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Effect of additives on the physicochemical properties of liquid suppository bases

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Abstract

To investigate the effects of additives on the physicochemical properties of in situ gelling and mucoadhesive liquid suppository base, gelation temperature, gel strength and bioadhesive force of liquid suppository base, poloxamer 407 (P 407) and poloxamer 188 (P 188) (15/15%) were evaluated in the presence of following additives: solvent (ethanol, propylene glycol, glycerin), ionic strength-controlling agent (sodium chloride) and pH-controlling agent (hydrochloric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate). Among the additives studied, sodium chloride, sodium monohydrogen phosphate and sodium dihydrogen phosphate increased to a great extent the gel strength and the bioadhesive force of P 407/P 188 (15/15%) with a decrease in gelation temperature. Glycerin slightly decreased the gelation temperature and slightly increased the gel strength and bioadhesive force. However, the addition of 1% of sodium chloride, sodium monohydrogen phosphate or sodium dihydrogen phosphate caused a greater than 60-fold increase in gel strength and over a tenfold increase in bioadhesive force with 2–4°C decrease of gelation temperature within optimal range, compared with P 407/P 188 (15/15%) alone. On the other hand, ethanol, propylene glycol and hydrochloric acid increased the gelation temperature and slightly decreased the gel strength and the bioadhesive force. Taken together, these findings indicate that the effect of additives on the physicochemical properties of liquid suppository bases depends on their bonding capacities, in that additives such as sodium chloride, sodium monohydrogen phosphate and sodium dihydrogen phosphate having strong cross-linking bonds with the components of liquid suppository base increase the strength and bioadhesive force of a gel compared to liquid suppository base alone, while additives such as ethanol, propylene glycol and hydrochloric acid having weaker hydrogen bonding result in a weaker response. Thus, sodium chloride and sodium phosphates appear to be promising additives for in situ gelling and mucoadhesive liquid suppository base, if used in adequate amounts.

Keywords: Liquid suppository base; Poloxamer; Gelation temperature; Gel strength; Bioadhesive force

1. Introduction

A conventional suppository is a solid dosage form which melts or softens in the rectum. Such a solid form suppository can cause patient discom-

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fort and lead to patient refusal, possibly lowering patient compliance. A solid type suppository which might reach the end of the colon, may also allow the carried drugs to undergo the first pass effect (Huang et al., 1987). Hence, the ideal suppository should be easy to administer without any pain during insertion and remain at the administered site to avoid the first pass effect in the liver and the gastrointestinal tract (Choi et al., 1998a,b; Kim et al., 1998).

To improve patient compliance when using conventional suppository, attempts have been made recently to develop in situ gelling and mucoadhesive liquid suppository bases composed of poloxamers, sodium alginate and polycarbophil, which exist as liquid in vitro but gell in vivo, by modulating the gelation temperature of poloxamer solution. The in situ gelling and mucoadhesive liquid suppository base was gelled at physiological temperature and was mucoadhesive to the rectal tissues. It also improved the bioavailability of a drug with good safety compared with conventional solid suppository (Choi et al., 1998a,b; Kim et al., 1998).

Poloxamer is a non-toxic copolymer of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) and has been used as a base for liquid suppositories. Aqueous solutions of poloxamer exhibit thermoreversible gelation, being liquids at low temperature and polymerizing to gels when exposed to physiological temperatures. Furthermore, poloxamers have been shown to cause no damage to mucosal membranes (Dumortier et al., 1991; Kim et al., 1999). Most studies with poloxamers have been focused mainly on modulating the gelation temperature of poloxamer solutions by modifying cross-linking agents and monomers (Schmolka, 1973; Holsman et al., 1984; Blackman and Ralske, 1989), by mixing the different series of poloxamers (Abhaham, 1994), by changing the weight of poloxamers (Schmolka, 1985), or by changing the pH and the ionic strength (Gilbert et al., 1987). The strength and bioadhesive force of gelled poloxamers are crucial factors in preparing suitable liquid suppositories that do not leak out from the anus and do not reach the end of colon after administration. However, there has been a lack of information regarding those factors.

To develop better in situ gelling and mucoadhesive liquid suppositories, additives such as solvents, ionic strength- and pH- controlling agents are required to dissolve or stabilize drugs. Therefore, in this study, the effects of these additives on the physicochemical properties of the in situ gelling and mucoadhesive liquid suppository bases were investigated.

2. Materials and methods

2.1. Materials

Poloxamers (P 407, P 188) were purchased from BASF (Ludwigshafen, Germany). Ethanol, propylene glycol, glycerin and sodium chloride were of USP grade. Sodium monohydrogen phosphate, sodium dihydrogen phosphate and hydrochloric acid were of analytical grade.

2.2. Preparation of liquid suppository base

Liquid suppository bases were prepared as previously described by Choi et al. (1998a,b) and Kim et al. (1998). In brief, various additives were dissolved in distilled water and the solution was cooled down to 4°C. Poloxamers were then slowly added to the solution with continuous agitation. Liquid suppository bases were kept at 4°C prior to use.

2.3. Measurement of gelation temperature

A 20-ml transparent vial containing a magnetic bar and 10 g of liquid suppository base was placed in a low-temperature thermostat water bath (Heto, Scandinavia). A digital thermosensor (Ika Labortechnik, RET digi-visc) connected to a thermistor was immersed in the liquid suppository base. Liquid suppository base was heated at a constant rate with constant stirring. When the magnetic bar stopped moving due to gelation, the temperature displayed on the thermistor was determined as the gelation temperature.

2.4. Measurement of gel strength

Liquid suppository base (50 g) was put in a 100-ml mass cylinder and gelled in a thermostat at 36.5°C. The apparatus for measuring gel strength (weight: 35 g) was then placed onto the liquid suppository base. The gel strength, which shows the viscosity of liquid suppository base at physiological temperature, was determined by the time (s) to penetrate the apparatus 5 cm down through the liquid suppository base. In cases where it took more than 10 min to drop the apparatus into the suppository base, various weights were placed on top of the apparatus. Then, gel strength was described by the minimal weights that pushed the apparatus 5 cm down through the suppository (Choi et al., 1998a,b; Kim et al., 1998).

2.5. Determination of bioadhesive force

The bioadhesive force of liquid suppository base was determined by using a measuring device as previouly described (Choi et al., 1998a,b; Kim et al., 1998). In brief, a section of tissue was cut from the fundus of rabbit rectus and secured with mucosal side out each to glass vial using a rubber band and an aluminum cap. The vials with the rectal tissues were stored at 36.5°C for 10 min. Next, one vial with a section of tissue was connected to a balance and the other vial was placed on a height-adjustable pan. Liquid suppository base was added onto the rectal tissue on the other vial. Then, the height of the vial was adjusted so that the liquid suppository base could be placed between the mucosal tissues of both vials. The weights were kept raised until the two vials were attached. Bioadhesive force, the detachment stress (dyn/cm^2), was determined from the minimal weights that detached two vials. The rectal tissue pieces were changed for each measurement.

3. Results and discussion

3.1. Effect of solvents

In this study, various additives were employed in liquid suppository base P 407/P 188 (15/15%) to develop suitable in situ gelling and mucoadhesive liquid suppository bases which would exhibit adequate gelation temperature for immediate polymerization to gel after insertion, good gel strength for easy insertion of suppository with no leakage from the anus after insertion, and suitable bioadhesive force for preventing the gelled suppository from reaching the end of the colon.

To investigate the effect of solvents on the physicochemical properties of liquid suppository base, 1.0–5.0% of ethanol, propylene glycol, or glycerin was added to P 407/P 188 (15/15%) and then its physicochemical properties such as gelation temperature, gel strength and bioadhesive force were evaluated.

In the absence of additives, P 407/P 188 (15/15%) exhibited gelation at 36°C which is within a suitable range for liquid suppository, 4 s gel strength, and 6.8×10^2 dyn/cm^2 bioadhesive force (Fig. 1).

The addition of ethanol or propylene glycol caused an increase in gelation temperature and a slight decrease in gel strength and bioadhesive force compared with P 407/P 188 (15/15%), whereas glycerin caused a small decrease in gelation temperature and a moderate increase in gel strength with a slight increase in bioadhesive force (Fig. 1). In the presence of 5.0% glycerin, the gelation temperature decreased by $\sim$1°C and the gel strength and the bioadhesive force increased 60 and 10%, respectively, compared with those in the absence of glycerin. The slight increase in bioadhesive force caused by glycerin appears to be due to its strong binding with oligosaccharide chains of rectal mucous membranes (Robinson and Robinson, 1990; Lenarets et al., 1987). In the contrast, in the presence of 5.0% of ethanol, the gelation temperature of P 407/P 188 (15/15%) increased by $\sim$4°C and the gel strength and the bioadhesive force decreased 49 and 12%, respectively, compared with those in the absence of ethanol. Propylene glycol had less effect on the gelation temperature (2.5°C $\uparrow$), gel strength (24% $\downarrow$) and bioadhesive force (9% $\downarrow$) than ethanol.

The differing effects of solvents on the physicochemical properties of liquid suppository base may be explained by the fact that weaker hydrogen bonding of ethanol and propylene glycol con-

taining one and two hydroxyl groups, respectively, compared to liquid suppository base causes weaker bonding in liquid suppository base, resulting in decrease in gel strength and increase in gelation temperature, while stronger hydrogen bonding of glycerin containing three hydroxyl groups compared to liquid suppository base, causes strong bonding in liquid suppository base, resulting in opposite results.

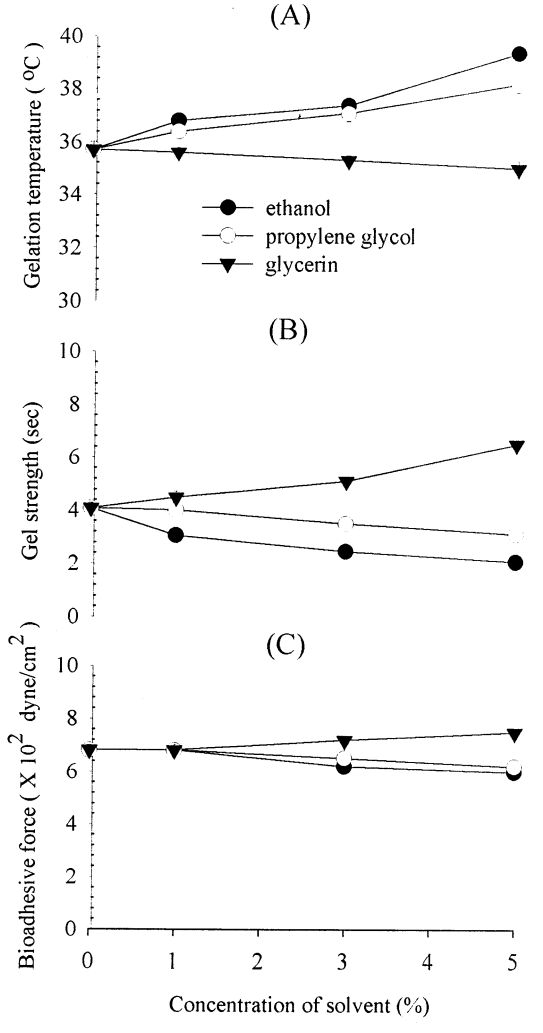

Fig. 1. Effect of solvents on the physicochemical properties of liquid suppository base, P 407/P 188 (15/15%). (A) Gelation temperature; (B) gel strength; (C) bioadhesive force. Each value represents the mean ± S.D. of five experiments.

3.2. Effect of ionic strength-controlling agent

The effect of ionic strength-controlling agent on the physicochemical properties of liquid suppository base was investigated by adding 0.1–1.0% of sodium chloride to P 407/P 188 (15/15%).

Sodium chloride reduced the gelation temperature and reinforced to a great extent the gel strength and the bioadhesive force of P 407/P 188 (15/15%) (Fig. 2). With the addition of 1.0% of sodium chloride, the gelation temperature decreased ~4°C and the gel strength and the bioadhesive force increased 84- and 12-fold, respectively, compared with those without sodium chloride. The great increase in gel strength and bioadhesive force caused by sodium chloride might have been attributed to strong cross-linking bonding of sodium salt with poloxamer (Miller and Drabik, 1984).

3.3. Effect of pH-controlling agents

A pH-controlling agent such as hydrochloric acid, sodium monohydrogen phosphate, or sodium dihydrogen phosphate, was added to P 407/P 188 (15/15%) to examine its effects on gelation temperature, gel strength and bioadhesive force.

Of the pH-controlling agents studied, hydrochloric acid when added to P 407/P 188 (15/15%) greatly increased the gelation temperature and slightly reduced the gel strength and the bioadhesive force compared with P 407/P 188 (15/15%) alone, whereas sodium monohydrogen phosphate and sodium dihydrogen phosphate slightly decreased the gelation temperature and considerably increased the gel strength and the bioadhesive force (Fig. 3). With the addition of 1.0% hydrochloric acid, the gelation temperature of P 407/P 188 (15/15%) increased ~6°C and the gel strength and the bioadhesive force of P 407/P 188 (15/15%) decreased 62 and 49%, respectively, compared with those of P 407/P 188 (15/15%) alone. However, with the addition of 1.0% of sodium monohydrogen phosphate or sodium dihydrogen phosphate, the gelation temperature decreased approximately 2°C and the gel strength and the bioadhesive force increased 61 ~ 65- and

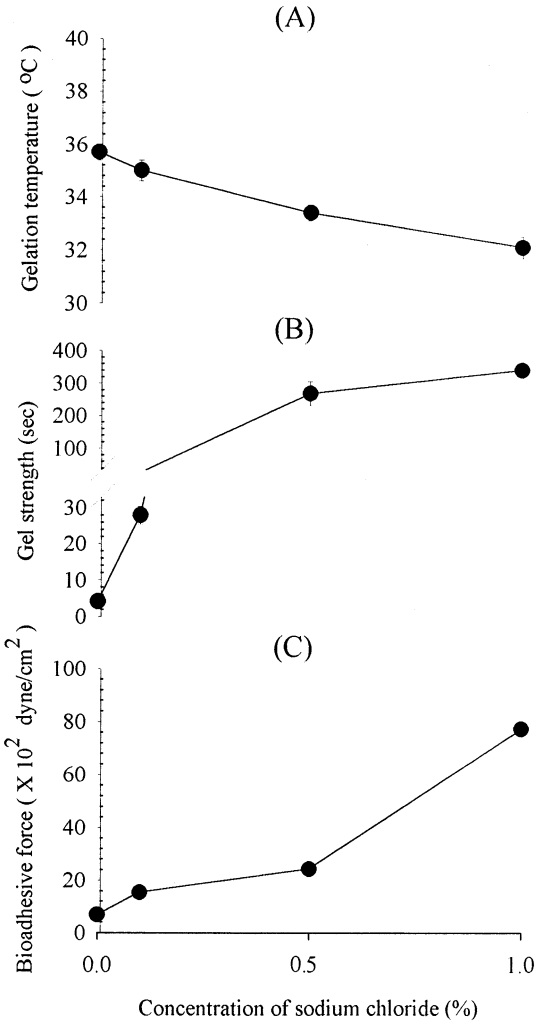

Fig. 2. Effect of ionic strength-controlling agent on the physicochemical properties of liquid suppository base P 407/P 188 (15/15%). (A) Gelation temperature; (B) gel strength; (C) bioadhesive force. Each value represents the mean ± S.D. of five experiments.

10.6 ~ 11.4-fold, respectively, compared with those of P 407/P 188 (15/15%) alone. The large increase in gel strength caused by both sodium phosphates might have been caused by strong cross-linking bonding of sodium salts with poloxamer (Miller and Drabik, 1984; Lenarets et al., 1987).

Among the additives examined in the present study, sodium chloride, sodium monohydrogen phosphate, and sodium dihydrogen phosphate caused a great increase in both gel strength and bioadhesive force of poloxamer solution with a decrease of gelation temperature within optimal range compared with poloxamer solution alone.

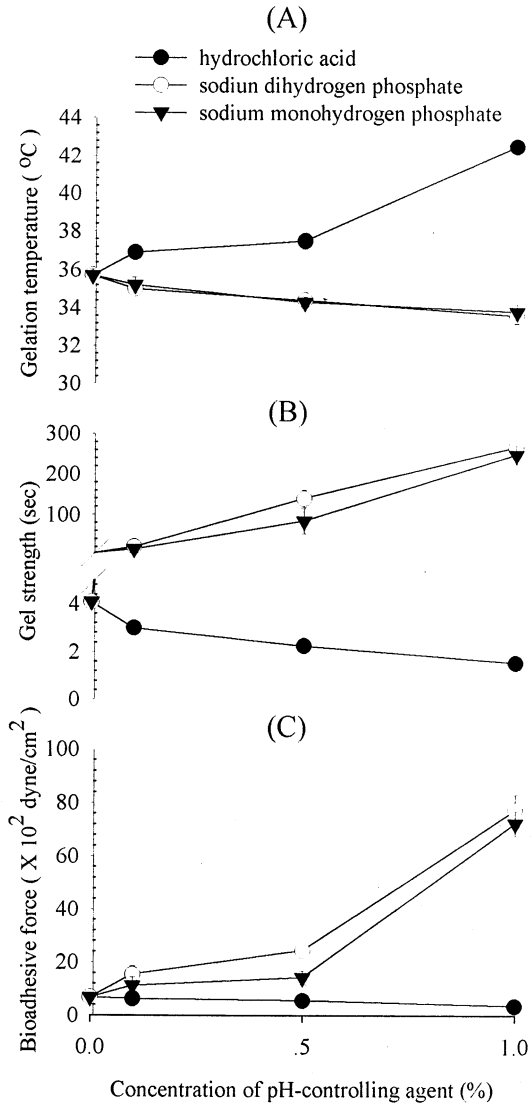

Fig. 3. Effect of pH-controlling agent on the physicochemical properties of liquid suppository base, P 407/P 188 (15/15%). (A) Gelation temperature; (B) gel strength; (C) bioadhesive force. Each value represents the mean ± S.D. of five experiments.

Poloxamer molecules exhibit an well-arranged zigzag configuration. The temperature-dependent gelation of liquid suppository base poloxamer solution may be explained by configurational change (Schick, 1966; Kramaric et al., 1992). As the temperature increases, the zigzag configuration of poloxamer may be transformed into a close-packed meander configuration, forming a more close-packed and more viscous gel.

As a possible mechanism by which solvents, ionic strength- and pH-controlling agents affected the physicochemical properties of liquid suppository base as observed in this study, it is speculated that sodium chloride, sodium monohydrogen phosphate and sodium dihydrogen phosphate, which form strong cross-linking bonds with poloxamer, could strengthen the bonding of cross-linked reticular liquid suppository base by placing them in the gel matrix, resulting in an increase in gel strength and a decrease in gelation temperature, whereas ethanol, propylene glycol, and hydrochloric acid, which have weaker hydrogen bonds, could weaken the bonding, resulting in a decrease in gel strength and an increase in gelation temperature (Schmolka, 1972; Choi et al., 1998a,b; Kim et al., 1998).

4. Conclusion

Taken together, it is concluded that the effects of additives on the physicochemical properties of liquid suppository bases depends on their bonding capacities, in that the presence of additives such as sodium chloride, sodium monohydrogen phosphate, and sodium dihydrogen phosphate having strong cross-linking bonds with the components of liquid suppository base causes greater strength and bioadhesive force of a gel with lower gelation temperature within optimal range compared to liquid suppository base alone, while the presence of additives such as ethanol, propylene glycol and hydrochloric acid having weaker hydrogen bonding causes weaker response. Thus, sodium chloride, sodium monohydrogen phosphate, and sodium dihydrogen phosphate appear to be promising additives for liquid suppository base, if added in suitable amounts.

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