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Performance qualification of a new hypromellose capsule: Part II. Disintegration and dissolution comparison between two types of hypromellose capsules

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ABSTRACT

This Part II paper describes the disintegration and dissolution aspects of the qualification of a new hypromellose capsule (HPMC Shell 2). This new capsule does not contain any gelling agent, and is manufactured by a thermal gelation process. Rupture time of the carrageenan-containing capsule (HPMC Shell 1) and HPMC Shell 2, as measured by an improved real-time detection method, showed only slight differences that did not manifest *in vivo*. The absence of a gelling agent appeared to give HPMC Shell 2 advantages in dissolution in acidic media and in buffers containing potassium ions. Slow drug release of HPMC Shell 1 in 0.1 M HCl was attributed to the interaction of carrageenan with drug compounds; whereas the presence of potassium ions, a gelling promoter for carrageenan, caused delay in capsule opening and larger capsule-to-capsule variation. Disintegration and dissolution performances of both hypromellose capsules are comparable in other dissolution media tested. Based on the superior dissolution performances and quality attributes in terms of physical, mechanical and processability that were detailed in Paper I, the new hypromellose capsule was satisfactorily qualified and has since been used in nearly 20 investigational new drug (IND) compounds.

1. Introduction

Gelatin capsules have long been the most commonly used two-piece hard capsules in the pharmaceutical industry because of good film-forming properties, ease of manufacture, and good solubility in biological fluids at body temperature. However there are many drawbacks of gelatin capsules that have been well documented in literature, such as reactivity with filled components (Rowe et al., 2003), interaction with anionic and cationic polymers (Cole et al., 1992), brittleness after exposure to low humidity, reaction with some drugs and excipients, and incompatibility with hygroscopic materials (Liebowitz et al., 1990). Another disadvantage of gelatin capsules that impacts both *in vitro* and *in vivo* release is the cross-linking reaction which occurs under accelerated storage conditions (e.g. 40 °C/75%RH) and, in some cases, can be facilitated by drugs and excipients. Water solubility of gelatin is reduced as a result of the cross-linking, and consequently, disintegration of the capsule shell as well as the drug release is retarded (Brown et al., 1998).

As an alternative to gelatin, cellulose type materials such as methylcellulose and hypromellose (HPMC) have gained popularity in the pharmaceutical industry. HPMC is non-ionic and is inert with most drugs and excipients, and it is a water-soluble material that is derived from plants. Replacement of hard gelatin capsules with HPMC capsules gained momentum after the mad cow disease scare in 1990s, which prompted Food and Drug Administration (FDA) to scrutinize the use of materials of animal origin in the drug products, and the HPMC capsules are particularly popular for the nutraceutical market. HPMC capsules possess physical properties comparable or superior to gelatin capsules (Ogura et al., 1998; Missaghi and Fassihi, 2006). However, unlike gelatin, HPMC alone does not gel at room temperature, consequently the thermal gelling properties of HPMC pose a challenge to the manufacture of HPMC capsules. Various gelling agents have been used as additives to the HPMC solution to facilitate gelation and film formation, including carrageenan, polysaccharide of tamarind seed, pectin, curdlan, gelatin, furcellaran, agar, gellan gum and others (Yamamoto et al., 1993; Cade et al., 2001). The use of carrageenan as gelling agent together with cations such as potassium ion, as the gelling promoter, was patented by Shionogi Qualicaps in the manufacture of the Quali-V® capsules (HPMC Shell 1) (Yamamoto et al., 1998; Matsuura and Tanjoh, 2003). HPMC Shell 1 was shown to have disintegration and dissolution properties and physico-mechanical characteristics comparable to those of hard gelatin capsule (Chiwele et al., 2000; Podczeck and Jones, 2002; El-Malah and Nazzal, 2007).

The HPMC Shell 1 capsule was chosen by Wyeth Pharmaceuticals as an alternative to hard gelatin capsules (HGCs) in the early 2000s, during an effort to replace animal derived products in product development of new chemical entities (NCEs) and clinical

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supply manufacture. The capsules were used in over 100 clinical products for over 30 NCEs from 2003 to 2006. Several problems with the HPMC Shell 1, however, were observed in the manufacture and testing of the drug products during this time. The two primary complaints were the high weight variation, which led to product sorting with a high rejection rate and low yield, and powder leakage during shipment and blister packaging, which presented quality and safety concerns. During this period of time, a new hypromellose capsule containing no gelling agent, VCaps Plus® (HPMC Shell 2), was developed by Capsugel and introduced in 2006. Rather than relying on a gelling agent, the new hypromellose capsule is made by a thermal gelling process using a hot-dip method. The process consists of dipping a pre-heated capsule forming pin into an HPMC water solution maintained at a temperature below the gel point temperature, withdrawing the pins and placing the pins in ovens at temperatures above the gelation temperature, and drying the film. HPMC gels on the surface of the heated pins and, as the pins are withdrawn, a HPMC film of a certain thickness is formed on the pins, and capsules are obtained after drying (Benameur, 2010). To qualify the new hypromellose capsule as a suitable replacement for use in drug development, Wyeth conducted a series of studies to evaluate and compare the performances of the two hypromellose capsule shells. Results of comparative studies in terms of physical, mechanical and processability were detailed in the Part I paper (Ku et al., 2010), which showed the HPMC Shell 2 to be superior or comparable to HPMC Shell 1 in these quality attributes.

In the period of time when HMPC Shell 1 was used in drug product development, slow *in vitro* dissolution caused by the interaction of carrageenan with buffering species containing divalent cations and potassium ion was also observed, although the issue can usually be resolved by choosing appropriate buffering species. Dissolution testing is one of the most important aspects in pharmaceutical development, and is a test most closely associated with the *in vivo* performance of a dosage form, and often used as a tool to predict and diagnose oral drug absorption (Dressman et al., 1998). Dissolution tests are conducted to screen formulations, for drug product quality control, to reveal *in vivo* performance of the drug products, and to establish bioequivalence for some drugs. Considering the importance of dissolution characteristics, comparative studies of the disintegration and dissolution of the HPMC Shell 1 and Shell 2 were conducted in dissolution media covering a wide range of pH values. Several Wyeth preclinical compounds were used as model compounds for the dissolution studies, and the results are the subject of this report. An improved method to determine rupture/opening time of capsule shells is also described.

2. Materials and methods

2.1. Empty capsule shells

Three types of capsule shells were evaluated in disintegration and dissolution comparison studies, hard gelatin capsule (HGC) from Capsugel, Quali-V® hypromellose capsule (HPMC Shell 1) from Qualicaps, and VCaps Plus® hypromellose capsule (HPMC Shell 2) from Capsugel. The HGC consists of pharmaceutical grade gelatin blend that meets global regulatory requirements. Because HGC is known to disintegrate and dissolve rapidly in aqueous media at body temperature, it is used in some case studies for direct comparison with the new hypromellose capsule (HPMC Shell 2). The major component for both HPMC capsules is hypromellose. However, there are two additional ingredients in HPMC Shell 1 (Quali-V®) capsule, carrageenan as the gelling agent and potassium chloride to promote gelling. The addition of carrageenan enables hypromellose to gel and form a film below its gelling point, while potassium enforces carrageenan gel strength. However, no gelling agent or promoter is used in HPMC Shell 2 (VCaps Plus®) because a thermal gelation process is used instead. The HGC used in tests is of grey color, which contains black iron oxide. The reddish brown color was selected for both HPMC capsules. Below are the lists of ingredients of the three capsule shells.

Composition of Quali-V® hypromellose capsule shell (HPMC Shell 1)

Ingredient	Quality specification
Carrageenan	NF/JPE
Potassium chloride	Ph. Eur./USP/JP
Titanium dioxide	Ph. Eur./USP/JP/E171
Synthetic iron oxide red	Ph. Eur./USP/JP/E172
Hypromellose	Ph. Eur./USP/JP
Water	USP

Composition of VCaps Plus® hypromellose capsules (HPMC Shell 2)

Ingredient	Quality specification
Titanium dioxide	USP/EU/FAO/WHO
FDA/E172 red iron oxide	NF/CFR21/95/45/EC/FAO/WHO
Hypromellose	EP/USP

Composition of hard gelatin capsules (HGCs)

Ingredient	Quality specification
Black iron oxide	95/45/EC; USP/NF; CFR 21
Titanium dioxide	Ph. Eur/USP/NF
Gelatin	USP/Ph. Eur./FAO/WHO

2.2. Chemicals

The various formulations were all made from commonly used excipients (microcrystalline cellulose, crospovidone, magnesium stearate) which were of NF grade. Chemicals used for dissolution media were all reagent grade or better. Caprylocaprol polyoxyl-8 glycerides (Labrasol®) was from Gattefosse, Saint-Priest, France. Diphenhydramine hydrochloride and psuedoephedrine hydrochloride were from Sigma–Aldrich, St. Louis, MO.

2.3. Capsule shell rupture time determination

Capsule rupture/opening time measurement was conducted with size #0 capsules of the two HPMC shells that were loosely filled with 180 mg diphenhydramine hydrochloride neat compound. The experiments were carried out using the USP dissolution Apparatus 2, i.e. Distek Evoluation 6100, at 50 rpm paddle speed. The dissolution apparatus is equipped with an in-line fiber optic UV detector manufactured by Leap Technologies, Inc., and a wavelength at 225 nm was chosen to continuously monitor UV absorption of the dissolution medium. The path length was 1 mm. Data were collected for every 10 s for 15 min. Disintegration was tested in four commonly used dissolution media, 0.1 M HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and 1% SLS in water, which were maintained at $37.0 \pm 0.5\,^{\circ}C$.

2.4. Test compounds

Nine Wyeth development compounds were chosen for the disintegration and dissolution evaluation. The formulation types/processes varied depending on the biopharmaceutical and physico-chemical properties of the compounds and the development needs. For the dissolution comparison, the same fill formulation (powder or granule) was manually encapsulated into the HPMC Shell 1 and HPMC Shell 2 and/or hard gelatin capsules.

2.5. Dissolution media and method

For the dissolution testing of the Wyeth compounds, a wide pH range of dissolution media was required, due to the different sol-

Table 1
Physico-chemical and biopharmaceutical properties of compounds in dissolution tests.

Compound	Form	BCS	pKa	Solubility in water (mg/mL)	Capsule strength (mg)	Dissolution media	Solubility in medium (mg/mL)	Sink ratio	Paddle speed (rpm)
1	Salt	4	4.7, 7.7 (base)	0.43	80	0.1 M HCl	23.9	269	50
2	Base	2	7.9, 4.7, 3.3	0.002	100	0.1 M HCl	43.3	390	50
3	Salt	1	8.9 (base)	73.7	75	0.1 M HCl	70.7	848	75
4	Salt	1	8.8 (base)	1.46	25	50 mM sodium acetate buffer pH 4.5	0.9	32	50
5	Salt	2	4.6, 7.6 (base)	0.58	80	50 mM sodium acetate buffer pH 4.5	6.3[a]	71	75
6	Acid	2	4.7 (acid)	0.05	120	50 mM sodium phosphate pH 6.8/0.1% CTAB	0.8	6	50
7	Acid	2	7.0, 9.5	0.04	25	30 mM sodium borate buffer pH 9.0/0.5%SLS	0.19	6.8	75
8	Neutral	2	Non-ionizable	0.02	250	1% SLS	0.32	1.2	100
9	Neutral	2	Non-ionizable	0.0005	80	1% SLS	0.061	0.7	75

[a] Solubility in pH 4.8 aqueous solution.

ubility characteristics of the compounds (Table 1). USP Apparatus 2 (paddles) was used for all dissolution experiments with dissolution bath from Distek Evolution 6100 or equivalent. An extra large sinker with a wire cage design and inert coating (Quality Lab Accessories, Part# CAPWHT-XL, approx. 1.32″ long with 0.46″ in diameter) was used for all dissolution tests. Temperature of the dissolution medium was maintained at 37 ± 0.5 °C. Six capsules were replicated in each test.

For some compounds, dissolution samples were assayed in-line directly using the Opt-Diss Fiber Optic UV system (Leap Technologies Inc.). The other compounds were analyzed using HPLC method with dissolution samples withdrawn and assayed at specified time points, typically 15, 30, 45, and 60 min. The same assay method by either HPLC or in-line fiber optics was used for a given compound in order to compare dissolution profile consistently across the three types capsule shells.

3. Results and discussion

3.1. Comparison of capsule disintegration

Before the material within a capsule can begin to dissolve, the capsule must first open so that the contents can establish contact with the dissolution medium. Attempts had been made to measure the initial break-up or rupture time of capsule shells using a ball bearing method (Chiwele et al., 2000), in which a stainless steel ball was placed in a capsule, whose body was immersed in a testing fluid, and the time that the ball fell through the capsule was recorded as the disintegration time. The testing device did not resemble the conventional USP disintegration or dissolution apparatus and, one could argue that the stainless ball could accelerate the capsule rupture as it weighed on the weakened shell. Nonetheless, the test provided useful comparison of rupture time between HGC and HPMC Shell 1 (Quali-V®) capsules in various fluids. As estimated from graphs shown in the paper, the disintegration time of size #0 HGC is similar in 0.1 M HCl and phosphate buffer at between 2 and 3 min, while that of size #0 HPMC is about 4 min in 0.1 M HCl and about 8 min in phosphate buffer.

In another study using a dissolution apparatus equipped with an in-line fiber optic UV detector, the rupture times of HGC and HPMC Shell 1 were compared by measuring the onset of the light scattering due to the formation of emulsion from the release of the liquid excipient Labrasol® inside the capsules (El-Malah and Nazzal, 2007). The capsule rupture times determined this way were similar to the results using ball bearing method. The HGC rupture time was 1.1–1.5 min in simulated gastric fluid (SGF) and 1.3–2.1 min in simulated intestinal fluid (SIF), while that of HPMC Shell 1 capsule was in the range of 2.8–3.8 min and 6.2–10.5 min, respectively. This study also showed that capsule size had minimal effect on the rupture time. Thus, both ball bearing and UV spectroscopic methods indicate that rupture time is somewhat longer for the HPMC Shell 1 capsule than HGC. Both studies also showed that rupture time of the hypromellose capsule was retarded in the phosphate buffer relative to the un-buffered acidic media. This has been attributed to salting out of HPMC in the presence of inorganic ions, which reduces its solubility, based on several studies on disintegration and dissolution of HPMC matrices and gels (Alderman, 1984; Mitchell et al., 1990; Kavanagh and Corrigan, 2004). It is also been reported that pH of the testing media does not have a significant impact on the dissolution of HPMC capsules as HPMC is a non-ionic polymer (Tochio et al., 2002).

The rupture time of HPMC Shell 2 capsule has not been reported in the literature. We attempted to apply the method developed by El-Malah and Nazzal (2007) and compare against rupture time of HPMC Shell 1 capsule, but we encountered a few issues. First, it could take some time for the Labrasol® emulsion to form, and we noticed that certain pigments/colorants from the capsule shell could interfere with the light scattering detection. In addition, we were concerned about the possibility of leakage of the liquid excipient from the junction between capsule cap and body without sealing or proper positioning of the capsule. Therefore, as an alternative we used the neat solid compound of the highly soluble diphenhydramine hydrochloride as the capsule fill, and UV absorption at 225 nm wavelength as the detection method. Diphenhydramine hydrochloride dissolves instantly upon contact with water, and has a chromophore that enables UV absorption detection. Once a capsule opens in the medium, the UV absorption of diphenhydramine can be immediately detected with the agitation of the medium by the paddles. The first uptick in the ascending slope of the drug release profile was taken as the rupture time. Using this method, we compared the disintegration/rupture of the two HPMC capsules in commonly used dissolution media, 0.1 M HCl, pH 4.5 sodium acetate buffer, pH 6.8 sodium phosphate buffer, and 1% SLS in water (Fig. 1).

The results indicate that HPMC Shell 1 tends to open up somewhat faster than HPMC Shell 2. This may be due to the presence of carrageenan, which appears to facilitate the dissolution of HPMC as it is soluble and hydrate easily. Without carrageenan, it appears to take a little longer for the more uniform HPMC film to hydrate and dissolve for HPMC Shell 2. The average capsule rupture time is in

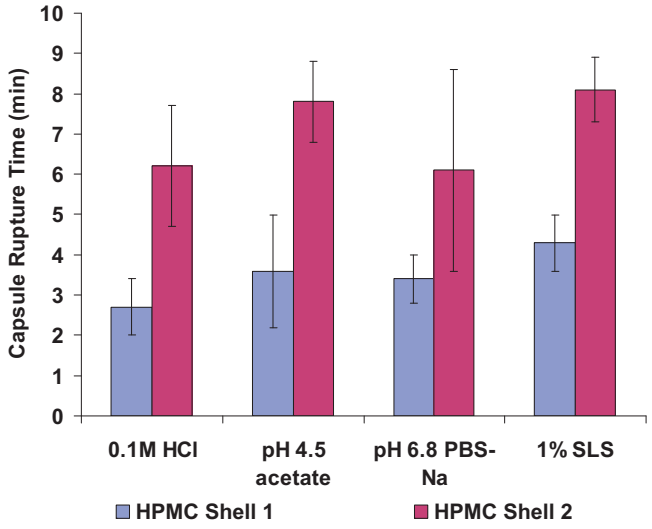

Fig. 1. Disintegration/rupture time of HPMC Shell 1 (Quali-V®) and HPMC Shell 2 (VCaps Plus®) in four dissolution media, 0.1 M HCl, pH 4.5 acetate buffer, pH 6.8 phosphate (sodium salt), and 1% SLS in water. The error bars represent standard deviation of six capsules.

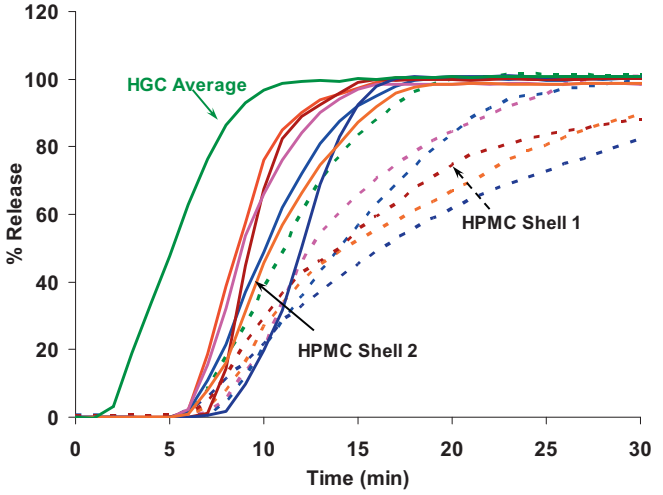

Fig. 2. Dissolution profiles of three capsules of Compound 1 formulation in 0.1 M HCl at 50 rpm paddle speed. HGC dissolution profile is shown as a bold solid line (for clarity, only the average of 6 capsules is shown). Six individual HPMC Shell 1 capsule dissolution profiles are shown as dashed lines, and six individual HPMC Shell 2 dissolution profiles as solid lines.

the range of 2.7–4.3 min for HPMC Shell 1 and 6.1–8.1 min for HPMC Shell 2 in various media. The Shell 1 rupture times determined by this method are in agreement with those reported in literature. As shown by the manufacturer (Qualicaps, 2009), capsule disintegration tends to start at the weakest point in the capsule that is the shoulder, splitting the capsule cap and body. Similar behavior was observed with the HPMC Shell 2 as well, which is not surprising when considering both HPMC capsules are manufactured using similar equipment with mold pins. Once the capsules open up, both HPMC capsule shells disintegrate and dissolve rapidly in the dissolution media. Although only one capsule size (size #0) is used in this study, it is expected that other capsule sizes would follow the same trend. Larger capsule may take slightly longer to rupture because of greater thickness, but the difference is quite small (El-Malah and Nazzal, 2007). The rupture time data are useful in understanding the disintegration behavior of the "empty" capsules in various media, and particularly, in understanding of the differences in dissolution profiles at early time-points seen in several case studies to be presented later.

The differences (<4 min) in capsule opening/rupture times between the two HPMC capsules are not expected to have significant impact on *in vivo* performance. Studies by others have shown that the *in vitro* rupture time or disintegration time of HPMC Shell 1 are generally slower than HGC in dissolution media at 37 °C (Chiwele et al., 2000; El-Malah and Nazzal, 2007), however, there is no significant difference in the *in vivo* capsule disintegration and dissolution times and thus no impact on the pharmacokinetic parameters (Tuleu et al., 2007). This is one of the important factors in the decision made by Wyeth to switch from HGC to HPMC Shell 1 for drug development in 2002, and the *in vivo* performance in animal and human for Shell 1 were satisfactory for over 30 compounds (Ku et al., 2010).

3.2. Capsule dissolution comparison

Dissolution of HGC and HPMC Shell 1 has been compared using the drug theophylline (Podczeck and Jones, 2002). The study showed that the *in vitro* dissolution performance of HPMC Shell 1 was comparable to or even exceeded that of HGC. This study also showed that formulation had the most significant impact on the capsule dissolution, and capsule material also had a large effect, whereas capsule fill weights and the tamping forces to form the plugs were found to have a minimal impact.

To evaluate the dissolution characteristics of HPMC Shell 2, we conducted dissolution tests of the two HPMC shells side by side, and in some cases together with HGC, using media with a range of pH values. Nine Wyeth development compounds were used. The physico-chemical properties such as solubility and pKa values of the compounds and dissolution parameters are listed in Table 1. The dissolution medium and solubility of the compound against the dose to be solubilized, i.e. sink ratio, are also shown in Table 1. For two thirds of Biopharmaceutical Classification System (BCS) Class 2 compounds in the table, surfactant additives were necessary to enhance solubility. For compounds developed in the earlier years, 50 rpm paddle speed was often used as it was used in the past with HGC and was considered sufficient for the HPMC capsules. It was later observed that there was variation in dissolution for multiple projects at 50 rpm, primarily due to the fact the capsule content was trapped under the broken capsule shells that hindered the drug release. Thus 75-rpm paddle speed was recommended to ensure consistency among capsules and batches of capsules. Paddle speed at 100 rpm was occasionally used when it was deemed necessary particularly because of poor solubility of a compound.

3.2.1. Capsule dissolution in 0.1 M HCl

Dissolution tests of Compounds 1, 2, and 3 were conducted in 0.1 M HCl. HGCs of Compounds 1 and 2 were also prepared for comparison. Dissolution apparatus equipped with in-line fiber-optic UV detection was used to test Compound 1 capsules (data were collected at 1 min interval) and dissolution profiles of Compound 1 in the three different capsules are shown in Fig. 2. The dissolution profiles show that HGC disintegrated and dissolved rapidly and reached complete release within 10 min overall. Capsule opening was slower for HPMC Shell 2 relative to HGC, as expected based on the previous capsule opening studies and our rupture time determination, so complete release was delayed until about 18 min accordingly, but the dissolution profiles were consistent among the HPMC Shell 2 capsules. The capsule opening time for HPMC Shell 1 was similar to that of HPMC Shell 2 in this case; however, the dissolution was more variable, and half of the Shell 1 capsules did not completely release within 30 min. To illustrate the variation, standard deviation values at several time points are shown in Table 2. For the slow releasing HPMC Shell 1 capsules, the disso-

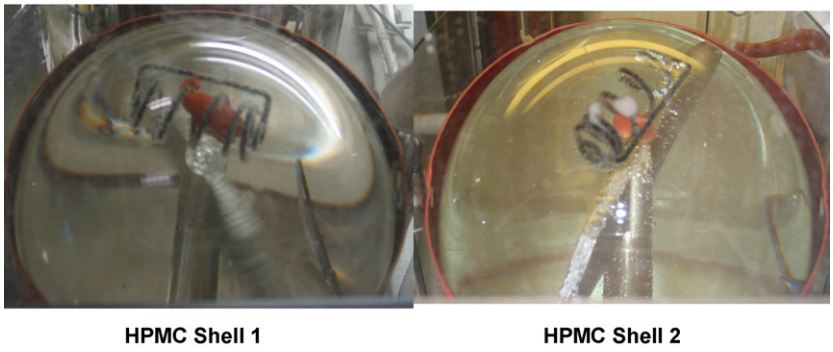

Fig. 3. Photographs of HPMC Shell 1 and Shell 2 capsules of Compound 1 in 0.1 M HCl after 30 min dissolution at 50 rpm paddle speed.

Table 2
Release of Compound 1 capsules in dissolution test.

Time (min)	HPMC Shell 1	HPMC Shell 2	HGC
15	59.8 (13.3)	94.2 (4.4)	100.1 (1.2)
30	93.5 (8.2)	99.8 (0.9)	100.6 (1.1)
45	99.5 (2.8)	99.8 (1.0)	100.8 (1.1)
60	101.7 (4.0)	100.0 (1.0)	100.9 (1.1)

Note: $N = 6$, Standard deviation in parentheses.

Table 3
Dissolution of Compound 2 capsules in 0.1 M HCl.

Time (min)	HPMC Shell 1	HPMC Shell 2	HGC
15	43.9 (41.0)	68.4 (11.7)	91.2 (3.7)
30	66.0 (32.9)	91.9 (2.9)	94.5 (3.3)
45	73.0 (27.3)	95.6 (1.2)	96.0 (3.0)
60	77.4 (23.3)	97.0 (1.0)	97.1 (2.8)

Note: $N = 6$, Standard deviation in parentheses.

lution profiles look like that of a controlled-release dosage form, even though the formulation is an immediate-release dosage form and compound solubility is not rate-limiting. The slower release of HPMC Shell 1 was also confirmed by the photographic images of capsules taken at selected time points during the dissolution test. Example photographs in Fig. 3 show that a significant portion of an HPMC Shell 1 capsule remains intact at 30 min, in contrast to an HPMC Shell 2 capsule that was almost completely dissolved.

The physico-chemical properties of Compound 2 were similar to Compound 1 (Table 1), but it was developed as a free base monohydrate. Dissolution samples were assayed by an HPLC method and dissolution profiles of the three capsules (Fig. 4) and standard deviation values (Table 3) show similar patterns and trends as seen with Compound 1. HGC dissolved most rapidly, followed by HPMC Shell 2 and then HPMC Shell 1. Although dissolution at the 15-min time point was somewhat variable for HPMC Shell 2, the variation quickly diminished at 30-min time point (Table 3). However, high variability in HPMC Shell 1 capsules persisted even at 60-min time point, and release was substantially slower (half of the capsules had 60% or less release at 60 min). Because Compound 2 is a free base, a requirement for longer time for wetting and disintegration of the formulation is reasonable. However, this does not explain the delay and variability seen only in HPMC Shell 1 capsules.

Compound 3 is another compound that was developed as a crystalline soluble salt form. It has a higher basic pKa value and reasonably good solubility throughout the physiological pH range, and it is classified as a BCS Class 1 compound because of high permeability. The dissolution was compared between two HPMC shells using an HPLC method for measurement. The dissolution profiles in Fig. 5 show that both capsules had essentially complete release within 15 min. Although the variability was slightly higher among HPMC Shell 1 capsules at 15 min, it diminished quickly by 30 min. Complete release was achieved for all the capsules within 30 min. The variability and the delayed release observed in HPMC Shell 1 for Compounds 1 and 2 were not seen in Compound 3. The comparison might be a little confounded because 75 rpm paddle speed was used for Compound 3 rather than 50 rpm used for earlier development Compounds 1 and 2.

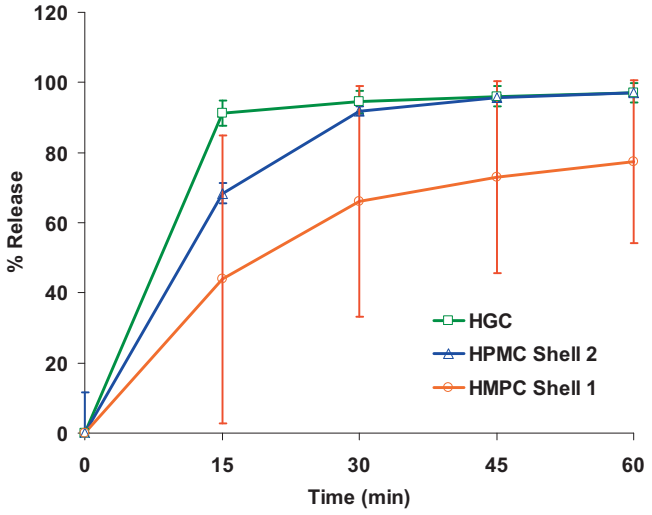

Fig. 4. Dissolution profiles of three capsules of Compound 2 formulation in 0.1 M HCl at 50 rpm paddle speed.

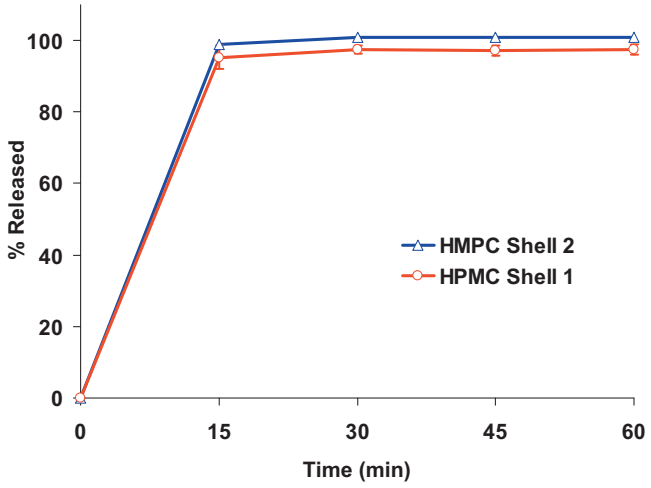

Fig. 5. Dissolution profiles of HPMC capsules of Compound 3 formulation in 0.1 M HCl at 75 rpm paddle speed.

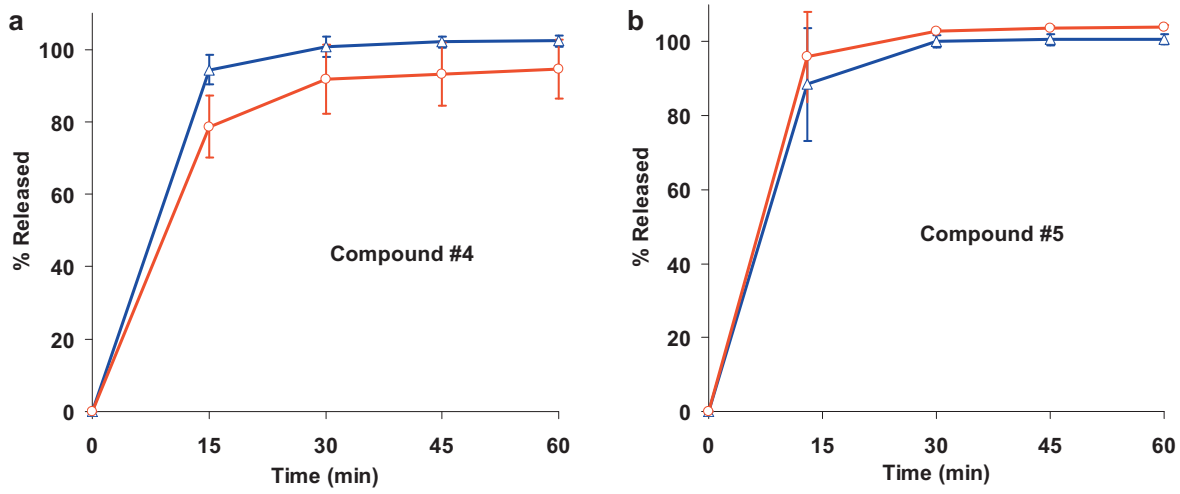

Fig. 6. Dissolution of (a) 25 mg Compound 4 and (b) 80 mg Compound 5 in pH 4.5 acetate buffer at 50 rpm and 75 rpm paddle speed, respectively. Symbols: ○ – HPMC Shell 1 capsules, △ – HPMC Shell 2 capsules.

The slow release of HPMC Shell 1 capsules observed with Compounds 1 and 2 suggests an interaction of the compounds with HPMC shell 1 that does not occur with HPMC shell 2. Since HPMC Shell 2 is almost 100% HPMC except for the pigments, the difference seen between the two HPMC shells are likely related to the gelling agent carrageenan in HPMC Shell 1. The hypothesis of a carrageenan-mediated retardation in the release rate of these compounds is supported by its use in controlled release dosage forms. Because of their unique properties as hydrocolloids, mixture of carrageenans or carrageenans with other cellulose ethers have been used in controlled-release hydrophilic matrices (Bonferoni et al., 1994, 1998; Hariharan et al., 1997; Nerukar et al., 2005; Picker, 1999a,b). With appropriate polymer mixture and ratio of drug to polymers, pH independent and near zero-order release can be achieved. Carrageenans have been found particularly useful in controlling the initial burst effect of basic drugs that is often observed in hydrophilic matrices, and in their ability to thicken and gel across wide pH range. It is noted that the acidic characteristics of the sulfate groups on carrageenans allow the ionic polymer–drug interactions to occur even in acidic environment (Bonferoni et al., 1998). In fact, lambda carrageenan was found to interact with diltiazem to form a slightly soluble complex by Bonferoni and co-authors, who isolated and characterized the complex (Bonferoni et al., 2000). The authors later developed a controlled-release tablet formulation based on this complex (Bonferoni et al., 2004). Controlled-release formulation of other basic compounds, such as chlorpheniramine (Bonferoni et al., 1994, 1998), tripelennamine (Hariharan et al., 1997), and sulbutamol (Bonferoni et al., 1994), have been developed using the carrageenan matrices; however, it is not clear if similar ionic interactions occur for these compounds and how the interaction might have impacted on the drug release.

The diltiazem–carrageenan complex offers clear evidence of the ionic polymer–drug interaction between carrageenan and some basic drug compounds (Bonferoni et al., 2000). Although lambda carrageenan was used in the diltiazem complex study, it is likely that similar polymer–drug interaction could occur between other carrageenan such as kappa carrageenan and some other basic drugs. Because carrageenan is present in the capsule shell (HPMC Shell 1) rather than in a matrix formulation, it is expected that the interaction with the drug compounds would vary from capsule to capsule, as was seen in the dissolution profiles of Compounds 1 and 2 in HPMC Shell 1. The interaction may be dependent on how the capsule is broken up and how much contact a capsule shell has with the formulation in the course of dissolution. However, this effect is clearly compound dependent. Any interaction between carrageenan in the HPMC Shell 1 capsule with Compound 3 was

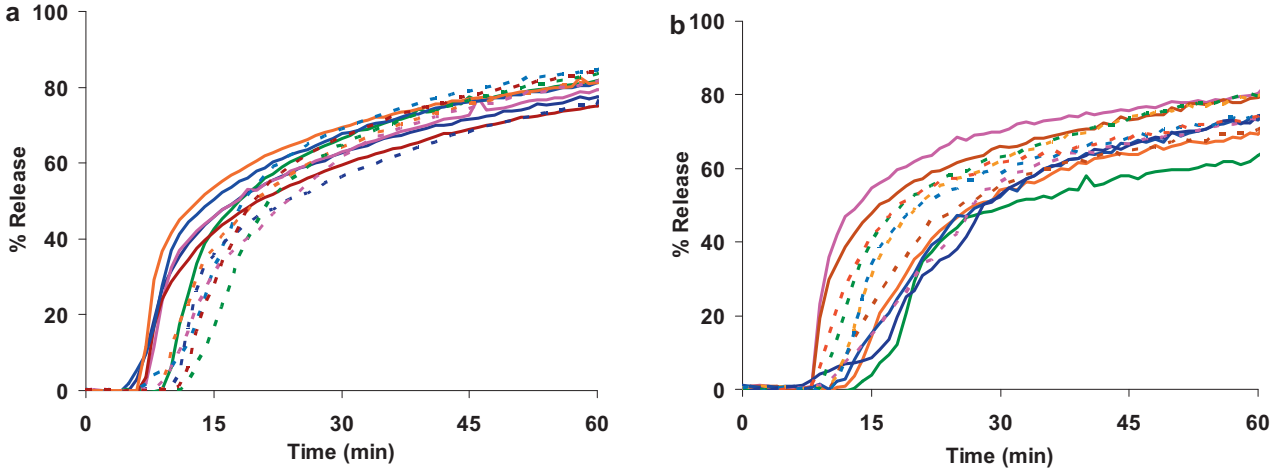

Fig. 7. (a) Dissolution profiles of HPMC Shell 1 (solid lines) and HPMC Shell 2 capsules (dashed lines) of Compound 6 in pH 6.8 sodium phosphate buffer with 0.1% CTAB at 50 rpm paddle speed. (b) Dissolution profiles of HPMC Shell 1 (solid lines) and HPMC Shell 2 capsules (dashed lines) of Compound 6 in pH 6.8 potassium phosphate buffer with 0.1% CTAB.

Table 4
Compound 6 dissolution data in sodium phosphate and potassium phosphate buffers.

Time (min)	Sodium phosphate buffer			Potassium phosphate buffer	
	HGC	HPMC Shell 1	HPMC Shell 2	HPMC Shell 1	HPMC Shell 2
15	46.3 (4.7)	46.7 (4.6)	29.9 (7.8)	24.1 (21.5)	30.4 (10.4)
30	61.7 (2.3)	64.8 (3.7)	63.7 (4.4)	57.4 (8.4)	59.3 (3.2)
45	71.5 (2.0)	74.0 (3.4)	75.1 (3.8)	67.3 (6.4)	69.2 (3.7)
60	77.5 (2.7)	79.3 (2.6)	81.7 (3.3)	73.4 (6.3)	75.3 (3.6)

Note: $N = 6$, standard deviation in parentheses.

apparently insignificant, as complete release was achieved rapidly within 15 min, and the difference between the two HPMC capsules was minimal. An additional dissolution experiment using a basic model compound (pseudoephedrine hydrochloride) also showed no difference in behavior between HPMC Shell 1 and Shell 2 (data not shown). One possible reason for this compound dependent behavior may be the fact that the molecular structures of Compounds 1 and 2 contain more than one basic site, allowing for multiple charge–charge interactions with carrageenan sulfonate groups, as opposed to just one interaction site for compound 3 or pseudoephedrine. Another possibility is the lower solubility of Compounds 1 and 2 relative to Compound 3 or pseudoephedrine being a contributing factor, and that more soluble compounds are less susceptible to this effect. The mechanism of interaction and the exact causes of the drug release retardation cannot be fully understood without further studies. However, these results indicate that HPMC Shell 2 is not subject to this effect, likely due to the absence of a gelling agent. The predecessor of HPMC Shell 2, VCaps®, was manufactured with a gellan gum as the gelling agent, and this capsule exhibited slow *in vitro* disintegration in acidic buffers and in stomach acid *in vivo*, which limited its applicability in pharmaceutical products (Cole et al., 2004). Thus, the lack of gelling agent in HPMC Shell 2 appears to offer an advantage in the *in vitro* dissolution in 0.1 M HCl media over HPMC Shell 1.

3.2.2. Capsule dissolution in pH 4.5 acetate buffer

Acetate buffer at pH 4.5 is one of the commonly used media for dissolution testing. A capsule shell comparison was therefore conducted in pH 4.5 acetate buffered media, using Compounds 4 and 5, which are basic compounds and were developed as soluble salts (Table 1). Both compounds belong to BCS Class 2 and have good solubilities at pH 4.5. As shown in Fig. 6, both compounds were almost completely dissolved at the 30-min time point for either of the HPMC capsule shells. The only anomaly observed was the variability for the HPMC Shell 1 capsules of Compound 4, which remained between 8 and 9% beyond the 15-min time point. Further examination of the individual capsule dissolution profiles revealed that it was attributed to the low release of one of the six capsules. It has been observed that during dissolution of Shell 1, fragments of the shell may sometimes trap the powder against the bottom of the vessel, hindering fast and complete release of the drug. This, of course, is an artifact that would not occur *in vivo*. This artifact can be minimized by using a higher paddle speed. In all other respects, the two types of HPMC capsules showed similar behaviors and the results are largely unremarkable.

3.2.3. Capsule dissolution in pH 6.8 phosphate buffers

It has been reported in the literature that the presence of potassium cations in the dissolution media hinders drug release from HPMC Shell 1 (Tochio et al., 2002; Cole et al., 2004; Honkanen et al., 2001), and our experiences also confirmed this retardation effect. Consequently sodium salt was recommended to replace potassium salt in the preparation of buffers for dissolution of HPMC Shell 1. It is known in the food industry, in which carrageenan is widely used as a stabilizer, that divalent cations and large group I cations such as potassium are effective in inducing gelation and enhancing gel strength of carrageenan at moderate concentrations (Watase and Nishinari, 1986; Doyle et al., 2002; Therkelsen, 1993; Piculell, 1995). Slow dissolution as a result of interaction with cations was also observed with the hypromellose capsule shell containing gellan gum (VCaps®) (Cole et al., 2004; Sanderson and Clark, 1984). Therefore, a comparison study was conducted in both sodium and potassium phosphate buffers at pH 6.8 to determine if potassium ion has an impact on HPMC Shell 2 dissolution. Compound 6 in Table 1 was used for these tests. Compound 6 is an insoluble free acid belonging to BCS Class 2. It is virtually insoluble in 0.1 M HCl and pH 4.5 acetate buffer. Solubility is increased in pH 6.8 sodium phosphate buffer as the compound is ionized beyond its pKa of 4.7. With the addition of surfactant hexadecyl trimethyl ammonium bromide (CTAB) at 0.1% in the dissolution medium, a sink ratio of 6 was achieved for the 120 mg capsule strength.

Dissolution profiles for the two HPMC capsules in sodium phosphate buffer with 0.1% CTAB are shown in Fig. 7a, and potassium phosphate in Fig. 7b. The dissolution data at selected time points are shown in Table 4. In sodium phosphate buffer, the profiles indicate the same trend in capsule opening time (HGC < HPMC Shell 1 < HPMC Shell 2) as what was determined in the rupture time study. This explains the lower release seen with HPMC Shell 2 capsules at the 15-min time point. No appreciable difference is discerned among the dissolution profiles at 30-min time point and beyond (Table 4). Capsules only reached about 80% release at 60 min, reflecting the poor solubility of the compound. The behavior of HPMC Shell 1 in potassium phosphate was quite different from that in sodium phosphate buffer. In potassium phosphate (Fig. 7b), two of the HPMC Shell 1 capsules appeared to open at a similar time (about 8 min) as in sodium phosphate, and these two capsules showed a very rapid initial dissolution rate. The other four HPMC Shell 1 capsules opened later to varying degrees; and these four capsules also showed substantially slower initial rates of dis-

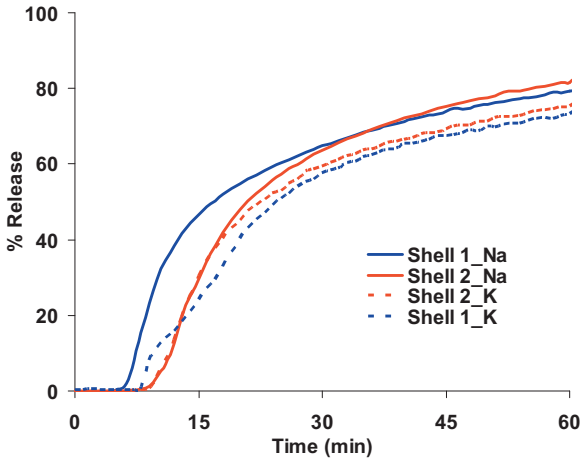

Fig. 8. Mean dissolution profiles ($N = 6$) of HPMC Shell 1 and HPMC Shell 2 capsules of Compound 6 in sodium phosphate and potassium phosphate at pH 6.8.

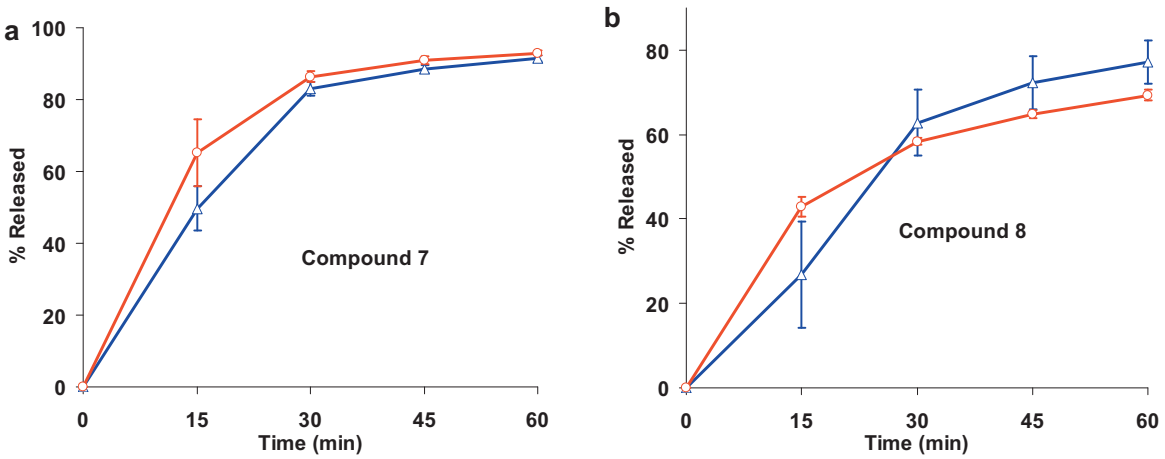

Fig. 9. Dissolution profiles of (a) Compound 7 and (b) Compound 8 in 1% SLS. Symbols: ○ – HPMC Shell 1 capsules, △– HPMC Shell 2 capsules.

solution (Fig. 7b). This significant effect of potassium ion on the dissolution behavior justifies the recommendation of avoiding the use of potassium for HPMC Shell 1. HPMC Shell 2, on the other hand, showed essentially the same dissolution behavior in either sodium or potassium phosphate buffer. This is illustrated clearly in Fig. 8, which shows the mean profiles of six capsules under each of the four conditions. Note that for HPMC Shell 2, the curves in sodium and potassium buffers are virtually indistinguishable during the first 15 min, whereas the HPMC Shell 1 shows substantially longer delay in potassium phosphate relative to sodium phosphate. Thus, it appears that the dissolution performance of Shell 2 is relatively insensitive to the presence of potassium ions in the media, and there does not appear to be any reason to restrict the use of potassium ion from dissolution media for Shell 2.

3.2.4. Capsule dissolution in 1% SLS media

Some pharmaceutical compounds are insoluble in water and also non-ionizable, meaning that pH adjustment has no impact on the solubility. Substantial amount of surfactants are usually added to the medium, i.e. water, to make dissolution testing possible. Formulations of Compounds 7 and 8 were used to evaluate capsule performance in the presence of the commonly used additive sodium lauryl sulfate (SLS). The use of 1% SLS helped increase solubility to allow measurement of dissolution, but sink ratios at 1.2 (Compound 7) and 0.7 (Compound 8) were far below the sink condition (ratio ≥ 6). Despite the low sink ratio, both HPMC capsules of Compound 7 (Fig. 9a) performed comparably, achieving about 90% release at 45 and 60 min. The lower release of HPMC Shell 2 at 15-min time point was a result of slower opening the capsules, as shown in the disintegration study. The flatter dissolution curves of Compound 8 (Fig. 9b) indicated its relatively slower dissolution rate, largely due to its lower sink ratio and much lower intrinsic solubility. The Shell 2 data of Compound 8 appeared somewhat peculiar because of the apparent increase in slope after 15-min time point compared to the slope before 15-min. However, this appearance is due to the time required for capsule opening. To illustrate this, it is useful to calculate the initial rates of dissolution with the time corrected for capsule opening. Based on the capsule opening time of 4.3 min for Shell 1 (Fig. 1) and 42.8% release at 15-min, a value of 4.0%/min for the initial slope (or dissolution rate) is obtained. For Shell 2 that has an opening time of 8.1 min (Fig. 1) and 26.8% release at 15-min, the initial dissolution rate is 3.9%/min based on the elapsed time of 6.9 min. Thus, when accounting for the time for capsules to open, the initial slopes obtained before 15-min time point for both HPMC capsules are essentially the same, indicating that the "peculiar" appearance of the Shell 2 curve in Fig. 9b is not related to any unusual dissolution behavior. The larger variation in Shell 2 for Compound 8 (Fig. 9b) is due primarily to 1 of 6 capsules that released 9–13% lower than the other capsules, similar to the case of Compound 4 in Shell 1 (Fig. 6). Although Shell 2 appeared to have higher release than Shell 1 at later time points, the small difference in our opinion is not significant enough to suggest any systematic interaction between the compound and either of the capsules, especially when considering the poor solubility characteristics of Compound 8. These data demonstrate that both capsules give satisfactory and comparable dissolution performance in 1% SLS media.

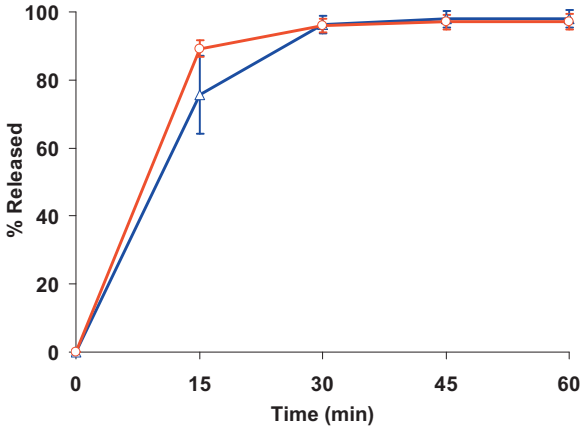

Fig. 10. Dissolution of 25 mg Compound 9 in pH 9.0 borate buffer with 0.5% SLS. Symbols: ○ – HPMC Shell 1 capsules, △– HPMC Shell 2 capsules.

3.2.5. Capsule dissolution in pH 9 borate buffer

We also conducted dissolution comparison in pH 9 borate buffer, which is a less frequently used dissolution medium but may occasionally be useful for weakly acidic compounds that require substantial increase in pH in order to afford solubility. Compound 9 was utilized for this test (Table 1). As in the case of the pH 4.5 testing, the results (Fig. 10) showed no significant difference between the two HPMC capsules with the exception of the slightly lower value for HPMC Shell 2 at the earliest time point (15-min), which could be reconciled by the slower opening time of HPMC Shell 2. No significant difference was noted at 30-min time point and beyond.

4. Conclusions

A comparison of capsule rupture/opening time between the two hypromellose capsule shells was conducted using a modi-

fied method from the literature. The results showed that the time required for HPMC Shell 2 to open was about 3–4 min longer than for HPMC Shell 1. This difference was consistent in the pH range of 1–6.8, and also in the presence of surfactant (SLS). In spite of the rupture time differences, both HPMC capsules show comparable *in vivo* performances, demonstrating rapid dissolution in animal and human pharmacokinetic studies (Ku et al., 2010).

Dissolution comparisons of the two hypromellose capsules were conducted over the pH range of 1–9. At pH 1 (0.1 M HCl), drug release for two of the three compounds in HPMC Shell 1 was hindered. This retardation effect was not seen for the same compounds/formulations in Shell 2. This different behavior was attributed to the interaction of these compounds with gelling agent carrageenan, which is present in Shell 1 but absent in Shell 2. In pH 6.8 phosphate buffers, HPMC Shell 1 showed a significant difference in behavior when switched from sodium to potassium phosphate buffer where, potassium, a gelling promoter for HPMC Shell 1, caused delay in capsule opening and substantial increase in variability of dissolution. This effect was also absent in HPMC Shell 2, which showed consistent dissolution behavior in either sodium or potassium phosphate buffer. At pH 4.5 and pH 9, dissolution behavior was similar between the two HPMC shells, the only minor difference being a slightly lower release at the earliest time point (15-min) for HPMC shell 2, which was attributed to the slightly longer capsule opening time for HPMC Shell 2. The two HPMC capsules were also found to perform comparably and satisfactorily in the dissolution media containing 1% SLS. Based on the superior dissolution performance and other quality attributes as detailed in Paper I (Ku et al., 2010), HPMC Shell 2 is satisfactorily qualified and used in nearly 20 investigational new drug (IND) compounds.

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