Effect of D-Sorbitol on the Thermal Gelation of Methylcellulose Formulations for Drug Delivery

Kunihiko Itoh,*[a] Tomoaki Hatakeyama,[a] Tomoki Kimura,[a] Tetsuya Shimoyama,[a] Shozo Miyazaki,[a] Antony D'Emanuele,[b] and David Attwood[c]

[a] *Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido; Ishikari-Tobetsu, Hokkaido 061–0293, Japan:* [b] *School of Pharmacy and Pharmaceutical Sciences, University of Central Lancashire; Preston PR1 2HE, U.K.: and* [c] *School of Pharmacy and Pharmaceutical Sciences, University of Manchester; Manchester M13 9PL, U.K.*

Received July 28, 2009; accepted November 5, 2009; published online November 16, 2009

The aim of this study was to examine the effect of D-sorbitol on the gelation characteristics of methylcellulose in aqueous solution. The addition of D-sorbitol at concentrations of between 25 and 30% (w/v) to 1.0—2.0% (w/v) methylcellulose solutions reduced the gelation temperature from approximately 53 °C to values between ambient and 37 °C and increased the strength of the gel. The *in vitro* release of acetaminophen (paracetamol) from 2.0% (w/v) methylcellulose gels containing 20—30% (w/v) D-sorbitol gel was diffusion-controlled.

Key words methylcellulose; D-sorbitol; gelation; acetaminophen

Methylcellulose is a water-soluble polymer derived from cellulose by methylation, and is extensively used as a binder or thickener in pharmaceutical, cosmetic, and food additives. Water-soluble methylcellulose solutions can form thermoreversible hydrogels in water on heating due mainly to a reduction of the hydrophobic association between methylcellulose chains and water at elevated temperatures. The gelation temperature of aqueous solutions of methylcellulose, however, is too high (approximately 53 °C) for use as an *in situ* gelling vehicle.

The effect of electrolytes on the gelation behaviour of methylcellulose has been extensively studied in the literature.[1—3] An electrolyte such as NaCl with salting-out properties has a greater affinity for water than methylcellulose resulting in the removal of water of hydration from the polymer and a lowering of its sol–gel transition temperature due to an enhancement of the hydrophobic association of methylcellulose chains. The gelation temperature of aqueous methylcellulose sols decreases significantly with increase of the electrolyte concentration. However, the electrolyte concentration required to reduce the gelation temperature to a suitable value to enable the methylcellulose to be used as an *in situ* gelling vehicle would be too high for oral administration to the patients. For example, methylcellulose solutions containing each of 0.7 M (4.1% (w/v)) NaCl, 0.7 M (7.7% (w/v)) $CaCl_2$ or 0.2 M (2.8% (w/v)) Na_2HPO_4 was approximately 32 °C.[4]

D-Sorbitol is about 60% as sweet as sucrose and is widely used as a taste-masking agent in oral dosage forms to disguise the bitter taste of drugs such as acetaminophen. We have reported the application of D-sorbitol as a taste-masking reagent for *in situ* gelling pectin formulation.[5,6] Levy and Schwarz have reported about the effect of adding nonelecrolytes (D-sorbitol, sucrose, glycerine, ethanol, polyethylene glycol and propylene glycol) on the gelation temperature of methylcellulose solution, and that the addition of 20% D-sorbitol to solution of 2% methylcellulose decreased the gelation temperature to 30 °C.[7] D-Sorbitol also represents a canonical salting-out cosolute.[8] It might therefore be expected that the addition of D-sorbitol would decrease the gelation temperature of aqueous methylcellulose solution as a consequence of its salting-out property.

In the present study we have investigated the influence of D-sorbitol on the gelation characteristics of methylcellulose sols and in particular its effect on the gelation temperature and gel properties with the aim of formulating a preparation suitable for oral administration as a liquid which would subsequently undergo *in situ* gelation to produce a gel depot suitable for sustained drug delivery. The formulations have been optimized to produce gelling and rheological properties suitable for oral administration and the *in vitro* drug release characteristics have been examined.

Experimental

Materials Methylcellulose (MCE-400, Lot. 7105564) was supplied by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). D-Sorbitol was obtained from Wako Pure Chemical Ind., Ltd. (Osaka, Japan). Acetaminophen (paracetamol) was obtained from Astellas Pharma Inc. (Tokyo, Japan). CALONAL® Syrup 2%, which is a commercial acetaminophen syrup supplied in Japan, was obtained from Showa Yakuhin Kako Co., Ltd. (Tokyo, Japan) and diluted to 1.0% (w/v) acetaminophen with ultra pure water. Ultra pure water was prepared by NANOpure® Diamond™ UF and UV/UF Systems (Barnstead International, Iowa, U.S.A.). All other reagents were of analytical grade.

Preparation of Methylcellulose Solutions The methylcellulose solutions containing D-sorbitol were prepared by gradually adding with constant stirring, weighed quantities of methylcellulose and D-sorbitol to about half of the required quantity of ultra pure water which was preheated at 70—80 °C. The solutions were made up to final volume with water and stirred thoroughly for 1 h at 50 °C and further for 1 h at 5 °C with ice-cooling. Methylcellulose solutions containing 1.0% (w/v) acetaminophen were prepared by adding the required amounts of acetaminophen to the methylcellulose solutions at 50 °C with stirring.

Determination of Gelation Temperature Gelation temperatures of methylcellulose solutions were measured by a sine-wave vibro viscometer (SV-10, A&D Co., Ltd., Tokyo, Japan) equipped with a water jacket through which water from a controlled temperature bath (NCB-1200, Tokyo Rikakikai Co., Ltd., Tokyo, Japan) could be circulated. Ten milliliters of the solution was gradually heated from 10 to 70 °C and the gelation temperature was determined from the sharp inflection point in the curve of viscosity *vs.* temperature resulting from the sudden increase of viscosity accompanying gel formation.

Measurement of Gel Strength The strength of the methylcellulose gels was measured using a rheometer (CR-500DX, Sun Scientific Co., Tokyo, Japan) according to the previously reported method.[9] Cylindrical gels (approximately 33 mm diameter and 10 mm height) were prepared as described above in a glass Petri dish (10 ml) and stored at 37 °C for 24 h. The gels were placed in the rheometer and raised at a rate of 60 mm/min so pushing a

* To whom correspondence should be addressed. e-mail: itou@hoku-iryo-u.ac.jp

probe slowly through the gel. The change in the load on the probe was measured as a function of the depth of immersion of the probe below the gel surface.

Measurement of Viscosity of Methylcellulose Solutions The viscosities of the methylcellulose solutions were determined at 5 °C with a cone and plate rotational viscometer with a cone angle of 1°34′ (TV-20H, model E, Tokyo Keiki Inc., Tokyo, Japan) using 1 ml aliquot of the sample. Measurements on each sol were performed in triplicate over a shear rate range of approximately 23—230 1/s, each shear rate sweep taking approximately 30 s.

Measurement of *In Vitro* Drug Release Measurement of the *in vitro* release of acetaminophen from methylcellulose solutions was carried out using plastic dialysis cells similar to that described previously.[10] The capacity of each half-cell was 4 ml and the surface area of the membranes was 2.67 cm^2. Commercial syrup (diluted to 1.0% (w/v) acetaminophen with ultrapure water) and methylcellulose solutions containing 1.0% (w/v) acetaminophen were placed in the donor compartment, and an equal volume of simulated gastric (pH 1.2) or intestinal (pH 6.8) fluid (as specified for the JP XV disintegration test) was placed in the receptor compartment. The gel donor phase and the aqueous receptor phase were separated by a dialysis membrane (Viskase® Co., Inc., Illinois, U.S.A.). The assembled cell was shaken horizontally at the rate of 60 strokes/min in an incubator at 37 °C. The total volume of the receptor solution was removed at intervals and replaced by fresh release medium. The concentration of acetaminophen in the samples was determined from the absorbance at a wavelength of 244 nm using a spectrophotometer (UV-1200, Shimadzu Co., Kyoto, Japan).

The diffusion coefficient, D, of methylcellulose gels was determined using the Higuchi equation, Eq. 1, for drug release from semisolid vehicles containing dissolved drug,[11]

$$Q = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \quad (1)$$

where Q is the cumulative amount of drug released per unit surface area, C_0 is the initial drug concentration, and t is the time. The diffusion constants were calculated from the gradients of the plots of Q *vs.* $t^{1/2}$.

Results and Discussion

Figure 1 shows the gelation temperatures of 1.0, 1.5 and 2.0% (w/v) methylcellulose solutions containing 0—30% (w/v) D-sorbitol. The gelation temperatures of 1.0, 1.5 and 2.0% (w/v) methylcellulose solutions in the absence of D-sorbitol were 54.13±0.39, 52.67±0.38 and 53.65±0.50 °C (n=4, mean±S.E.), respectively. Gelation temperatures were decreased to below 37 °C by the addition of D-sorbitol at a concentration greater than about 25% (w/v); for example 1.0, 1.5 and 2.0% (w/v) methylcellulose solutions containing 25% (w/v) D-sorbitol gelled at 36.81±0.35, 33.96±0.12 and 32.99±0.12 °C (n=4, mean±S.E.), respectively. Concentrations of D-sorbitol greater than 30% (w/v) produced gelation at temperatures too close to ambient for use in the design of *in situ* gelling vehicles.

2.0% (w/v) methylcellulose solutions showed shear thinning non-Newtonian flow properties; an increase of viscosity at low shear rate was observed as the concentration of added D-sorbitol increased over the range 20—30% (Fig. 2). The solutions had a suitable fluidity for ease of swallowing and could be particularly appropriate for administration to dysphagic patients.

Increasing amounts of D-sorbitol increased the strength of 2.0% (w/v) methylcellulose gels as seen from the stress–strain curves of Fig. 3. The rheological profile of the gels is typical of that of the elastic gels reported for other polysaccharides such as xyloglucan and gellan[9] the sudden decrease of stress after the maximum indicating a brittle system. Values of the stress immediately before collapse, which may be used as a guide to gel strength, were 3.09, 5.86 and 6.22 kN/m^2 for methylcellulose gels containing 20, 25 and 30% (w/v) D-sorbitol, respectively. These data suggest that D-sorbitol may be acting as a dehydration agent in a similar manner to "salting-out" electrolytes such as NaCl, which enhance the thermal aggregation of methylcellulose.

The release profiles of acetaminophen from 2.0% (w/v) methylcellulose gels without added D-sorbitol and with D-sorbitol concentrations over the range 20—30% (w/v) are

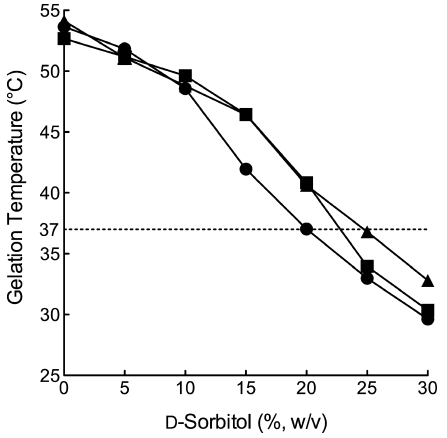

Fig. 1. Effect of D-Sorbitol Concentration on the Gelation Temperature of Methylcellulose Solutions of Concentrations (% (w/v)) of ▲, 1.0; ■, 1.5 and ●, 2.0

Each value is the mean±S.E. of 4 determinations.

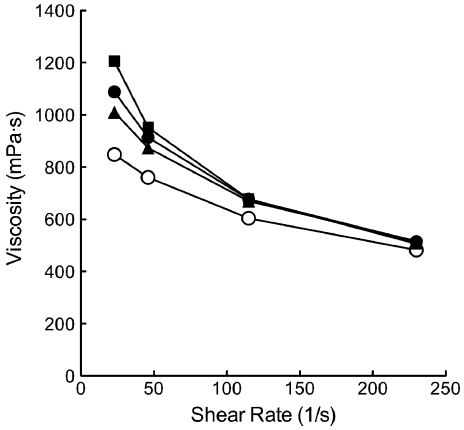

Fig. 2. Viscosity at 5 °C of 2.0% (w/v) Methylcellulose Solutions Containing D-Sorbitol at Concentrations (% (w/v)) of ○, 0; ▲, 20; ●, 25 and ■, 30

Each value is the mean±S.E. of 3 determinations.

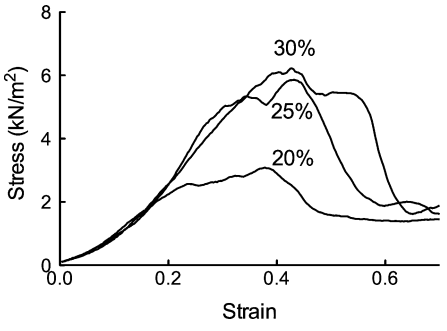

Fig. 3. Stress–Strain Curves at 37 °C of 2.0% (w/v) Methylcellulose Gels Containing D-Sorbitol with Concentrations (% (w/v)) as Indicated

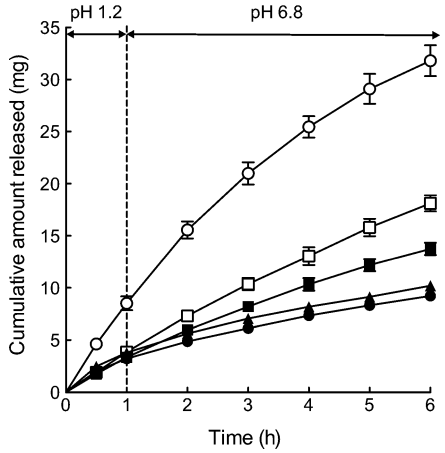

Fig. 4. *In Vitro* Release of Acetaminophen at 37 °C from ○, Commercial Syrup; □, 2.0% (w/v) Methylcellulose Gel, and 2.0% (w/v) Methylcellulose Gels Containing D-Sorbitol at Concentrations (% (w/v)) of ▲, 20; ●, 25 and ■, 30 Plotted as Cumulative Release against Time

Each value is the mean±S.E. of 4 determinations.

compared in Fig. 4 with that from a commercial syrup (CALONAL® syrup) containing 1.0% (w/v) acetaminophen. The receptor solutions of the diffusion cell were changed after 1 h from simulated gastric fluid at pH 1.2 to a simulated intestinal fluid at pH 6.8 to mimic gastrointestinal transit. The pK_a of acetaminophen is 9.5,[12] and consequently there will be no change in the state of ionization of this drug accompanying this pH change.

Methylcellulose solutions containing D-sorbitol formed gels in the donor cell within 30 min. The release profiles of 2.0% (w/v) methylcellulose gels containing both 20 and 25% (w/v) D-sorbitol were similar; the gel structure was maintained despite the change of pH, for the 6 h duration of the release measurements. In contrast, drug release from the 2.0% (w/v) methylcellulose/30% (w/v) D-sorbitol gel was more rapid and visual observation of the contents of the donor cell after 6 h showed evidence of gel erosion. Although the D-sorbitol-free methylcellulose solution did not form a gel, drug release from this solution was slower than that from the commercial syrup because of its higher viscosity.

Plots of cumulative release from the methylcellulose/D-sorbitol gels as a function of square root of time were linear in accordance with Eq. 1 indicative of diffusion-controlled release. The values of the diffusion coefficients, D ($\times 10^{-6}$ cm^2/s), calculated from the gradients of these plots were 5.95±0.52, 5.28±0.41 and 15.00±1.65 (n=4, mean±S.E.) for methylcellulose gels containing 20, 25 and 30% (w/v) D-sorbitol, respectively.

In summary, our study has demonstrated that the addition of 25—30% (w/v) D-sorbitol to methylcellulose solutions of concentrations 1.0—2.0% (w/v) reduces the gelation temperature to values between ambient and body temperature. Gels formed *in vitro* by 2.0% (w/v) methylcellulose solutions containing 25% (w/v) D-sorbitol released acetaminophen *in vitro* by a diffusion-controlled mechanism over a period of 6 h and retained their gel structure over the pH range 1.2—6.8. Our study suggests that these formulations may have potential application as *in situ* gelling vehicles for the sustained delivery of drugs.

Acknowledgements The authors are grateful to Dr. H. Kokubo of Shin-Etsu Chemical Co., Ltd. for the kind gift of methylcellulose. This work was supported in part by "High-Tech Research Center" Project for Private Universities: matching fund subsidy was from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Grant-in-Aid for the 2009—2010 Research Project of the Research Institute of Personalized Health Sciences, Health Sciences University of Hokkaido.

References

1) Xu Y., Li L., Zheng P., Lam Y. C., Hu X., *Langmuir*, **20**, 6134—6138 (2004).
2) Xu Y., Wang K. C., Li L., *Langmuir*, **20**, 646—652 (2004).
3) Xu Y., Li L., *Polymer*, **46**, 7410—7417 (2005).
4) Liang H. F., Hong M. H., Ho R. M., Chung C. K., Lin Y. H., Chen C. H., Sung H. W., *Biomacromolecules*, **5**, 1917—1925 (2004).
5) Miyazaki S., Kubo W., Itoh K., Konno Y., Fujiwara M., Dairaku M., Togashi M., Mikami R., Attwood D., *Int. J. Pharm.*, **297**, 38—49 (2005).
6) Itoh K., Kubo W., Fujiwara M., Watanabe H., Miyazaki S., Attwood D., *Biol. Pharm. Bull.*, **29**, 343—347 (2006).
7) Levy G., Schwarz T. W., *J. Am. Pharm. Assoc.*, **47**, 44—46 (1958).
8) Shar P. P., Roberts C. J., *J. Phys. Chem. B*, **111**, 4467—4476 (2007).
9) Miyazaki S., Takahashi A., Itoh K., Ishitani M., Dairaku M., Togashi M., Mikami R., Attwood D., *Drug Dev. Ind. Pharm.*, **35**, 780—787 (2009).
10) Miyazaki S., Takeuchi S., Yokouchi C., Takada M., *Chem. Pharm. Bull.*, **32**, 4205—4208 (1984).
11) Higuchi W. I., *J. Pharm. Sci.*, **51**, 802—804 (1962).
12) Fairbrother J. E., "Analytical Profiles of Drug Substances," Vol. 3, ed. by Florey K., Academic Press, New York, 1974, pp. 1—109.