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Synthesis and Characterization of HPMC Derivatives as Novel Duodenum-Specific Coating Agents

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HPMC (Hydroxypropyl methylcellulose) was chemically modified, using maleic anhydrides, to obtain pH-sensitive HPMCAM (Hydroxypropyl methylcellulose acetate maleate) polymers for use as novel duodenum-specific coating agents. The pharmaceutical properties of HPMCAM, such as film forming, acid values, pH-sensitive values, water vapor permeability, tensile strength and Tg, were investigated, and found to show good film forming properties. The pH-sensitive values were 3.0 to 3.7. *In vitro* results demonstrate that HPMCAM could completely suppress drug release within 2h in a simulated gastric fluid (pH 1.2) and rapidly release the drug in a simulated pathological duodenal fluid (pH 3.4). These results indicate that HPMCAM might be a useful material for a duodenum-specific drug delivery system.

Key words: Duodenum-specific, Hydroxypropyl methylcellulose acetate maleate (HPMCAM), pH-Sensitive

INTRODUCTION

A duodenal ulcer (DU) is a multifactorial disease, with a lifetime prevalence of approximately 10% (Sohn, et al, 1998). The risk factors include first-degree relatives with the disease, alcohol abuse, cigarette smoking and stress, etc. A DU is prone to recrudesce and may cause other concurrent diseases, such as hemorrhage and perforation, and may even lead to concretization. Recently, numerous studies have demonstrated that *helicobacter pylori* (*H. pylori*) infection is strongly associated with DU (M.R. Konorev, 2001). Eradiation therapy for *H. pylori* using various antibiotics, such as metronidazole, amoxicillin or clarithromycin, is now widely recognized as playing a critical role in improving and/or preventing gastrododenal diseases. The duodenum, the initial part of the intestines, is about 25 cm long. Drugs taken by oral administration always go quickly through the duodenum and do not reach their effective concentration at the pathological site; therefore, can not completely eradiate *H. pylori*. Furthermore, since therapeutic regimens for DU are not duodenum-specific, sometimes not enough of the drug will be left in the duodenum after degradation by digestive enzymes in the stomach. Therefore, to develop a duodenum-specific drug delivery system, which can deliver the drugs directly to the duodenum for their release to an effective concentration, is very important for the treatment of DU.

Under natural physiological condition, after 24 hours fasting, the pH value of gastric juice in stomach has been found to be between 1.3~1.8, and rarely exceeds 2.0, while those of the duodenal juice and jejunum are 4~5 and 6~7, respectively. The sufferers of a DU, due to their relatively higher stomach discharge rate, have a lower duodenal juice pH about 2.9~4.0 (Mela GS, *et al.*, 1992). Therefore, a macromolecular film coating agent, with a pH-sensitive value around 2.9~4.0, may be used as a duodenum-specific coating agent. However, commercially available coating agents are commonly soluble in the pH range 1.0 to 2.0, such as Eudragit VI (pH 1.2~1.5), or 5.0 to 7.0, such as hydroxypropyl methylcellulose phthalate (HPMCP) (pH 5.5~5.8 or higher), cellulose acetate phthalate (CAP, pH 6.0 or higher), hydroxypropyl methylcellulose acetate succinate (HPMCAS, pH 5.5~7.1 or higher) and eudragit II (pH 6.0 or higher) and III (pH 7.0 or higher). HPMC (Hydroxypropyl methylcellulose) has been modified, using trimellitic acid, with varying degrees of substitution,

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to develop the novel enteric coating agent, hydroxypropyl methylcellulose trimellitate (HPMCT), which is soluble at around pH 4.0, so would dissolve quickly after transfer from the stomach to the intestine, thereby maximizing the bioavailability of acid-susceptible, poor absorbable drugs (Hiroyasu KokuBo *et al.*, 1997). However, the pH for solubility of these polymers is higher than that of the duodenal ulcer environment. Therefore, it is of interest to develop polymers with a pH-sensitive range of 2.9 to 4.0 to ensure the coating film is dissolved in the duodenum to allow an effective concentration for therapy.

In the present study, the synthesis and characterization of a duodenum-specific drug delivery system is reported for the first time. Berberine chloride (BER·HCL), which is an active principles extracted from the Traditional Chinese Medicine-R*hizoma coptidis* (huang-lian), was chosen as a model drug, as clinical experiments have shown it to have similar antibacterial activity against *H. pylori in vivo*, but less side effects than antibiotics, such as metronidazole, amoxicillin or clarithromycin. (Wang-ying, *et al.*, 2003). HPMC was modified, using maleic acid, to develop a pH-sensitive macromolecule material-HPMCAM (Hydroxypropyl methylcellulose acetate maleate). The pharmaceutical properties, such as film forming, acid values, pH-sensitive values, water vapor permeability, tensile strength and Tg, were investigated. The *in vitro* release of berberine chloride tablets coated with HPMCAM was also studied. We hypothesize that "the press-coated tablets can carry the therapeutics directly to the duodenum without drug release in the stomach, allowing the released drug to accumulate at the surface of the pathological ulcer, thereby achieving the function of a duodenum-specific and eradiation therapy for *H. pylori*." Also, the tablets could be separately coated with stomach-specific and duodenum-specific coating agents, and then taken by patients suffering from gastroduodenal ulcers, which at the same time would fulfill the eradiation therapy for *H. pylori* for the treatment of gastroduodenal ulcers and other gastroduodenal diseases.

MATERIALS AND METHODS

Materials

The hydroxypropyl methylcellulose (HPMC 2910, 6 mPa·s, 2% aqueous solution at 20°C) was obtained from Colorcon Coating Technology Limited, Shanghai, P.R, China; the maleic anhydrides, acetic anhydrides and acetic acid, chemical grade, were obtained from Zibo Chemical Co. Ltd., Tianjing, China; and the berberine chloride (BER·HCL) from Xixiao Chinese Medicine Co. Ltd., Chengdu, China. All other chemicals and reagents used were of commercially available analytical grade.

Modification of HPMC

For the synthesis of the hydroxypropyl methylcellulose acetate maleate (HPMCAM), 5 g of HPMC 2910 was dissolved in 31 g of acetic acid in a kneader at 85 to 90°C, and then appropriate amounts of maleic anhydrides, acetic anhydrides and 2 g of sodium acetate, used as a catalyst, were added. The reaction was allowed to proceed at 85 to 90°C for 5 h, and then 10 g of purified water were poured into the mixture. After cooling to room temperature, 3.5 g of concentrated hydrochloric acid was added to the mixture, which was then poured into an excess amount of purified water to separate the polymer. The crude polymer was washed with water, and then dried to afford HPMCAM-1~9 (Table I).

Identification of HPMCAM

IR spectra were recorded on a Nicolet 200SXV spectrophotometer and the ^{1}H-NMR spectra run at 400 MHz on a Brucker-Ac-200 spectrometer, with the chemical shifts shown in ppm downfield from tetramethylsilane.

Determination of pH-sensitive values

The obtained polymers were dissolved in methanol/methylene chloride 1:1 (v/v), the solutions cast on glass plates and dried to form films 30 to 50 μm thick. The films were cut into 3 mm square pieces. The dissolution pH of the film was measured at 37±0.5°C in a simulated gastric fluid (pH 1.2) and phosphate buffer with pH values from 2.5 to 4.5 by observing whether 20 mg of the films dissolute completely in 2 h. The lowest pH value at which a film dissolved was the pH-sensitive value for that film.

Determination of acid value

Approximately 80 mg of the cast films (naturally dried for 12 h, removed and dried under vacuum for 3 h at around 50°C) were accurately weighted, and then dissolved in an excessive amount of NaOH solution (0.1 M,

Table I. Acid and Sensitive pH values of the different HPMCAM

No.	HPMC: CA: MA (The ratio of quality)	Acid value (mgNaOH/1gHPMCAM)	pH-sensitive value
HPMCAM-1	1: 1.0: 0.40	126.85±0.028	3.7
HPMCAM-2	1: 0.8: 0.40	144.58±0.057	3.3
HPMCAM-3	1: 0.6: 0.40	153.53±0.087	3.0
HPMCAM-4	1: 0.8: 0.36	129.82±0.009	3.5
HPMCAM-5	1: 0.6: 0.36	143.05±0.062	3.3
HPMCAM-6	1: 0.4: 0.36	148.14±0.029	3.2
HPMCAM-7	1: 0.8: 0.28	122.55±0.012	3.7
HPMCAM-8	1: 0.7: 0.28	128.83±0.041	3.6
HPMCAM-9	1: 0.4: 0.28	144.71±0.061	3.3

CA= Acetic anhydrides MA= Maleic anhydrides

20 mL). Titrations were carried out using 0.1 M standard HCl solution, with phenolphthalein as the indicator.

Determination of Tensile Strength of the cast film

The cast film was cut into a dumbbell-like strip, and then one end hung on the hob, with a conical flask tied to the other end. Water was evenly dripped through a funnel into the conical flask until the film ruptured. The total weight of the water and the conical flask were obtained and the width and thickness of the ruptured part determined using Vernier calipers (Guo SR, *et al.*, 1998).

Determination of water vapor permeability of the film

The small bottle method was adopted to obtain the water vapor permeability of the films. Briefly, the films were fixed with glue over vials (size: 5×1.97 cm) filled with dried silica gel. After accurately weighing, the vials were stored in a desiccator at 37°C, with 75%RH and weighted every 12 h. The permeability coefficient, J, was calculated (MU Xiao-hong, *et al.*, 1994).

Determination of scanning calorimetery (DSC) measurement

The glass transition temperatures (Tg) of HPMCAM and HPMC were measured using a PERKIN-ELMER differential scanning calorimeter at temperatures ranging forming from 20 to 250°C, at a scanning rate of 10°C/min.

Preparation of core tablets

The wet granulation method was applied for the preparation of the granules for the core tablets (Eiji Fukui, *et al.*, 2001). A powder consisting of 30 g BER·HCL, 31.2 g pregelatinized starch and 2.6 g carboxyl methyl starch was kneaded with 20 mL of 2.5%(w/v) polyvinylpyrrolidone ethanol solution as the binder. The wetted mass was forced through a 1000 μm screen. The granules were then dried and sized by passing through a 710 μm screen. Magnesium stearic acid was mixed with the granules as a lubricant.

For the preparation of core tablets, the tableting was performed under a compression force of 4 kg/mm^2. A fleet-concave-faced punch, 5.5 mm in diameter, was used, and core tablets containing 30 mg of BER·HCL per 65 mg tablet were obtained.

Preparation of press-coated tablets with HPMCAM

The HPMCAM-5, 6 and 8 were dissolved in a mixture of acetone and ethanol [1:1(v/v)] to make 2% solutions, with dibutyl phthalate and Tweens 80 then added to the solutions. There was an approximate 4% weight increase of the core tablets due to coating process (Kokako, *et al.*, 2001).

In vitro dissolution tests of BER·HCL press-coated tablets

A dissolution study was performed, using the basket method, as described in the 2000 edition of the Chinese Pharmacopoeia, with a rotation speed of 120 rpm at 37°C. For the initial 2 h, the study was conducted in the 1000 mL of 0.1 mol·L^{-1} HCl, followed by dissolution in a series of phosphate buffers (adjusted with citric acid and disodium phosphate). Aliquots were collected manually at predetermined time intervals, and analyzed for berberine chloride content, at 263 nm, using a UV spectrophotometer.

RESULTS AND DISCUSSION

Modification and identification of HPMCAM

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, by adjusting both the kinds of carboxylic acid and the degree of substitution, coating agents with certain pH-sensitive values can be prepared.

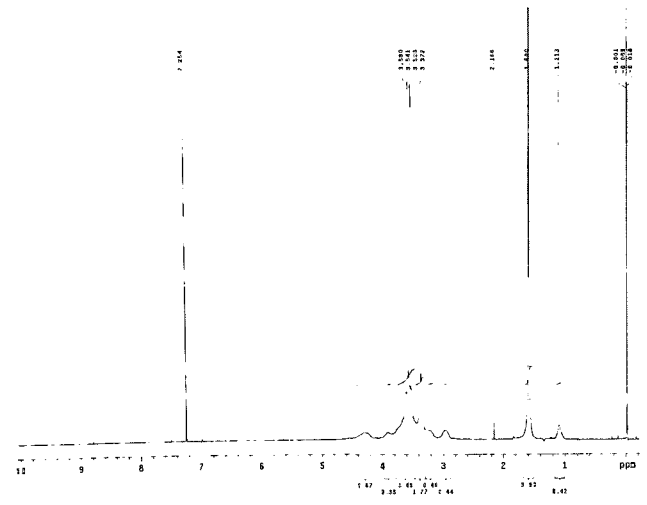
The structure of HPMCAM was proved by IR and ^{1}H-NMR (Fig. 1). The IR spectrum showed an ester (COOR) absorption peak at 1749 cm^{-1}, which suggested the formation of an ester. The ^{1}H-NMR of HPMCAM displayed a broad singlet at δ_H6.3~6.4, which was assigned to the hydrogen of MA. Also, a signal at δ_H 2.0~2.3 was attributed to the hydrogen of an acetyl [pointed out by arrow in Fig. 1(B)]. The entire spectrum above suggested the target polymer had been synthesized.

Acid value and pH-sensitive value

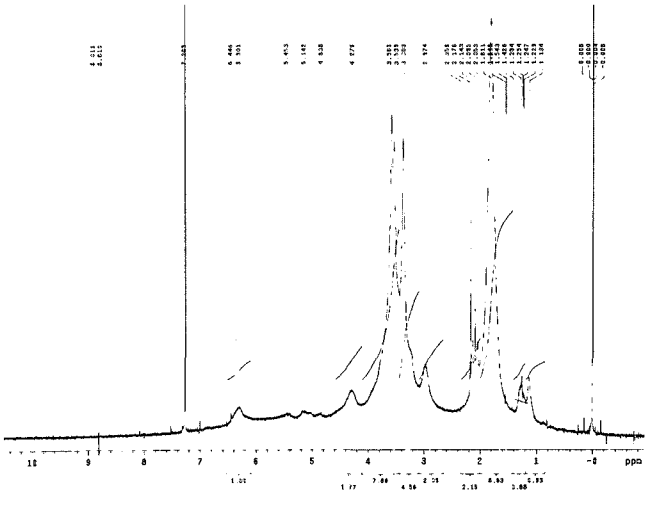
By adjusting the ratio of materials, a series of HPMCAM with various levels of substitution were obtained. HPMC solution is stable between pH 3.0~11.0. However, when reacted with maleic anhydrides, the stable pH is changed by the carboxylic acid substituents. Table I demonstrates that, for HPMCAM, there was a direct link between the acid value and maleic anhydrides ratio, but an inverse link between the acid value and acetic anhydrides ratio. The pH-sensitive value was consistent with acid values, which were both determined in the buffer solution. The pH-sensitive value can be controlled within the range 3.0~3.7 by adjusting the Maleic anhydrides and acetic anhydrides ratios.

Tensile strength of the film

The tensile strengths of the films were calculated using: tensile strength = weight/outside cross section area (width × thickness), and that of the HPMCAM film was 3222.24 N/cm^3. It has been reported that the tensile strength of a good film should range from 2000 to 6000 N/cm^3, indicating the HPMCAM film has a suitable tensile strength.



(A) HPMC



(B) HPMCAM-6

Fig. 1. ^{1}H-NMR spectra of HPMC (A) and HPMCAM-6 (B)

Water vapor permeability of the film

According to Ficks Law Q=J·ΔP·A·T/L, where Q: quantity of the water vapor permeated (g); ΔP: the difference in the water vapor pressure between the two sides of the film (kPa); A: permeating area (m^2); L: thickness of film (mm); T: permeating time (h); J: coefficient of the water vapor permeability ($g \cdot mm \cdot kPa^{-1} \cdot m^{-2} \cdot h^{-1}$).

The water vapor permeability of the film can be expressed by J, which means when L, A and ΔP are 1 mm, 1 m^2 and 1.333 kPa (0.75 cm·Hg), respectively, J is the mass of water vapor having permeated the film during 1 h (g). ΔP=P=Φ·Ps= 75%×6.274 kPa (The water vapor pressure of the silica gel side of the film is zero, then ΔP is the water vapor pressure of the other side; Ps is the water vapor pressure of saturated air at a given temperature; Φ means the relative humidity outside the bottle is 75%).

Table II. Comparison of the permeability coefficients of the different coating agents

Material	The water vapor permeability velocity equation	Correlation coefficient(r)	The permeable coefficient(J)
HPMCAM-3	Q=0.008131+0.002380T	0.9972	0.04993
HPMCAM-5	Q=0.005308+0.001873T	0.9976	0.03929
HPMCAM-6	Q=0.006647+0.002077T	0.9975	0.05809
HPMCAM-8	Q=0.006783+0.001788T	0.9964	0.08752
HPMC E6	Q=0.001281+0.002490T	0.9945	0.1215
Cellulose acetate	Q=0.072291+0.004728T	0.9978	0.03761
Ethyl cellulose	Q=0.044701+0.004144T	0.9990	0.6485

he thicknesses (L), as measured with Vernier calipers, were HPMCAM-3 0.04 mm, HPMCAM-5 0.03 mm, HPMCAM-6 0.04 mm, HPMCAM-8 0.06 mm, HPMC E_6 0.09 mm, CA 0.01 mm, and EC 0.2 mm respectively.

Permeability coefficients of films made of different material ratios are showed in Table II.

As a coating material, the polymer should have a good water vapor permeability to prevent humidity from permeating through the film into the core tablet. The above results show that, as the ratio of material varies, the moisture absorptions of various polymers are different. The J values of HPMCAM-3, 5, 6 and 8 were 0.04993, 0.03929, 0.05809 and 0.08752, respectively, which were similar to those of cellulose acetate (0.03761), but much smaller than those for HPMC (0.1215) and Ethyl cellulose (0.6485). The results also demonstrated the potential of HPMCAM as a good duodenum-specific coating agent.

Glass transition temperature (Tg)

Tg is an important parameter of macromolecular polymers. With respect to coating agents, the higher the Tg, the harder and more fragile the coating will become, and in some cases may even cause the coating to break. The Tg of HPMC is 156.48°C, while that of HPMCAM is 147.48°C. This also shows the potential of HPMCAM as a good duodenum-specific coating agent.

In vitro dissolution tests of BER·HCL press-coated tablets

Here, simulated gastric fluid (pH 1.2) was used to mimic the environment of the stomach, with phosphate buffer (pH 3.4) as simulated pathological duodenal juice. As seen from Fig. 2(A), the release behavior of the BER·HCL core tablets was similar to that in the simulated gastric (pH 1.2) and pathological duodenal fluids (pH 3.4). Both cause the quick release, reaching the maximum concentration in around 12 min. This kind of release behavior goes against the treatment of duodenal ulcers, whereas the press-coated tablets prepared in this study reach the anticipated objective of this experiment. That is: they were hardly

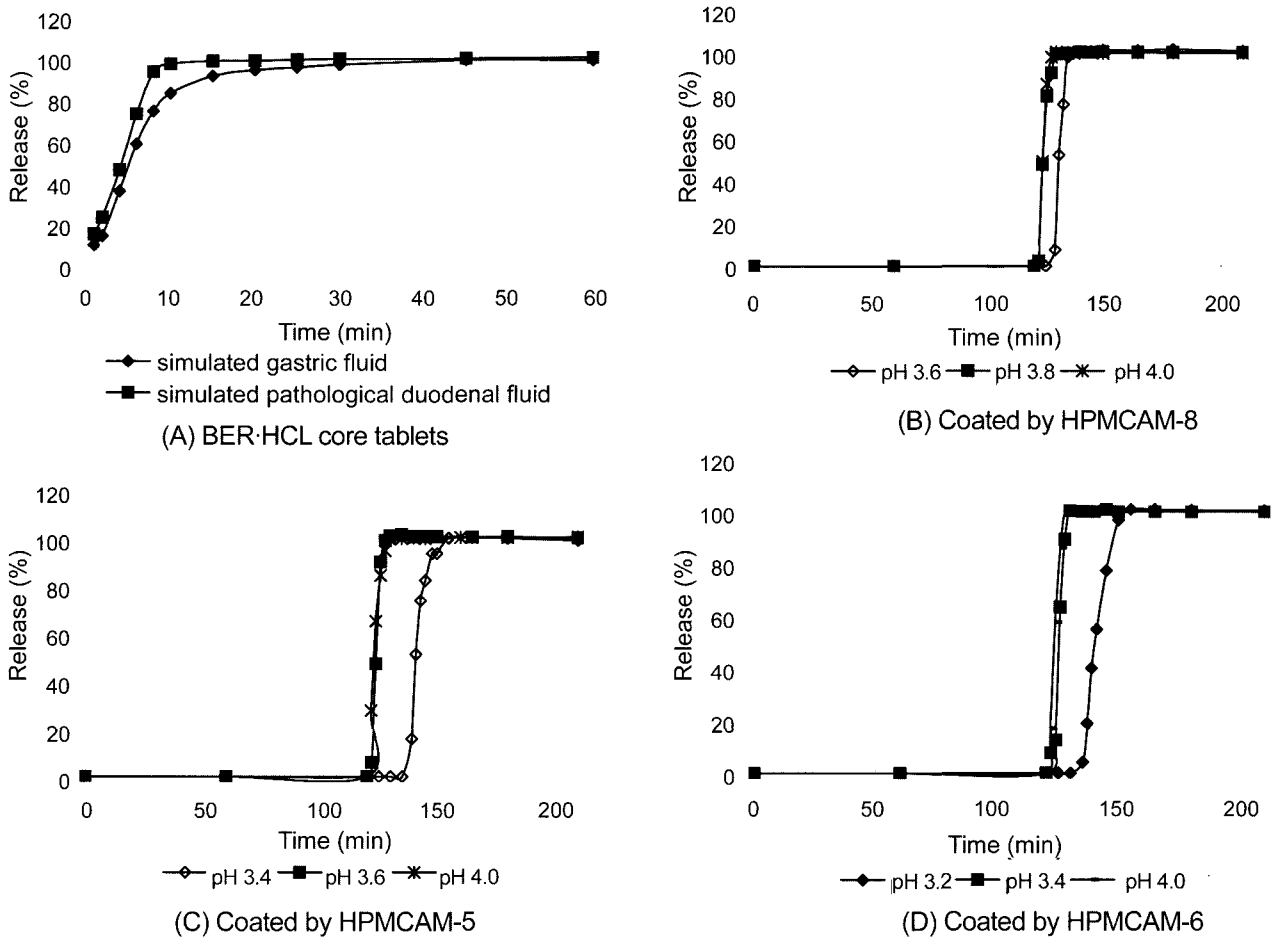


Fig. 2 (A) is the release curve of the BER·HCL core tablets in simulated gastric (pH1.2) and pathological duodenal (pH 3.4) fluids. Figs. 2 (B), (C) and (D) are the cumulated release curves of the BER·HCL tablets coated by HPMCAM-8, HPMCAM-5 and HPMCAM-6, respectively. They were first kept in simulated gastric fluid (pH1.2) for 2 h, and then transferred into buffer solutions at pH 3.2, 3.4, 3.6, 3.8 and 4.0.

soluble in the simulated gastric fluid, but had good solubility in the simulated pathological duodenal fluid, reaching their maximum concentration, ensuring the drug accumulated on the surface of duodenal ulcer, thereby achieve the maximum effect.

A series of polymers (HPMCAM-5, 6 and 8) with different pH-sensitive values were prepared, and tablets coated with these polymers were studied. From Figs. 2 (B), (C) and (D), the BER·HCL in HPMCAM-5, 6 and 8 coated tablets was not released in the simulated gastric fluid (pH 1.2) during the 2 h study period. Then the drug in the HPMCAM-6 coated tablets was released quickly into the pH 3.4 medium, reaching a maximum concentration at 8 min, while there was a 15 min lag time in the pH 3.2 medium. The BER·HCL in the HPMCAM-5 coated tablets was released quickly in the pH 3.6 medium, reaching a maximum concentration at 8 min, while there was a 15 min lag time in the pH 3.4 medium. The drug in the HPMCAM-8 coated tablets was released quickly in the pH 3.8 medium, reaching a maximum concentration at 8 min, but with a 9 min lag time at pH 3.6. Of the HPMCAM polymers, HPMCAM-6 had the lowest pH-sensitive value, at 3.4, so would seem to be the most suitable polymer for a duodenum-specific coating agent.

The above results indicate that by adjusting the ratios of HPMC/ Maleic anhydrides/ acetic anhydrides, HPMCAM with different acid values can be prepared. As the pH-sensitive values vary with the acid value, coating agent targeted toward different locations can be prepared.

In conclusion, a series of polymers, with different pH-sensitive value, can be obtained by adjusting the ratios of HPMC/Maleic anhydrides/ acetic anhydrides. From the *in vitro* tests, the pH-sensitive value of HPMCAM-6 was found to be around 3.4, which is suitable for a duodenum-specific treatment, and may be used as a duodenum-specific coating agent.

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REFERENCES

Hiroyasu, KokuBo, Sakae, OBARA, Katsuyoshi, MINEMURA, and Takashi TANAKA. Development of cellulose derivatives as novel enteric coating agents soluble at 3.5~4.5 and higher. *Chem. Pharm. Bull.,* 45, 1350-1353 (1997).

Guo, S. R., Fang, X. L., Huang, H. Q. ,and Hu, X., Synthesis and Application of Novel Acrylic Resin as Enteric Coating, *Acta Pharmaceutica Sinica*, 33, 860-863 (1998).

MU, Xiao-hong, ZHANG, Ru-hua, and ZHU, Hong-jie, The Water Vapor Permeability of Free Film of Hydroxypropylmethyl Cellulose Phthalate (HPMCP) and Effect of Additives. *Zhong Guo Yao Xue Za Zhi*, 29, 470-473 (1994).

Kokubo, Hiroyasu and Nishiyama, Yuichi, U.S.Patent 6258799 (2001).

Konorev, M. R., Eradication of *Helicobacter pylori* from the stomach and duodenum of patients with duodenal ulcers. *Int. J. Antimicrobial Agents*, 17, 425-426 (2001).

Eiji, Fukui, Nobuteru, Miyamura, and Masao Kobayashi, An *in vitro* investigation of the suitability of press-coated tablets with hydroxypropylmethylcellulose acetate succinate (HPMCAS) and hydrophobic additives in the outer shell for colon targeting. *J. Control Release,* 70, 97-107 (2001).

Mela, G. S., Savarino, V., and Vigneri, S., Optimizing the information obtained from continuous 24-hour gastric pH monitoring. *Am. J. Gastroenterol,* 87, 961-966 (1992).

Sohn, Natalie. Dyspepsia and ulcers. *Primary Care Update for OB/GYNS.* 5, 24-27 (1998).

Wang-ying and Wang xian-bing, China medicinal therapeutics to *Helicobacter pylori. China Med. Bull.*, 3, 40-44 (2003).