

***In Vitro* and *in Vivo* Pharmacoscintigraphic Evaluation of Ibuprofen Hypromellose and Gelatin Capsules**

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Purpose. To evaluate the *in vitro* and *in vivo* characteristics of hypromellose (HPMC) capsules prepared using a gellan gum and potassium gelling system compared to conventional hard gelatin capsules.

Methods. The *in vitro* dissolution of ibuprofen gelatin and HPMC capsules was determined using the USP and TRIS buffers at pH 7.2. The effect of pH and composition of the media was determined using a model drug that is soluble throughout the pH range 1.2 to 7.2. In an 11 subject four-way crossover study, the gastrointestinal performance of ibuprofen gelatin and HPMC capsule formulations was evaluated using scintigraphy and pharmacokinetics following fasted and fed dosing.

Results. Acid conditions and the presence of K⁺ cations hinder HPMC capsule opening, whereas in water, dissolution is identical to that of gelatin. These effects are related to the nature of the gel network that is formed in the presence of cations. No significant difference in esophageal transit was observed. Although the *in vivo* opening times of HPMC capsules were longer than for their gelatin counterparts, no significant difference in the regulatory important pharmacokinetic metrics of C_{max} and AUC was found between ibuprofen, gelatin and HPMC capsules.

Conclusions. The *in vitro* performance of HPMC capsules differ from gelatin, which will require modification to dissolution testing methodology for certain drugs. However, for the class II BCS drug ibuprofen, the two capsule types were not statistically different when comparing AUC and C_{max} values, which suggests that the *in vitro* differences have reduced *in vivo* relevance.

KEY WORDS: capsules; dissolution; gelatin; hypromellose; pharmacoscintigraphy.

INTRODUCTION

For many years, gelatin was the material most commonly used to manufacture capsules. An injection molding system using starch (1) never gained wide acceptance due to the need for different capsule filling equipment. However, companies recently have successfully manufactured capsules from hypromellose (HPMC), which has provided consumers with a choice between gelatin and alternative polymers (2–4). HPMC is produced from plant-derived material and today is used when dietary concerns or religious beliefs require an alternative to gelatin or when the technical characteristics of

gelatin present a challenge to the drug formulation. It has an inherently lower equilibrium moisture content than gelatin, and the role of water as a plasticizer is less important. It also does not contain reactive groups that can potentially interact with fill materials, especially under hot and humid conditions. An early attempt to produce capsules with HPMC made use of its thermo-gelling properties by dipping heated pins into an aqueous solution of HPMC to induce gelling (5,6). Although a capsule was commercially produced, many technical difficulties were associated with this technique leading to a search for an improved process.

Gelatin is a self-gelling agent, and when a solution above a minimum critical concentration is cooled below 40°C, a three-dimensional gel network is formed. This allows gelatin capsules to be produced by dipping pins at ambient temperature into a gelatin solution. By the addition of a gelling agent to a solution of HPMC, it is possible to produce an equivalent gel network and thereby allow capsules to be formed using the conventional process. Many gelling agents have been considered, such as agar, pectin, and curdlan, but experience has shown that the two most suitable materials are carrageenan and gellan gum (7,8).

Gellan gum is a microbial polysaccharide produced by the organism *Sphingomonas elodea* in a fermentation process. It has a linear tetrasaccharide repeating sequence with one carboxyl group per repeat unit. Carrageenans are algal (seaweed) polysaccharides consisting of high-molecular-weight linear sulfated galactan chains. In solution at the dipping stage, both gelling agents exist as disordered coils. On cooling, the chains associate by the formation of double helices. Gelation occurs by subsequent aggregation of these helices to form a continuous, three-dimensional network. Because both polysaccharides are negatively charged, gelation is promoted by cations that suppress the electrostatic repulsion between the helices and allow aggregation to occur. Divalent metal ions are particularly effective in inducing gelation of gellan (9) and carrageenan (10,11), but large group I cations, such as K⁺, also give strong gels at moderate salt concentrations (9,12–16).

It has been reported that the presence of potassium cations in the dissolution media influence the release of drug (4,17) from HPMC capsules, but little attention has been paid to a systematic evaluation of capsule composition on *in vitro* or *in vivo* product behavior. In this paper, we report on the *in vitro* and *in vivo* pharmacoscintigraphic properties of HPMC capsules that contain gellan gum as a gelling agent, compared to conventional hard gelatin capsules. Comparisons will also be drawn, using data from the literature, with HPMC capsules that contain carrageenan as the gelling agent.

MATERIALS AND METHODS

Materials

Conventional gelatin capsules size 1, natural transparent, were used in the study and compared with size 1 capsules made from HPMC, in which the gelling system was gellan gum and potassium acetate. Data comparing the physical characteristics of gelatin and HPMC capsules, such as permeability and moisture content and its influence on capsule properties, have been reported (2,3). Machines for filling cap-

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sules are designed for the commonly used gelatin product. For a new capsule to find industrial acceptance, its form should be as close as possible to the existing product. As is the case for gelatin capsules, the HPMC capsules were produced by a dip molding process.

Drug Selection and Radiolabeling Strategy

Over 50% of new drugs in development are either class II or IV in terms of the Biopharmaceutics Classification System and therefore possess low aqueous solubility. As a consequence, there is more insoluble drugs to be delivered by capsules during early clinical evaluation in the near future. Ibuprofen is a typical class II drug that is routinely used in pain relief medication and has a requirement for fast onset (18). Previous studies have shown that the drug is rapidly absorbed from the small intestine producing peak serum levels in 1 to 2 h with an elimination half-life of about 2 h. A 200 mg dose of drug was formulated to provide rapid release from gelatin capsules in pH 7.2 phosphate buffer with traditional fill excipients [61 mg microcrystalline cellulose (Avicel PH 101) and 2 mg magnesium stearate]. The capsule formulations were radiolabeled for scintigraphic evaluation using conventional labeling strategies involving the previously validated approach of blending ^{111}In -labeled Amberlite IPP-69 resin capsule contents prior to filling (19).

After oral administration, the capsule is first exposed to the acidic environment of the stomach, and any interaction with the gelling system can potentially affect drug release. However, as a weak acid, ibuprofen is insoluble at acidic pH and therefore is not a good marker of *in vitro* capsule properties. Therefore, to assess *in vitro* release of the capsules over the whole range of pH values, acetaminophen (280 mg) was filled into comparable capsules.

In vitro Dissolution

In vitro release characteristics of ibuprofen were assessed using the USP Apparatus II at 50 rpm, in 900 ml of 37°C potassium phosphate buffer pH 7.2. Apparatus II was selected to facilitate visual observation of the capsule during dissolution. Due to the potential interaction of potassium cations with gellan gum, dissolution tests were also carried out in Tris (hydroxymethyl) aminomethane (TRIS) buffer at pH 7.2. *In vitro* release characteristics of acetaminophen were also assessed using the USP Apparatus II at 50 rpm in 900 ml of 37°C water, 0.1 N HCl, pH 1.2, sodium acetate buffer USP, pH 4.5, potassium phosphate buffer USP, pH 7.2, sodium phosphate buffer, pH 7.2, and TRIS buffer, pH 7.2.

Study Design

The objective of the clinical study was to both compare the *in vivo* disintegration properties of the capsules with and without the presence of food and to correlate these intestinal events with simultaneously collected pharmacokinetic data. Therefore, a four-way randomized crossover study was undertaken to evaluate the intestinal performance of ibuprofen gelatin and HPMC capsule formulations using a combination of scintigraphy and pharmacokinetics (pharmacoscintigraphy) in a group of 11 healthy male and nonpregnant female subjects following fasted and fed dosing. The clinical protocol was approved by an independent ethics committee, and dos-

ing of radiolabeled product was approved by the ARSAC division of the UK Department of Health. Each subject provided written informed comment, and there was a minimum washout of 2 days between each administration.

Imaging Requirements

Prior to dosing, two anterior anatomical markers containing 0.05 MBq ^{111}In were taped to the skin in the same transverse plane as the cardiac sphincter and pylorus, respectively. Subjects were asked to sit in front of the gamma camera prior to dosing, to provide an anterior view extending from the buccal cavity to the upper margin of the stomach. In order that images could be acquired immediately after dosing, the preparations were administered with the volunteers correctly positioned in front of the camera.

In the fasted state, the ^{111}In -labeled (1MBq) capsules were dosed with 240 ml of water labeled with 4MBq of $^{99\text{m}}\text{Tc}$ diethylenetriaminepentaacetic-acid (DTPA) to identify the key anatomical landmarks of the intestine. For the fed dosing, a standardized high fat meal (1300 Kcal) was radiolabeled using a previously validated approach involving scrambled eggs radiolabeled with 4MBq $^{99\text{m}}\text{Tc}$ sulfur colloid (20). Labeling of the solid phase of the meal had the advantage of allowing the relationship between gastric emptying of the capsule contents and the meal to be examined.

Anterior scintigraphic images were recorded using a gamma camera (General Electric Maxicamera, Milwaukee, WI) fitted with a medium energy parallel hole collimator. Esophageal transit of the capsule was recorded, while the subject was seated, as a dynamic study of 360 sequential images, each 0.5 s in duration (i.e., 180 s of dynamic imaging). Thereafter, anterior static images (each 50 s in duration) were taken continuously for a maximum of 45 min post-dose with the subject standing in front of the camera, and then every 15 minutes until 4 hours post-dose. Subsequently, images were collected at 6, 8, and 12 h post-dose. If the dosage form failed to disintegrate within 45 min, images were obtained as frequently as possible until disintegration was observed. The subjects remained moderately active during the study period.

Blood Sampling

Venous blood samples (6.5 ml) were withdrawn via cannula or by venepuncture according to the following time schedule: 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h post-dose. The samples were centrifuged at approximately 1600g for approximately 10 min at approximately 4°C. The resulting plasma fraction was frozen in labeled polypropylene tubes at approximately -20°C until the end of each study period and then at approximately -80°C until required for assay.

Scintigraphic Data Analysis

The scintigraphic data from the study were analyzed to obtain the following parameters:

- a) esophageal transit time of the capsule;
- b) anatomical location and time of initial capsule disintegration.
- c) anatomical location and time of complete capsule disintegration.

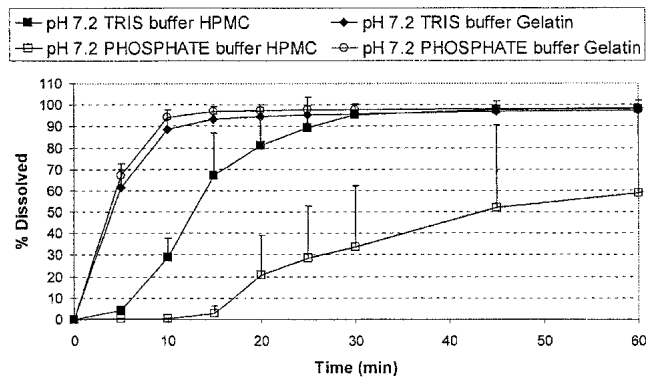


Fig. 1. Dissolution of ibuprofen from gelatin and HPMC capsules in potassium phosphate and TRIS buffers at pH 7.2. Bars represent std.dev. (n = 6).

d) gastric emptying time of capsule contents (initial and complete);

e) gastric emptying time of labeled food or drink (initial and complete).

Bioanalytical, Pharmacokinetic, and Statistical Analysis

Plasma samples were analyzed for ibuprofen using a previously validated HPLC/UV assay with an LOQ of 0.1 ng/ml. Pharmacokinetic analysis of the ibuprofen plasma concentration-time data obtained was performed using appropriate noncompartmental techniques to obtain estimates of the following pharmacokinetic parameters:

- maximum plasma concentration (C_{max});
- time to reach C_{max} (t_{max});

c) time of first quantifiable sample (t_{lag});

d) area under the concentration-time curve from dosing to infinity ($AUC_{0-\infty}$).

The plasma concentration data were reviewed in order to determine the highest concentration achieved (C_{max}) and the time of its first occurrence post-dose (t_{max}).

Log transformation of the key pharmacokinetic data was undertaken prior to statistical analysis using SAS v8.1. Each parameter was then subject to an analysis of variance with subject, treatment, and period as factors. Statistical differences were examined and significance at the 5% level reported.

RESULTS

In vitro Dissolution

In vitro release profiles of ibuprofen from gelatin and HPMC capsules in phosphate and TRIS buffers pH 7.2 are shown in Fig. 1. In both buffer solutions, as expected, the dissolution of ibuprofen from gelatin capsules was both rapid and complete. For HPMC capsules in the standard USP potassium phosphate buffer, a lag time of 15 min was observed before significant drug was released. Release was also variable and incomplete even after 60 min. When TRIS buffer was used, ibuprofen release occurred much more quickly and was almost complete after 30 min, even under the relatively gentle stirring conditions of 50 rpm.

In vitro release of acetaminophen from gelatin and HPMC capsules in the various media studied are shown in Table I. The dissolution of acetaminophen from gelatin capsules, like that of ibuprofen, was rapid and complete. Release of acetaminophen from HPMC capsules in water and TRIS

Table I. Dissolution of Acetaminophen from Gelatin and HPMC Capsules (Mean and Range, n = 6)

Dissolution media	Time (min)	Percentage acetaminophen in solution	
		Gelatin	HPMC
Distilled water	15	39 (34-46)	41 (29-47)
	30	85 (73-93)	90 (86-97)
	45	99 (98-100)	99 (98-100)
pH 1.2	15	40 (37-47)	2 (1-3)
	30	87 (75-94)	6 (4-13)
	45	99 (98-100)	12 (8-21)
	60	—	19 (13-26)
Sodium acetate buffer USP pH 4.5	15	39 (32-48)	16 (9-26)
	30	89 (77-98)	56 (40-80)
	45	99 (95-101)	83 (68-98)
	60	—	99 (95-101)
Potassium phosphate buffer USP pH 7.2	15	38 (31-52)	5 (2-8)
	30	87 (70-98)	32 (16-56)
	45	100 (97-101)	56 (27-91)
	60	—	83 (53-101)
Sodium phosphate buffer pH 7.2	15	43 (38-54)	15 (7-21)
	30	75 (66-92)	46 (29-67)
	45	91 (83-100)	68 (52-90)
	60	98 (94-100)	79 (67-95)
TRIS buffer pH 7.2	15	54 (38-70)	36 (26-45)
	30	89 (72-95)	76 (71-90)
	45	98 (94-99)	95 (91-99)
	60	100 (9-100)	99 (98-100)

HPMC, hypromellose.

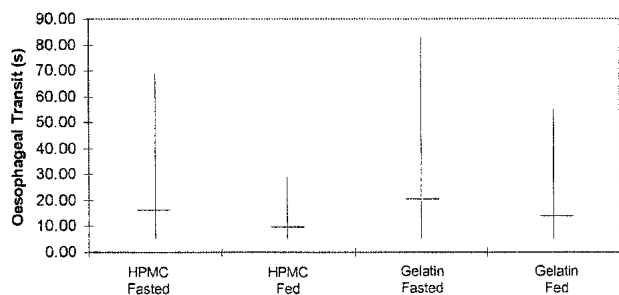


Fig. 2. Esophageal transit data for gelatin and HPMC capsules in healthy volunteers as assessed by gamma scintigraphy [min to max plus mean ($n = 11$)].

buffer pH 7.2 was comparable to that from gelatin capsules. However, in acid conditions, the HPMC capsule remains practically intact with very little drug release. In potassium phosphate buffer, release of acetaminophen was delayed and variable, whereas when the cation present is sodium at pH 4.5 and 7.2, release of acetaminophen is less delayed.

Esophageal Transit

Esophageal transit findings are provided in Fig. 2. Esophageal hold-up is often defined as transit time longer than 20 s (21). However, though there are a very small number of subjects in this study with examples of such hold-up, in no individual was transit ever delayed for longer than 90 s. Eight out of 44 administrations showed periods of esophageal stasis; 3 for HPMC and 5 for gelatin.

Capsule Disintegration and Gastric Emptying

The capsule disintegration data are outlined in Table II, and the gastric emptying properties are summarized in Table III. Initial disintegration of the gelatin capsule following fasted dosing occurred on average at 0.13 ± 0.06 h post-dose (range, 0.03 to 0.22 h), and complete disintegration occurred at 0.24 ± 0.14 h post-dose (range, 0.03 to 0.43). In the fed state, initial disintegration of the same capsule was delayed until 0.39 ± 0.36 h post-dose (range, 0.11 to 1.33 h) and was complete at average at 1.22 ± 0.80 h post-dose (range, 0.11 to 2.10 h).

For the HPMC capsule after an overnight fast, disintegration occurred on average at 0.47 ± 0.17 h post-dose (range, 0.13 to 0.69 h) and was complete at 0.69 ± 0.29 h post-dose (range, 0.25 to 1.18 h). In the post-prandial state, disintegration of the HPMC capsule administered after a high fat breakfast occurred on average at 1.00 ± 0.37 h post-dose (range,

0.48 to 1.73 h) and was complete at 1.61 ± 0.65 h post-dose (range, 1.03 to 3.08 h).

Pharmacokinetic Data

The pertinent pharmacokinetic data for the two preparations dosed in the fasted and fed state are provided in Table IV. The T_{max} values occurred at 2 h post-dose following either capsule in fasted subjects, and thereafter the plasma concentrations declined in a biphasic manner. However, in fed subjects the T_{max} was delayed until 4 h post-dose. After the maximum, the mean plasma concentrations of ibuprofen declined monoexponentially. The C_{max} values of ibuprofen were higher in the fasted state compared to fed dosing following dosing of either capsule. However, there were no statistical differences between the capsule types suggesting that capsule substrate had little or no impact on rate of drug absorption. T_{lag} occurred at either 1 or 1.5 h post-dose in fasted subjects following administration of the HPMC capsule and ranged from 0.25 to 1 h post-dose following administration of its gelatin counterpart. In fed subjects, T_{lag} was much more variable and generally occurred at 3 h post-dose following administration of the HPMC preparation and ranged from 0.5 to 4 h following dosing of gelatin capsule.

The $AUC_{0-\infty}$ values of ibuprofen were higher in fasted subjects than in fed subjects following administration of either preparation. However, there was no statistical difference in the extent of absorption between the respective capsule substrates dosed in the fasted or fed state.

DISCUSSION

In the majority of volunteers, esophageal transit was very rapid (<20 s) with no significant difference between gelatin and HPMC capsules. This contrasts with studies (22,23) carried out with isolated pig esophagus tissue that showed significant differences between gelatin and HPMC capsules. The findings of this human study question the clinical relevance of such isolated tissue tests. As a consequence, the current recommended practice for administration of oral dosage forms such as gelatin products remains valid for HPMC capsules.

To be able to manufacture HPMC capsules using the conventional dipping process, addition of a gelling agent is necessary. Currently, either carrageenan (HPMC_{carr}) or gelatin gum (HPMC_{gellan}) are used in commercially available capsules. As shown in Table I and Fig. 1, the *in vitro* opening time of gelatin capsules is independent of the composition of the dissolution media. In the case of HPMC_{gellan} capsules, the opening time is dependant on both pH and composition of the

Table II. *In vivo* Disintegration of Ibuprofen Gelatin and HPMC Capsules as Assessed via Gamma Scintigraphy (Mean \pm SD; $n = 11$)

Capsule type	Dietary state	Initial disintegration		Complete disintegration	
		Mean \pm SD (h)	Mean (min)	Mean \pm SD (h)	Mean (min)
Gelatin	Fasted	0.13 ± 0.06	8	0.24 ± 0.14	14
HPMC	Fasted	0.47 ± 0.17	28	0.69 ± 0.29	41
Gelatin	Fed	0.39 ± 0.36	23	1.22 ± 0.80	73
HPMC	Fed	1.00 ± 0.37	60	1.61 ± 0.65	97

HPMC, hypromellose.

Table III. Gastric Emptying Properties for Gelatin and HPMC Capsules as Assessed via Gamma Scintigraphy (Mean \pm SD; n = 11)

Capsule type	Dietary state	Initial gastric emptying		Complete gastric emptying	
		Capsule (h)	Water/food (h)	Capsule (h)	Water/food (h)
Gelatin	Fasted	0.28 \pm 0.12	0.10 \pm 0.04	1.69 \pm 0.67	1.74 \pm 0.77
HPMC	Fasted	0.82 \pm 0.27	0.16 \pm 0.08	1.81 \pm 0.87	1.41 \pm 0.71
Gelatin	Fed	2.13 \pm 0.82	1.14 \pm 0.78	6.08 \pm 2.24	6.12 \pm 1.68
HPMC	Fed	2.17 \pm 0.46	1.07 \pm 0.69	4.80 \pm 0.58	5.31 \pm 0.92

HPMC, hypromellose.

dissolution media. If water is used as the dissolution medium, gellan gels dissociate because of diffusion of cations out of the network resulting in rapid film disruption of HPMC_{gellan} capsules and fast drug release. The same will occur for carrageenan (15), and this effect has also been observed for HPMC_{carr} (2,3) capsules. However, in acid conditions, the two gelling agents behave differently. Carrageenan at pH 1.2 behaves in the same way as in water (14), because the sulfate groups, having very low pK_a, retain their negative charge, which disrupts helix-helix aggregates by electrostatic repulsion when the gel-forming cations diffuse into the surrounding acidic solution. This effect has been reported in dissolution studies with HPMC_{carr} capsules (2). The carboxyl groups of gellan gum, however, have a much higher pK_a (~3.4), and therefore convert into the uncharged (-COOH) form at low pH, with consequent elimination of electrostatic repulsion between the helices (9). Gellan gels, therefore, are less soluble at pH 1.2 (16). The capsule, however, comprises acid-soluble HPMC distributed within the matrix of gellan and in reality any agitation, such as exists in the GI tract or during dissolution/disintegration testing, would be expected to aid disintegration of the gel system by erosion, enabling drug to be released from the capsule.

When the dissolution medium contains sufficient gel-forming potassium cations, dissociation of the aggregates is hindered with the result that the gel from gellan and carrageenan retains its structure and the solubility is reduced. When the buffer solution contains sodium cations, disruption of the film is faster than if potassium cations are present. The reason for this difference is thought to be due to the binding efficiency with which ions of different size can fit into potential sites on the helices. Behavior in TRIS buffer, which contains no metal cations, is similar to that in water. The mechanisms involved with the different cations can be explained as follows (24):

- 1) Divalent metal ions promote aggregation by site binding between pairs of carboxyl groups on neighboring helices.
- 2) Monovalent metal ions bind to the surface of individual helices, thus lowering their charge-density and reducing the electrostatic barrier to aggregation.
- 3) Large organic cations, such as tetramethylammonium (9) and the (CH₂OH)₃CNH₃⁺ ions present in TRIS buffer, are incapable of binding to gellan helices and induce gelation only at very high concentrations, by nonspecific screening of electrostatic repulsion between the helices.

In both the *in vivo* fasted and fed state, gelatin capsules disintegrate faster than HPMC_{gellan} capsules. The initial disintegration time of gelatin capsules of 8 min agrees well with previously reported values (25). The lower solubility of the HPMC_{gellan} film observed *in vitro* is reflected in the slower *in vivo* disintegration time (Table II) and the lag time before ibuprofen was first detected (Table IV). The acid conditions of the fasted stomach and interactions with cations present in the breakfast are responsible for this observed effect. However, when the classical pharmacokinetic parameters of C_{max} and AUC are considered, gelatin and HPMC_{gellan} capsules were found not to be statistically different in both the fasted and fed state. This is in agreement with the findings of previous workers (4,22) in which HPMC_{carr} capsules were used and suggests that the type of gelling system used in HPMC capsules would not appear to significantly influence bioavailability as defined by C_{max} and AUC. The slightly delayed lag time following fasted dosing in detection of plasma ibuprofen for HPMC_{gellan} capsules compared to gelatin could influence the bioavailability of class I and III BCS drugs for which gastric emptying can critically influence absorption. However, as 50–60% of NCEs are poorly soluble, (class II and IV), the slower *in vivo* disintegration time of HPMC capsules would not be expected to influence the regulatory important phar-

Table IV. Pharmacokinetic Comparison for Ibuprofen Gelatin and HPMC Capsules (Mean \pm SD; n = 11)

Capsule type	Dietary state	AUC _{0-∞} (μg · h/ml)	C _{max} (μg/ml)	t _{max} (h)	t _{lag} (h)
Gelatin	Fasted	45.6 \pm 11.9*	13.1 \pm 2.8‡	2.0 \pm 1.0	0.6 \pm 0.3
HPMC	Fasted	48.6 \pm 11.5*	15.4 \pm 4.6‡	2.3 \pm 1.0	1.2 \pm 0.2
Gelatin	Fed	40.4 \pm 14.8†	8.1 \pm 3.2§	4.4 \pm 1.6	2.1 \pm 1.0
HPMC	Fed	41.5 \pm 10.3†	10.1 \pm 4.0§	3.7 \pm 0.5	2.8 \pm 0.7

HPMC, hypromellose.

* p = 0.29.

† p = 0.42.

‡ p = 0.36.

§ p = 0.13.

macokinetic metrics. It is also interesting to observe that following fed dosing, the lag time is largely independent of capsule type, presumably due to the delayed gastric emptying observed following post-prandial administration acting to largely normalize the differences observed in capsule disintegration. This observation is extremely important because many hydrophobic and lipophilic class II/IV drugs are dosed in the fed state to improve bioavailability, and in such situations choice of capsule substrate will have even less impact on the pharmacokinetic metric performance based on the findings of this research.

For drugs such as ibuprofen that are soluble at basic pH, it is clear that the specified USP phosphate buffer is not appropriate to monitor the dissolution profile from HPMC capsules with either gelling system, either as a quality control tool or as a development tool in establishing IVIV correlations. The same also holds true for drugs which require acidic dissolution media filled into HPMC_{gellan} capsules.

Gelatin is unique in its properties of being an amphoteric gelling agent that is soluble in both gastric as well as intestinal media. Alternatives to gelatin, however, require the addition of gelling systems such as polysaccharides, which require metal cations to promote the formation of a gel structure. These gels in turn are also sensitive to the presence of metal cations or acids that are often present in dissolution media. This study illustrates that future work will need to be devoted to developing new bio-relevant dissolution media for non gelatin capsules.

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