Drug Development and Industrial Pharmacy, 35:34–42, 2009

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040802144229

informa
healthcare

Carboxymethyl Mungbean Starch as a New Pharmaceutical Gelling Agent for Topical Preparation

Ornanong S. Kittipongpatana, Siriporn Burapadaja, and Nisit Kittipongpatana
Department of Pharmaceutical Sciences, Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand

An application of carboxymethyl mungbean starch (CMMS) as a gelling agent in the topical pharmaceutical preparation was investigated. CMMS was prepared using specific conditions that yielded a high-viscosity product. Polymer gels and gel bases were prepared at 1–10% (wt/wt), and physicochemical studies were carried out in comparison with four standard gelling agents: carbopol 940 (CP), hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC), and sodium carboxymethyl cellulose (SCMC). Piroxicam was used as a model drug to study the drug release profile of the gel formulations. The tackless, greaseless, and transparent CMMS gels exhibited pseudoplastic behavior with thixotropy at concentrations less than 5% (wt/wt). At a concentration of 5% (wt/wt) and higher, the semisolid gels showed plastic flow characteristics. Viscosity and X-ray diffraction results indicated a good compatibility between CMMS and the acidic piroxicam. No precipitation of piroxicam or phase separation was observed during a stability test. The release rate of piroxicam from 3% (wt/wt) CMMS gel was 1,003.79 ± 105.08μg/cm^2, which was comparable with 947.66 ± 133.70μg/cm^2 obtained from a 0.5% (wt/wt) carbopol formulation. The release profiles of both formulations were consistent and remained unchanged after 2 months' storage. Viscosity played an important role in controlling the release rate of low concentration CMMS formulations by regulating the drug diffusion. At a concentration of 5% (wt/wt) CMMS and higher, the release rates of piroxicam were not significantly different. A plausible explanation based on the nature of the gelling agent was proposed. Stability and drug release profiles of CMMS and commercial gelling agents were compared. The results supported the potential use of CMMS as a new, effective gelling agent for topical gel preparation.

Keywords gelling agent; mungbean starch; gel base; carboxymethyl starch; modified starch; piroxicam gel

INTRODUCTION

Topical gel preparation has been and remains one of the most popular and important pharmaceutical dosage forms. This semisolid formulation has the main advantage of allowing the drug to be absorbed directly at a specific site and bypassing the first-pass metabolism at the liver. As a result, the therapeutic effects of the drugs are achieved effectively whereas the systemic side effects can be avoided or minimized. Examples of drugs commonly prepared in topical gel form include gastrointestinal (GI)-irritating nonsteroidal antiinflammatory drugs (NSAIDs) (Chena et al., 2006; El Gendy, Jun, & Kassem, 2002; Güngör & Bergişadi, 2003; Mohammed, 2001; Özsoy, Güngör, & Cevher, 2004) and antibacterial (Hassan, Mohammed, & Sabour, 2003), antifungal (Ning, Guo, Pan, Chen, & Gu, 2005; Shishu & Aggarwal, 2006), local anesthetic (Abdel-Hamid, Abdel-Hady, El-Shamy, & El-Dessouky, 2006; Welin-Berger, Neelissen, & Bergenstahl, 2001), and antihistaminic agents (Tas, Özkan, Savaser, & Baykara, 2004).

The formulation of an effective gel requires the use of an appropriate gelling agent, usually a polymer. The preferred characteristics of such polymer include the inertness, safety, and biocompatibility with other ingredients, good adhesion to mucous membrane, permission of drug permeation while not being absorbed into the body, irritation-free, and preferably biodegradable (Zatz & Kushla, 1996). When in the formulation, the polymer should exhibit good swelling, syneresis, and rheological properties suitable for solidifying or stiffening the system. A number of gelling agents have been commercially employed in the preparation of topical gels, including the synthetic carbomers (Patel et al., 2006) and the semisynthetic cellulose derivatives (Mohammed, 2001; Tas, Özkan, Savaser, & Baykara, 2003). As the number of newly formulated topical gel products containing drugs and chemicals continues to increase in recent years (Choi & Shin, 2007; Dua et al., 2006; Kikwai et al., 2005) and expand into the products containing natural compounds or extracts (Marquele-Oliveira, Fonseca, de Freitas, Fonseca, 2007; Özer, Mutlu, & Kivçak, 2007), coupled with the concerns over the safety of the totally synthetic materials, the development of new gelling agents from natural sources has regained the attention. Examples of biopolymers reported as gelling agents for topical preparation are carrageenan (Mangione et al., 2007), xanthan gum (Chena et al., 2006), and

Address correspondence to Ornanong S. Kittipongpatana, Faculty of Pharmacy, Chiang Mai University, Department of Pharmaceutical Sciences, Suthep Road, A. Muang, Chiang Mai, 50200 Thailand. E-mail: ornanong@pharmacy.cmu.ac.th

chitosan (Tsai, Hsu, Fang, & Lin, 1999). A number of studies have also been reported for mixed polymers (Jimé nez, Fresno, & Ramírez, 2007; Liu, Lin, Li, & Liu, 2005). Different types of polymer may undergo gelation through different mechanisms. For examples, CP solution gelatinized upon the addition of alkaline molecules such as triethanolamine (TEA) to nullify the acidic groups, allowing the polymer chains to align closer together forming networks (Patel et al., 2006). Gelation of cellulose derivatives generally occurred through the entanglement of swollen polymer chains upon exposure to water. In some cases, specific components are required for gel formation, e.g., κ-carrageenan forms gel in the presence of K^+ (Mangione et al., 2007).

Starch, an abundantly and inexpensively available, inert, and biodegradable polymer, has been considered as one of the candidates for use as gelling agent. However, the application of native starch in this aspect has been discouraged mainly because a high concentration and heating are required to obtain viscous gel, the opacity of the gel, and the lesser stability compared with other gelling agents. Modification of native starch by physical, chemical, or enzymatical means yields modified starches with different and generally improved physicochemical properties that allowed the use as more efficient pharmaceutical excipients. A number of studies have been carried out on the preparation of modified starches and related materials and their application as a gelling agent, including a cross-linked corn starch–polyvinyl alcohol with glutaraldehyde (Pal, Banthia, & Majumdar, 2008), dextrin (Carvalho, Gonçalves, Gil, & Gama, 2007), and carboxymethyl dextran (Zhang, Tang, Bowyer, Eisenthal, & Hubble, 2005). Biodegradable hydrogels with absorbency in pure water of as high as 120 g-water/g-dry gel have also been synthesized based on esterification of potato starch and succinic anhydride (Yoshimaru, Yoshimaru, Seki, & Fujioka, 2006).

Carboxymethyl starch (CMS), an anionic, water-soluble, etherified starch, has been employed as a thickening agent in foods long before the investigations for pharmaceutical uses. The safety of CMS has been vouched by its inclusion in the United States Pharmacopeia (USP) and the British Pharmacopoeia (BP). Our previous report on the physicochemical properties of carboxymethyl mungbean starch (CMMS) prepared using different type of solvents and conditions showed that the carboxymethylation carried out using methanol as a solvent at suitable temperature and reaction time yielded CMMS with the highest viscosity, and higher than CMSs prepared from other types of native starches (Kittipongpatana, Sirithunyalug, & Laenger, 2006). A subsequent study (Kittipongpatana & Sirithunyalug, 2006) showed that CMMS could be used as a pharmaceutical suspending agent, with the efficiency comparable with that of xanthan gum and sodium carboxymethyl cellulose (SCMC). The syntheses of chemically cross-linked potato CMS and radiation cross-linked maize CMS for the preparation of biodegradable hydrogel have been reported (Nagasawa, Yagi, Kume, & Yoshii, 2004; Siedel et al., 2004).

This work reports an application of a high-viscosity CMMS as a new gelling agent for the preparation of topical gel formulation, in comparison with the use of four commercial gelling agents, carbopol 940 (CP), hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC), and SCMC. Piroxicam, a water-insoluble, weakly acidic (pK_a = 6.3) NSAID, was used as a model drug. Physical/visual appearances, physicochemical properties, drug release profiles, and products stability are key parameters investigated. The potential use of CMMS as a gelling agent is summarized.

MATERIALS AND METHODS

Materials and Reagents

Mungbean starch (100%) was a gift from Sitthinan Co. Ltd. (Bangkok, Thailand (Pine brand, Thai Industrial Standard, TIS 948–2533). Chemicals and solvents used in the preparation and analysis of modified starches were of AR grade or equivalent. Double-distilled commercial grade methanol was used to wash the final products. Standard commercial gelling polymers included CP, HPMC (Methocel™ E4M), MC (Methocel™ A4M), and SCMC. Piroxicam was a gift from Siam Pharmaceutical Co. Ltd. (Bangkok, Thailand) Chemicals used to prepare gel formulations were of pharmaceutical grade or equivalent.

Methods

Preparation of Carboxymethyl Mungbean Starch

A high-viscosity CMMS was prepared and the physicochemical properties were determined according to the procedures previously described by Kittipongpatana et al. (2006). In brief, 40 g of monochloroacetic acid was dissolved in 200 g of methanol, and then, while stirring, 140 g of native mungbean starch powder was added into the solution followed by 80 mL of 50% sodium hydroxide solution. The mixture was heated to 70°C where it was maintained for 60 min, with continuous stirring. At the end, the reaction was stopped by neutralization with glacial acetic acid. The liquid supernatant was decanted and the powder product was washed several times with 80% methanol and finally with 100% AR grade methanol. The modified starch was oven-dried at 50°C for 24 h and was passed through sieve no. 60.

Preparation of Polymer Gels, Gel Bases, and Piroxicam Formulations

CP was used at concentrations 0.5, 1, and 1.5% (wt/wt), whereas HPMC, MC, and SCMC were used at concentrations 2–4% (wt/wt). CMMS was tested at concentrations 1–10% (wt/wt). The polymer gels were prepared by mixing the polymer powder at specified concentrations with distilled water, and then allowed to fully swell overnight before use. In case of CP, an addition of TEA was required to adjust pH to 7.2 for maximum swelling. The gel bases (100 g) composed of polymer (varied concentration), 10 mL propylene glycol, 8 mL denatured alcohol,

and 1.5 mL TEA and adjusted to weight with distilled water. For the medicated formulation, 0.5 g of an antiinflammatory model drug piroxicam was dissolved in TEA and added into the gel base. The viscosity and clarity of each polymer gel, gel base, and gel formulation were determined and compared. The spreadability and general appearances and the pH of each formulation were also noted.

Physicochemical Properties of Gel Samples

Viscosity, clarity, and X-ray diffraction pattern were evaluated for gel samples prepared freshly and those stored for 2 months at room temperature. X-ray diffraction analysis was also conducted on samples treated through eight heating–cooling (HC) cycles. Each cycle consisted of a cold storage at 8°C for 2 days and a warm storage at 45°C for 2 days (Kittipongpatana & Sirithunyalug, 2006).

Viscosity

Apparent viscosity of each polymer gel, gel base, and gel formulation was measured using a Brookfield R/S-CPS rheometer. The measuring system was CC48 DIN. The mode used was controlled shear rate (CSR). The measured parameters consisted of three steps: (1) an increase of the shear rate from 0 to $100\,s^{-1}$ in 1 min, (2) held at $100\,s^{-1}$ for 1 min, and (3) a decrease of the shear rate from 100 to $0\,s^{-1}$ in 1 min. All measurements were performed in triplicate, at a controlled temperature of 25 ±1°C. The data were analyzed with a Brookfield Rheo 2000 software. The apparent viscosity for all samples in this study was measured at a shear rate of $100\,s^{-1}$. Viscosity was expressed in Pa.s. The experiment was carried out on a freshly prepared sample and was repeated on a sample kept for 2 months at room temperature.

Gel Clarity

A sample of polymer gel or gel base (2.5 mL) was placed in a disposable cuvette, and the absorption was measured at 700 nm on a spectrophotometer against a water blank.

X-Ray Diffraction of Piroxicam Gel

X-ray diffraction patterns of gel bases and piroxicam gel formulations were recorded in the reflection mode on a Siemens D-500 X-ray diffractometer. Diffractograms were registered at Bragg Angle (2θ) = 5–40° at a scan rate of 5° per minute.

Release Profile of Piroxicam from Gel Preparations

A gel sample (~10 g) was carefully filled, to avoid any air bubbles, inside a 10-mL cylindrical glass bottle of 22 mm diameter (release area = $3.80\,cm^2$). A sheet of Spectra/Por®7 regenerated cellulose membrane (MWCO 1000, Spectrum Laboratories Inc., Rancho Dominguez, CA, USA) was then firmly placed on top and tightly secured with a rubber band. The bottle was inversely submerged in a 400-mL beaker containing 200 mL phosphate buffer (pH 7.4) and equipped with stirring and temperature-controlling devices. The release test was carried out at a controlled stirring rate of 200 ± 10 rpm and a temperature of 37 ± 1°C. At 5, 10, 15, 30, 60, 120, 180, and 240 min, 3 mL of the buffer containing the released piroxicam was withdrawn from the beaker and 3 mL of fresh phosphate buffer was added into the beaker to maintain the original volume. The withdrawn sample was taken to measure the UV absorbance at 243 nm and the amount of piroxicam release from the gel formulation was calculated based on a standard curve of piroxicam. Each sample was tested in at least triplicate. The release profiles and the amounts of piroxicam released were compared among different gel formulations. The experiment was carried out for both the samples prepared freshly and those stored for 2 months at room temperature.

Statistical Analysis

Descriptive statistic was used to describe the physical properties and visual appearance of the products. The differences in the viscosity and the amount of piroxicam released among samples containing different types and amounts of gelling agents were statistically analyzed using Student's *t* test at a 95% confidence level ($p < .05$).

RESULTS AND DISCUSSION

Preparation and Physicochemical Properties of CMMS and CMMS Gels

CMMS was obtained as an off-white powder. The degree of substitution (DS) was determined to be 0.35. The powders were soluble in unheated water; a 1% (wt/vol) solution yielded a pH of 7.8 and a viscosity of 0.41±0.1 Pa.s (at SR $100\,s^{-1}$). These and other physicochemical properties (SEM, XRD) were in agreement with those previously reported (Kittipongpatana et al., 2006). When dispersed in water and stirred to fully dissolved, CMMS formed clear, flowable gel at concentrations between 1 and 4% (wt/wt), with A_{700nm} between 0.053 and 0.366. At a concentration of 5% (wt/wt) or higher, the gel became thick and viscous, which suggested a potential use as a sole gelling agent. The viscosities of CMMS polymer gel, gel base, and piroxicam formulation containing CMMS at concentrations of 1–10% (wt/vol) are shown in Figure 1.

An increase in the viscosity was proportional to the concentration of CMMS. And while the apparent viscosity of the polymer gel, especially at CMMS concentrations of 1–4%, was significantly higher than that of the gel base, the differences among the viscosity of the gel base and the piroxicam formulation at the same CMMS concentration was mostly not significant. This result indicated that the composition(s) of the gel base, mostly likely TEA, affected the viscosity of the polymer, whereas the acidity of the model drug piroxicam had no or very little effect to CMMS gel. At all concentrations studied, CMMS gel formulations were tackless, greaseless, and easily washable.

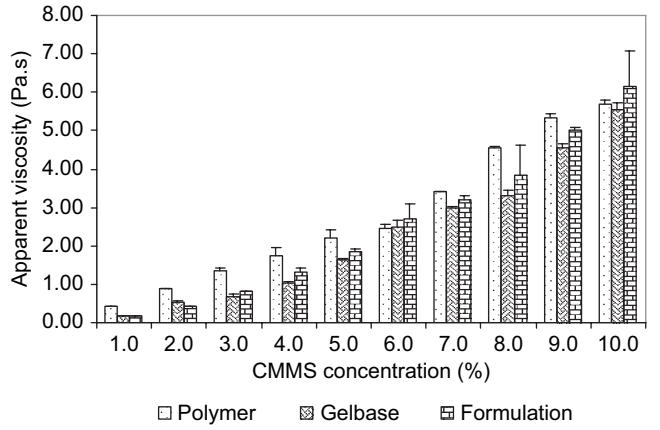

FIGURE 1. Apparent viscosity (Pa.s, at shear rate $100\,s^{-1}$) of polymer gels, gel bases, and 0.5% (wt/wt) piroxicam gel formulations containing 1–10% (wt/wt) concentration of CMMS as a gelling agent. The measured parameters in a controlled shear rate (CSR) mode consisted of (1) an increase of the shear rate from 0 to $100\,s^{-1}$ in 1 min, (2) held at $100\,s^{-1}$ for 1 min, and (3) a decrease of the shear rate from 100 to $0\,s^{-1}$ in 1 min. The temperature was controlled at 25 ± 1°C. Error bars indicate ± SD (n = 3).

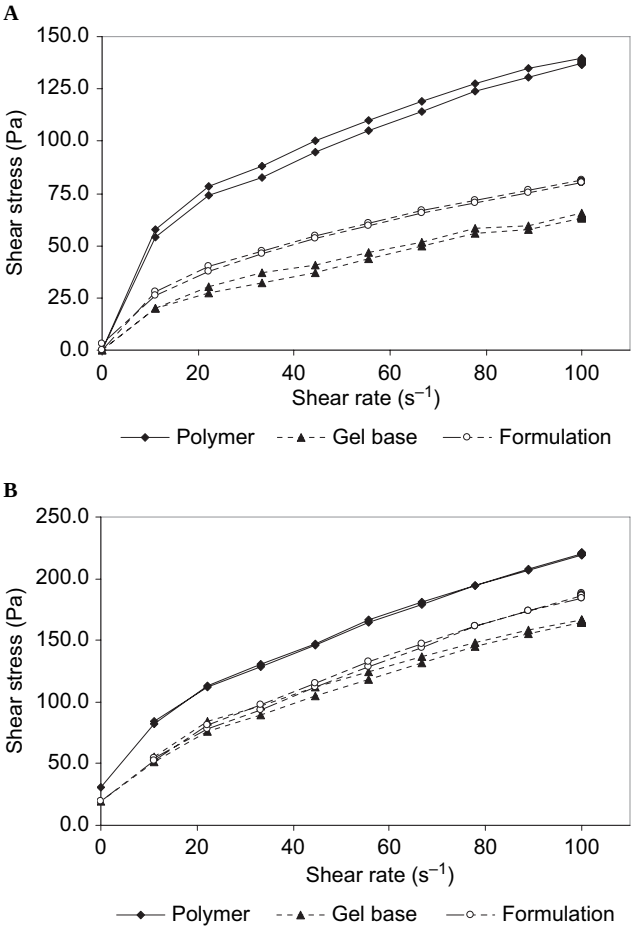

FIGURE 2. Rheological profiles of polymer gels, gelbases, and 0.5% (wt/wt) piroxicam formulations containing (A) 3% (wt/wt) CMMS; (B) 5% CMMS as gelling agent. The measured parameters in a controlled shear rate (CSR) mode consisted of (1) an increase of the shear rate from 0 to $100\,s^{-1}$ in 1 min, (2) held at $100\,s^{-1}$ for 1 min, and (3) a decrease of the shear rate from 100 to $0\,s^{-1}$ in 1 min. The temperature was controlled at 25 ± 1°C.

Starch gel was known to exhibit pseudoplastic flow characteristics (Lin & Luo, 2005). Rheological profile of low concentration CMMS gel (3%, wt/wt) was shown to follow pseudoplastic pattern, with thixotropy (Figure 2A). This flow behavior remained intact as CMMS gel was used to prepare the gel base and the formulation. As the concentration was increased to 5% (wt/wt), a higher viscosity was accompanied by an observation of a yield value, a shear stress value above zero at which the material started to flow, in all three samples (Figure 2B). Yield value is an indication of a plastic flow behavior and a characteristic of a gel dosage form (Buhse et al., 2005; Marriott, 2002). This type of behavior change is known to occur in carbomer solutions, in which a pseudoplastic flow is observed at low concentrations whereas a plastic flow is exhibited at higher concentrations (Bhargawa, Nicolai, & Oza, 1996). Both pseudoplastic and plastic flows are known characteristics of gel formulations, with a recent literature citing a plastic flow as preference (Buhse et al., 2005). Based on these physicochemical properties and visual appearance, 3 and 5% (wt/wt) CMMS were selected as representatives for comparison with the commercial gelling agents.

Physicochemical Properties of Commercial Gel Bases and Formulations

The pHs of all but one commercial gel bases ranged between 8.8 and 9.2 mainly due to the presence of the alkalinic TEA required for the dissolution of piroxicam in the formulation. The exception was the CP formulation in which the acidity of the acrylic acid polymer counteracts the alkaline effect to pH between 7.4 and 7.5, at which the viscosity of the gel was maximized. Comparison among the viscosity and clarity of polymer gels and gel bases containing varied concentrations of different commercial gelling agents are shown in Table 1.

For CP and SCMC, the viscosities of the polymer gel and the gel base were not significantly different, suggesting that the effects of the gel base compositions on the polymer viscosity were minimal. However, the acidity of piroxicam affected the viscosity of CP and SCMC as evident by a slight but significant decrease in the viscosities of the piroxicam formulations compared with those of the gel bases (12–57% for CP and 12–30% for SCMC). In the case of MC and HPMC, the viscosity of the gel base decreased significantly compared with that of the polymer gel (31–45% for MC and 15–45% for HPMC) and further decreased when piroxicam was added to prepare formulation (18–58% for MC and 47–87% for HPMC). Clarity of gel formulations, determined as the absorbance at 700 nm ($A_{700\,nm}$), showed that CP was the best gel base in terms of clarity, followed by SCMC, whereas MC and HPMC showed a significant degree

TABLE 1
Apparent Viscosity (Pa.s ± SD, at Shear Rate 100 s^{-1}) of Polymer Gels, Gel Bases, and 0.5% (wt/wt) Piroxicam Gel Formulations and Clarity of Formulations Prepared Using Varied Concentrations of Different Gelling Agents

Polymer	Concentration (%, wt/wt)	Apparent Viscosity at 100 s^{-1} (Pa.s±*SD*)			A_{700nm}
		Polymer Gel	Gel Base	Formulation	
CP	0.5	5.55 ± 0.37	5.69 ± 0.57	2.46 ± 0.12*	0.157
	1.0	7.80 ± 0.26	8.75 ± 0.19*	7.03 ± 0.28	0.158
	1.5	8.92 ± 1.04	9.28 ± 0.65	8.15 ± 0.18	0.160
HPMC	2	2.51 ± 0.59	2.08 ± 0.22	0.28 ± 0.08*	0.668
	3	9.47 ± 2.15	8.04 ± 0.17	3.14 ± 0.40*	1.050
	4	24.99 ± 0.82	13.63 ± 0.80*	7.20 ± 0.09**	1.068
MC	2	10.55 ± 3.13	7.30 ± 0.39*	3.10 ± 0.25**	0.681
	3	24.83 ± 1.17	13.65 ± 1.19*	9.29 ± 2.81**	0.760
	4	25.45 ± 0.14	16.61 ± 0.71*	13.64 ± 0.38**	0.908
SCMC	2	2.34 ± 0.18	2.23 ± 0.11	1.95 ± 0.19*	0.107
	3	6.51 ± 0.13	6.85 ± 0.61	4.82 ± 0.99*	0.202
	4	13.55 ± 2.56	11.64 ± 0.68	9.74 ± 1.14*	0.285

Values across the same row with the different number of * (ie none, *, **) indicated a statistically significant difference.

of opacity. Based on the viscosity and general appearances, the formulations containing 0.5% (wt/wt) CP, 2% (wt/wt) MC, 3% (wt/wt) SCMC, and 3% (wt/wt) HPMC were selected as representatives for each type of gelling agent.

X-Ray Diffraction of CMMS Gel Samples

XRD of piroxicam powder (Figure 3A) showed crystalline peaks in which the pattern and the values were in agreement with a reported literature (Ambrogi et al., 2007). The disappearance of all the peaks from the freshly prepared piroxicam–CMMS gel sample (Figure 3C) indicated that the drug was completely dissolved in the gel formulation. After subjecting to HC cycles, piroxicam remained soluble in the gel (Figure 3D) as the XRD of the gel formulation showed similar pattern to that of the gel base (Figure 3B) and no crystalline peaks was detected.

Release Profile of Piroxicam from Gel Formulation

The drug release from a gel preparation generally occurs by the diffusion of drug molecules through the gel network or by erosion or dissolution of the gel texture at the contact interface (Conti et al., 2007). The results showed that as the concentration of CMMS in the gel formulation was increased from 1 to 4% (wt/wt), the amount of piroxicam released into the buffered medium was gradually decreased from 5.38 ± 0.23 mg (1.42 ± 0.06 mg/cm^2) to 2.91±0.14 mg (766.61 ± 36.48 μg/cm^2) at 240 min. Further increase of CMMS concentration in the formulation to 5% (wt/wt) and above, however, showed only slight effect on the drug release as the amounts of piroxicam detected in the medium were between 2.56 ± 0.10 mg (673.18 ± 25.76 μg/cm^2) at 5% (wt/wt) and 2.34 ± 0.38 mg (615.04 ± 99.24 μg/cm^2) at 10% (wt/wt) (Figure 4), despite a continued increase in the formulation viscosities. Rheological properties were known to be related to the gel structure, interchain interactions, and polymer chain entanglements (Michailova, Titeva, Kotsilkova, Krusteva, & Minkov, 1999), which in turn affected drug release and diffusion processes (Welin-Berger et al., 2001). The results suggested that the release rate was influenced by not only the viscosity but also other factors. The nature of the polymer composing the vehicle and other components of the formulation are known to play a role in controlling the release rate and permeability of the drug (Özsoy et al., 2004; Tas et al., 2003). In the case of formulations with 1 and 2% (wt/wt) CMMS which appeared thin, transparent, and easily pourable, the low viscosities of the formulations (0.16 ± 0.00 to 0.43 ± 0.00 Pa.s) allowed the diffusion of drug molecules from the inner part of the container to the membrane–medium contact surface where they passed through the membrane and dissipated into the buffered medium. This is in agreement with a previous suggestion that the drug release rate was governed by both the diffusion through the gel and the diffusion through the membrane or skin (Choi & Shin, 2007). These clear liquid formulations, which displayed Newtonian or pseudoplastic flow behavior, were technically defined as topical solutions (Buhse et al., 2005). Formulations with 3 and 4% (wt/wt) CMMS were more stiff but still slightly pourable. The release rate depended on the dissolution of the drugs at the contact surface, and also a small amount of drugs diffused through the gel textures of medium viscosities (0.80 ± 0.00 to 1.32 ± 0.09 Pa.s). As the viscosity increased, the amount of drug diffusion through the gel became lesser, thus the decrease of the

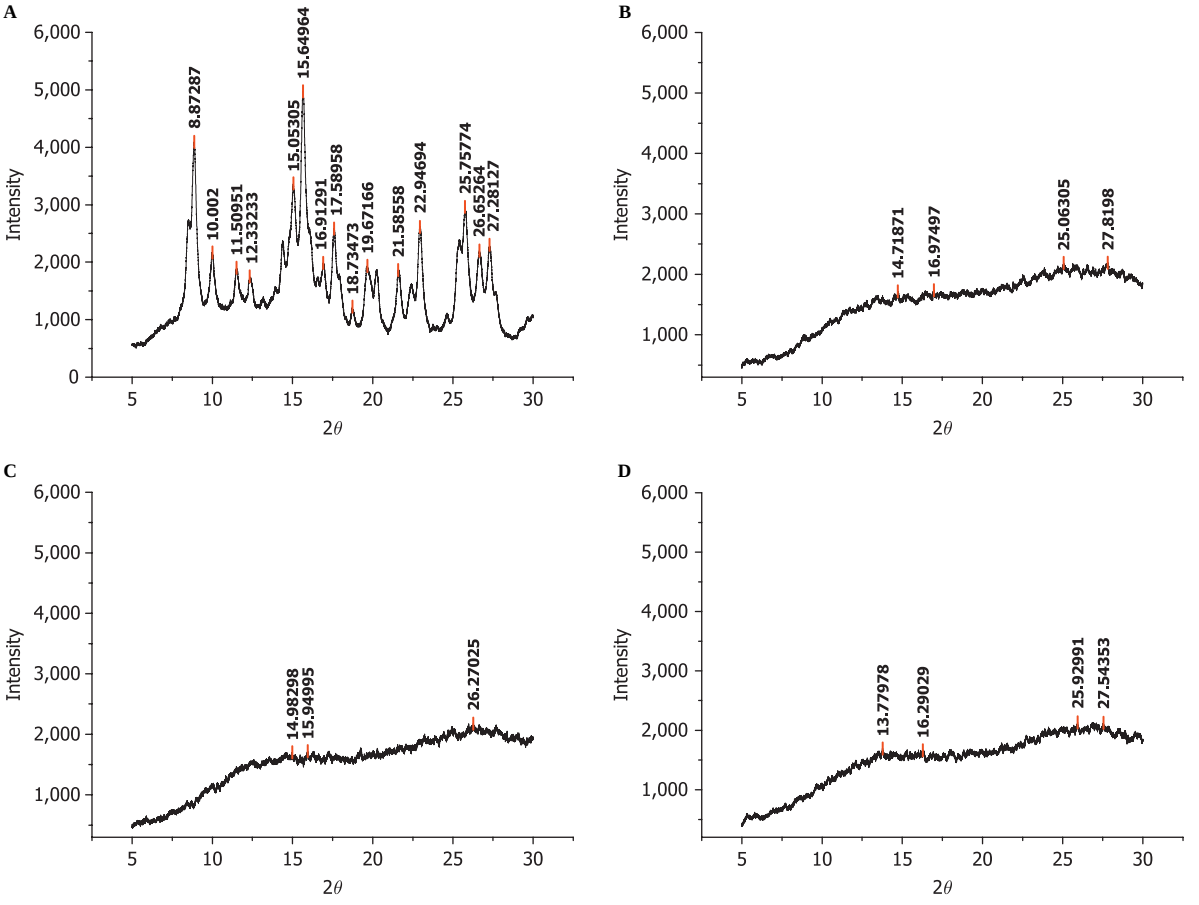

FIGURE 3. Representative XRD of (A) piroxicam powder, (B) CMMS gel base, (C) freshly prepared piroxicam CMMS gel, and (D) 0.5% (wt/wt) piroxicam gel formulation kept under heating–cooling (HC) cycles. Diffractograms were registered at Bragg Angle (2θ) = 5–40° at a scan rate of 5° per minute on a Siemens D-500 X-ray diffractometer.

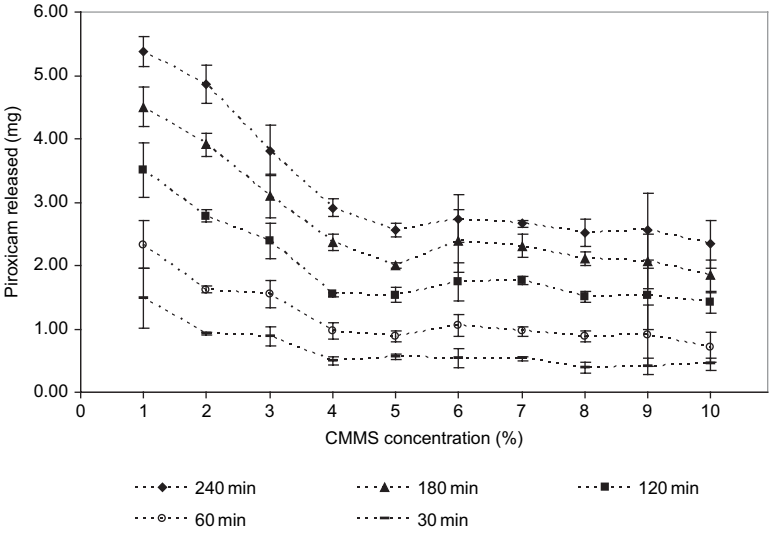

FIGURE 4. Release profiles of piroxicam from gel formulations containing different concentrations of CMMS as a gelling agent through a Spectra/Por®7 membrane (MWCO 1000, area 3.80 cm^2) into a phosphate buffer solution (pH7.4) at 37 ± 1°C. Each line represented a release amount, calculated based on UV absorption at 243nm, at a specific time (from 30 to 240min). Values are average of five replicates and are expressed with ± *SD*.

release rate. At 5% (wt/wt) CMMS and higher, the formulations exhibited true semisolid behaviors i.e., not flow, not pourable. Such appearance indicated a formation of an entanglement network system in the solution which was suggested to take place when the polymer concentration exceeded a critical concentration. While the evidences supported that 5% (wt/wt) represented a critical concentration at which CMMS formed a semisolid gel system, the explanation for the similar rates of piroxicam release observed in formulations with 5–10% (wt/wt) CMMS required a closer inspection. An increase in the polymer concentration is usually accompanied by an increase in the viscosity, which normally results in a decrease of drug release from the formulation (Tsai et al., 1999). A plausible explanation in this case is that because the diffusion of piroxicam molecules were restricted by the high viscosities of the gels, the release rates of these formulations were solely regulated by the dissolution of the gel at the contact surface, allowing free drug molecules to diffuse through the membrane. Because CMMS was a hydrophilic starch derivative and was in a completely soluble form in all formulations, dissolution of drugs from gel base occurred readily and consistently resulting in a similar amount of drug release regardless of the viscosity.

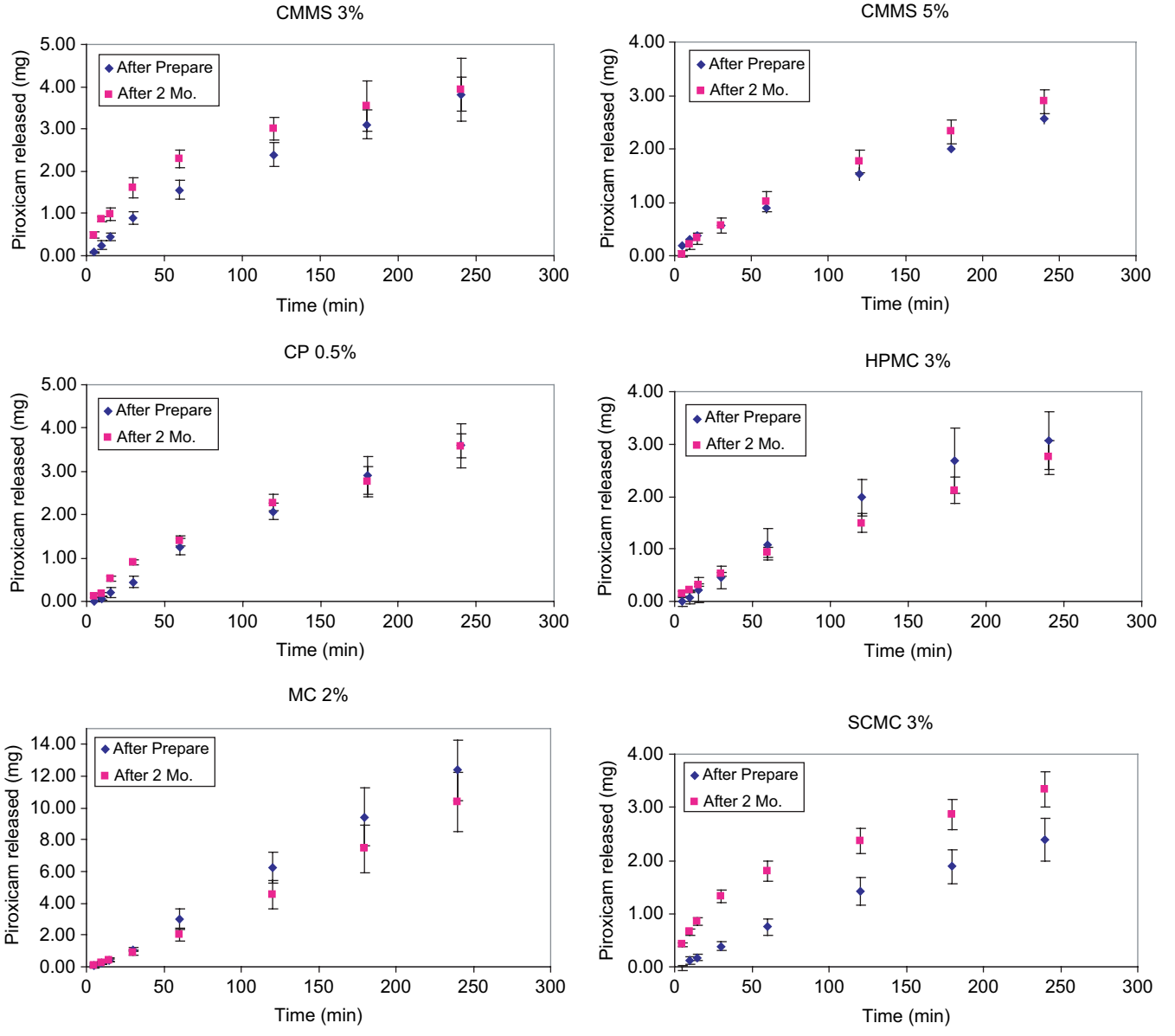

FIGURE 5. Release profiles of piroxicam from gel formulations containing different types of gelling agent through a Spectra/Por®7 membrane (MWCO 1000, area 3.80 cm^2) into a phosphate buffer solution (pH 7.4) at 37 ± 1°C. Drug release was determined freshly after prepare versus after 2 months storage at room temperature. Values are average of five replicates and are expressed with ± *SD*.

The amounts of piroxicam released from formulations containing 5% (wt/wt) CMMS or above were between 45 and 50% of that released from the 1% (wt/wt) CMMS formulation.

The release profiles of piroxicam formulations containing different types of gelling agent determined freshly after preparation and after 2 months' storage at room temperature are shown in Figure 5. Despite the difference in the viscosities, formulations containing 3% (wt/wt) CMMS and 0.5% (wt/wt) CP showed release profiles that were not statistically different ($p < .05$), both when determined after preparation and after 2 months' storage. Both formulations also showed excellent stability as the profiles determined after preparation and after 2 months' storage were not significantly different. Similarly, formulation containing 3% (wt/wt) HPMC showed steady release of piroxicam that was statistically comparable with that of 5% (wt/wt) CMMS formulation ($p < .05$). In contrast, freshly prepared 3% SCMC formulation exhibited lower release of piroxicam compared with those containing CP, HPMC, and CMMS. This is explained by the higher viscosity of the SCMC formulation than that of other formulations, which is similar to a result reported previously (Tas et al., 2003). A significantly higher release of piroxicam from the sample kept for 2 months compared with the freshly prepared was observed. This difference indicated that SCMC formulation was less stable than the CP and CMMS formulations. Formulation containing 2% MC was stable after 2 months' storage but overall showed a much higher rate of drug release compared with other gelling agents.

CONCLUSIONS

High-viscosity CMMS can be used as a sole gelling agent in the preparation of a pharmaceutical gel at a concentration of 3% (wt/wt) or higher. CMMS gel exhibited a pseudoplastic flow with thixotropic behavior at low concentrations and a plastic flow with yield value at higher concentrations. Both flow characteristics suggested that CMMS was suitable for the preparation of topical gel with good spreadability. The solubility of CMMS in unheated water and the clarity and viscosity of the resulting CMMS gel allowed the preparation of a stable, good visual appearance, greaseless, and washable gel preparation. The release of piroxicam from the gels of low (<5%, wt/wt) CMMS concentrations was dictated by the diffusion of drug molecules through the gel texture, whereas at CMMS concentrations of 5% (wt/wt) and higher, the dissolution of gel controlled the amount of drug release. Drug release rates and patterns of the selected CMMS formulations were comparable with those of CP and HPMC. In addition to the advantage of being prepared from an abundantly available and the least expensive natural polymer, CMMS gel showed good stability and compatibility with the acidic piroxicam at 2 months' storage time in comparison with gels of commercial polymers, thus suggesting possible use as a gelling agent in the preparation of other topical NSAIDs as well as other acidic molecules. CMMS could also be used in combination with other commercial gelling agents to obtain copolymer gel base with improved or different texture and properties suitable for active ingredients with various characteristics.

ACKNOWLEDGMENTS

The authors thank Suteera Watanageebudtra for the technical assistance in the laboratory work. We thank Siam Pharmaceutical Co. Ltd. for providing the model drug piroxicam and Sitthinan Co. Ltd. for providing the native mungbean starch. This work was supported by a grant from BIOTEC Thailand (Contract No. BT-B-01-CM-10-5001).

REFERENCES

Abdel-Hamid, S. M., Abdel-Hady, S. E., El-Shamy, A. A., & El-Dessouky, H. F. (2006). Formulation of an antispasmodic drug as a topical local anesthetic. *Int. J. Pharm., 326*, 107–118.

Ambrogi, V., Perioli, L., Marmottini, F., Giovagnoli, S., Esposito, M., & Rossi, C. (2007). Improvement of dissolution rate of piroxicam by inclusion into MCM-41 mesoporous silicate. *Eur. J. Pharm. Sci., 32*, 216–222.

Bhargawa, H. N. Nicolai, D. W., & Oza, B. J. (1996). Topical suspensions. In H. A. Lieberman, M. M. Rieger, & G. S. Banker (Eds.), *Pharmaceutical dosage forms: Disperse systems* (2nd. ed., Vol. 2, p. 206). New York: Marcel Dekker.

Buhse, L., Kolinski, R., Westenberger, B., Wokovich, A., Spencer, J., Chen, C. W. Turujman, S., Gautam-Basak, M., Kang, G. J., Kibbe, A., Heintzelman, B., & Wolfgang, E. (2005). Topical drug classification. *Int. J. Pharm., 295*, 101–112.

Carvalho, J., Gonçalves, C., Gil, A. M., & Gama, F. M. (2007). Production and characterization of a new dextrin based hydrogel. *Eur. Polym. J., 43*, 3050–3059.

Chena, H., Changa, X., Dub, D., Lia, J., Xua, H., & Yanga, X. (2006). Microemulsion-based hydrogel formulation of ibuprofen for topical delivery. *Int. J. Pharm., 315*, 52–58.

Choi, J. S., & Shin, S. C. (2007). Preparation and evaluation of pronoprofen gel for percutaneous administration. *Drug Dev. Ind. Pharm., 33*, 19–26.

Conti, S., Maggi, L., Segale, L., Machiste, E. O., Conte, U., Grenier, P., & Vergnault, G. (2007). Matrices containing NaCMC and HPMC 1. Dissolution performance characterization. *Int. J. Pharm., 333*, 136–142.

Dua, K., Sara, U. V. S., Ramana, M. V., Agrawal, A., Garg, V., Soni, N., Kumar, P., & Mehta, D. K. (2006). Formulation and evaluation of topical bases of aceclofenac. *Ind. Pharm., 5*, 73–75.

El Gendy, A. M., Jun, H. W., & Kassem, A. A. (2002). In vitro release studies of flurbiprofen from different topical formulations. *Drug Dev. Ind. Pharm., 28*, 823–831.

Güngör, S., & Bergişadi, N. (2003). In vitro release studies on topical gel formulations of nimesulide. *Pharmazie, 58*, 155–156.

Hassan, M. A., Mohammed, F. A., & Sabour, E. A. (2003). Formulation and evaluation of ciprofloxacin hydrochloride and norfloxacin topical gel. *S.T.P. Pharma. Sci., 13*, 195–201.

Jiménez, M. M., Fresno, M. J., & Ramírez, A. (2007). Rheological study of binary gels with carbopol® ultrez™ 10 and hyaluronic acid. *Chem. Pharm. Bull., 55*, 1157–1163.

Kikwai, L., Babu, R. J., Prado, R., Kolot, A., Armstrong, C. A., Ansel, J. C., & Singh, M. (2005). In vitro and in vivo evaluation of topical formulations of spantide II. *AAPS PharmSciTech., 6*, E565–E572.

Kittipongpatana, O. S., Sirithunyalug, J., & Laenger, R. (2006). Preparation and physicochemical properties of carboxymethyl mungbean starches. *Carbohydr. Polym., 62*, 105–112.

Kittipongpatana, O. S., & Sirithunyalug, J. (2006). Development of suspending agent from sodium carboxymethyl mungbean starches. *Drug Dev. Ind. Pharm., 32*, 609–620.

Lin, H., & Luo, X. (2005). Progress of research on rheological properties and application of starch. *Shipin Gongye Keji., 26*, 183–185.

Liu, J., Lin, S., Li, L., & Liu, E. (2005). Release of theophylline from polymer blend hydrogels. *Int. J. Pharm., 298*, 117–125.

Mangione, M. R., Giacomazza, D., Cavallaro, G., Bulone, D., Martorana, V., & San Biagio, P. L. (2007). Relation between structural and release properties in a polysaccharide gel system. *Biophys. Chem., 129*, 18–22.

Marquele-Oliveira, F., Fonseca, Y. M., de Freitas, O., & Fonseca, M. J. V. (2007). Development of topical functionalized formulations added with propolis extract: stability, cutaneous absorption and in vivo studies. *Int. J. Pharm., 342*, 40–48.

Marriott, C. (2002). Rheology. In M. E. Aulton (Ed.), *Pharmaceutics: The science of dosage form design*, (2nd ed., pp. 41–58). London: Harcourt Publishers.

Michailova, V., Titeva, St., Kotsilkova, R., Krusteva, E., & Minkov, E. (1999). Influence of aqueous medium on viscoelastic properties of carboxymethylcellulose sodium, hydroxypropylmethyl cellulose, and thermally pre-gelatinized starch gels. *Colloids Surf., A: Physicochem. Eng. Asp., 149*, 515–520.

Mohammed, F. A. (2001). Topical permeation characteristics of diclofenac sodium from NaCMC gels in comparison with conventional gel formulations. *Drug Dev. Ind. Pharm, 27*, 1083–1097.

Nagasawa, N., Yagi, T., Kume, T., & Yoshii, F. (2004). Radiation crosslinking of carboxymethyl starch. *Carbohydrate. Polym., 58*, 109–113.

Ning, M., Guo, Y., Pan, H., Chen, X., & Gu, Z. (2005). Preparation, in vitro and in vivo evaluation of liposomal/niosomal gel delivery systems for clotrimazole. *Drug Dev. Ind. Pharm*,*31*, 375–383.

Özer, Ö., Mutlu, B., & Kivçak, B. (2007). Antityrosinase activity of some plant extracts and formulations containing ellagic acid. *Pharm. Biol, 45*,519–524.

Özsoy, Y., Güngör, S., & Cevher, E. (2004). Vehicle effects on in vitro release of tiaprofenic acid from different topical formulations. *IL Farmaco, 59*, 563–566.

Pal, K., Banthia, A. K., & Majumdar, D. K. (2008). Effect of heat of starch on the properties of starch hydrogels. *Mater. Lett., 62*, 215–218.

Patel, M., Patel, B., Patel, R., Patel, J., Bharadia, P., & Patel, M. (2006). Carbopol: A versatile polymer. *Drug Delivery Tech., 6*, 32–34, 36, 38, 40–43.

Siedel, C., Kulicke, W. M., Hess, C., Hartmann, B., Lechner, M. D., & Lazik, W. (2004). Synthesis and characterization of cross-linked carboxymethyl potato starch ether gels. *Starch/Stärke, 56*, 157–166.

Shishu, & Aggarwal, N. (2006). Preparation of hydrogels of griseofulvin for dermal application. *Int. J. Pharm., 326*, 20–24.

Tas, Ç., Özkan, Y., Savaser, A., & Baykara, T. (2003). In vitro release studies of chlorpheniramine maleate from gels prepared by different cellulose derivatives. *IL Farmaco, 58*, 605–611.

Tas, Ç., Özkan, Y., Savaser, A., & Baykara, T. (2004). In vitro and ex vivo permeation studies of chlorpheniramine maleate gels prepared by carbomer derivatives. *Drug Dev. Ind. Pharm, 30*, 637–647.

Tsai, C. J., Hsu, L. R., Fang, J. Y., & Lin, H. H. (1999). Chitosan hydrogel as a base for transdermal delivery of berberine and its evaluation in rat skin. *Bio. Pharm. Bull, 22*, 397–401.

Welin-Berger, K., Neelissen, J. A. M., & Bergenstahl, B. (2001). The effect of rheological behaviour of a topical anaesthetic formulation on the release permeation rates of the active compound. *Eur. J. Pharm. Sci., 13*, 309–318.

Yoshimaru, T., Yoshimaru, R., Seki, C., & Fujioka, R. (2006). Synthesis and characterization of biodegradable hydrogels based on starch and succinic anhydride. *Carbohydrate. Polym., 64*, 345–349.

Zatz, J. L., & Kushla, G. P. (1996). Gels. In H. A. Lieberman, M. M. Rieger, & G. S. Banker (Eds.), *Pharmaceutical dosage forms: Disperse systems* (2nd. ed., Vol. 2, pp. 399–421). New York: Marcel Dekker.

Zhang, R., Tang, M., Bowyer, A., Eisenthal, R., & Hubble, J. (2005). A novel pH- and ionic-strength-sensitive carboxy methyl dextran hydrogel. *Biomaterials, 26*, 4677–4683.