Application of Extremely Low Viscosity Methylcellulose (MC) for Pellet Film Coating[1)]

Hiroyasu KOKUBO,* Sakae OBARA, and Yuichi NISHIYAMA

Specialty Chemicals Research Center, Shin-Etsu Chemical Co., Ltd., 28–1 Nishifukushima, Kubiki, Nakakubiki-gun, Niigata 942–8601, Japan. Received June 29, 1998; accepted August 20, 1998

Pellet film coating has very limited applicability compared with tablet film coating, because of the problem of sticking during fluidized bed operation. We have prepared an extremely low viscosity methylcellulose (MC) (4 mPa·s), and examined its solution and film properties and its suitability for pellet film coating.

MC lost its adhesiveness at a relatively high moisture content and pellet film coating could be achieved without agglomeration of the pellets within a reasonable operating time. The coated pellets were covered with a continuous film of MC, and drug release from the coated pellets was as rapid as that from the core. These findings suggest that MC (4 mPa·s) is applicable for pellet film coating in an aqueous system.

Key words methylcellulose; low viscosity; pellet; film coating; tackiness measurement; thermal gelation

Film coating with hydroxypropyl methylcellulose 2910 (HPMC) has been used in the pharmaceutical industry since the 1950's to provide taste-masking or light protection of tablets.[2)] Subsequent improvements in coating equipment and techniques led to a switch from organic solvent-based systems to aqueous systems. However, problems such as peeling, sticking, or logo-bridging can occur in aqueous film coating due to slow vaporization of water in comparison with that of organic solvents.[3,4)] There is a potential demand for pellet film coating in order to prevent chemical interactions between active ingredients and excipient or to protect coated pellets with function of enteric or sustained-release properties during compression to make a pellets in tablet formulation. However, great difficulty is encountered in pellet film coating due to the problem of sticking during fluidized bed operation, especially when the coating occurs in an aqueous solution system.

Film coating has been extensively studied in the pharmaceutical industry. The mechanical properties of HPMC films and solutions have been thoroughly studied.[3,5—8)] The hydroxypropylcellulose (HPC) coating system has a significantly lower vaporization efficiency and HPC films are quite tacky when compared with HPMC.[9)] MC has the lowest thermal gelation temperature among water-soluble cellulose ethers,[10)] and might be less adhesive. However, although there is considerable information on aqueous latex coating systems for pellets,[11)] little work has been done on water-soluble polymer coating. To our knowledge, all pellet film coating methods so far employed require extremely long operating times, thus necessitating the use of an organic solvent system.

In our previous study,[12)] we evaluated several water-soluble cellulose ethers as binders, and found that MC lost its adhesiveness at a higher water content than the others. In this study, we extended that work to examine the feasibility of pellet film coating with an extremely low viscosity MC (4 mPa·s).

Experimental

Materials Water-soluble cellulose ethers used were hydroxypropylcellulose (HPC: HPC EF-P, JP, Shin-Etsu Chemical Co.), hydroxypropyl methylcellulose 2910 (HPMC: Pharmacoat 603, 606 and 615, USP, Shin-Etsu Chemical Co.) and methylcellulose (MC: Metolose SM-15, JP, Shin-Etsu Chemical Co.). The sample of extremely low viscosity MC (MC: Metolose SM-4, JP, Shin-Etsu Chemical Co.) was prepared by acid-catalyzed hydrolysis. Table 1 shows the viscosity of a 2% aqueous solution of each cellulose ether measured at 20 °C with an Ubbelohde-type viscometer and the substitutents contents measured by the JP method. Plasticizer used was glycerin (Wako Pure Chemical Ind. Co.). Theophylline (Shiratori Pharmaceutical Co.) was used as a model drug in the pellets.

Viscosity and Thermal Gelation Measurements Various amounts of cellulose ethers were dissolved in purified water, and the viscosity of the solutions was measured at 20 °C with an Ubbelohde-type viscometer. The thermal gelation temperature was determined as the clouding point of the solutions by elevating the temperature at the rate of 1 °C/min.

Film Strength The aqueous solutions having a viscosity around 1000 mPa·s were each poured onto a glass plate and dried at 40 °C for 8 h to form a film of 100 μm thickness. After removal from the glass plate, the obtained films were cut into 1 cm×12 cm pieces and stored in 52% relative humidity at 25 °C for 3 d until the mechanical tests were performed. Plasticized films were prepared in a similar manner.

The mechanical properties of the films were evaluated by using a test apparatus (Auto Graph, Model DSS-10T-S, Shimadzu Co.). The initial length of the film specimens was 10 cm, and the extension speed was 10 mm/min. Film specimens with physical damage were discarded. The test was carried out at 25±2 °C and 50±2% relative humidity. The stress-strain curves were recorded for each sample, and the values of tensile strength and elongation at break were calculated.

Solubility of the Films Films were cut into 1 cm squares for the dissolution test. The dissolution time of the films was measured at 37 °C in purified water, JP 1st fluid (pH 1.2) and JP 2nd fluid (pH 6.8) using the JP disintegration test method.

Tackiness of the Binder Solution[12)] Tackiness of HPC, HPMC (3 mPa·s) and MC (4 mPa·s) aqueous solutions was measured using a rheological measuring instrument (Rheo Meter, Model NRM-2010J-CW, Fudoh Ind. Co.) under the following conditions: clearance between the glass plate (lower plate) and the circular metal plate (upper) of 30 mm in diameter was set at 1 mm, and the press and remove stroke was controlled at 5 times/min at 5 mm/sec stroke speed. One ml of aqueous solution (approx. 28%; dry basis) was placed on the glass plate, and the instrument was run continu-

Table 1. Characteristics of the Water-Soluble Cellulose Ethers Used

Type	Methoxyl (%)	Hydroxypropoxyl (%)	Viscosity (mPa·s)[a)]
HPMC (3 mPa·s)	29.0	8.9	3.02
HPMC (6 mPa·s)	29.0	8.9	5.74
HPMC (16 mPa·s)	29.0	8.9	16.0
MC (4 mPa·s)	28.9	—	4.16
MC (16 mPa·s)	28.9	—	15.8
HPC	—	62.3	5.56

a) 2% aqueous solution at 20 °C.

* To whom correspondence should be addressed.

Table 2. Operating Conditions

Item	Conditions
Machine	Flow coater FLO-5 (Freund Ind. Co.)
Coating solution	7% aq. solution
Coating amount	8% based on core pellets
Charge	5 kg of pellets
Spray gun	Schlick type, nozzle 1.2 mm in diameter
Atomizing air pressure (kPa)	300
Atomizing air flow (ml/min)	210
Gun position	40 cm from pellet bed surface
Drying air flow (m^3/min)	4.0
Supply air temperature (°C)	80
Spray feed rate (g/min)	50, 80, 100
Exhaust air temperature (°C)	47, 39, 35
Pellet bed temperature (°C)	51, 44, 39

ously under a gentle drying air flow at room temperature. The change of tackiness was measured in terms of the separating force between the two plates, and the change of moisture content of the test solution was determined by weighing.

Pellet Coating The coating experiment was conducted as follows. Spherical pellets prepared by the wet-granulation extrusion method containing 60% theophylline (particle size: 16 mesh on, 1.0%; 18 mesh on, 89.1%; 22 mesh on, 9.1%, 22 mesh pass, 0.8%) were coated with 7% aqueous solutions of MC (4 mPa·s) and HPMC (3 mPa·s) using a conventional fluidized bed coating apparatus (Flow coater FLO-5, Freund Ind. Co.) until the polymer consumption reached 8% based on the core pellets. The coating was done at several spray feed rates, and percent agglomeration of the coated pellets was evaluated in terms of the 16 mesh on fraction. The process variables are listed in Table 2.

The dissolution rate of the coated pellets was measured in purified water for 60 min at 37 °C according to the JP XIII dissolution test method (rotating basket, 100 min^{-1}). The amount of theophylline released was monitored by measuring the UV absorbance at 270 nm.

Results and Discussion

Solution Properties The relationship between concentration and viscosity of the aqueous solutions of HPMC and MC is shown in Fig. 1. MC solutions showed an almost linear relationship between concentration and viscosity, and are more viscous than HPMC solutions of equivalent concentration at high concentrations. Assuming that the optimal viscosity of a coating solution is below 100 mPa·s in order to maintain the fine particle size of the sprayed mist, the optimal polymer concentration would be below 4% for the lowest viscosity grade of MC (16 mPa·s) that is currently available. This is too low compared with the value of 7% for the regular film coating agent HPMC (6 mPa·s); the operating time would be almost doubled. MC (4 mPa·s) showed the same viscosity of 100 mPa·s as HPMC (6 mPa·s) at a polymer concentration of 7%. This suggests that MC (4 mPa·s) solution might be usable for pellet coating at a sufficiently high polymer concentration to give a reasonable coating time.

The thermal gelation properties of water-soluble cellulose ethers are well known, and the thermal gelation temperature is dependent on the contents of substituents and the concentration of the solutions.[10] In this experiment, we determined the gelation temperature in terms of the clouding point of the polymer solution instead of viscosity because of the very low viscosity. The relationship between concentration and thermal gelation temperature of the aqueous solutions is shown in Fig. 2. The thermal gelation temperature for both MC (4 mPa·s) and HPMC (3 mPa·s) decreased as the polymer concentration was increased. MC showed a lower thermal

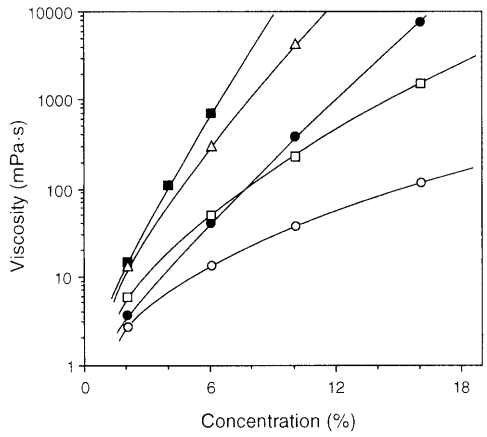

Fig. 1. Relationship between Concentration and Viscosity of Polymer Aqueous Solutions

○, HPMC (3 mPa·s); □, HPMC (6 mPa·s); △, HPMC (16 mPa·s); ●, MC (4 mPa·s); ■, MC (16 mPa·s).

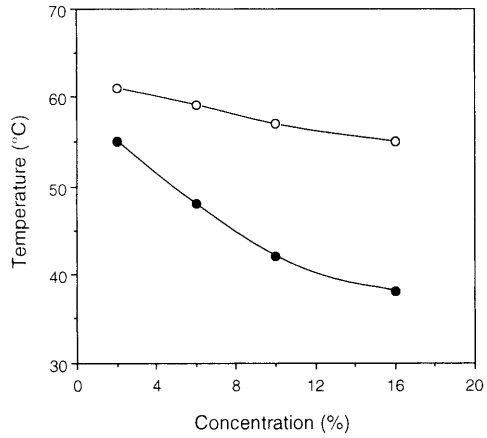

Fig. 2. Relationship between Concentration and Thermal Gelation Temperature of Polymer Aqueous Solutions

○, HPMC (3 mPa·s); ●, MC (4 mPa·s).

gelation temperature than that of HPMC. The difference was especially large at higher polymer concentrations. At 16% polymer concentration, the thermal gelation temperature of MC (4 mPa·s) lay below 40 °C. This is close to the pellet bed temperature (Table 2), implying that the MC in the sprayed solution will readily change from a solution to a gel state during the coating operation in a fluidized bed. If this is so, it would influence the tackiness of the solution during drying, as will be discussed later.

Film Properties The relationship between polymer viscosity and tensile strength of the films is shown in Fig. 3. The film strength decreased as the polymer viscosity decreased reflecting the lower degree of polymerization, especially for MC (4 mPa·s). The plasticized film strength and the maximum elongation are shown in Table 3. The combination of MC and glycerin afforded better mechanical properties, being tough and flexible, than the combination of HPMC and glycerin. For pellet film coating, film properties are not critical in practical terms, because the pellet is usually spherical and small, in contrast to the shape of tablets, and the stress on the films that arises from shrinking during drying is small and well-distributed.

The dissolution time of the films was measured according

to the JP XIII disintegration test method. HPMC and HPC films dissolved in various buffer solutions within 5 min. MC films did not dissolve within the test period of 120 min due to the low thermal gelation temperature (below 37 °C under the test conditions), but changed into a white gel and broke up into small pieces in 10 to 20 min.

Tackiness of the Polymer Solutions In our previous study[12] on water-soluble cellulose ethers as granulation binders, MC lost its adhesiveness at a higher water content than the other cellulose ethers. The water content transition pattern and the tackiness of HPMC, MC and HPC solutions are shown in Fig. 4. Plasticized solutions of MC and HPMC were also evaluated, and the values of moisture content at the point of loss of adhesiveness are summarized in Table 4. At below 45.5% moisture (dry basis; 31.3%, wet basis), HPMC and HPC solutions changed to the gel state, but HPC maintained its adhesiveness in the gel state until the moisture content fell to 16.2% (dry basis; 13.9%, wet basis), whereas HPMC lost its adhesiveness immediately upon conversion to the gel state.[12] These findings are consistent with reports that HPC films are flexible and quite tacky,[9,13] requiring lower spray feed rates of the solution compared with the regular HPMC film coating agent. MC showed a transition at the beginning of this test, and lost its adhesiveness below 125.8% moisture (wet basis; 55.7%, dry basis). The plasticized solutions lost their adhesiveness at higher moisture contents in comparison with the unplasticized solutions. A higher spray feed rate can be applied for such plasticized solutions in tablet film coating. These results suggest that MC can be used at a higher spray feed rate than HPMC, and has great potential for pellet film coating.

Pellet Coating A 5 kg scale fluidized bed was employed to assess the feasibility of pellet film coating with MC. Mi-

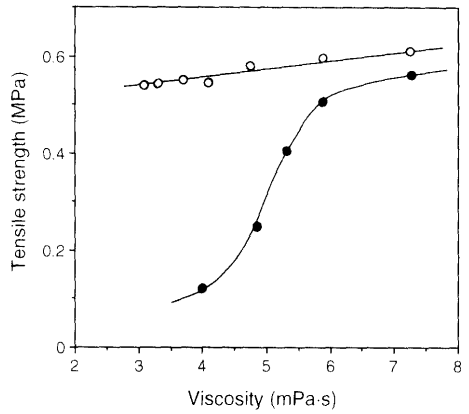

Fig. 3. Relationship between Viscosity and Tensile Strength of Polymer Films

○, HPMC (3 mPa·s); ●, MC (4 mPa·s).

Table 3. Film Strength and Maximum Elongation of MC and HPMC

Polymer	Unplasticized	Plasticized[a]
Film strength (MPa)		
HPMC (16 mPa·s)	61	25
HPMC (3 mPa·s)	56	5
MC (16 mPa·s)	71	33
MC (4 mPa·s)	42	19
Elongation (%)		
HPMC (16 mPa·s)	12.7	2.5
HPMC (3 mPa·s)	4.9	0.8
MC (16 mPa·s)	24.8	26.0
MC (4 mPa·s)	2.1	3.6

a) MC and HPMC were plasticized with 30% glycerin based on the polymer.

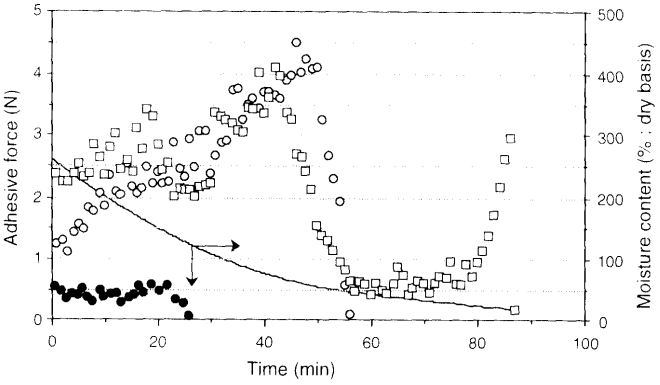

Fig. 4. Tackiness and Water Content Transition Patterns of Binder Solutions

○, HPMC (3 mPa·s) solution; ●, MC (4 mPa·s) solution; □, HPC solution; ——, moisture.

Table 4. Water Content at Loss of Adhesiveness

Polymer mixture	Water content (%)[a]
HPMC	45.5 (31.3)
30% plasticized[b]	62.1 (38.3)
MC	125.8 (55.7)
30% plasticized[b]	151.3 (60.2)
HPC	16.2 (13.9)

a) Dry basis (wet basis). *b*) Glycerin.

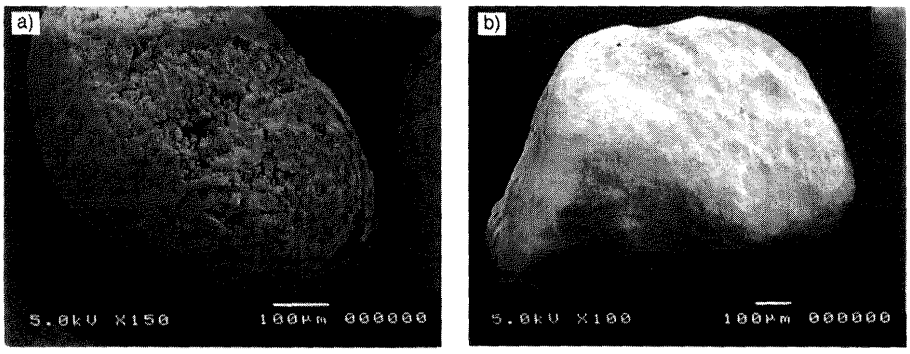

Fig. 5. Microscopic Views of the Coated and Uncoated Pellets

a) core pellet, b) pellet coated with MC (4 mPa·s).

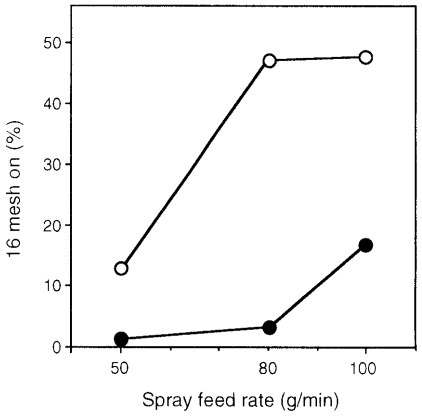

Fig. 6. Relationship between Agglomeration Rate (16 mesh on) and Spray Feed Rate

○, HPMC (3 mPa·s); ●, MC (4 mPa·s).

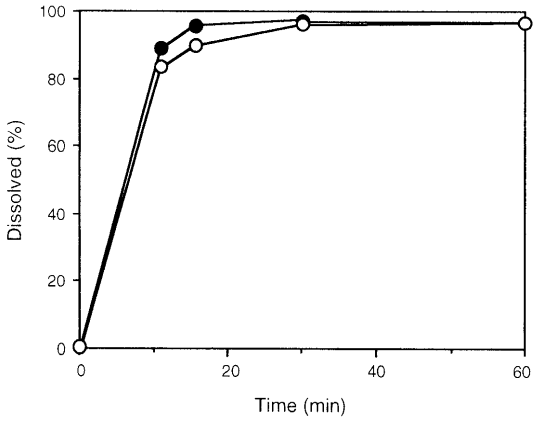

Fig. 7. Dissolution Profiles of Pellets Coated with MC (4 mPa·s) and Core Pellets

○, core pellets; ●, MC (4 mPa·s).

croscopic views of a core pellet and a pellet coated with MC (4 mPa·s) are shown in Fig. 5. The agglomeration rate was evaluated by means of sieve analysis, and the results are shown in Fig. 6. The coated pellets were covered with a continuous film of MC (Fig. 5). By using the MC solution, pellet coating could be achieved with almost no agglomeration until the spray feed rate reached 100 g/min. On the other hand, over 10% agglomeration was observed with HPMC solution at the spray feed rate of 50 g/min, despite its lower viscosity in comparison with that of the MC solution. This result demonstrates that MC (4 mPa·s) is a suitable polymer for pellet film coating using a fluidized bed coating apparatus.

The dissolution profile of theophylline pellets coated with MC is shown in Fig. 7. The drug release was as rapid as the release from the core, even though the film did not dissolve, as mentioned above. MC appears to be available as an alternative to HPMC as a water-soluble polymer coating agent, and is superior to HPMC for pellet film coating.

Conclusion

We have examined the solution and film properties of an extremely low viscosity grade of MC (4 mPa·s) to assess the feasibility of using this polymer for pellet film coating. The results may be summarized as follows. 1) The MC solution could be used at the same polymer concentration as a regular film coating agent, HPMC (6 mPa·s). 2) The thermal gelation temperature of MC was lower than that of HPMC, and thus the MC solution lost its adhesiveness on drying at an earlier stage than the HPMC solution. 3) Coating experiments with the MC solution did not result in agglomeration of the pellets, though serious agglomeration was observed when HPMC solution was used. These results were well explained by the results of tackiness measurements of MC and HPMC. 4) Pellets coated with MC showed quick dissolution of the drug, similar to that seen with usual water-soluble film coating. Based on these results, the extremely low viscosity MC (4 mPa·s) is expected to be suitable for use as a pellet film coating agent to prevent chemical interactions among components or to protect coated pellets during compression. It is also clear that tackiness measurement is a useful technique to evaluate film coating solutions.

References

1) A part of this study was presented at the 23rd Conference on Pharmaceutical Technology, Chiba, July 1998.
2) Endicott C. J., Dallavis A. A., Dickinson H. M. N., United States Patent 2991085 April 7 (1959).
3) Rowe R. C., "Defects in Aqueous Film-Coated Tablets, in Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms," 2nd ed., ed. by McGinity J. W., Marcel Decker, Inc., New York and Basel, 1997, pp. 419—440.
4) Rowley F., *Pharm. Technol.*, **15**(10), 68—72 (1991).
5) Rowe R. C., *J. Pharm. Pharmacol.*, **32**, 116—119 (1980).
6) Rowe R. C., *J. Pharm. Pharmacol.*, **35**, 205—207 (1983).
7) Okhamafe A. O., York P., *J. Pharm. Pharmacol.*, **37**, 449—454 (1985).
8) Okhamafe A. O., York P., *J. Pharm. Pharmacol.*, **37**, 849—853 (1985).
9) Reiland T. L., Seitz J. A., Yeager J. L., Brusenback R. A., *Drug Dev. Ind. Pharm.*, **9**, 945—958 (1983).
10) Nagura S., Nakamura S., Onda Y., *Kobunshi Ronbunshu*, **38**, 133—137 (1981).
11) Fukumori Y., "Coating of Multiparticulates Using Polymeric Dispersions, in Multiparticulate Oral Drug Delivery," ed. by Ghebre-Sellassie I., Marcel Decker, Inc., New York and Basel, 1994, pp. 79—111.
12) Kokubo H., Nakashima C., Sunada H., *Chem. Pharm. Bull.*, **46**, 488—493 (1998).
13) Park H. J., Testin R. F., Vergano P. J., Weller C. L., *J. Food Sci.*, **58**, 1361—1370 (1993).