Development of Cellulose Derivatives as Novel Enteric Coating Agents Soluble at pH 3.5—4.5 and Higher¹⁾

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Hydroxypropyl methylcellulose (HPMC) was selected as a base polymer to develop novel enteric coating agents for acid protection which can dissolve at pH around 4, and was modified with trimellitic acid or maleic acid at various degrees of substitution. These carboxylic acids have higher dissociation constants and higher solubility in water than the carboxylic acids of existing enteric coating polymers. The synthesized polymers were micronized and dispersed in aqueous medium to determine their pK_a values by potentiometric titration. The pH of dissolution and the water vapor permeability of the cast films prepared from organic solutions were also evaluated. Hydroxypropyl methylcellulose trimellitate (HPMCT) showed good acid resistance, and the pH at which it dissolves can be controlled in the range of pH 3.5 to 4.5 by varying the content of trimellityl groups and the methoxyl substitution of the base polymer.

Key words acid protection; enteric coating; trimellitic acid; hydroxypropyl methylcellulose; hydroxypropyl methylcellulose trimellitate; potentiometric titration

Solid enteric pharmaceutical preparations are provided with an enteric coating which protects a drug with low acidic resistance from the attack of gastric juice, simultaneously protecting the gastric mucosa from irritation by the drug and not being dissolved till it reaches the intestine; accordingly, the drug exhibits its effect within the intestine. There is a difference in pH in going from stomach to intestine: gastric juice with pH values ranging from 1.5 to 3.5 and intestinal environments with pH ranging from 3.6 to 7.9 were reported.^{2,3)} Commercially available enteric coating agents of both cellulosic and acrylic polymers are soluble in the pH range from 5.0 to 7.0 (Table 1). However, in drugs with poor and limited absorbability in the gastro-intestinal tract, it is desirable to ensure that the coating is dissolved as early as possible by reducing the dissolution pH thereof, in order to maximize the drug absorption.⁴⁻⁶⁾ It is therefore of interest to develop polymers soluble at more acidic pH than conventional enteric coating polymers.

Enteric coating polymers having carboxyl groups in their undissociated form have very low solubility in water; as the pH is raised, the equilibrium shifts to the formation of the ionized form with increasing water solubility. Thus, the pH at which cellulosic enteric polymers become soluble can be controlled by adjusting both the kind of carboxylic acid and the degree of substitution. In the present study, we examined the feasibility of modifying hydroxypropyl methylcellulose (HPMC) with trimellitic acid and maleic acid to develop acid protective coating materials soluble at pH around 4. Six derivatives were synthesized and evaluated.

Experimental

Polymer Synthesis For the synthesis of hydroxypropyl methylcellulose trimellitate (HPMCT), 700 g of HPMC 2910 or 2208 (8 mPa·s, 2% aqueous solution at 20°C) was dissolved in 2100 g of acetic acid (reagent grade) in a 5 l kneader at 70°C, and then an appropriate amount of trimellitic anhydride (Wako Pure Chemical Industries) and 275 g of sodium acetate (reagent grade) as a catalyst were added and the reaction was allowed to proceed at 85 to 90°C for 5 h. After the reaction, 1200 g of purified water was poured into the reaction mixture, and the resultant

mixture was poured into an excess amount of purified water to precipitate the polymer. The crude polymer was washed well with water and then dried to afford HPMCT-1, 2, 3 or 4. Hydroxypropyl methylcellulose acetate maleate (HPMCAM) was synthesized similarly using a mixture of acetic and maleic anhydrides in place of trimellitic anhydride, affording HPMCAM-1 and 2 (see Table 3).

Solubility of Polymer Films The obtained polymers were dissolved in a mixture of dichloromethane:ethanol (1:1 by weight), and the solution was poured onto a glass plate and dried to form a film of 100 μ m thickness. Films were cut into 1 cm squares for the dissolution test. The dissolution time of the films was measured at 37°C in McIlvaine buffer solutions of various pH values using the JP disintegration test method.

Potentiometric Titration of the Polymer Dispersions The synthesized polymers were micronized and dispersed in aqueous medium (polymer concentration: 0.01 mol/l) to determine the pK_a values by potentiometric titration. The titration was carried out by adding a calculated amount of alkali to the polymeric dispersion to obtain a given degree of neutralization (α : based on free carboxyl groups) and measuring the pH of the dispersion after it reached equilibrium. In the case of a monobasic weak acid, the pH at $\alpha=0.5$ is equivalent to the pK_a value. We presumed that this theory could be applied to the present polymers to determine the pK_a values.⁷⁾ At the same time, the amount of alkali required to dissolve the polymer was also determined.

Water Vapor Permeability of the Film Films of 100 μ m thickness were

Table 1. Dissolution pH of Existing Enteric Polymers

Polymer	Dissolution pH
Cellulosic	
Cellulose acetate phthalate (CAP)	6.2 ^{a)}
Hydroxypropyl methylcellulose phthalate (HPMCP)	
HP-55	5.5 ^{b)}
HP-50	5.0 ^{b)}
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	
AS-L	5.5 ^{b)}
AS-M	6.0 ^{b)}
AS-H	6.8 ^{b)}
Acrylic	
Eudragit L30D-55	5.5 ^{c)}
Eudragit L-100	6.0 ^{c)}
Eudragit S100	7.0 ^{c)}

a) Technical data from Eastman Chemical Co. b) Technical data from Shin-Etsu Chemical Co. c) Technical data from Röhm GmbH.

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placed over vials filled with saturated sodium chloride aqueous solution. The vials were stored in a desiccator containing calcium chloride for several days and then were weighed. The value of water vapor permeability was calculated from the change of weight.

Coating Experiment The coating experiment was conducted as follows. Spherical pellets containing 2% riboflavin were coated with a solution of the polymer, in a mixture of water:ethanol (3:7 by weight) using a conventional fluidized bed coating apparatus until the polymer consumption reached 20% based on the core pellets. The dissolution rate of the coated pellets was measured in the JP 1st (pH 1.2) for 2 h and then the buffer solution was changed to McIlvaine buffer solution of various pH values at 37 °C according to the JP dissolution test method (rotating basket, 100 rpm). The amount of riboflavin release was monitored by UV at 444 nm.

Results and Discussion

Strategy of Polymer Synthesis The substituents of cellulose-based enteric polymers have an important influence on the pH-solubility relationship and acid resistance. Many kinds of polymers have been investigated as enteric coating agents.⁸⁾ The substituents of hydrophobic car-

boxylic acid groups lead to higher pH soluble polymers. Hexahydrophthalic or tetrahydrophthalic acid derivatives of HPMC had higher pH solubility than the phthalic acid derivatives reported.⁹⁾ Considering pK_a values and water solubility characteristics (Table 2), we selected trimellitic acid and maleic acid as candidate substituents for the synthesis of polymers soluble at lower pH, to compare with existing polymers containing phthalic acid and succinic acid, respectively. We employed trimellitic acid at various levels of substitution (Table 3). Maleic acid was incorporated together with acetic acid to obtain an appropriate level of hydrophobicity. Total substitution of maleic acid and acetic acid combined was fixed at around 0.85 degree of substitution per glucose unit, which represents approximately 80% of the possible substitution sites of the base polymer.

pH Solubility Relationship of the Polymers The degrees of substitution of the synthesized polymers are listed in Table 3. The relationship between the pH and the dissolution time of cast films of the aromatic derivatives of both synthesized and existing polymers is shown in Fig. 1. HPMCT was soluble at a lower pH range of 3.5 to 4.5, as we had expected, compared with the conventional enteric polymers HP-50 and HP-55. HPMCT differs from HP-50 and HP-55 in the contents of both trimellityl and methoxyl groups.

The relationship between the pH and the dissolution time of cast films of the aliphatic derivatives of both synthesized and existing polymers is shown in Fig. 2. Hydroxypropyl methylcellulose acetate maleate (HPMC-AM), which differs from the conventional enteric polymers, AS-L, AS-M and AS-H, in the contents of both maleyl and acetyl groups, was dissolved at a lower pH range of 3.5 to 4.5.

pH Titration and Water Vapor Permeability of the Polymers The results for aromatic derivatives of HPMCT-3 and HP-50 are shown in Fig. 3. The pH titration curves of HPMCT-3 lay under that of HP-50 in both purified water and 0.1 M NaCl aqueous solution. The pK_a values of both polymers in purified water coincided well with the pH values of film dissolution. In the presence of an electrolyte, NaCl, the dissociation increased, as expected for a polyelectrolyte.⁷⁾ Similar patterns were obtained with

Table 2. pK_a Values and Solubility in Water of Carboxylic Acids Used in This Study

Carboxylic acid	pK_a value	Solubility in water (/100 g water)
Trimellitic acid	2.49 ^{a)}	2.1 g ^{c)}
Phthalic acid	2.75 ^{b)}	0.6 g ^{c)}
Maleic acid	1.75 ^{a)}	Free ^{c)}
Succinic acid	4.00 ^{a)}	7.7 g ^{c)}

a) "Kagakuinran," 4th ed., Maruzen Co., Tokyo, 1993. b) "Encyclopaedia Chimica," Kyoritsu Shuppan Co., Tokyo, 1963. c) "The Merck Index," 9th ed., Merck and Co., Rahway NJ, 1976.

Table 3. Carboxyl, Methoxyl and Hydroxypropoxyl Substitution of Samples Used in This Study

Polymer	Methoxyl ^{a)}	HPO ^{b)}	Phthalyl or trimellityl ^{a)}	Succinoyl or maleyl ^{a)}	Acetyl ^{a)}
Aromatic					
HPMCT-1	1.87	0.24	0.65	—	—
HPMCT-2	1.87	0.24	0.28	—	—
HPMCT-3	1.41	0.20	0.64	—	—
HPMCT-4	1.41	0.19	0.30	—	—
HPMCP HP-55	1.87	0.24	0.66	—	—
HPMCP HP-50	1.86	0.24	0.40	—	—
Aliphatic					
HPMCAM-1	1.87	0.24	—	0.51	0.35
HPMCAM-2	1.87	0.24	—	0.33	0.46
HPMCAS AS-L	1.87	0.24	—	0.41	0.48
HPMCAS AS-M	1.87	0.24	—	0.28	0.57
HPMCAS AS-H	1.87	0.24	—	0.15	0.68

a) Degree of substitution. b) Hydroxypropoxyl molar substitution.

Fig. 1. pH-Solubility Relationship of Films of Aromatic Derivatives
McIlvaine buffer solutions were used. T-1, HPMCT-1; T-2, HPMCT-2; T-3, HPMCT-3; T-4, HPMCT-4.

Fig. 2. pH-Solubility Relationship of Films of Aliphatic Derivatives
McIlvaine buffer solutions were used. AM-1, HPMCAM-1; AM-2, HPMCAM-2.

Fig. 3. pH Titration Curves of the Aromatic Derivatives
Arrows indicate the test medium: purified water (upper line)→0.1 M NaCl aqueous solution (lower line). —, soluble; ---, insoluble.

the other polymers. The dissolution point also shifted to smaller values of pH and greater values of the degree of neutralization.

The results for aliphatic derivatives of HPMCAM-1 and AS-L are shown in Fig. 4. The pH titration curves of HPMCAM-1 lay under that of AS-L in both purified water and 0.1 M NaCl aqueous solution. The pK_a values of both polymers in purified water were consistent with

Fig. 4. pH Titration Curves of the Aliphatic Derivatives
Arrows indicate the test medium: purified water (upper line)→0.1 M NaCl aqueous solution (lower line). —, soluble; ---, insoluble.

Fig. 5. Relationship between Degree of Substitution and Dissolution pH of Polymer Films

-----, HPMCT (base polymer HPMC 2910); —, HPMCT (base polymer HPMC 2208); —, HPMCAM; ---, HPMCP; —, HPMCAS. The degree of substitution of the aliphatic derivatives is expressed by the acetyl group.

the pH of film dissolution. These findings were similar to those in the case of the aromatic derivatives. The dissolution point also shifted to smaller values of pH, though the degree of neutralization of HPMCAM-1 fell to zero. This suggested that HPMCAM-1 will dissolve or swell in ordinary buffer solutions and show insufficient acid resistance.

The relationship between degree of substitution and pH of dissolution of the polymers employed in this study is shown in Fig. 5. HPMCT and HPMCAM were soluble at lower pH, the value of which can be controlled in the range of pH 3.5 to 4.5 by adjusting the substituent contents.

The results of water vapor permeability of HPMCT-3, HP-55, HP-50 HPMCAM-1 AS-L AS-M and AS-H are listed in Table 4. This permeability of HPMCT-3 was found to be $80 \text{ g/m}^2 \cdot 24 \text{ h}$, while that of HPMCAM-1 was $190 \text{ g/m}^2 \cdot 24 \text{ h}$ when measured as described in Experimental.⁷⁾ These values were almost equivalent to their analog of aromatic and aliphatic derivatives, respectively.

Dissolution Properties of Pellets Coated with HPMCT
The dissolution behavior of riboflavin pellets coated with 20% HPMCT-3 is shown in Fig. 6. The acid resistance was sufficient, and the pellets dissolved rapidly at pH over 4.0. Almost no drug release was observed at pH 3.5.

Table 4. Water Vapor Permeability of Samples Used in This Study

Polymer	Permeability (g/m ² ·24 h)
Aromatic	
HPMCT-3	80
HPMCP HP-55	90
HPMCP HP-50	100
Aliphatic	
HPMCAM-1	190
HPMCAS AS-L	170
HPMCAS AS-M	190
HPMCAS AS-H	210

Fig. 6. Dissolution Profiles of Pellets Coated with HPMCT-3

The dissolution test was conducted by the JP basket method at 100rpm in McIlvaine buffer solutions. ○, pH 3.5; □, pH 4.0; △, pH 4.5.

Conclusion

We examined the effect of introducing trimellitic acid or maleic acid substituents into HPMC on the pH-solubility relationship to develop novel enteric coating materials for

acid protection soluble at lower pH. The new polymers all dissolved at lower pH than existing polymers, and the pH values at which films of these polymers dissolved coincided well with their pK_a values. The aromatic derivatives (HPMCT) exhibited superior acid and moisture resistance in comparison with the aliphatic derivatives (HPMCAM). The dissolution pH of HPMCT could be controlled by adjusting the trimellityl and methoxyl contents within the range of pH 3.5 to 4.5. Hydroxypropyl methylcellulose trimellitate (HPMCT) is an interesting candidate for a new enteric or acid protective coating agent which would dissolve quickly after transfer from the stomach to the intestine, thereby maximizing the bioavailability of acid-susceptible, poorly absorbable drugs.

References

- 1) A part of this study was presented at the 117th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March 1997.
- 2) "Remington's Pharmaceutical Sciences," 14th ed., Mack Publishing Co., Easton, Pennsylvania, 1970, pp. 1689–1691.
- 3) Kubiak E., Long S., Ryan G. W., Wagner J. G., *J. Am. Pharm. Assoc. Sci. Ed.*, **49**, 133–139 (1960).
- 4) Doi Y., Fujimoto H., Ito M., Iwamoto K., Kitamura K., Maekawa H., Ogura T., Takagishi Y., *Jpn. J. Antibiot.*, **30**, 631–638 (1977).
- 5) Aita K., Doi Y., Imagawa T., Ito M., Kawai S., Matsuda S., Nishimura K., Sakamoto T., Sonoyama T., Yasuda M., *Jpn. J. Antibiot.*, **38**, 813–821 (1985).
- 6) Lappas L. C., McKeeham W., *J. Pharm. Sci.*, **56**, 1257–1261 (1967).
- 7) Hoshi N., Kokubo H., Nagai T., Obara S., "Application of HPMC and HPMCAS to Film Coating of Pharmaceutical Dosage Forms, in Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms," 2nd ed., ed. by McGinity J. W., Marcel Dekker, Inc., New York and Basel, 1997, pp. 177–225.
- 8) "Remington's Pharmaceutical Sciences," 13th ed., Mack Publishing Co., Easton, Pennsylvania, 1965, pp. 604–605.
- 9) Koyanagi S., Ogawa K., Onda Y., Yamamoto A., U. S. Patent 3870702 (1975) [*Chem. Abstr.*, **77**, 168614s (1972)].