. A 1:1 weight ratio was chosen because it maximizes the likelihood of observing an interaction. Thermograms were obtained at a rate of 10°C/min in heating scans between 0 and 90°C with an empty aluminum pan as a reference. The melting point of indium was used for calibration.

Statistics

The effect of flavors on the gelling point of the aqueous poloxamer solution was evaluated statistically using a one-way ANOVA. A P value < 0.05 was considered significant.

RESULTS AND DISCUSSION

Viscosity and gelling point of poloxamer 407 aqueous solution

In order to validate the experimental methodology, the viscosity of the 20, 25 and 30% (w/w) aqueous poloxamer solutions were measured, and the viscosity of these solutions was plotted as a function of temperature (Fig. 1).

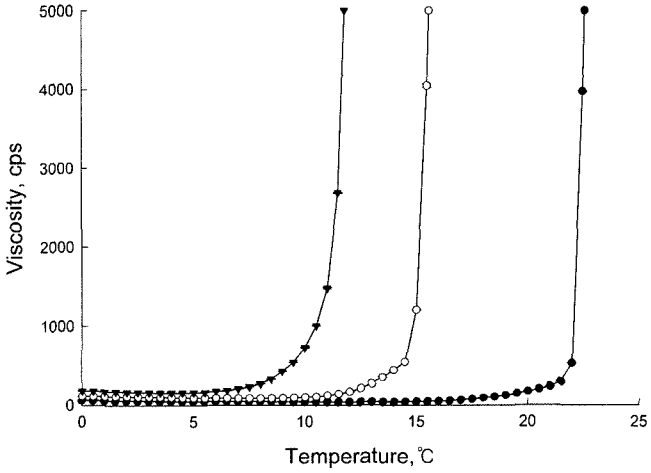

Fig. 1. Viscosity profiles of aqueous poloxamer 407 solution at different temperatures (Mean±S.D., n=3). Key : ●; 20% poloxamer, ○; 25% poloxamer, ▼; 30% poloxamer.

Table II. Comparison of the gelling point of aqueous poloxamer 407 solution determined with two different methods (unit : °C)

Poloxamer 407 concentration	Gelling point	
	Viscosity method	Miyazaki's method[2]
20%	21.9 ± 0.0[1]	21.5 ± 0.1
25%	14.5 ± 0.0	15.5 ± 0.1
30%	10.3 ± 0.0	10.2 ± 0.1

[1]Mean ± S.D. (n=3)
[2]Yakuzaigaku 51(1), 36-43 (1991).

As expected, the 30% (w/w) poloxamer 407 solution showed the highest viscosity and the lowest gelling point. The gelling points of these poloxamer solutions were quite reproducible, as shown in Table II. The gelling points obtained using the present method were similar to those reported Miyazaki *et al.* (1991). There is no distinct difference between the two methods.

Effect of monoterpenes on the viscosity of aqueous poloxamer 407 solution

Monoterpenes are one of the frequently used flavors for the topical preparations, particularly for the topical analgesics. In order to evaluate the effect of monoterpenes on the viscosity and gelling point of poloxamer solutions, menthol, camphor, thymol, cineole, limonene and geraniol were added to poloxamer 407 solutions at concentrations of 0.1, 0.2, 0.5 and 1.0%. Among them, menthol and camphor could only be added to the poloxamer solution up to a concentration of 0.5% because they are not completely soluble at 1.0%.

Fig. 2 shows the gelling points of poloxamer solutions containing different kinds of monoterpenes. The gelling point of the poloxamer solution decreased with increasing monoterpene concentration in the polymer solution, which was attributed to the fact that the viscosity of the aqueous poloxamer 407 solutions increased in proportion to the amount of monoterpenes added. Among the monoterpene type flavors, thymol had the largest effect on the viscosity of the poloxamer 407 solutions. When thymol was added to the solution at a concentration of 1.0%, the gelling point of the poloxamer solution was reduced to approximately 20°C. However, cineole reduced the gelling point of the poloxamer solution to only 14°C. All the monoterpene type flavors evaluated in this study increased the viscosity

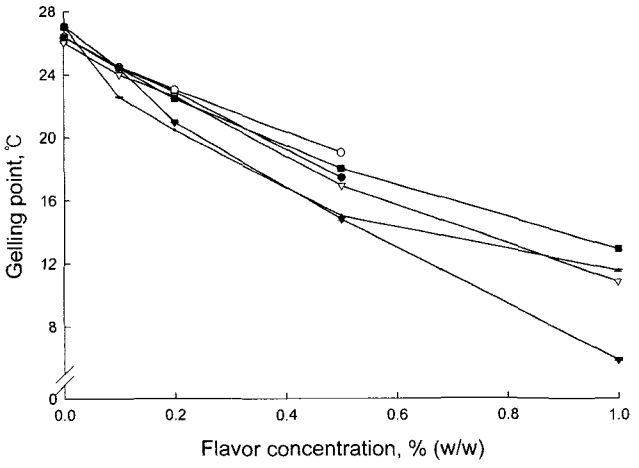

Fig. 2. Effect of monoterpene type flavors on the gelling point of aqueous poloxamer 407 solution (Mean±S.D., n=3). Key : ●; menthol, ○; camphor, ▼; thymol, ▽; geraniol, ■; cineole, • ; limonene.

of the aqueous poloxamer 407 solution, and hence, decreased the gelling point.

Effect of esters on the viscosity of aqueous poloxamer 407 solution

In order to evaluate the effect of the ester type flavors on the viscosity and gelling point of the poloxamer 407 solutions, benzyl acetate, linalyl acetate, ethyl phenyl glycidate, phenyl ethyl acetate, terpinyl acetate and ethyl cinnamate were added to the poloxamer 407 solution at concentrations of 0.1, 0.2, 0.5 and 1.0%. However, only up to 0.5% menthyl acetate could be added, which appeared to be the maximum solubility of the flavor in the poloxamer solution. The viscosity of the poloxamer solution increased in proportion to the amount of ester added to the solution. Consequently, the gelling point was found to be inversely proportional to the concentration of the esters added. Fig. 3 shows the gelling point of the aqueous poloxamer solution containing ester type flavors. All the esters decreased the gelling point of the aqueous poloxamer solution significantly. At a concentration of 1.0%, linalyl acetate, which had the greatest effect on the viscosity of the polymer solution among the ester-type flavors, reduced the gelling point of poloxamer solution to 15.5°C and ethyl phenyl glycidate, which had the least effect on the polymer solution, reduced the gelling point to approximately 14.4°C.

Gilbert *et al.* (1987) investigated the effect of a series of benzoic acid derivatives on the gelation properties. They reported that the more lipophilic ester produced a larger decrease in the gelling point of a poloxamer 407 solution than a hydrophilic ester. They explained this phenomenon by the hydrophobic binding ability of the esters to the poloxamer 407 chains, and found that the para-hydroxy benzoates bound to polyethylene glycols. The flavors evaluated in this study have lipophilic portion and also have a similar structure to para-hydroxy benzoate. In addition, the hydrophilic end chains of poloxamer 407 consist of the same PEO chains with PEGs. Therefore, it is believed that the flavors bind to the PEO chains and promote dehydration. As a result, they may cause an increase in the entanglement of the adjacent micelles and produce gelation at lower temperatures.

Effect of alcohols on the viscosity of poloxamer 407 aqueous solution

Eugenol, citronellol, cinnamyl alcohol, phenethyl alcohol and terpineol were added at different concentrations to the aqueous poloxamer solution to determine the influence of various alcohol type flavors on the viscosity and gelling point of aqueous poloxamer 407 solutions. All the alcohol type flavors investigated in this study decreased the gelling point of the aqueous poloxamer 407 solution. 1.0% phenethyl alcohol decreased the gelling point of the solution to only 6°C and cinnamyl alcohol decreased the gelling point to approximately 10°C. In the case of citronellol, the gelling point of the poloxamer solution was decreased to 16°C. In general, the gelling point was inversely proportional to the concentration of alcohols, as shown in Fig. 4. In the view of the structure, alcohol type flavors are similar to ester type flavors. Cinnamyl alcohol, phenethyl alcohol and eugenol have a benzene ring, a lipophilic portion, and hydrophilic portion. Citronellol and terpineol have hydrogenated carbon chains, which represent lipophilic and hydrophilic alcohol groups. Therefore, the hydrophilic portions of the flavors may bind to the PEO chains of poloxamer 407, and accelerate the entanglement of the polymeric micelle through a hydrophobic interaction. As a result, they appear to induce the

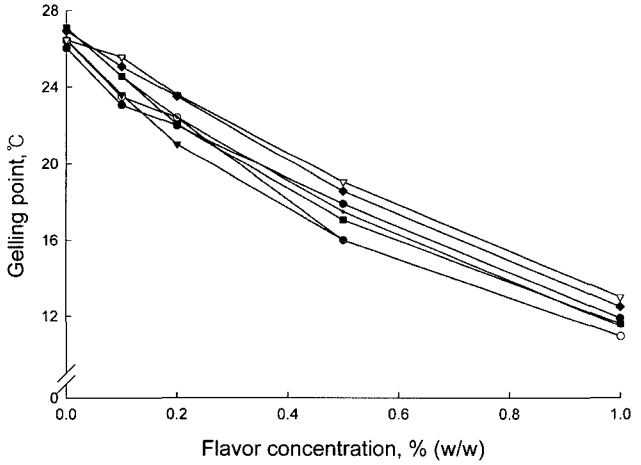

Fig. 3. Effect of ester type flavors on the gelling point of aqueous poloxamer 407 solution (Mean±S.D., n=3). Key : ●; benzyl acetate, ○ ; linalyl acetate, ▼; menthyl acetate, ▽; ethyl phenyl glycidate, ■; terpinyl acetate, • ; ethyl cinnamate, ◆; phenylethyl acetate.

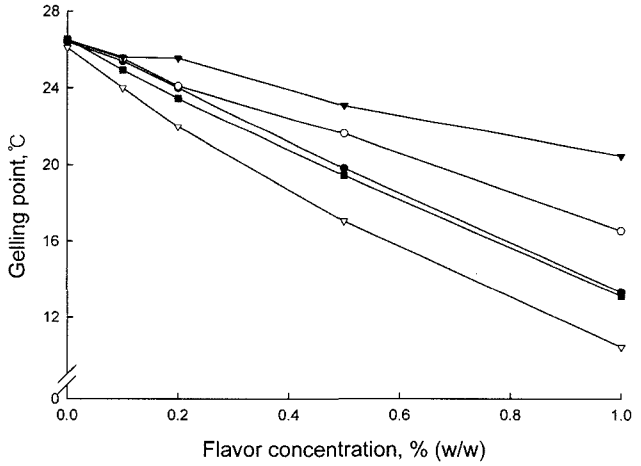

Fig. 4. Effect of alcohol type flavors on the gelling point of aqueous poloxamer 407 solution (Mean±S.D., n=3). Key : ●; eugenol, ○; cinnamyl alcohol, ▼; phenethyl alcohol, ▽; citronellol, ■; terpineol.

gelation of the poloxamer solution at lower temperatures.

Effect of aldehydes and ketones on the viscosity of aqueous poloxamer 407 solutions

Ethylvanillin, cinnamaldehyde, n-decyl aldehyde, and vanillin are classified as aldehyde type flavors and β-ionone and *p*-methyl acetophenone are typical examples of ketone type flavors. The effect of aldehyde·ketone type flavors on the viscosity and gelling point of the poloxamer 407 solution was examined by adding them to the poloxamer solution at concentrations of 0.1, 0.2, 0.5 and 1.0%. Among them, only up to 0.5% methyl acetophenone could be added to the polymer solution, which appeared to be the maximum solubility of the flavor in the poloxamer solution.

All the aldehyde·ketone type flavors evaluated in this study, except for vanillin and ethylvanillin, decreased the gelling point of the poloxamer 407 solution, as shown in Fig. 5. n-Decyl aldehyde, at 1.0%, which had the greatest effect on the poloxamer solution among the aldehyde·ketone-type flavors, lowered the gelling point of the solution to approximately 16°C. The addition of ionone at the concentration of 1.0% lowered the gelling point of the poloxamer solution to 15.5°C. They contain both lipophilic and hydrophilic portions. These flavors can bind to the hydrophilic end chains of poloxamer 407, and enhance the entanglement between the adjacent micelles. As a consequence, the poloxamer solution may form gel at lower temperatures.

On the other hand, the viscosity and gelling point of the poloxamer 407 solutions were unaffected by vanillin and only slightly by ethylvanillin. As shown in Fig. 5, the addition of vanillin into the aqueous poloxamer 407 solution did not alter the gelling point of the solution. In the case of vanillin and ethylvanillin, the lipophilic benzene ring is mixed to hydrophilic functional groups. Therefore, they cannot interact with poloxamer.

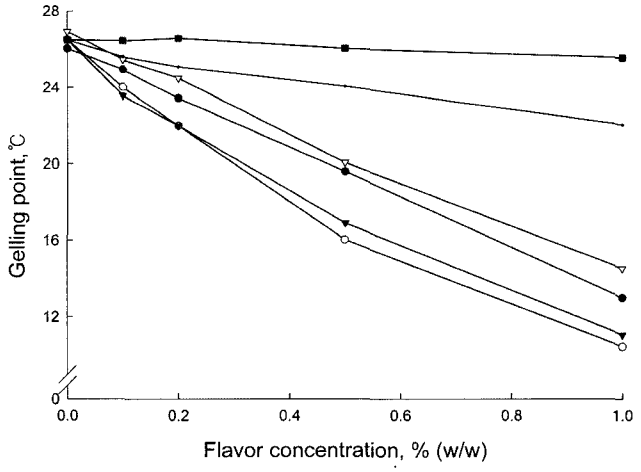

Fig. 5. Effect of aldehyde·ketone type flavors on the gelling point of aqueous poloxamer 407 solution (Mean±S.D., n=3). Key : ●; cinnamaldehyde, ○; n-decyl aldehyde, ▼; ionone, ▽; methyl acetophenone, ■; vanillin, • ; ethylvanillin.

Effect of lactones on the viscosity of poloxamer 407 aqueous solution

In lactone type flavors, jasmin lactone, cyclopentadecanolide, ethylene brasylate, coumarin and γ-undecalactone were examined. Among them, coumarin was added to the poloxamer solution up to only 0.5% because it to be its maximum solubility in the poloxamer solution. In the aqueous poloxamer 407 solution containing coumarin, unlike the monoterpenes and ester type flavors, the viscosity and gelling point of poloxamer 407 aqueous solution were unaffected, as shown in Fig. 6. Coumarin has a different structure from the other compounds that increased the viscosity of the poloxamer solution. The electrons of oxygen conjugate with the double bond of the ring resulting in virtually little hydrophilic property. This may disturb the interaction between the poloxamer and coumarin. As a result, the addition of coumarin did not appear to have an influence on the viscosity of the poloxamer solution.

Thermal analysis

Thermal analysis was performed to examine the interactions between poloxamer 407 and flavors. Fig. 7 shows the thermograms of poloxamer 407, coumarin and a 1:1 physical mixture. Poloxamer 407 showed a single endothermic peak with an onset of 153.2°C and a maximum occurring at 155.6°C. Coumarin exhibited a sharp endothermic peak with an onset of 68.0°C and a maximum occurring at 69.6°C. The physical mixture of poloxamer 407 with coumarin showed the characteristic

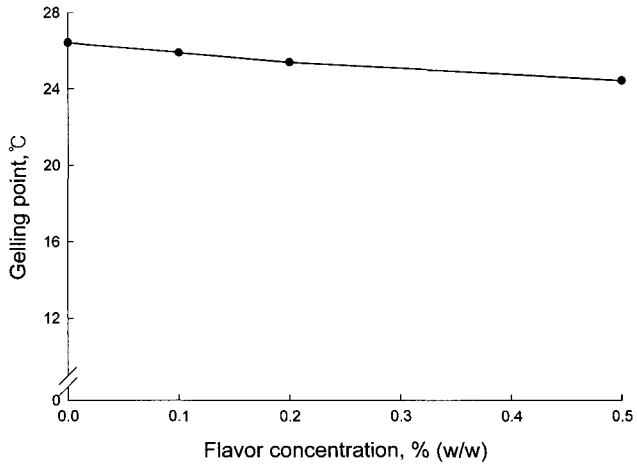

Fig. 6. Effect of coumarins on the gelling point of aqueous poloxamer 407 solution (Mean±S.D., n=3). Key : ●; coumarin.

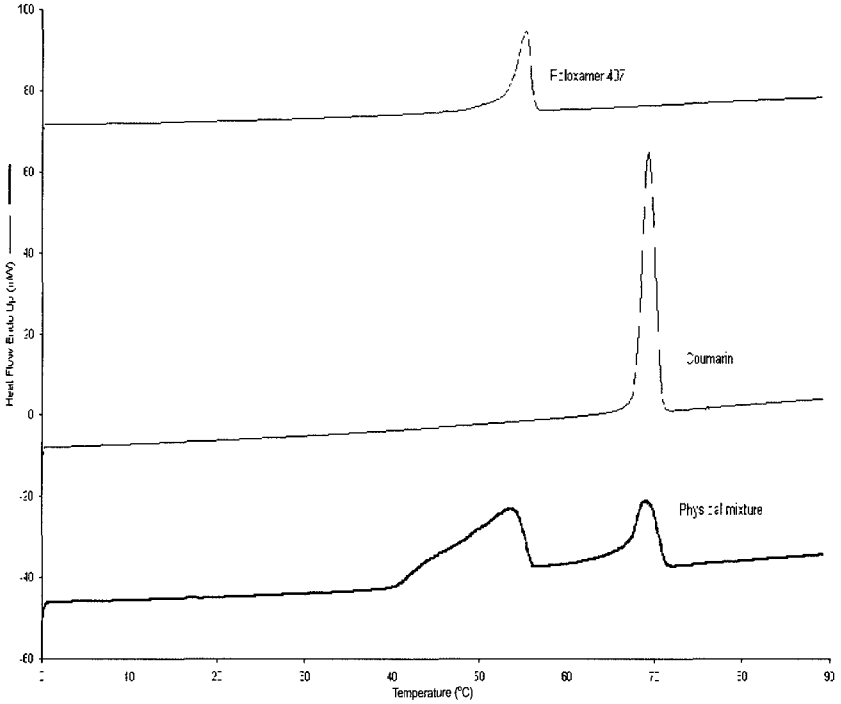

Fig. 7. DSC thermograms of poloxamer 407, coumarin and their 1:1 physical mixture

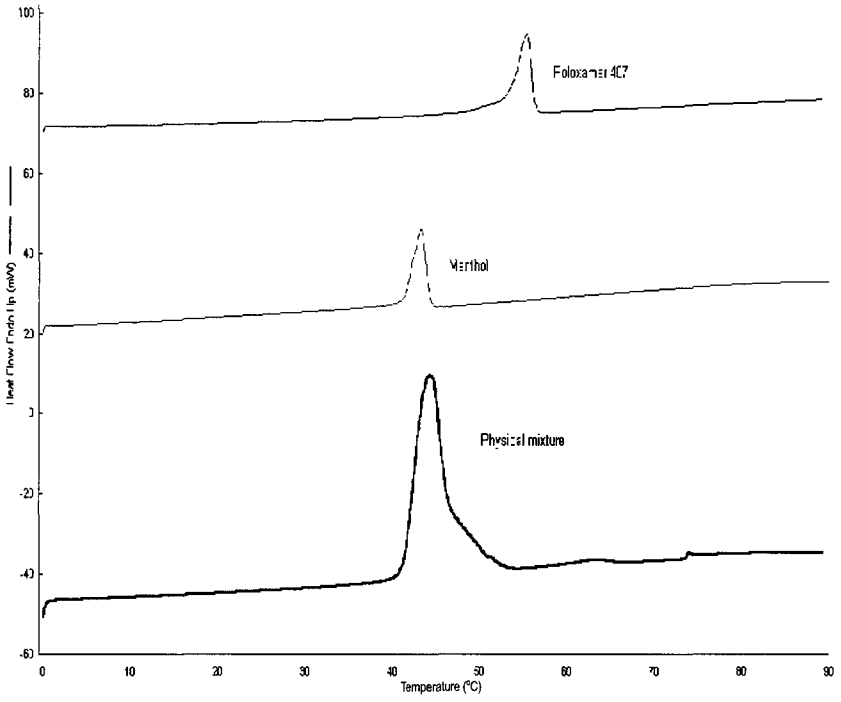

Fig. 8. DSC thermograms of poloxamer 407, menthol and their 1:1 physical mixture

features of both poloxamer 407 and coumarin, indicating no interaction between them.

The thermal behavior of menthol was quite similar to that of coumarin by reducing the maximum by approximately 25°C. However, a 1:1 mixture with poloxamer showed a different thermal behavior. In the DSC thermogram, the poloxamer 407-menthol physical mixtures demonstrated a broad endothermic peak at 40-53°C instead of the characteristic features of poloxamer 407 and menthol. This suggests an interaction between them. Fig. 8 shows the thermograms of menthol, poloxamer 407 and their 1:1 physical mixture. The thermal behavior of

thymol was similar to that of menthol. Cineole did not show any endothermic or exothermic peak. However, its 1:1 physical mixture with poloxamer 407 showed a broadening of the poloxamer 407 endothermic peak along with a shift to a lower temperature indicating a poloxamer 407-cineole interaction. In the thermogram of poloxamer 407 mixed physically with cinnamyl alcohol, both the characteristic endothermic peak of poloxamer 407 and cinnamyl alcohol shifted to a lower temperature and broadened broadly. This change in the thermogram might due to the interaction between poloxamer 407 and cinnamyl alcohol.

CONCLUSIONS

In order to examine the effects of flavors on the physical properties of the poloxamer solution, monoterpene-, ester-, alcohol-, aldehyde·ketone- and lactone-type flavors were incorporated into the poloxamer 407 solution at various concentrations, and the viscosity of the solutions was measured. The gelling point of the poloxamer solutions was measured from viscosity vs. temperature curves. Most of flavors increased the viscosity of the poloxamer aqueous solution and decreased the gelling point of poloxamer 407 aqueous solution in proportion to amount added. Coumarin, vanillin and ethylvanillin did not have an influence on the viscosity and gelling point of the poloxamer 407 solutions. DSC thermal analysis indicates the interaction between poloxamer and most of the flavors evaluated in this study. The flavors may bind to the hydrophilic end chains of poloxamer, promoting dehydration and causing gelation of the polymer solution at lower temperatures. Therefore, when a pharmaceutical preparation is formulated with poloxamer and flavors, it is important to consider that flavors can affect the viscosity and gelling point of the poloxamer solution.

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