capsules

How polymer science is changing the functional role of capsules

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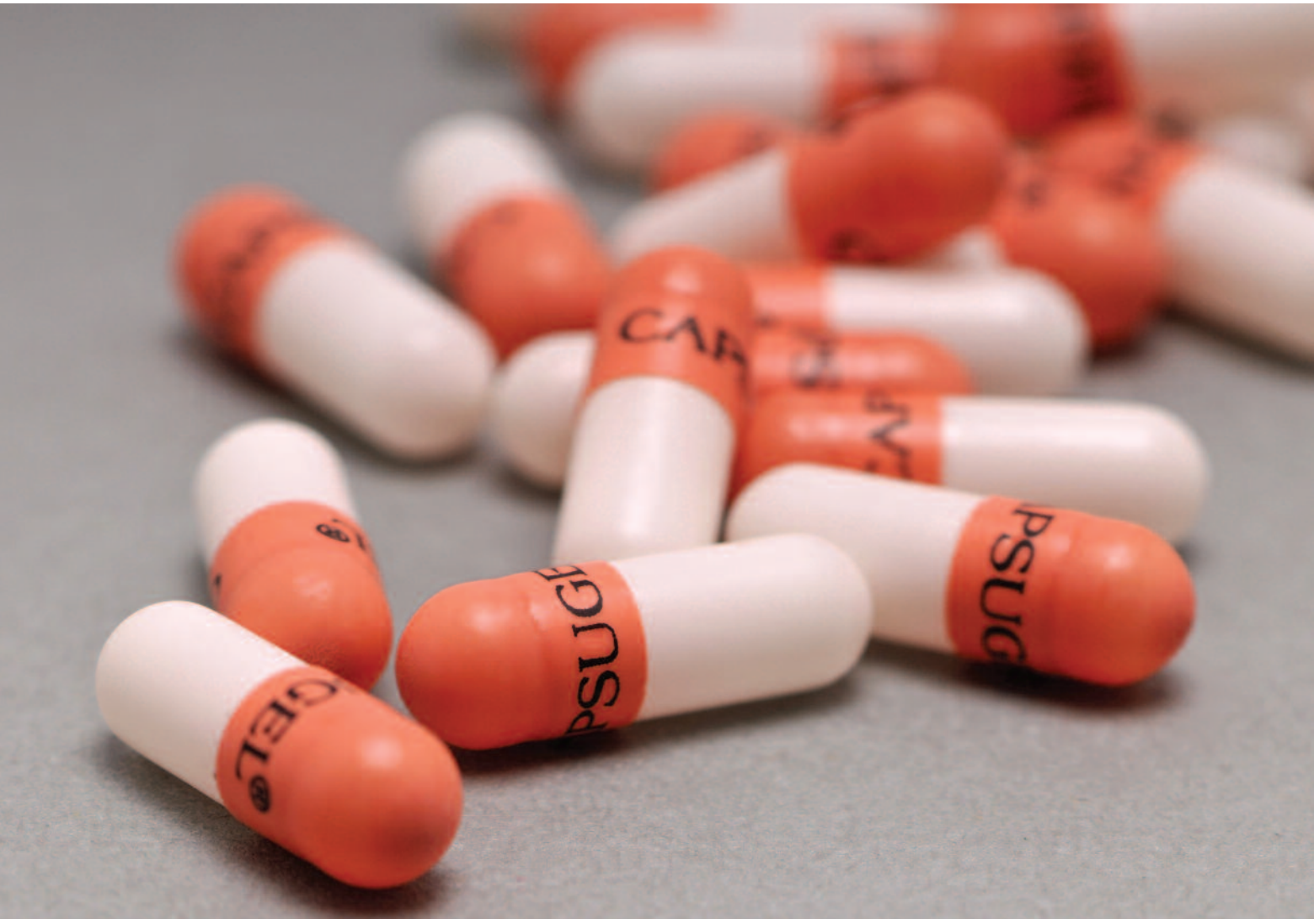
Capsugel



New developments in polymer science and engineering are broadening the role that capsules play in drug delivery, formulation science, and medical research. Today's array of capsules enables formulators to offer safer, more effective treatments for patients and consumers.

Never have so many drug delivery systems based on hard capsules been available to pharmaceutical manufacturers and physicians. Today, they can choose from a variety of options to achieve immediate, delayed, controlled, site-specific, or colon-targeted release. These technologies enable capsule-based formulations to improve bioavailability, meet the clinical needs for specific plasma time-course profiles, avoid site-specific degradation in the GI tract, and improve the efficacy of drug products. In these areas and others—particularly

pulmonary delivery—two-piece (hard) capsules are playing a leading role. This article summarizes important developments in hard capsules over the last 10 years, including the most recent innovation: A non-gelatin capsule that offers enteric protection and delayed release without using a functional coating.

Controlled- and targeted-release formulations

Targeting the upper small intestine for release can lead to high local API levels and rapid absorption, while targeting the colon can help treat irritable bowel syndrome, ulcerative colitis, and other disease states. Depending on whether delayed release or site-specific targeting is required, there are three main approaches: timed release, pH-controlled release, and enzymatic release.

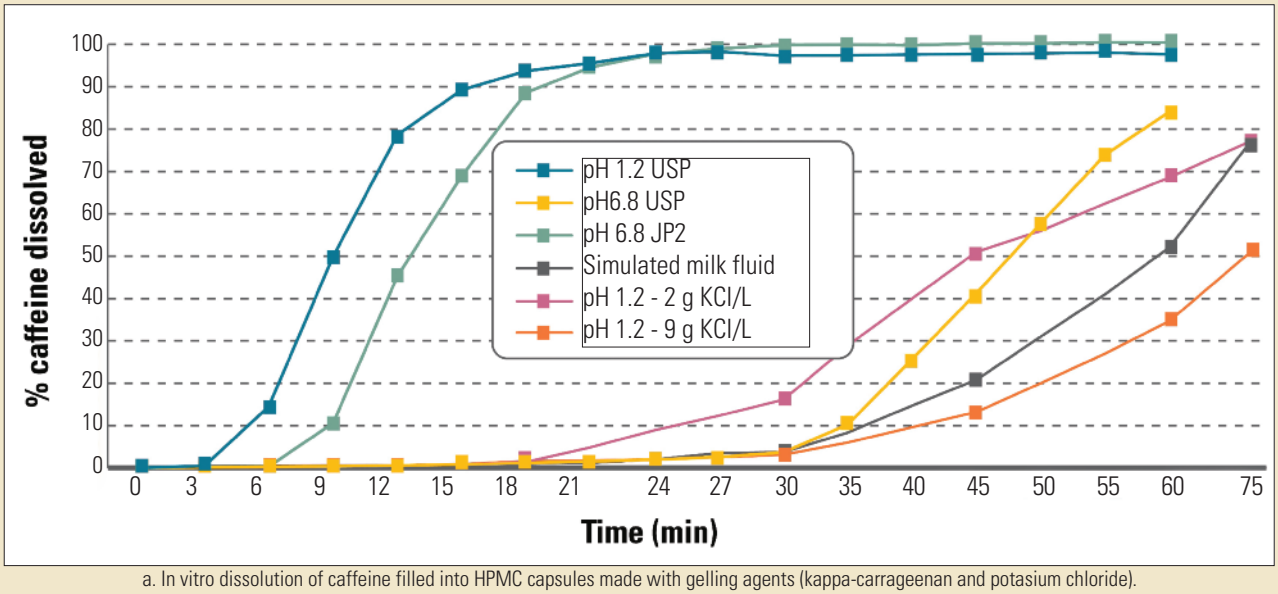
Timed release formulations use functional coatings that erode slowly, independent of pH, or they include a matrix that releases the active as the matrix erodes or when erosion is complete. With pH-controlled release, formulators take advantage of the increase in pH going from the stomach to the small intestine and use an enteric polymer coating with an appropriate profile. The coating renders the dosage form insoluble at the lower pH of the stomach to upper small intestine, yet soluble at the higher pH of the distal small intestine. Enzymatic release uses starch-based coatings that resist digestion in the stomach and small intestine, but are degraded by microbial enzymes when the dosage form reaches the colon.

Early HPMC capsules

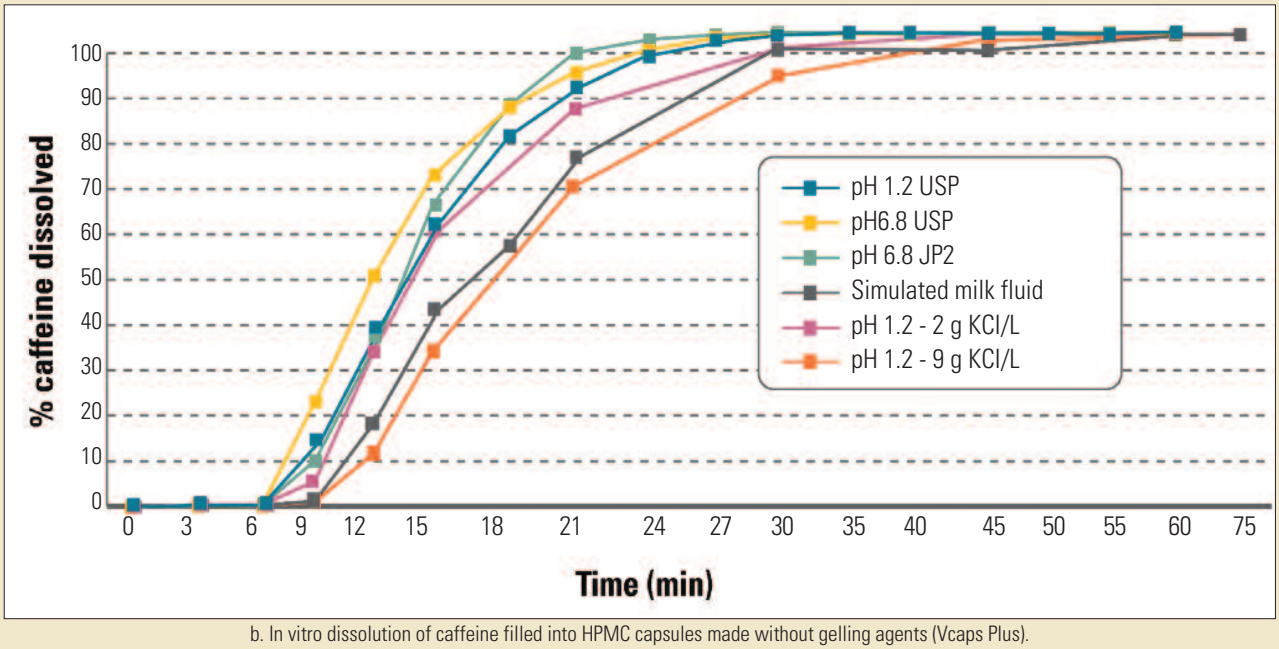
Capsules are widely used to administer both solid and liquid drug products. Most hard capsule shells are made of gelatin or hydroxypropyl methylcellulose (HPMC). This latter polymer emerged nearly two decades ago to meet the need for a non-animal-derived alternative to gelatin. In addition, HPMC is more compatible with

FIGURE 1

Comparison of dissolution performance of HMPC capsules made with and without gelling agents



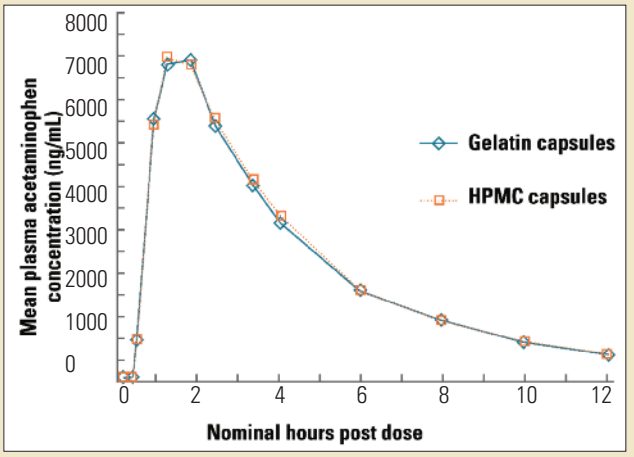
a. In vitro dissolution of caffeine filled into HPMC capsules made with gelling agents (kappa-carrageenan and potasium chloride).



b. In vitro dissolution of caffeine filled into HPMC capsules made without gelling agents (Vcaps Plus).

FIGURE 2

In vivo bioequivalence study comparing acetaminophen encapsulated in gelatin capsules with HPMC capsules made by thermo-gelation



Notes: N=24. HPMC capsules are Vcaps Plus, and gelatin capsules are Coni—Snap.

hygroscopic materials and avoids the crosslinking that can occur with gelatin under accelerated storage conditions. Its ability to withstand temperature excursions without a change in performance and to meet religious and dietary requirements makes HPMC an important capsule polymer.

In 2006, Capsugel offered a new version of its HPMC capsule, Vcaps Plus, that contains no gelling agents, a cause of variable in vitro dissolution. Instead of gelling agents, the capsules are made using a thermo-gelation process at temperatures higher than those of the traditional process. Eliminating the gelling agents gives the capsules pH-independent disintegration, which was shown in a human biostudy involving three APIs to give bioequivalence compared with a gelatin capsule [1]. Figures 1 and 2 compare the in vitro and in vivo performance of gelatin capsules and Vcaps Plus capsules.

The capsules have several advantages over those made from gelatin. In-house studies of Vcaps Plus capsules have shown they undergo no changes in color, transparency, loss on drying, disintegration, dissolution, or filling performance at low temperatures. Nor have we observed changes in disintegration, dissolution, or mechanical performance at elevated temperatures. Study results also indicate that because the capsules have a lower water content overall (less than 6 percent at ambient conditions), they may reduce moisture transfer from the capsule to the encapsulated product, which helps maintain product stability. Furthermore, because water is not needed as a plasticizer, the capsules are less likely to break, even in dry conditions, which helps maintain stability. They are also well suited for moisture-sensitive ingredients and can be dried to a lower moisture level—as low as 3 percent—for low-water-activity applications.

Fixed-dose combinations

Both gelatin and HPMC capsules can over-encapsulate single- and multi-layer tablets, API-layered multiparticulates, liquid fills, as well as filled capsules. A capsule-in-capsule technology we offer uses specialized liquid-filling techniques and equipment to place a prefilled smaller capsule into a larger, liquid-filled capsule. The smaller inner capsule can contain a liquid, solid, or semi-solid formulation. Based on the formulation or product requirements, either or both capsules can be made of gelatin or HPMC and coated, if desired, to achieve enteric protection or provide colonic drug delivery. These and other fixed-dose combination products can improve both the therapeutic effect and patient compliance. Products with a dual-release profile, such as pulsatile- or combination-release functionality, enable formulators to target more than one area of the GI tract.

Acid-resistant capsules

Launched in 2011 and intended for the nutraceutical market, Capsugel's DRcaps are delayed-release capsules geared toward delivering acid-sensitive ingredients. These capsules protect the ingredients from fully releasing and disintegrating in the stomach, then allow complete dissolution in the intestine. They also mask unpleasant tastes and odors without using shellac or artificial coatings. With a moisture content of 4 to 6 percent at 50 percent relative humidity, the capsules enhance the stability of moisture-sensitive probiotics. They are also suitable for liquid fills (photo).

DRcaps capsules protect ingredients from fully releasing and disintegrating in the stomach, then allow complete dissolution in the intestine. They accept powder and liquid fills.

A number of studies have been conducted with DRcaps, including one that evaluated acid resistance in a capsule-in-capsule format. In this study, pure acetaminophen was filled into different sizes of capsules, which were then filled into other capsules. Next, the double capsules were subjected to in vitro dissolution and disintegration tests. The results showed that the capsule-in-capsule format using DRcaps significantly increased acid resistance (pH 1.2) and delayed dissolution in a pH 6.8 JP2 buffer. Under disintegration test conditions, the double DRcaps did not exhibit any significant delay at the pH 6.8 JP2 stage. The study also showed that the capsules' acid resistance is not affected by the presence of as much as 40 percent alcohol (ethanol) in the dissolution media, which

may help prevent alcohol dose dumping in delayed-release products [2]. The results of an earlier study showed that a single DRcaps capsule offered similar protection in the presence of as much as 40 percent alcohol in JP2 protocol dissolution studies with caffeine. That same study also showed that "stacked" DRcaps extended acid protection of the formulation [3]. The combined results confirm that DRcaps capsules can be considered for use in extended delayed-release formulations.

Acid-resistant capsules protect ingredients from early activation by stomach acid and then release them completely in the intestines.

A human in vivo study of DRcaps that used gamma scintigraphy also documented their ability to delay delivery of acid-sensitive ingredients. The capsules protected the ingredients from early activation by stomach acid, and then released them completely in the intestines. The capsules began to release in a mean time of 52 minutes after ingestion (45 minutes later than an immediate-release capsule), and completely released the ingredients in a mean time of 72 minutes after ingestion. For the majority of subjects, complete release took place in the intestine [4,5].

Another study—the results of which appeared in medical journals—described how investigators at Massachusetts General Hospital used DRcaps for an unusual treatment of a serious medical problem. They used prescreened frozen fecal material from healthy donors to treat recurrent diarrhea caused by a Clostridium difficile infection, a major cause of morbidity and mortality. The capsules obviated the need for invasive procedures and thereby eliminated procedure-related complications and reduced the cost of treatment. Among the 20 patients treated, 14 had clinical resolution of diarrhea after the first administration and remained symptom-free at 8 weeks. The six non-responders were re-treated and five of them had resolution of diarrhea. The overall rate of clinical resolution of diarrhea was 90 percent [6].

Capsules with full enteric protection

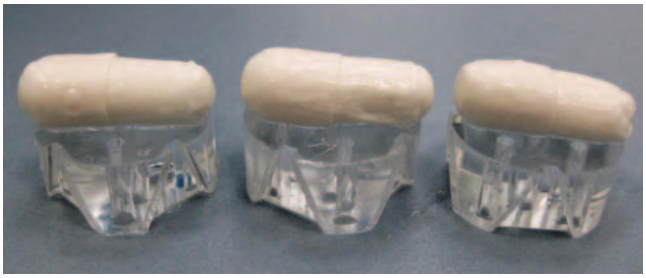
In 2015, Capsugel introduced its enTRinsic drug delivery technology. These capsules provide full enteric protection and targeted release of acid- and heat-sensitive ingredients in the upper GI tract without using functional coatings. Examples include nucleotides, peptides, vaccines, and live biotherapeutic products. The intrinsically enteric capsules, which use approved pharmaceutical polymers, have been shown to rapidly release at pH 5.5, allowing optimal absorption in the upper GI tract. The technology also enables formulators to accelerate product development of acid-labile or gastric-irritating compounds because the capsules eliminate the preparation, application, scaleup, and process validation steps associated with functional coatings.

In vitro and in vivo evaluations have confirmed that the capsules provide enteric protection. One test of their in vitro disintegration and dissolution performance involved esomeprazole magnesium trihydrate (EMT). In that test, enteric-coated EMT pellets in gelatin capsules (Nexium) were selected as an acid-labile model compound for which gastric stability is limited—similar to peptides, nucleotides, and vaccines. The EMT formulation was placed in enTRinsic capsules for comparison with capsules whose manufacturer claimed were acid resistant [7]. The results: The intrinsically enteric capsules showed no significant discoloration after 2 hours in acid media, indicating little to no degradation. Conversely, the capsules said to be acid resistant showed clear evidence of degradation, deformation, and content release. The EMT capsules filled into the enTRinsic capsules also showed quick dissolution of the gelatin capsules with no dissolution of the pellets at the acid stage, and complete dissolution of the pellets at the buffer stage, with a mean of 94 percent of EMT dissolved after 30 minutes.

In late 2016, Capsugel introduced a functional capsule that provides a second alternative for enteric protection and delayed release without using a functional coating. The capsules, Vcaps Enteric, use a polymer blend of HPMC and hydroxypropyl methylcellulose acetate succinate (HPMC-AS). While the polymer blend differs from what the enTRinsic capsules use, Vcaps Enteric offer a similar benefit: simpler enteric delivery from early-stage development to commercial manufacturing.

Vcaps Enteric capsules use a polymer blend of HPMC and HPMC-AS to provide enteric protection and delayed release without using a functional coating.

These latest enteric capsules comply with relevant EP, JP and USP monographs and have been evaluated in vitro across a number of compounds. The results show they protect the stomach from aggressive APIs and delay release to provide maximum absorption. Vcaps Enteric capsules work with all but the most sensitive APIs. (For highly sensitive molecules—including peptides, nucleotides, and vaccines—enTRinsic capsules are a better option because they use an impervious polymer.) In addition to eliminating the need for enteric coating, Vcaps Enteric and enTRinsic capsules provide product differentiation, allow lifecycle management, and offer the potential to make intellectual property claims.



Vcaps Enteric capsules after 2 hours in gastric conditions (pH 1.2). They were not sealed or banded.

The future of functional capsules

In vivo tests show that soluble compounds are well absorbed from both gelatin and HPMC capsules. In most cases, capsules of either material perform similarly, but in some applications they don't.

HPMC capsules, for example, can interact with poorly soluble APIs in a way that leads to a lower crystallization rate in the GI tract. This can be important when there are supersaturated APIs in the intestine, as can occur when dosing either a high-energy salt form or a weakly basic API. In those cases, HPMC capsules can help maintain supersaturation by inhibiting crystallization. The degree to which crystallization inhibition affects in vivo performance depends on the particular application, but HPMC has the potential to play a role as a functional excipient that improves bioavailability [8].

Capsules made from an HPMC-HPMC-AS polymer blend are inherently enteric, simplifying the move from early-stage development to commercial manufacturing.

Among the molecules Capsugel has formulated at its Bend, OR, site, approximately 40 percent are weakly basic, with a basic pKa between 2 and 7, and almost all the compounds are poorly water soluble. This indicates that there are many compounds that could benefit from HPMC capsules.

Today's HPMC capsules are more than an alternative to gelatin capsules. They offer an array of opportunities to improve drug delivery. From research to human dosing, HPMC capsules provide predictable delivery of simple immediate-release formulations and address the complex needs of targeted release, moisture protection, and enteric delivery. The variety of HPMC capsules now available, combined with a host of innovative strategies and technologies for drug delivery, offer a new means of addressing the challenges of today's APIs and provide a platform to develop patient-centric formulations that incorporate the next generation of molecules in development. *T&C*

References

1. Stegemann S., Vishwanath S., Kumar R., Cade D., Lowery M., Hutchison K., Morgen M., Goodwin A., and Lee C. Comparative human in-vivo study of an immediate release tablet over-encapsulated by gelatin and hydroxypropyl methyl cellulose capsules: Impact of dissolution rate on bioequivalence. Am. Pharm. Rev. 18(7) (2015) 38-45.

2. Cade D, Groshens E, He XW. Alcohol dose dumping for controlled release formulations: Is DRcaps acid resistant capsule an option? Poster W4209, annual meeting of the American Association of Pharmaceutical Scientists, October 2014, San Diego, CA.

3. He XW, Groshens E, et al. Prolonged gastric acid resistance using a new double hypromellose capsule approach. Poster W4158, annual meeting of the American Association of Pharmaceutical Scientists, October 2015, Orlando, FL.

4. Amo R. DRcaps capsules achieve delayed release properties for nutritional ingredients in human clinical study. Capsugel-commissioned study conducted by Bio-Images Research, Glasgow, Scotland (2014).

5. Hodges LA, Stevens HNE, Connelly SM, Cade D, Lee C. Novel HPMC capsules display acid resistant behaviour: A scintigraphic imaging study. Poster W5173, annual meeting of the American Association of Pharmaceutical Scientists, October 2014, San Diego, CA.

6. Youngster I et al. Oral, capsulized, frozen fecal microbiota transplantation for relapsing clostridium difficile infection. JAMA 312(17) (2014) 1772-1778.

7. Benameur H. Enteric capsule drug delivery technology: Achieving protection without coating. Drug Development & Delivery, 18(5) (2015) 34-37.

8. Richardson M and Morgen M. Next generation HPMC capsules bioequivalence and functional performance. Sponsored content, Pharm Tech, March 2016.

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