ADVERTORIAL

How Polymer Science is Changing the Functional Role of Capsules

New developments in polymer science are broadening the role that capsules play in drug delivery, formulation science and medical research. Today options exist to achieve immediate, delayed, controlled, site-specific or colon-targeted release. Specialized capsules can now play a functional role in improving bioavailability, meet the clinical needs for specific plasma time-course profiles, avoid site-specific degradation in the GI tract, and improve drug efficacy for patients.

DRUG RELEASE WITH HARD CAPSULES

Hydroxypropyl methylcellulose (HPMC) polymer capsules were developed to meet the industry need for a non-animal-derived alternative. HPMC provides greater compatibility with hygroscopic materials and avoids cross-linking that can occur with gelatin under accelerated storage conditions. The ability to withstand temperature excursions without a change in performance and meet religious and dietary requirements make HPMC an important capsule polymer.

Capsugel's introduction of an HPMC capsule manufactured through thermo-gelation provided a means of eliminating gelling agents, a cause of variable *in vitro* dissolution. This gave the new HPMC capsules pH independent disintegration, and was shown in a human biostudy to provide bioequivalence compared to a gelatin capsule.[1]

ACID-RESISTANT CAPSULES

Launched in 2011, DRcaps™ capsules have delayed release properties and are designed for sufficient enteric protection or gastric resistance for nutritional market application. These capsules protect the ingredients from fully releasing in the stomach, and allow complete dissolution in the intestine – a gamma scintigraphy study showed an average of 52 minutes to first opening.[2] DRcaps were also studied using a capsule in capsule concept. Their *in vitro* dissolution and disintegration tests used a double-wall DRcaps capsule which significantly increases the acid resistance (pH1.2) and delays dissolution in the pH6.8 JP2 buffer. In the test, the double DRcaps did not exhibit any significant delay at the pH6.8 JP2 stage. The study showed that DRcaps acid resistance is not affected by the presence of up to 40 percent alcohol (ethanol) in the dissolution media, which may help prevent alcohol dose dumping in delayed-release products. The results also confirmed that these capsules can be considered an option as an extended delayed-release oral dosage form.[3]

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 *Clostridium difficile* (*C. difficile*) infection (CDI), a major cause of morbidity and mortality. The capsules obviated the need for invasive procedures, 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 eight weeks. The six non-responders were re-treated, with five patients having a resolution of diarrhea. The overall rate of clinical resolution of diarrhea was 90 percent.[6]

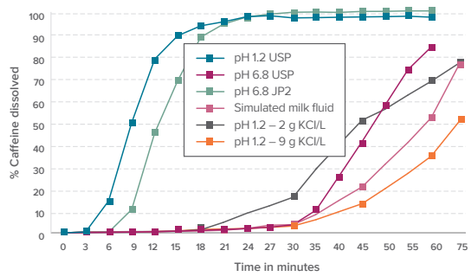
FULL ENTERIC PROTECTION FOR PHARMACEUTICAL APPLICATIONS

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

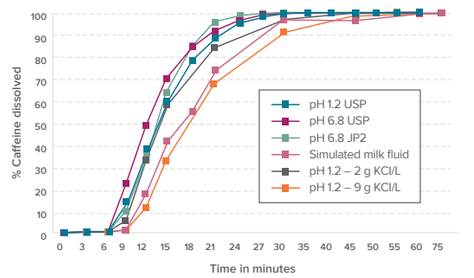
These enteric capsules comply with relevant EP, JP and US Pharmacopeia monographs and have been evaluated *in vitro* across a number of compounds. The results show they protect the stomach from aggressive APIs and delay release to provide maximum absorption. Vcaps® Enteric capsules work with all but the most sensitive APIs.

Dissolution variations introduced by gelling systems in HPMC capsules

Influence of gelling systems on HPMC capsules in dissolution testing



In vitro dissolution of caffeine in Vcaps® Plus capsules



ENTERIC PROTECTION FOR HIGHLY SENSITIVE SMALL AND LARGE MOLECULES

The enTRinsic™ drug delivery technology provides full enteric protection and targeted release of acid- and heat-sensitive active ingredients to the upper GI tract without the use of functional coatings. Examples include nucleotides and peptides, vaccines and live bio therapeutic 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 accelerated product development of acid-labile or gastric-irritating compounds because the capsules eliminate the preparation, application, scale-up and process validation steps associated with functional coatings.

LOOKING FORWARD WITH FUNCTIONAL CAPSULES

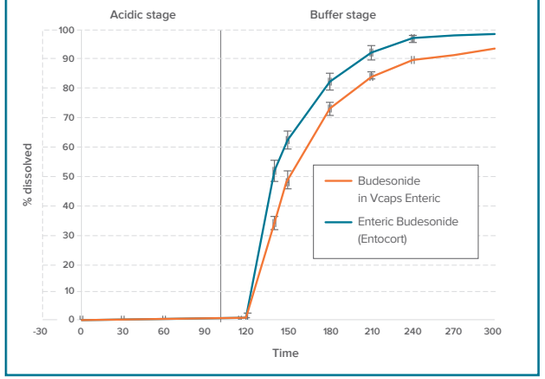
In-vivo tests have shown that soluble compounds are well absorbed from both HPMC-based Vcaps® Plus and gelatin capsules. In most cases, capsules of either material perform similarly, but in some applications they don't.

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-based capsules can help maintain super-saturation by inhibiting crystallization. The degree to which crystallization inhibition affects *in-vivo* performance will depend on a particular application, but HPMC has the potential to play a role as a functional excipient which improves bioavailability.[5] Capsugel's Bend, OR, formulators predict approximately 40 percent of molecules are weakly basic, having a basic pKa between 2 and 7, and almost all these compounds are poorly water soluble. This indicates that there are many compounds that could benefit from HPMC-based capsules.[6]

SUMMARY

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 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.

Enteric release without the need for coating with Vcaps® Enteric capsules



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Capsugel®