Relationship between Solubility of Chitosan in Alcoholic Solution and Its Gelation

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A cationic polymer, chitosan (CHI) is anticipated to be a potent component in several dosage forms involving transdermal drug delivery systems (TDDS). Solubility of CHI and its gelation in alcoholic aqueous solutions were investigated. Elasticity of the gel containing 3% CHI, 2% oxalic acid, as a crosslinking agent, and ethanol (EtOH) and/or 1,3-butyleneglycol (BG) was also evaluated by a rheometer. The CHI solubility in the gel was dependent on the solubility parameters of the mixed solvent. High elasticity was observed in the CHI gel when an alcoholic solvent giving low solubility of CHI was used. A good correlation was found between the gel elasticity and the relative gel concentration (=concentration of CHI in gel/solubility of CHI in gel). Since the polarity of mixed solvents also affected the thermodynamic activities of drugs and penetration enhancers, optimization of the vehicle composition for TDDS is important to assure suitable drug efficacy.

Key words chitosan; gelation; ethanol; 1,3-butyleneglycol; solubility parameter

Several polymer materials have been utilized in a number of pharmaceutical preparations and potential drug delivery systems (DDS).[1,2] Selection and/or use of polymers are very important in the formulation design, since a polymer–drug interaction is one of the major determinants of the quality of a pharmaceutical preparation. On the other hand, aqueous solutions containing ethanol (EtOH) and other alcohol are thought to be a practical chemical enhancer to increase permeation of drugs through biological membrane because of their safety and strong enhancing effect.[3,4] EtOH has already been used in several marketed transdermal DDS (TDDS). Most of them are a liquid reservoir type of TDDS, in which active drugs and penetration enhancers are dissolved in reservoir solvents and are sealed by drug-permeable membranes.[5—7] With the liquid reservoir type of TDDS it is difficult to maintain an effective application area because of change of patient position and there is a high risk of breaking the membranes. Selection of a highly viscous gel for the reservoir medium may relieve these problems.

We have reported that the skin permeation of morphine was enhanced by a mixed solvent system of *l*-menthol, EtOH and water,[4] and the enhancing effect was influenced by several polymers.[8] The latter study[8] indicated that the skin permeation of morphine as a basic compound was increased by chitosan (CHI) as a cationic polysaccharide, while it was decreased by carboxyvinylpolymer as an anionic polymer.

In the present study, we investigated the solubility and gelation of CHI in aqueous solutions containing alcohols in detail to obtain further information on CHI as a new pharmaceutical additive suitable for TDDS.

Experimental

Materials CHI was supplied by Ajinomoto Co., Inc. (Marine Dew PC-100, M.W. 450000—900000, Tokyo, Japan). The CHI has a degree of deacetylation of about 50%. EtOH, isopropanol, propyleneglycol and glycerol were purchased from Wako Pure Chemical Industries Co., Ltd. (Osaka, Japan). 1,3-Butylene glycol (BG) was purchased from Tokyo Chemical Industries Co., Ltd. (Tokyo). Other chemicals were of reagent grade.

Evaluation of Effect of Alcohols on the CHI Solubility Different ratios of alcohol and purified water were mixed in a transparent glass vial, and CHI was added at concentration of 3% to the mixed solvent. Since CHI is insoluble in neutral solutions, acetic acid was added at concentration of 2% to each vial. CHI was dispersed and dissolved by stirring with a vortex mixer and ultrasonication. The obtained solution was stored at 32 °C for 48 h in an incubator, and uniformity of CHI in the solution was judged visually. The maximum concentration of alcohol which allowed complete dissolution of CHI in the solution was called the "critical concentration."

Preparation of CHI Gel and Evaluation of CHI Solubility in the Gel Various amounts of CHI and 2% oxalic acid as a crosslinking agent were added to several mixed solutions of EtOH, BG and water in a transparent glass vial. They were mixed rapidly to obtain a clear solution or gel as above, and the resulting solutions or gels were stored at 32 °C for 48 h. The transparency of the gel was optically checked. The maximum concentration of CHI which retained the uniformity and transparency of the gel was regarded as "CHI solubility".

Evaluation of CHI Gelation Stress relaxation of CHI gel was measured by a rheometer (NRM-2002J, Fudo Kogyo Co., Ltd. Tokyo), which had a circular flat plunger (diameter 20 mm, thickness 1 mm) jointed to a sensor and a rising sample stand. Since the same strain was not achieved for each CHI gel, the stress relaxation was examined at four different constant strains. The CHI gel in a glass vial (volume 50 ml, internal diameter 32 mm, height 75 mm) rose at the rate of 30 mm/min and stopped at a strain in the range of 0.02 to 0.2. Modulus of elasticity of the CHI gel was calculated at each point using the following equation:

$$E=\frac{F\cdot L}{a\cdot l}$$

where E is modulus elasticity, F and L represent stress and initial length of the CHI gel, respectively, and a and l are area of the plunger and compressed length of the CHI gel. The maximum and stationary moduli, E_0 and E_∞, of elasticity were obtained from the time course of E. E_0 and E_∞/E_0 at a strain of 0.04, which were obtained by a regression equation of the moduli of elasticity against the strains, were used for indices of gel strength and maintenance of shape, respectively. For instance, $E_\infty/E_0=1$ was expressed as a complete elastic body.

Results and Discussion

Effect of Alcohols on CHI Solubility The influence of different polarities of alcohols added to the aqueous solution on the CHI solubility was evaluated. Figure 1 shows the critical concentration of alcohols to retain a condition in which 3% CHI was clearly dissolved. The alcohols are arranged in the order of polarity in Fig. 1.[9] The highest critical concen-

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tration was observed for glycerol, which has the highest polarity among the alcohols tested. The result suggested that solubility of CHI could be affected by the polarity of the mixed solvent.

Aqueous solutions containing EtOH and/or BG were used for the gel preparation to evaluate the effect of polarity of the mixed solvent system on the CHI solubility in the CHI gel.[5,10] Figure 2A shows CHI solubility in the gel containing EtOH and water. Solubility of CHI in water was 10%, which was the maximum value in this series. CHI solubility decreased almost linearly with the EtOH content, and in 50% EtOH was less than 0.1%. Figures 2B and 2C show CHI solubility in the gel containing EtOH, BG and water; the solubility increased with increase in BG/EtOH ratio. Since the polarity of BG is higher than that of EtOH, hydrophilicity of the mixed solvent increases with increase in the ratio.

The solubility parameter (SP) of each mixed solvent was calculated to determine the relationship between solvent polarity and the CHI solubility.[11] Figure 3 illustrates the CHI solubility in each mixed solution against corresponding SP value; the solubility in the gel had a tendency to increase with the SP value. The SP value of CHI itself seemed to be higher than that of the mixed solvent system. The CHI solubility in highly polar solvents could be high because of low dissolution heat and high solvation of amino group or hydroxyl group, as true of the dissolution behavior of polymer described by Flory.[12]

Effect of Alcohols on Gelation of CHI The viscoelastic properties of the CHI gel were measured to learn the effect of alcohols on the gelation of CHI. Figure 4 shows E_0 and E_∞/E_0 at several compositions of the gel in which E_0 is the maximum elasticity and E_∞/E_0 is maintenance of its shape. These values in the EtOH–water mixed solvent system containing 3% CHI and 2% oxalic acid varied with the EtOH content in the gel (Fig. 4A). At 40% EtOH, E_0 and E_∞/E_0 were 9.4×10^3 (N/m^2) and 0.64, respectively. Both values were maximum in this series. For the gel containing 50% EtOH, phase-separation was observed, *i.e.*, CHI was deposited, and the values of E_0 and E_∞/E_0 were lower than those of 40% EtOH. On the other hand, the gel containing 50% BG was uniform and the values of E_0 and E_∞/E_0 were higher than those of 50% EtOH (Fig. 4C). In the gel containing both EtOH and BG (Fig. 4B, C), the values of E_0 and E_∞/E_0 decreased with an increase in the BG/EtOH ratio, and the highest values were observed in the gel containing 40% EtOH and 10% BG. Substitution of only 10% in 50% EtOH by BG led to a significant change in the elasticity of CHI gel. These results suggest that the gel elasticity depends on the polarity of the mixed solvent rather

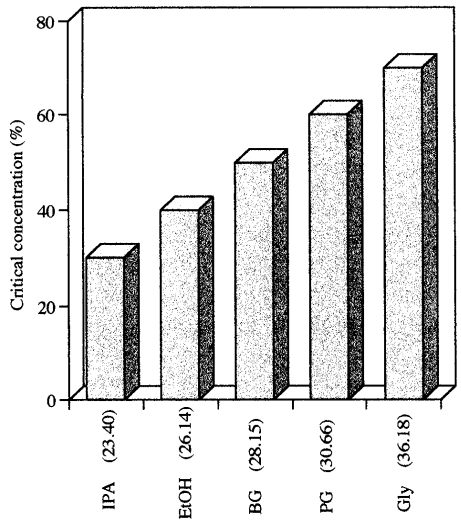

Fig. 1. Critical Concentration of Alcohol in 3% CHI Solution Containing 2% Acetic Acid

IPA, isopropanol; PG, propyleneglycol; Gly, glycerol: (SP of each alcohol in parentheses, $(J/cm^3)^{1/2}$).

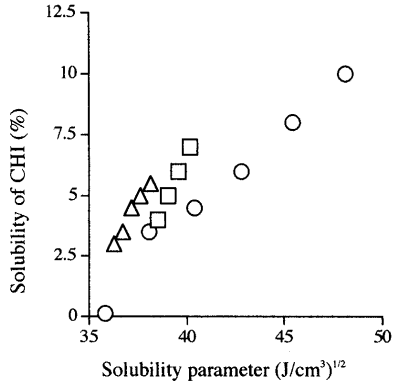

Fig. 3. Relationship between SP of Mixed Solvent and Solubility of CHI in the Gel Containing 2% Oxalic Acid

Data in Fig. 2 were re-plotted as the relationship between SP and solubility.
○, 0—50% EtOH/water (Fig. 2 A); □, EtOH+BG (total 40%)/water (Fig. 2 B); △, EtOH+BG (total 50%)/water (Fig. 2 C).

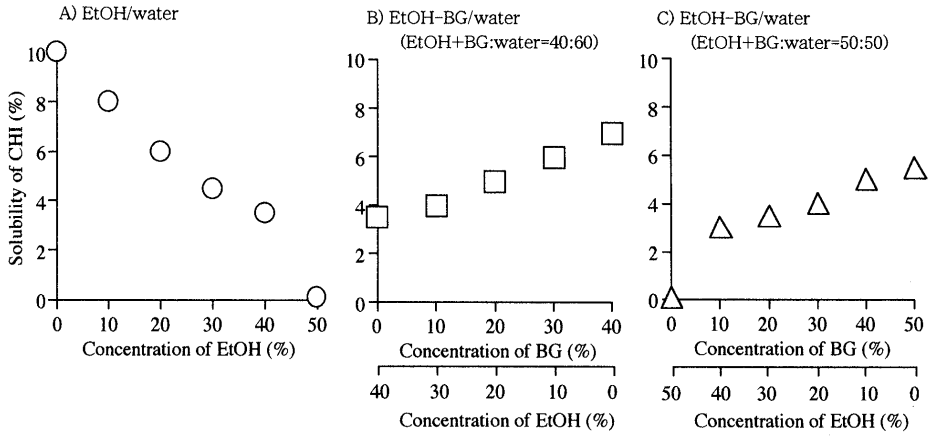

Fig. 2. Solubility of CHI in the CHI Gel Containing Alcohols and 2% Oxalic Acid

A) 0—50% EtOH/water; B) EtOH+BG (total 40%)/water; C) EtOH+BG (total 50%)/water.

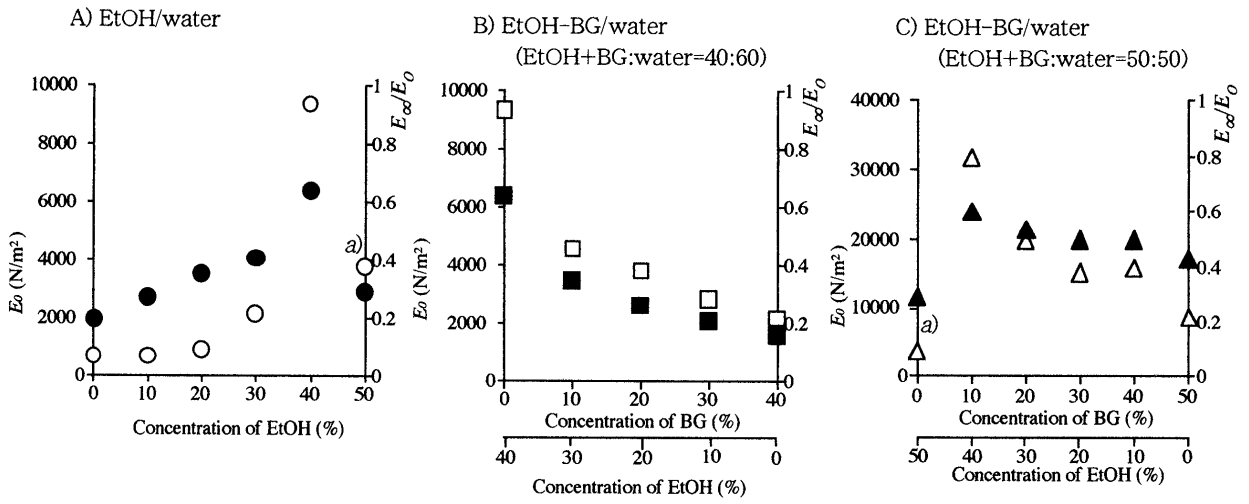

Fig. 4. E_0 and E_∞/E_0 of 3% CHI Gels Containing Alcohols and 2% Oxalic Acid

A) 0—50% EtOH/water; B) EtOH+BG (total 40%)/water; C) EtOH+BG (total 50%)/water: E_0 (○, □, △), E_∞/E_0 (●, ■, ▲): *a*) Phase-separation occurred.

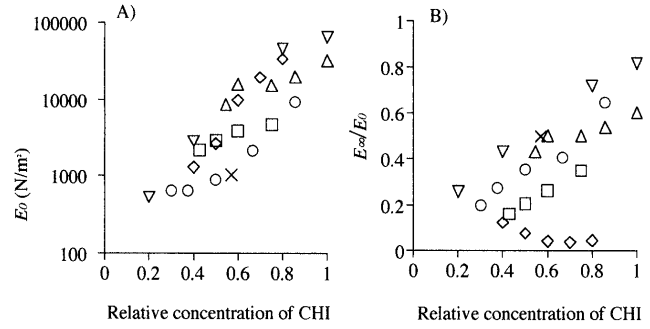

Fig. 5. Relationship between E_0 and E_∞/E_0 and Relative Concentration of CHI (Concentration / Solubility of CHI in the Gel Containing 2% Oxalic Acid)

○, 3% CHI, 0—50% EtOH/water; □, 3% CHI, EtOH+BG (total 40%)/water; △, 3% CHI, EtOH+BG (total 50%)/water; ◇, 4—8% CHI/water; ▽, 1—5% CHI, 20% EtOH, 30% BG/water; ×, 2%CHI, 40% EtOH/water.

than on the chemical structure of solvents. CHI dissolved in a solvent in which it is poorly soluble, could effectively act for the gelation. The kind and content of alcohols are important in preparation of a CHI gel in which the alcohols act as skin penetration enhancers for TDDS.

High elasticity was observed in the CHI gel, which was uniform and consisted of an alcoholic solution in which CHI had low solubility. Relative concentrations of CHI in several alcoholic gels were calculated to examine the relationship between CHI solubility in the alcoholic solution and elasticity of the gel as follows:

relative concentration=(concentration of CHI / solubility of CHI)

E_0 and E_∞/E_0 were plotted against these values. E_0 and E_∞/E_0 values of CHI gel containing various concentrations of CHI (1—8%) were added to the data in Fig. 4, which was observed in the CHI gel containing 3% CHI. Figure 5A shows a semi-logarithmic plot of E_0 against the relative concentration of CHI, suggesting a positive correlation. Figure 5B shows a linear plot of E_∞/E_0 against the relative concentration of CHI; it suggests a positive correlation between solubility of CHI and elasticity of its gel, except in the case of CHI gel without alcohols. The exceptional behavior observed in the system without alcohols is not fully understood, and further study to clarify possible differences in gelling behavior of CHI in aqueous systems with and without alcohols is needed.

Conclusion

This study examined the relationship between CHI solubility in alcoholic solution and its gelation. The results suggest that the polarity of mixed solvents affects not only the solubility of CHI but also elasticity of the gel. Since the polarity of mixed solvents also affects the thermodynamic activity of drugs and penetration enhancers, such as l-menthol,[13] it is clear that optimization of the composition of vehicle for TDDS is important.

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