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Hard Gelatin and Hypromellose (HPMC) Capsules: Estimation of Rupture Time by Real-Time Dissolution Spectroscopy

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ABSTRACT The objective of this study was to measure rupture time of gelatin and hypromellose (hydroxypropyl methylcellulose or HPMC) capsules using a novel approach based on real-time dissolution spectroscopy. Rupture time was measured in standard dissolution apparatus at a constant temperature using a dip-type fiber-optic probe. Labrasol released from the capsules was treated as the marker of the rupture process. Light scatter generated by the emulsified labrasol was detected by an ultrafast monochromator at scan rates approximating 24,000 nm/min. This technique was validated by measuring the dissolution time of gelatin capsules. Rupture times of hypromellose capsules were studied as a function of capsule size, capsule grade, and dissolution medium. Statistical correlations were analyzed by ANOVA. Rupture time of hypromellose capsules was dependent on both the medium and the grade of the capsule, and was independent of capsule size. The composition of the dissolution medium contributes to the rupture time of the capsules and should be considered when fast release and quick biological response is desired. Release delay, however, may not manifest itself in vivo and the time to maximum plasma concentration may not be significant.

KEYWORDS Hard gelatin capsules, Hypromellose capsules, HPMC capsules, Real-time spectroscopy, Dissolution, Dosage forms

INTRODUCTION

Nowadays there is a growing interest in novel processing technologies and analytical techniques, such as real-time spectroscopy, to ensure the safety and efficacy of drug products. The food and drug administration (FDA) assembled a subcommittee in 2001 to look into establishing guidelines for the use of quality testing methods. These methods comprise the process analytical technologies (PATs), which were designed to improve efficiencies in both manufacturing and regulatory processes through an integrated approach to quality control. The PAT initiative hinges on four

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main components: data analysis, process analytical tools, process monitoring, and continuous feedback (Willis, 2004).

Dissolution testing serves as a measure of quality control. Traditional dissolution testing involves the removal of several aliquots of dissolution medium, at specified time intervals, followed by sample analysis. The four basic means of sampling from a dissolution vessel are manual sampling, sipping to a flow cell, and semiautomatic and full automatic collection into high-performance liquid chromatography vials. The main disadvantage of these techniques is the limited number of data points that can be generated, which may result in a less than ideal representation of the dissolution profile. Another drawback is the possibility of a sampling error caused by filtration, drug adsorption, or volume correction.

Ultraviolet (UV) spectroscopy, which employs the measurement and quantitation of ultraviolet absorption by an analyte, is a proven technique. The use of UV fiber-optic probes immersed in the dissolution medium allows real-time analysis without transfering the samples outside the vessels for testing. Monitoring dissolution test by real-time spectroscopy eliminates many of the limitations encountered by the traditional sampling techniques. In addition to an increase in accuracy and precision, a major advantage of the real-time in situ approach is the frequency of sample analysis and subsequently, the greater "data density" available for analysis

A promising application of the real-time analysis of dissolution media is the characterization of lipid-based drug delivery systems. Recently, a turbidimetric method was developed to study the release and emulsification of Coenzyme Q_{10} lipid formulations (Nazzal et al., 2002). Unlike the turbidimetric technique, which relies on flow-through assembly, a fiber-optic dip-probe directly immersed in the dissolution medium could provide accurate and precise measurement of phenomena, such as the capsule rupture time, which is problematic and seldom discussed in official pharmacopoeia. To demonstrate this utility, a real-time spectrometer with a fiber-optic probe was used in this study to measure the rupture time of capsule shells. Rupture time was defined in this study as the time elapsed from the moment the capsule is released into the dissolution medium to the moment of first rupture. First rupture is the point when a hole of significant size is formed in the shell that allows water to flow into the capsule and enables the release of the fill material into the dissolution medium. Therefore, labrasol, a liquid fill material, was used as a marker of the rupture process. Labrasol has a fast self-emulsification rate and yields a background scatter that could be detected at very low concentrations ($<$0.1 mg%) within a broad wavelength range. This procedure is expected to yield more precise results than the reported approach described by Chiwele (2000) which relies on the sound generated by a steel ball falling from the ruptured capsule shell. The objective of this study was, therefore, to demonstrate the utility of real-time spectroscopy in predicting the rupture time of hard gelatin and hypromellose (HPMC) capsules in simulated gastric and intestinal dissolution media.

The two-piece hard shell capsule was first patented by Lehuby in 1846 (Jones, 1987). Since then, gelatin has been the primary material used in the manufacture of hard shell capsules. It is readily soluble in biological fluids at body temperature and is a good film forming material. However, some properties of gelatin films are disadvantageous. For instance, gelatin shells could become brittle if stored at low relative humidities or when filled with hygroscopic materials (Nazzal & Wang, 2001). Interaction between gelatin proteins and aldehyde groups in the fill material can reduce the solubility of the capsule shells due to the cross-linking of the gelatin (Carstensen & Rhodes, 1993; Digenes et al., 1994). It is sometimes desirable to use alternative materials in the manufacture of the hard shell capsules. Several materials have been tested to partially or fully replace gelatin as the shell forming material. Among the alternatives, hypromellose (HPMC) was shown to fulfil all the requirements for a two-piece hard shell capsules in terms of manufacturability and filling properties (Chiwele et al., 2000). Capsules made with hypromellose as the film forming agent may contain carrageenan and potassium chloride in small quantities to lower the thermal gelation temperature of hypromellose and to enhance gelation (Matsuura & Yamamoto, 1993; Harwood & Johnson, 1994).

MATERIALS AND METHODS

Materials

Hard gelatin capsules, and pharmaceutical and nutritional grade hypromellose (hydroxypropyl methylcellulose or HPMC) capsules (Quali-V®) were provided, as a generous gift, by Qualicaps, Inc. (NC). Caprylocaproyl macrogolglycerides (Labrasol) was obtained from Gattefossé (Saint-Priest Cedex, France). Water, which was used to prepare the dissolution media, was freshly prepared by a combination of demineralization and reverse osmosis using a NANOpure system (Barnstead, Dubuque, IA). Potassium phosphate, sodium hydroxide, sodium chloride, and hydrochloric acid were purchased from Spectrum Quality Products, Inc. (NJ). Simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2), without pancreatin, were prepared according to the USP28 – NF23.

Capsule Preparation

Gelatin and hypromellose capsules were evaluated in this study. Four sizes–00, 0, 1, and 3–and two hypromellose grades–pharmaceutical and nutritional–were used. With the aid of a syringe, capsules of different grades and sizes were manually filled with labrasol. Special care was taken to ensure no external contamination with the fill material. The weight of the fill material was unified between the capsules of equal size. Weight differences between the smaller and larger capsules had no effect on study outcome. To further eliminate the effect of the fill material (if any) on the dissolution of capsule shells, capsules were freshly prepared (less than 2 min) before the start of the experiments. At the beginning of each experiment, a capsule was placed in a coiled stainless steel sinker and released into the dissolution vessel. The release of capsules into the medium was synchronized with the spectroscopic data-acquisition as outlined in the following section.

Real-time Dissolution Study

The rupture-time of hard gelatin and hypromellose capsules was determined in a USP Type II dissolution apparatus (VK 7000, Varian Inc., Cary, NC), set at a rotating paddle speed of 50 rpm and a bath temperature of 37°C ± 0.5, in 500 mL of either simulated gastric fluid (pH 1.2) or phosphate buffer (pH 7.2) as the simulated intestinal fluid. Absorbance of the transmitted light before and after the release of labrasol into the dissolution medium was measured in real-time mode between 300 and 700 nm at a rate of five scans per min for 25 min using a Cary 50 spectrophotometer (Varian Inc, Cary, NC). The Cary fiber-optic dip-probe unit is a dual beam, ratio recording, rapid scanning high-performance ultraviolet-visible spectrophotometer. The unit uses reflective dielectrically coated optical components. Spectral analysis was facilitated by the use of a dip-type probe submerged in dissolution medium parallel to the rotating shaft and connected via fiber-optic probe to the spectrometer. Fiber-optic cables carry monochromatic light signals generated by the UV-probe, in the test media, to the spectrophotometer. Vessel covers were fitted snugly enough to eliminate any evaporation or contamination.

RESULTS AND DISCUSSION

Rupture-time of hard capsules is an important parameter to consider when developing a pharmaceutical product. It is often not possible to separate the release time of the fill formulation from the rupture-time of the capsule shell. The latter depends on the shell rupture and dissolution properties, but is strongly overlaid by the properties of the fill material (Jones, 1972). For example, Nazzal (2002) demonstrated that an increase in chremophor EL concentration in the fill material of a hypromellose capsule delayed the release of the formulation into the dissolution medium. Lipid release was measured using a flow-through turbidimetric method. Delayed release was attributed to the formation of a viscous gel at the lipid–water interface, which was more prominent at higher surfactant concentrations. This was deemed independent of the rupture time of the capsule shell. In the present study, a modified method was sought, which could precisely determine the rupture-time of hard shell capsules. A real-time dip-type fiber-optic system was used to measure the increase in absorbance associated with the labrasol released from the capsules. Ultrafast measurements were possible by using a high-speed electronically synchronized phase stepped monochromator with a maximum scan rate of 24,000 nm/min. The authors believe that this test method, which is capable of differentiating the rupture-time of capsules of different materials under different testing conditions, could be adopted as a standard approach to study the dispersion and emulsification of lipid formulations from their perspective dosage forms.

Figs. 1a and b, are representative 3D and 2D plots, respectively, showing the release and dispersion of labrasol from a ruptured nutritional hypromellose capsule size (3) in simulated gastric fluid at pH 1.2. These plots were generated using the SigmaPlot software (version 8, Systat Software Inc. Richmond, CA). Rupture time was determined by a change in spectral absorbance caused by the emulsification of the marker (labrasol) into the dissolution medium, which is clarified by the 2D contour plot (Fig. 1b) depicting the progression of the rupture process.

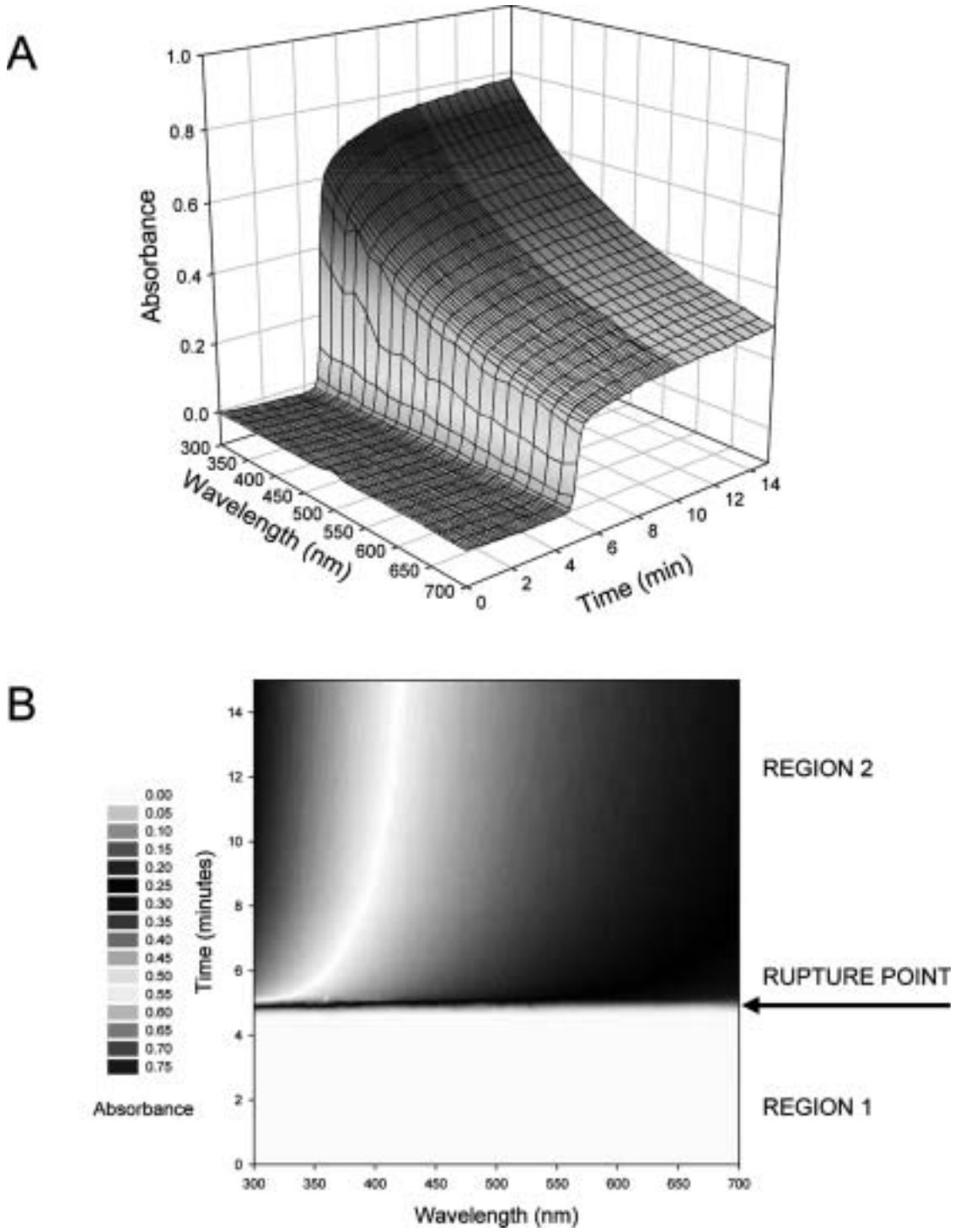

FIGURE 1 **A Representative 3D Surface Plot (a) and a 2D Contour Plot (b) Showing The Release and Dispersion Of Labrasol From a Ruptured Hard Shell Capsule.**

This figure shows two distinctive regions; "region 1", which represents the time before the appearance of the marker, and "region 2", which represents the increase in absorbance intensity as the labrasol is released from the tiny holes in the capsules. The horizontal line at the interface between the two regions represents the rupture time of capsule shells.

Design Validation

To verify the validity of the real-time spectroscopic method, the rupture times of hard gelatin capsules were measured in simulated gastric fluid (pH 1.2) and in phosphate buffer (pH 7.2). Results were compared with the reported data in the literature. Rupture times of the hard gelatin capsules are shown in Figs. 2 and 3. Rupture time ranged between 1.1 and 1.5 min in simulated gastric fluid and between 1.3 and 2.1 min in simulated intestinal fluid. The increase in rupture time observed in phosphate buffer was in agreement with the reported data (Hüttenrauch, 1971; Elliott, 1972). ANOVA, analysis of variance, was performed to determine the significance of capsule size and the pH of the dissolution medium on rupture time at a standard probability value (p-value) of 0.05 (JMP IN software, SAS Institute Inc. Cary, NC). The results of the

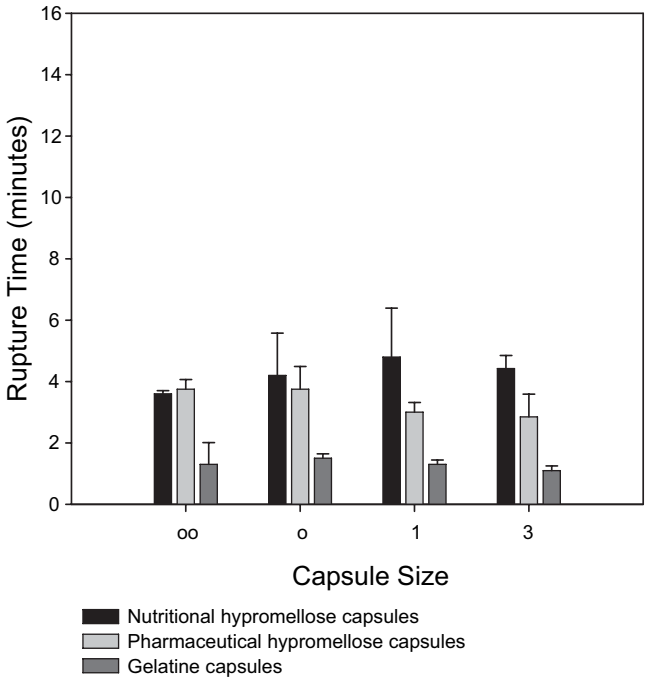

FIGURE 2 **Shell Rupture Time in Simulated Gastric Fluid (pH 1.2).**

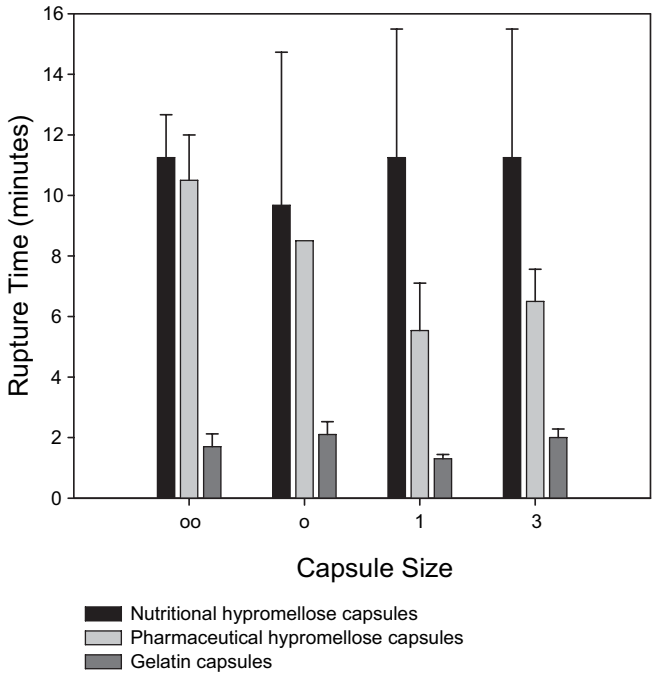

FIGURE 3 **Shell Rupture Time in Simulated Intestinal Fluid (pH 7.2).**

TABLE 1 **ANOVA Test for Gelatin Capsules**

Source	Degrees of freedom	Sum of squares	F Ratio	p-Value
DM*	1	0.903	7.078	0.029
Capsule size	3	0.508	1.327	0.332
DM × capsule size	3	0.428	1.118	0.398

*DM: Dissolution medium (simulated gastric fluid and simulated intestinal fluid).

ANOVA analysis showing the main effects and the interaction effects are given in Table 1. As seen from the table, the interaction terms were insignificant and there was no significant difference between the different capsules sizes in either simulated gastric fluid (p-value 0.5581) or simulated intestinal fluid (p-value 0.2497). pH of the dissolution medium, however, had a significant effect ($p < 0.05$) on the rupture time of hard gelatin capsules. It was reported that melting and dissolution properties of gelatin could be altered by pH depending on the origin of the gelatin (Jones, 1987). Ionic strength of the dissolution medium could also contribute to the extended disintegration of the capsules given the presence of ionic (side groups) functionalities in gelatin. An increase in the ionic strength of the dissolution medium was reported to considerably prolong

the disintegration time of lactose-filled hard gelatin capsules (Hüttenrauch, 1971).

Rupture Time of Hypromellose Capsules

The relationships between hypromellose capsule size–both pharmaceutical and nutritional grades–and rupture time in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) are shown in Figs. 2 and 3, respectively. Analysis of variance (ANOVA) was used to test the effect of capsule grade, capsule size, and dissolution medium on rupture time. The results of the ANOVA are given in Table 2. The interaction terms between the dissolution medium (DM), capsule size, and capsule grade were insignificant ($p > 0.05$). Therefore, only main effects were evaluated in the subsequent discussion.

Capsule Size

Rupture time of the nutritional capsule-grade ranged from 3.6 to 4.8 min in SGF and from 9.67 to 11.25 min in SIF. Rupture time of the pharmaceutical grade ranged from 2.85 to 3.75 min in SGF and from 6.15 to 10.5 min in SIF. The relationship between the mean rupture time of the hypromellose capsules, as calculated by the least square technique, and rupture time is depicted in Fig. 3a. ANOVA results listed in Table 2 indicate that the size of the hypromellose capsules, regardless of grade and dissolution medium, has insignificant effect on rupture time ($p < 0.05$), i.e., there is no significant difference between different capsule sizes.

TABLE 2 **ANOVA Test for Hypromellose (HPMC) Capsules**

Source	Degrees of freedom	Sum of squares	F Ratio	*p*-Value
DM*	1	249.705	57.7936	<.0001
Grade	1	29.819	6.901	0.017
Size	3	5.347	0.413	0.746
DM × grade	1	8.191	1.896	0.185
DM × size	3	7.142	0.551	0.654
Grade × size	3	15.482	1.194	0.339

*DM: Dissolution medium (simulated gastric fluid and simulated intestinal fluid).

Dissolution Medium

Simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2) were used as the dissolution media in this study. The relationship between the dissolution medium and mean rupture time is shown in Fig. 3b. As given in Table 2, dissolution medium has a statistically significant effect on the rupture time of hypromellose capsules ($p < 0.001$). Rupture time increased in the simulated intestinal fluid (pH 7.2). The pH of the dissolution medium, however, is not expected to have an effect on the dissolution of the nonionic hypromellose polymer. The pH of the test media was reported to have a minimal effect on the dissolution of acetaminophen from hypromellose capsules (Tochio, et al., 2002). Instead, differences in salt concentration, ionic strength, and activity coefficient between the two dissolution media are the critical factors that contribute to the delay in rupture time and disintegration of hypromellose capsules. To clarify this argument, ionic strength and activity coefficient of the two dissolution media were calculated using the following equations:

$$\textit{Ionic strength}: I = \frac{1}{2}\sum m_i Z_i^2$$

$$\textit{Activity coefficient}: \log f = -0.509 Z_+ Z_- \sqrt{I}$$

[m_i is the molarity of the ion with a charge Z_i, f is the mean activity coefficient, Z_+ is the charge on the cation, Z_- is the charge on an anion, and I is ionic strength].

Ionic strength and mean activity coefficient of the SIF were 0.305 and 0.143, respectively. Ionic strength and mean activity coefficient for the SGF were 0.106 and 0.681, respectively. It is evident that rupture time increased with an increase in ionic strength. This is attributed to the salting out of the HPMC polymer by the inorganic ions, particularly the phosphate ions, present in the dissolution medium. Increase in ionic strength forces the polymer chains to loose water of hydration, which is caused by the competing ions for the available water molecules. The effect of ionic strength on hypromellose is in agreement with the reported data (Alderman, 1984; Mitchell et al., 1990; Kavanagh and Corrigan, 2004). The concentration of potassium ions is also an important contributor of increased disintegration time. It is well documented that potassium ions

reduce the solubility of carrageenan (Bonferoni, et al., 2000). This factor is critical because carrageenan is used in the manufacture of some grades of HPMC capsules. The effect of potassium ions on the dissolution of hypromellose capsules was reported by Tochio (Tochio, et al, 2002), who also concluded that the dissolution profile from HPMC capsules does not change in a medium containing low concentrations (<12.5 mM) of potassium ions.

Capsule Grade

The grade of the hypromellose capsules had a significant effect ($p < 0.05$) on rupture time (Table 2). Nutritional grade had a higher mean rupture time that the pharmaceutical grade. This effect is depicted in Fig. 4c. The difference in rupture time could be attributed to the additives required to manufacture each grade of capsules, the grade/molecular weight of hypromellose used, and/or the process involved in their manufacture. This information, however, is proprietary and was not available to the authors.

CONCLUSION

Real-time dissolution spectroscopy is an efficient technique to measure rupture time and to monitor the release of fill formulations from capsules. The size of the gelatin and hypromellose (HPMC) capsules had insignificant effect on rupture time. Rupture time, however, was significantly lower in the simulated gastric fluid (pH 1.2) than the simulated intestinal fluid (pH 7.2). This effect was not attributed to pH, as hypromellose is a nonionic polymer. Higher salt concentration in the SIF, particularly potassium ions, and subsequently, higher ionic strength, is believed to be the primary factor contributing to the delayed rupture of the capsules. The grade of the hypromellose capsules was also found to have a significant effect on rupture time. This might be due to the type of additives or grade and/or molecular weight of hypromellose used to prepare the capsules. In practical aspect, special attention should be given to the composition of the dissolution medium when using hypromellose capsules as the desired dosage form. While hypromellose capsules have many advantages over the conventional gelatin capsules, special consideration should be given to rupture time, particularly when a fast biological response is desired. It is important to emphasize, however, that delayed disintegration of hypromellose capsules may not manifest itself in vivo and the time to maximum plasma concentration may not be significant.

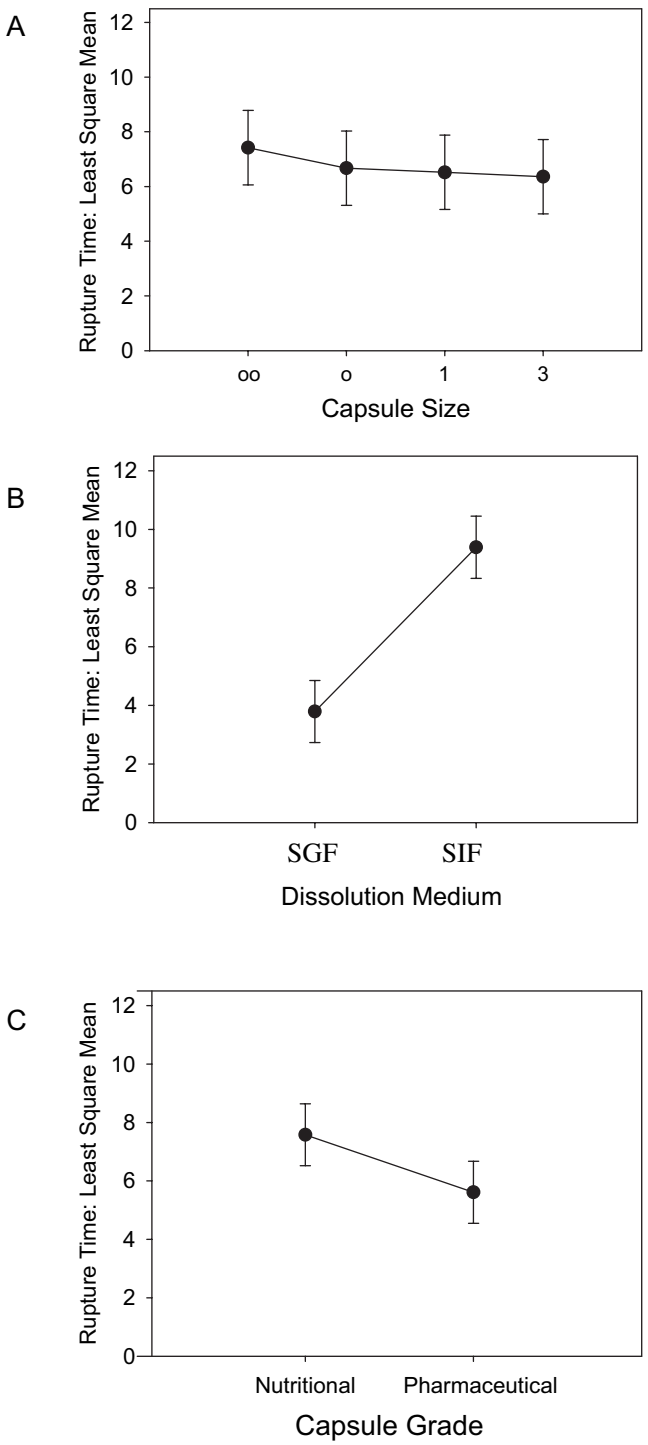

FIGURE 4 **The Relationship Between the Mean Rupture Time of Hypromellose (HPMC) Capsules and Capsule Size (a), Dissolution Medium (b), And Capsule Grade (c).**

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