March 2017

Simple Steps to Speed Encapsulated Drug Development

Challenged to shorten your drug development timeline? Discover eight encapsulation ideas for fast-tracking this process.

OVERVIEW

In the pharmaceutical industry, speed to market is essential for gaining a competitive position. New encapsulation technologies now make it possible to streamline research and development activities, improve product development, and jump-start time to market. Novel capsule polymers can also give a drug additional functionality and expand its applications. Therefore, choosing the right capsule polymer from the get-go is critical.

HPMC CAPSULES

Gelatin capsules have long been considered robust for numerous applications, but they have a "window of opportunity" in terms of their moisture sensitivity. It is often recommended that these types of capsules be stored at 35–65% relative humidity to ensure that the gelatin maintains a water content of 12–16%. Straying too far below these levels can cause the capsules to become brittle. On the other hand, exceeding moisture limits can deform the capsules, thus preventing them from performing well in encapsulation equipment.

Such sensitivity to moisture is one key reason for the growing interest in hydroxypropyl methylcellulose (HPMC) polymer capsules (such as Capsugel's Vcaps® Plus HPMC). Not only do they protect the formulation and enhance performance, but they also do not rely on water content for pliability. As shown in Figure 1, the HPMC "window of opportunity" is larger than that of gelatin capsules, with the ideal moisture content being 2–9% for HPMC versus 12–16% for gelatin. *(Figure 1)*

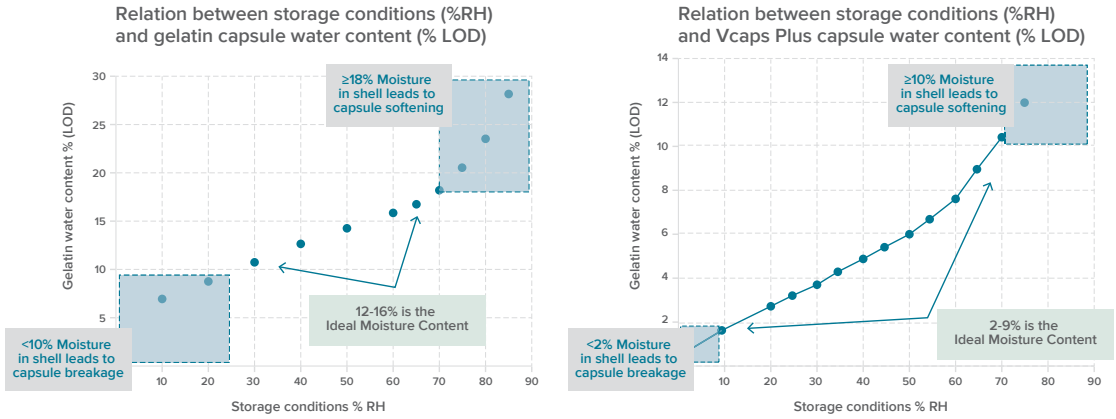
But not all HPMC capsules provide an equivalent change from gelatin capsules. HPMC capsules can be made with or without a gelling system. When a gelling system is used, dissolution variability will always be introduced. Figure 2 shows how much variability occurs with *in vitro* dissolution of caffeine-filled HPMC capsules produced with a gelling system.

Products encapsulated in HPMC capsules without a gelling system do not have these variations. Capsugel's Vcaps® Plus capsules, for instance, are made with a proprietary thermal gelation process that demonstrates reliable dissolution regardless of changes in pH and ionic strength *(Figure 2)*.

CASE STUDY: DISSOLUTION LAG TIME

Customers often voice concerns about an apparent lag time in the initial dissolution and disintegration of HPMC capsules. After six minutes, it appears that dissolution has just started *(Figure 2)*.

VCAPS® PLUS HPMC CAPSULES



- The dimensional product specifications are identical to gelatin capsules (same dipping pins are used)
- Capsule weight specifications similar to gelatin capsules
- Capsule colors and imprints similar to gelatin
- Water content and mechanical properties differ significantly by polymer

Figure 1: General characteristics of Vcaps® Plus HPMC capsules.

DISSOLUTION VARIATIONS INTRODUCED BY GELLING SYSTEMS

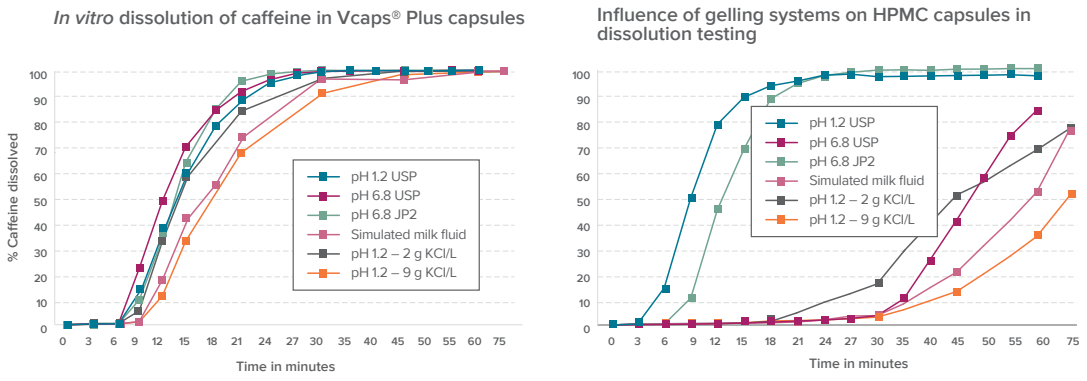


Figure 2: On left, in-vitro dissolution of caffeine filled in hypromellose capsules (HPMC) produced with gelling systems (kappa-carrageenan and potassium chloride). Dissolution profiles are dependent on the pH and ionic strength of the dissolution media.

On right, caffeine in-vitro dissolution in various dissolution media of HPMC by thermo-gelation (Vcaps® Plus). Dissolution profiles of products encapsulated with thermo-gelled Vcaps® Plus capsules demonstrate independence of the pH and ionic strength of the media.

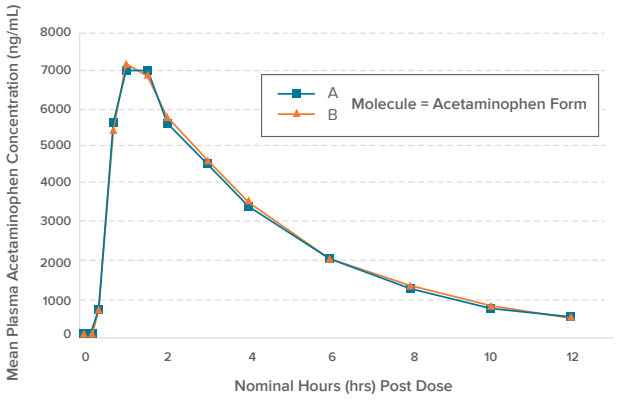
To investigate this issue, Capsugel commissioned an in-vivo study to compare the performance of Vcaps® Plus HPMC capsules made with thermal gelation with hard gelatin capsules.

Investigators recruited 24 healthy men to take part in this randomized, two-way crossover study. Vcaps® Plus HPMC capsules — General Excedrin® Extra Strength caplets were selected as the study material as they contain three different biomarkers (i.e., for acetaminophen, aspirin, and caffeine), each with a separate biopharmaceutical classification for solubility. An Excedrin® Extra Strength caplet was added to both the Vcaps® Plus HPMC capsule and to a hard-gelatin capsule. The capsules were dosed according to the study protocol and various pharmacokinetic parameters were collected.

The results involving the acetaminophen marker indicate that neither the difference in the polymer type nor the slight lag time in HPMC disintegration affected product performance in-vivo *(Figure 3)*. Both had nearly identical performance, with high confidence intervals. The results with both the aspirin and caffeine markers affirm the same in-vivo performance noted in the acetaminophen marker showing near matches to their gelatin encapsulated counterparts with high confidence intervals in each case.

This study suggests that HPMC capsules can broaden the space for two-piece capsule application in drug development and manufacturing, provided that the capsules are made without a gelling system.

ACETAMINOPHEN IN VCAPS® ENTERIC CAPSULES



In-vivo results and statistical analysis

N=24

PK Parameter	Least Squares Geometric Means of Treatment:		Ratio (%)	Intrasubject %CV	90% CU of Ratio
	Gelatin capsules	HPMC capsules			
log(C_{max})	8.5	8.1	103.9	21.8	(93.4, 115.6)
log(AUC_{0-t})	29.1	29.3	99.0	7.9	(95.3, 102.9)
log($AUC_{0-\infty}$)	31.1	31.4	99.0	7.9	(95.2, 102.9)

Figure 3: In-vivo testing of acetaminophen in Vcaps® Enteric capsules.

ACCELERATING EARLY DRUG DEVELOPMENT

Drug developers often must use enteric-coated particulates or capsules to deliver drug compounds past the low-pH of the gastric environment or to improve a drug's performance through delayed release.

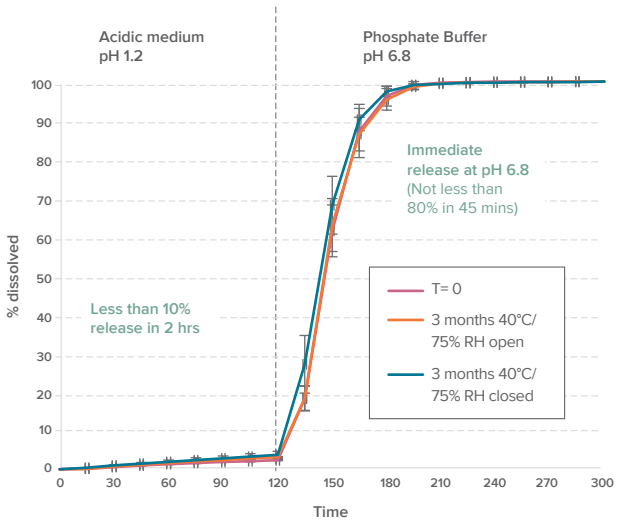
A new functional encapsulation technology (Capsugel's Vcaps® Enteric capsules) achieves enteric protection and delayed release without the need for a functional coating. Having noncomplex enteric options in early drug development offers a faster way for drug developers to evaluate new chemical entities that require acid protection.

Two-piece Vcaps® Enteric hard capsules are made with a thermal gelation process from widely used HPMC and enteric cellulosic materials. The capsule's enteric properties reside within the polymer itself, rather than an exterior coating. Also, the capsules do not require additional processing steps such as sealing or banding.

During a two-stage test protocol, less than 10% of the product was released after two hours at a gastric pH. A quick release occurred when the capsule was added to the higher pH buffer of the second stage *(Figure 4)*.

ACETAMINOPHEN API DISSOLUTION TEST DATA

- Two-piece intrinsically enteric hard capsules
- Mix of HPMC together with pharmaceutical grade cellulosic enteric derivative (widely accepted and used for over 20 years in the pharma industry)
- Manufactured via Capsugel's thermogelling process
- Water content: Less than 7%
- Fully compliant to USP/EP/JP monographs for enteric release



Method: spiral sinkers used for capsules (float w/o sinkers), 2-stage test with 2-hours gastric (750mL, HCl 0,1N) pH 1,2 then medium added at 2 hours to final: 1000mL phosphate buffer USP, pH 6.8; Acetaminophen UV detecon = 300nm; n=6.

Figure 4: Dissolution tests of acetaminophen in Vcaps® Enteric capsules.

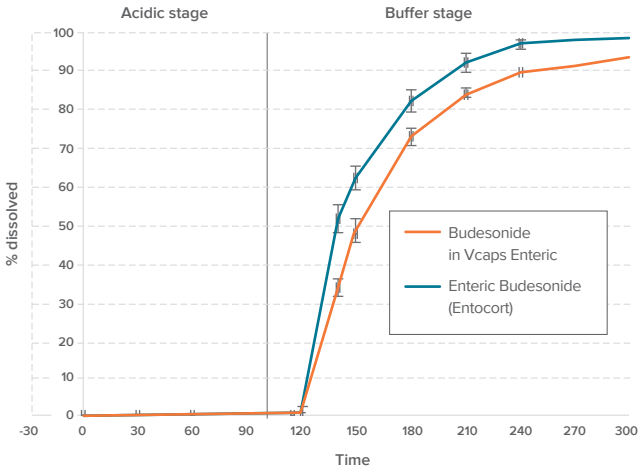
In a separate study, the dissolution of budesonide encapsulated in Vcaps® Enteric was compared with enteric-coated budesonide. A two-stage dissolution protocol was used. As seen in Figure 5, both routes provide good enteric protection and opened quickly at higher pH levels, offering similar release profiles.

BUDESONIDE DISSOLUTION

Budesonide
(ENTOCORT®, AstraZeneca)

- Gelatin capsule containing enterically coated microgranules
- Delayed release is favorable to the active principle absorption

Vcaps® Enteric as potential alternative to enteric-coated microgranules in capsule



Test Conditions: n=6 ; spiral sinkers used for capsules (float w/o sinkers), 2-stage test with 2 hours gastric (500mL, 100mM HCl) then medium added at 2-hours to final: 1000mL 95mM phosphate buffer w/0.5% Kolliphor HS15, pH 6.8; 100 rpm, Test Ref: IRD384-068 (HPLC-UV)

Budesonide pure API directly filled in Vcaps Enteric

Figure 5: Enteric release without the need for coating with Vcaps® Enteric capsules.

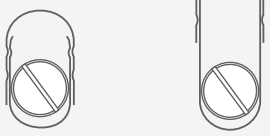
PRODUCTS TO HELP STREAMLINE CLINICAL STUDIES

Several other encapsulation products also help to streamline clinical studies. Three options include:

Capsules (such as DBcaps®) that are shorter and wider than standard-size capsules, which enables a wider range of tablet and capsule sizes to be overencapsulated than standard capsules for double-blind clinical trials and makes them easier to swallow. Direct encapsulation saves time and resources compared to other modes of blinding such as the creation of placebo products and/or removal of identification marks. These features improve patient compliance, which is important when multiple daily doses are needed. It is also harder to break the sealing without visible evidence of tampering.

IMPROVES PATIENT COMPLIANCE

Actual Sizes



DBcaps size C

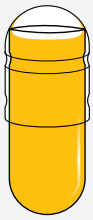
Standard Size 0

PATENTED LOCKING MECHANISM HELPS PREVENT BREAKING THE BIND

Dual locking rings

Extended length cap

For preclinical studies, some small-size capsules (such as PCcaps® Capsules) can be used to dose the API alone. Since no excipient formulation time is needed, developers can get proof-of-concept results more efficiently.



Locking ring prevents accidental separation of cap after filling

Small size is ideal for rats and guinea pigs. Not suitable for mice or rodents below 150g weight.

All Color Capsules combine several FD&C or iron oxide dyes that can extract to 18 possible color options in one capsule. This variety allows formulators to move forward with stability studies before a final color selection is made *(Figure 6)*.

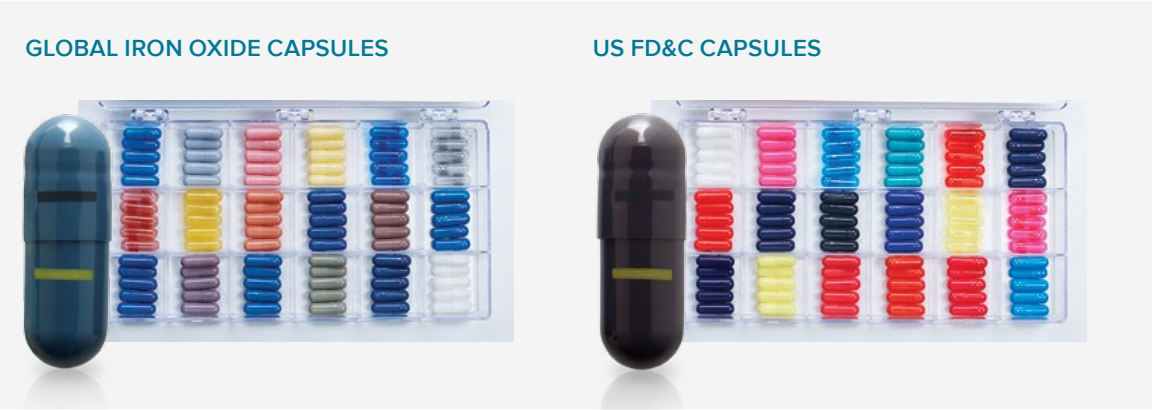


Figure 6: Extraction cases demonstrate that 18 color capsules that can be extracted from the All Color Capsule.

MICRO-DOSING TECHNOLOGY

Micro-dosing may be defined as the process of dispensing a precise amount of a drug substance into a capsule to administer to human subjects in early phase clinical trials. This approach allows for pharmacokinetic observations to determine if the drug substance is a viable candidate to proceed to the next phase of product development. These early determinations are significant prior to a substantial investment in development of a drug product. Precision weighing of drug substances into capsules can be conducted using Xcelodose® systems. These instruments allow for precise dispensing of the drug substance into capsules from 100 µg to 200 mg per dose depending on the drug substance physical characteristics (particle size distribution, flow), including 100% weight verification of each unit produced. This approach limits drug substance usage and waste generation in order to produce the dosage form, allows for multiple dose strengths to be produced using the same process, and has the ability to streamline formulation and analytical development. Formulation development activities, such as excipient compatibility, can be conducted after initial clinical assessments of the powder in capsule or in parallel, allowing cost conscious options in for drug development.

	Xcelodose® 120S	Xcelodose® 600S
Application	Pre-clinical evaluations and small-scale clinical trial manufacture. 	Clinical trial manufacture and small-scale manufacture. High throughput unit for longer runs and greater fill weights 
Typical Throughput	60-100 capsules/hr. dependent upon dosing levels & API characteristics	250-300 capsules/hr. dependent upon dosing levels & API characteristics
Capsule Handling	Manually loaded, semi automatic indexing	Fully automatic capsule handling and filling

Figure 7: Xcelodose® precision powder micro-dosing systems

Capsugel's proprietary Xcelodose® Precision Powder Micro-dosing Systems facilitate this microdosing or powder-in-capsule approach by providing accurate, consistent, and automated fill across compound types inclusive of very lowdose applications. It is estimated that these systems reduce product development time by up to 17 weeks *(Figure 7)*.

LIQUID FILLED HARD CAPSULE TECHNOLOGY

Liquid filled hard capsule technology (LFHC) has now established a well-recognized position in the pharmaceutical industry, as a dosage form to be considered for compounds with low solubility or bioavailability issues. This increased popularity can be attributed in part to its simplicity in manufacturing design and technology transfer process combined with a versatility in providing solutions to wide range of formulation challenges. The technology lends itself well to addressing key challenges faced by the formulator when developing new chemical entities and further enhancing existing products. These challenges may include improving bioavailability, delivering highly potent and low dose dosage forms, combination products, modified and targeted delivery as well as specialist applications such as abuse deterrence.

Furthermore LFHC technology can shorten the development lifecycle through efficient technology transfer. The process is simple; a non-aqueous liquid is filled into the body of a hard shell capsule using precision pumps, the caps are placed on the bodies and a seal or band is applied at the join. The capsules used in the filling process can be either gelatin or HPMC. In comparison to a typical tabletting process which can involve up to seven steps, the process of LFHC can be completed in just three; preparation of the mix (compounding), filling of the capsules, and banding (or sealing) (Figure 8). With the small number of process steps, one of the key advantages of LFHC is the ease of scalability, which allows direct transfer from the lab through pilot scale to commercial manufacture. The reduced number of steps offers a more straightforward process validation which can assist in achieving a smoother regulatory journey.

In addition, where a customer's Active Pharmaceutical Ingredient (API) is in short supply, the use of LFHC technology can minimize the API requirements at the early clinical stages of the project by offering smaller batch sizes which are reasonably representative of the process on a larger scale.

LFHC technology is well-suited to address a number of formulation and processing challenges, which can potentially accelerate the drug development process with the ultimate goal of reaching the market in a faster time-frame. *(Figure 8)*

Figure 8: Liquid filled hard capsules – Increased speed to market with fewer process steps

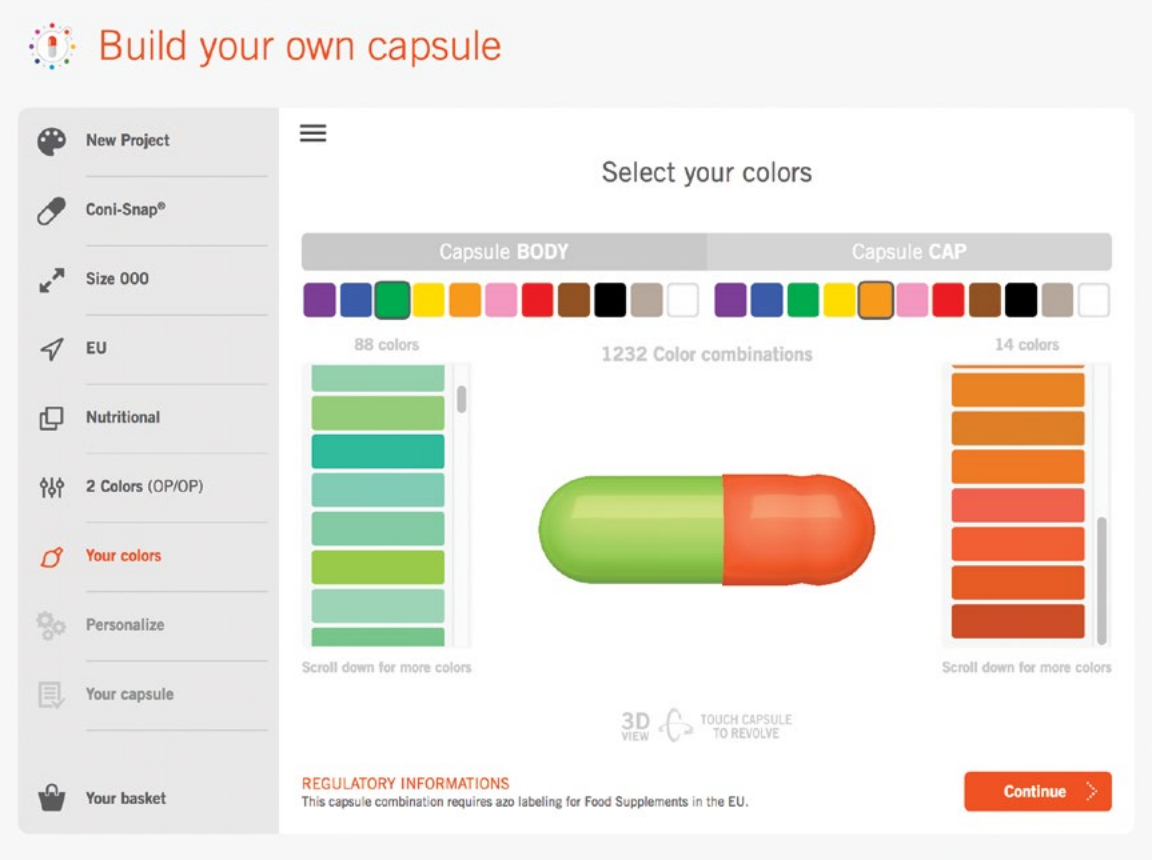


Figure 9: Build your own capsule tool.

BRAND AND COLOR DEVELOPMENT

Selecting the correct color for a capsule is a complicated issue that not only affects a company's market position, but also its regulatory compliance and consumer acceptance. In fact, capsule color even plays a role in the perceived efficacy of a drug. One study of four different colored placebo capsules suggested that patients' perceptions of pain relief varied widely. Red placebos were thought to offer moderate pain relief while yellow ones provided minimal relief.

To facilitate the selection process, Capsugel's Build Your Own Capsule tool with a regulatory overlay allows users to build and request capsules in a variety of sizes, materials, colors, and color combinations, thus supporting fast drug development *(Figure 9)*. The tool is available at Capsugel.com/Knowledge-Center/Build-Your-Own-Capsule.

CONCLUSION

Drug developers are often tasked with bringing drugs to and through clinical phases quickly. Novel encapsulation technologies not only support faster time to market, but also offer cost savings and can have a positive impact on advancing capsule-based projects.

Capsugel®

FOR MORE INFORMATION CONTACT US AT
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