

A sponsored
whitepaper.

Next-Generation HPMC Capsules Bioequivalence and Functional Performance



Matt Richardson, PhD
Pharmaceutical
Business Development
Manager, Capsugel

By: **Matt Richardson, PhD and Michael Morgen, PhD**

Introduction

Hydroxypropylmethylcellulose (HPMC) is not a new material to pharmaceuticals. It has been used and well vetted in pharmaceutical formulations for many years. Capsules made of HPMC are not novel either they have been part of the pharmaceutical industry for several years. Recent advances in the development and manufacture of HPMC capsules, have led to an expansion of their use.

An increasing percentage of new compounds are being evaluated in HPMC capsules at the onset of formulation studies either as the capsule of choice or in simultaneous studies with hard gelatin capsules. This is a change in the dynamic of capsule formulations as HPMC capsules were previously only considered as a last resort or a fail-safe formulation option.

Two-piece capsules made from HPMC have been used as an alternative to gelatin (HGC) when challenged with chemically incompatible actives or hygroscopic and/or moisture-sensitive ingredients. Second generation HPMC capsules are different from both first generation HPMC capsules and gelatin capsules. New HPMC polymers have eliminated the use of secondary gelling agents and use a thermo-gelation for film formation, resulting in performance profiles close to gelatin.

Gelatin is a chain of amino acids that requires no additive to gel on its own; it is self-gelling which occurs at a particular concentration when the temperature of the solution reaches $< 40^{\circ}\text{C}$. As it comes out of solution, it forms a three-dimensional chain network. After drying, the capsule has about 12 to 15% water content, which is important for maintaining flexibility. When the water content goes out of that range significantly, it has an effect on the performance of gelatin. Thus, the integrity of the gelatin structure is dependent upon controlling both water content and temperature.

HPMC capsules, in contrast, are a cellulose-based material derived from plant sources, usually wood pulp. Depending on the degree of substitution and viscosity of the products, HPMC can be further separated and classified into different grades associated with the chain link of the polymer and viscosity.

Initial HPMC capsules were made under similar process conditions as hard gelatin capsules, using cooled stainless steel pins dipped into a hot solution of HPMC. The solubility of HPMC, however, is lower in hot water than cool water. So to help stabilize the polymer in solution, gelling systems comprised both a gelling agent and a gelling promoter to assist in polymer film formation.

As customers tested that first generation HPMC capsule, they experienced variability in physical attributes, most notably in the dissolution of encapsulated formulations. Upon further



Michael Morgen, PhD
Senior Principal
Scientific, Bend
Research

SPONSORED BY

CAPSUGEL®

Pharmaceutical
Technology™

investigation, it was shown that the variability was attributed to the use of gelling agent and gelling promoter. Thus, it became clear that an alternative process was needed in which gelling systems were not used at all.

This led to research on the manufacture of HPMC capsules without gelling systems. Taking advantage of the solubility of HPMC in cool water, which allowed for a more uniform concentrated solution of HPMC, shell formation is achieved by a thermo-gelatin process around the dipping pins. Hot stainless steel pins are dipped into a cool solution, allowing for the HPMC to deposit as a solid film on a stainless steel. The capsules are then finalized much like any other two-piece hard capsule would be, regardless of the polymer.

This process is a complete reversal of the traditional hard capsule manufacturing process. Capsugel's second-generation capsules are called Vcaps® Plus. The capsule process completely avoids the addition of gelling system producing HPMC capsules that have properties that are quite unique.

Physico-Chemical Characteristics of HPMC Capsules

With respect to the dimensions of the capsule, HPMC capsules are identical to the size and shape of gelatin capsule because the same dipping pins are used. A vast array of color and imprint choices are available through both gelatin and the Vcaps® Plus capsule. Water content, however, is the most notable difference between the physical nature of the HPMC and gelatin capsule (Figure 1).

Moisture content for HGCs is ideal at 12-15%. That represents the safe storage window of about 35 to 65% relative humidity for a gelatin capsule. Should the moisture level in the capsule drop too low, concerns of brittleness are heightened and if the capsules gain too much moisture, they then begin to lose their shape.

With HPMC capsules, however, the different polymer lends itself to a different result. The ideal moisture range is 2 to 9% for an HPMC, allowing for a wider operating range according to the relative humidity. The average moisture content for HPMC capsules is about 5 to 6% water. When either moisture sensitivity or hygroscopic actives are being formulated, this differential in the water content could be important.

A tube test device was used to evaluate and compare capsule mechanical properties (Figure 2). The device drops a 100-gram weight at distance of 8 cm onto the capsule, and the resultant capsule is examined for signs of cracking or shattering. 50 capsules each of HPMC and HGC were equilibrated

Figure 1: General characteristics—water content.

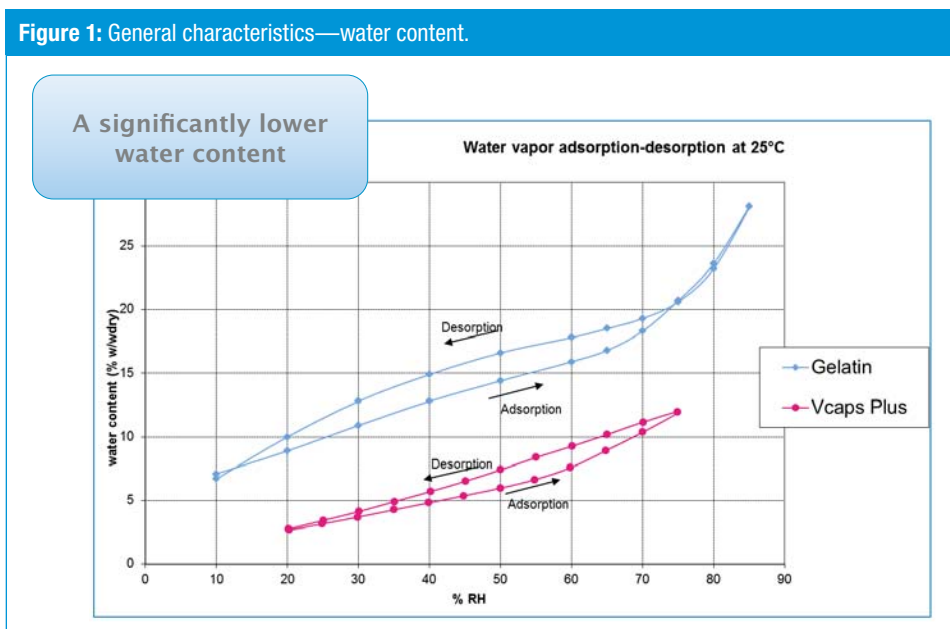


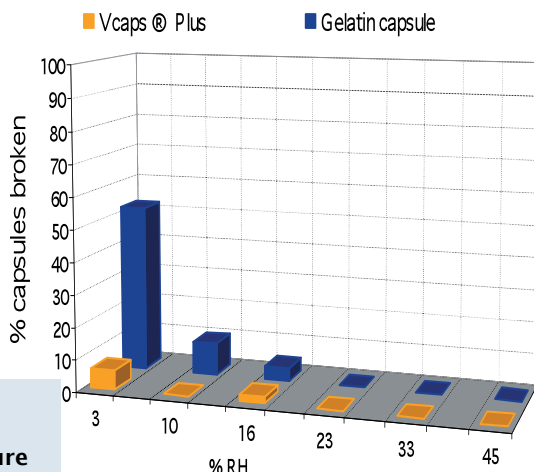
Figure 2: General characteristics—mechanical resistance.

'Tube Test' used to evaluate and compare capsule mechanical properties



CONCLUSION

HPMC (Vcaps® Plus) capsules present high mechanical resistance even at low moisture levels



at various relative humidities and then subjected to the tube test evaluation. This graph shows the percentage of broken or damaged capsules at the various equilibrated relative humidity levels. An increasing percentage of gelatin capsules broke as the relative humidity levels dropped, corresponding to a lower amount of moisture in the gelatin shell.

HPMC, however, does not show the same level of brittleness at the lower humidity levels. Whereas gelatin uses the water as a plasticizer to remain flexible, HPMC does not, and as a result, maintains its robust nature at lower moisture levels. This allows for storage in drier conditions as well as has significant implications when desiccants are used to protect formulations.

Another characteristic that shows an interesting difference between Vcaps® Plus and gel-based HPMC polymers is weight variation. Gelatin has the lowest amount of variability in weight. Vcaps® Plus capsules are manufactured through the thermo-gelation (shell 2), which shows a better weight consistency than the HPMC capsule, which does contain a gelling system (shell 1) (Figure 3).

The Vcaps® Plus HPMC capsule showed a 3.29% relative standard deviation compared with the first-generation capsule containing a gelling system, which showed an almost twice weight variability at 6.45% relative standard deviation. This suggests that, capsule-to-capsule and batch-to-batch, variability would be lower using HPMC capsules that do not contain a gelling system.

Another notable difference is the ability for the HPMC capsules to better tolerate heat deviation or hot storage conditions.

Recommended storage conditions for gelatin capsules would be placed in a 15 to 25 °C. HPMC capsules actually show heat resistance well past that of gelatin. Figure 4 shows there no change in the HPMC, the Vcaps Plus capsule, even up as high as 60, 70, and 80 °C.

Dissolution Characteristics of HPMC Capsules

Understanding the impact of gelling systems on the first generation HPMC capsule with regard to disintegration and dissolution drove the production of the manufacture of the second generation HPMC capsule. The goal was to have an alternative polymer capsule with great disintegration and dissolution performance with little to no variability.

In the inset of the graph of Figure 5, the disintegration rate of Vcaps® Plus is similar but slightly higher compared to gelatin. This effect is more pronounced when one compares the dissolution rates of caffeine in both gelatin and Vcaps Plus thermo-gelation HPMC capsules.

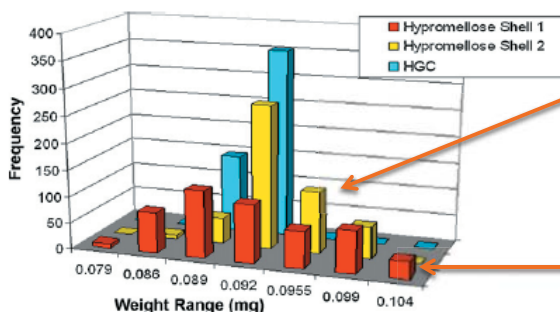
Gelatin quickly releases the contents, allowing for dissolution to occur rapidly while Vcaps Plus does not appear to allow dissolution until approximately 5 minutes into dissolution testing. This dissolution lag time is common to all HPMC capsules, both first and second generations. HPMC capsules have less water than gelatin capsules, and as a result, HPMC needs a hydration period to pull water into the matrix and allow disintegration to begin. Gelatin already contains 12 to 16% water so it doesn't need the same hydration period.

Figure 6 shows dissolution variability in HPMC capsules

Figure 3: General characteristics—weight variation.

Capsule weight variation.

Criteria (±target)	Acceptable rate (%)		
	Hypromellose Shell 2 Size #0	Hypromellose Shell 1 Size #0	Capsugel HGC Size #0
5.0%	85.2%	53.2%	100%
7.5%	97.8%	78.4%	100%
10.0%	100.0%	89.2%	100%
Average wt. (mg)	94.5	92.7	92.0
Maximum wt. (mg)	102.6	107	95.2
Minimum wt. (mg)	85.5	79	87.5
RSD	3.29%	6.45%	1.44%



Vcaps® Plus - Shell 2 had a 3.29% RSD

HPMC/Gelling System - Shell 1 had a 6.45% RSD

that contain gelling systems (carrageenan and potassium salts). A variety of dissolution media were tested to produce the data shown. As the differences in the media are investigated further, the implications of the variability begin to show up more fully.

Variance is reduced by eliminating the gelling system. In vitro dissolution profiles of products encapsulated with Vcaps® Plus demonstrate independence of the pH and ionic strength of media (Figure 7).

In Vivo Performance of HPMC Capsules

If variability is noted in vitro with ionic media, then an *in vivo* concern should be suspect as well. A study presented in the International Journal of Pharmaceutics showed a dose escalation experiment in humans to investigate the performance of Vcaps® Plus *in vivo*. The study demonstrated that the HPMC capsule opened consistently across the dose escalation range with the median T_{max} observed at each case in one hour (Figure 8). This is indicative that the shell disintegrates quickly, allowing for the subsequent dissolution and absorption of the immediate release compound tested. Results of that study confirmed that the capsules had an excellent performance *in vivo* and further confirmed the viability of Vcaps® Plus HPMC capsules made by thermo-gelation.

To further study the performance of Vcaps® Plus with different types of compounds and to understand *in vivo* performance, a bioequivalence study was performed, the details of which are outlined in Figure 9.

Figure 10 shows the results for the acetaminophen PK parameters. At the top is the graph of the main plasma concentration of acetaminophen over time. The plot for the hard gelatin capsule is shown in red. The plot for the Vcaps® Plus

Figure 4: General characteristics—higher stability range.

Higher stability under accelerated and extreme accelerated conditions

HPMC (Vcaps® Plus) can tolerate extreme temperatures, from -18° C to 90° C

Disintegration & dissolution

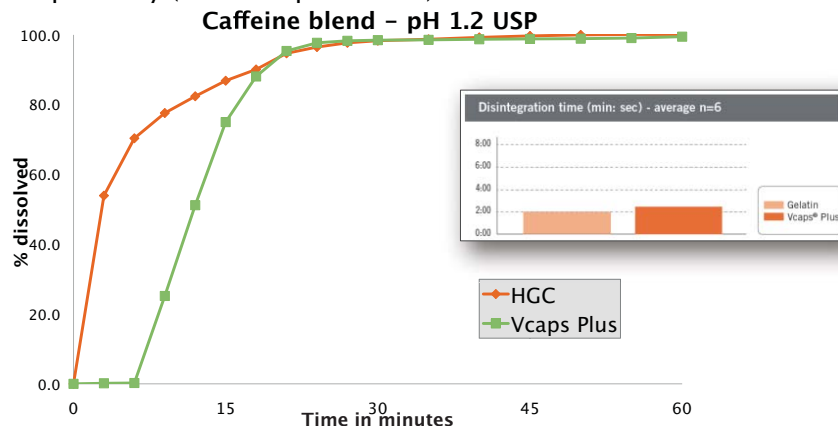
Temperature	Room conditions	40 °C	50°C	60°C	70°C	80°C	90°C
Gelatin hard capsules	No change			Test not applicable as capsules are deformed, sticking together and partly molten			
Vcaps Plus capsules	No change						

Mechanical resistance (brittleness, breakage)

Temperature	Room conditions	40 °C	50°C	60°C	70°C	80°C	90°C
Gelatin hard capsules	No change			Test not applicable as capsules are deformed, sticking together and partly molten			
Vcaps Plus capsules	No change						

Figure 5: Comparing disintegration and dissolution.

- Disintegration time similar
- Dissolution time between gelatin and HPMC (Vcaps® Plus) encapsulated products differs from 2 – 3 min and 7 – 8 min respectively (due to rupture time)



HPMC capsule is shown in blue. The results are nearly identical for the mean plasma concentration levels.

The statistical analysis is shown in the table below the graph. The max and area under the curve values match up quite nicely for acetaminophen and give a high confidence interval showing the equivalency of the encapsulated forms of acetaminophen between hard gelatin and the thermo-gelation HPMC capsule containing no gelling system.

The results for the acetylsalicylic acid PK parameters are

Figure 6: Dissolution variations introduced by gelling systems.

Dissolution profile dependent on pH and ionic strength of the dissolution media

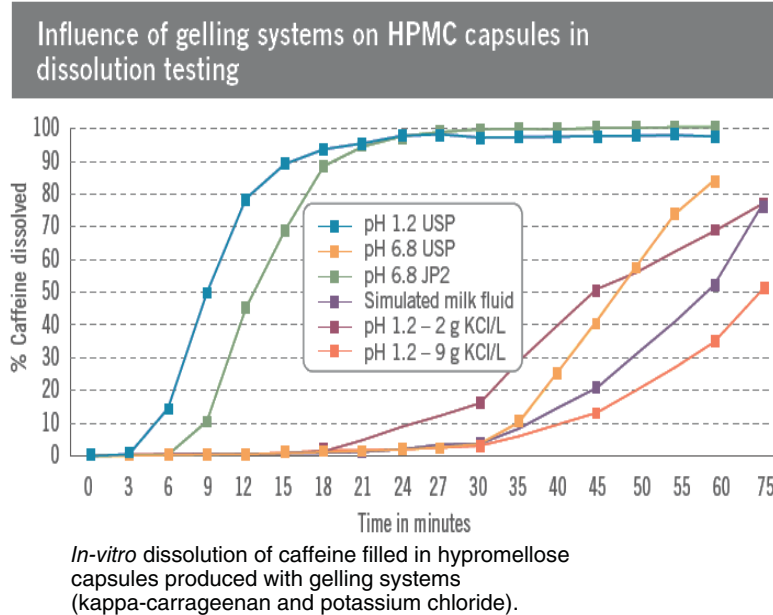
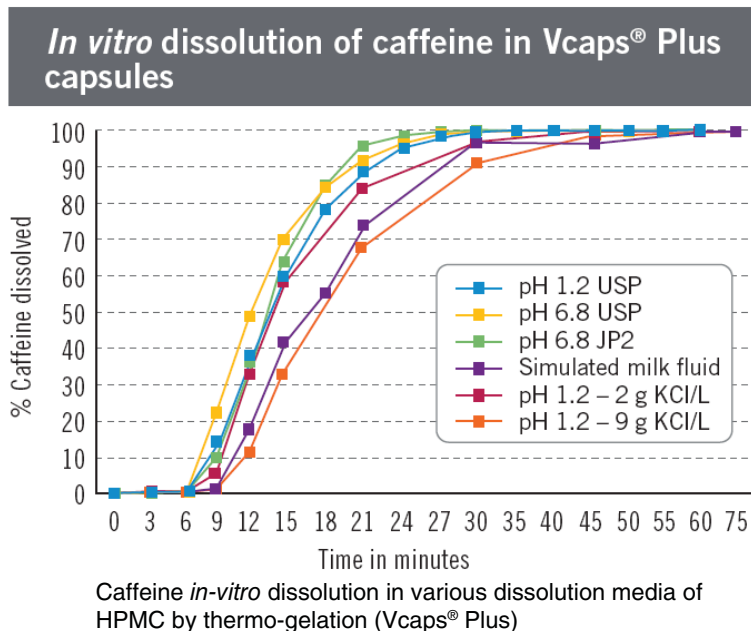


Figure 7: Variances reduced by eliminating the gelling system.

Dissolution profiles of products encapsulated with thermo-gelled Vcaps® Plus capsules demonstrate independence of the pH and ionic strength of the media.



shown in **Figure 11**. The results show a nearly identical match for the mean plasma concentration levels. Collectively, equivalency of the encapsulated forms of acetylsalicylic acid, whether in hard gelatin or Vcaps® Plus HPMC, is demonstrated.

The results for the caffeine PK parameters are seen in **Figure 12**. In the graph of the mean plasma concentration of caffeine over time, a similar data trend is presented when comparing the product encapsulated in hard gelatin capsule. Caffeine shows *in vivo* equivalency between encapsulated forms in hard gelatin and HPMC without a gelling agent.

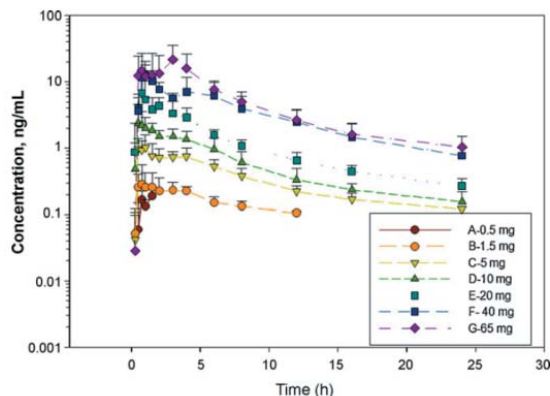
It can be concluded that there is no significant *in vivo* difference that comes from using an HPMC capsule that contains no gelling system. HPMC capsules have been shown to broaden the space for two-piece capsule applications in pharmaceutical product development and manufacturing. Characteristics and performance of HPMC capsules differ according to their manufacturing process, with those manufactured through a thermo-gelatin process closely reaching gelatin-like quality and *in vivo* performance.

Finally, *in vitro* dissolution and *in vivo* bioequivalency studies demonstrate that Vcaps® Plus is a good candidate for new APIs currently in development in gelatin--as well as potential switches for products registered in gelatin to the more robust HPMC capsule.

Figure 8: Published *in-vivo* performance.

In-vivo bioavailability studies performed on experimental compounds

- Dose escalating studies revealed the median T_{max} in each case at 1 hour, which was indicative of fast *in-vivo* shell disintegration and immediate release of the compound.

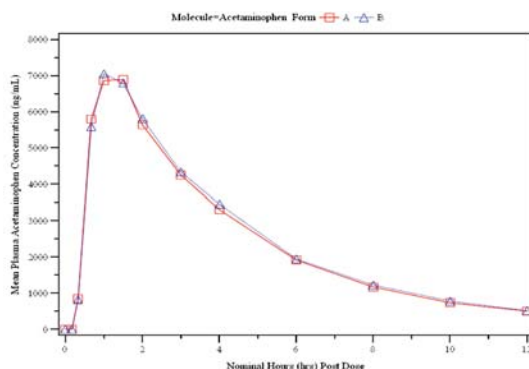
**Figure 9:** Bio-equivalence study design.

- Single-center, open label, single dose, randomized 2-way crossover study in 24 male healthy subjects under fasted conditions
- Excedrin® Extra Strength caplets as a sensitive marker for *in-vivo* dissolution and absorption of caffeine (65 mg), acetylsalicylic acid (250 mg) and acetaminophen (250 mg)
- Excedrin Extra Strength caplets were filled into HGC or Vcaps® Plus size 00 capsules. Subjects each took two.
- *In-vitro* dissolution test was carried out according to the USP-29 monograph for “acetaminophen, aspirin and caffeine tablets” using a USP dissolution apparatus 2 at 100 rpm [USP 29]
- *In-vivo* PK parameters: AUC_{0-t} , $AC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, C_{max} and T_{max} for acetaminophen, acetylsalicylic acid, total salicylate, unbound salicylic acid and caffeine

Figure 10: Acetaminophen.

In-vivo results and statistical analysis

N=24



In-vitro Modeling and Early Research into HPMC as a Functional Excipient

Using the three actives from the bioequivalence study described above, pharmacokinetic modeling of acetaminophen was performed to show that the *in vivo* profiles obtained were consistent with expectations, and to show the sensitivity of the PK profiles to the drug release profiles from the capsules (**Figure 13**).

In this modeling, two things were varied: the lag time for release of drug from capsule while keeping the dissolution rate constant; and the dissolution rate while keeping the lag time constant. The actual *in vitro* dissolution curves from HPMC and gelatin capsules are shown in the upper left. The upper right shows the resulting simulated PK curves for various lag times ranging from a few minutes to two hours. The bottom plot shows the effect of dissolution lag time on C_{max} , AUC , and T_{max} . And as expected, the C_{max} and AUC don't change appreciably whereas the T_{max} gets pushed out to longer times within increasing lag times.

Figure 14 shows the constant lag time with varying dissolution rate constants, which, although not seen experimentally, was modeled to assess the sensitivity of PK profile to dissolution rate. The modeling suggests no change in the AUC , and a decrease in C_{max} with decreasing dissolution rate, as expected.

We've seen that the soluble compounds are well absorbed in Excedrin have PK profiles for HPMC-based Vcaps® Plus and gelatin capsules that are expected to be similar. But there are applications for which the two capsule materials might perform differently.

Figure 11: Acetylsalicylic acid.

In-vivo results and statistical analysis

N=24

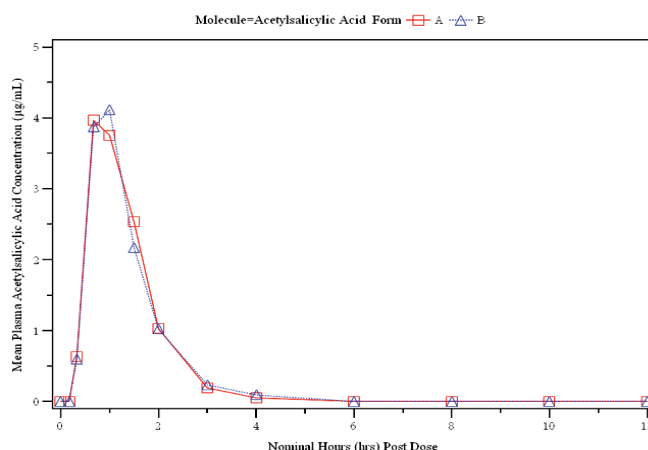
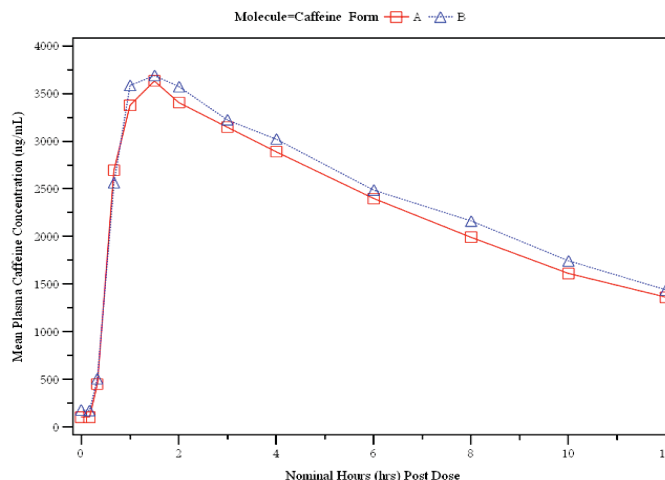


Figure 12: Caffeine.

In-vivo results and statistical analysis

N=24



Favorable HPMC drug interactions can lead to a reduced crystallization rate of drugs in the GI tract for poorly soluble drugs when using HPMC-based capsules. This can be important when there are super-saturated drugs in the intestine that can result from dosing either a high energy salt form, an amorphous form, or a weak basic API. In these cases, HPMC-based capsules can help maintain that super-saturation by inhibiting crystallization of the drug.

Evaluating Four Weakly Basic Drugs in Vcaps Plus vs. Gelatin

With the goal of developing a method to evaluate potential for capsule materials to inhibit precipitation/crystallization, four weakly basic drugs were evaluated: Erlotinib, Gefitinib, Ketoconazole, and Dipyridamole. All are relatively soluble in the ionized state in the low pH gastric environment, but have lower solubility at neutral intestinal pH, which can lead to a highly super-saturated state of the drug in the intestinal environment *in vivo*.

We would expect the sustainment of the drug to depend on the drug concentration relative to the gastric and intestinal solubility of the drug, as well as on the tendency of the API to crystallize, and on the type of capsule used. For all four of the drugs, we saw improvement of sustainment using the HPMC-based capsules relative to gelatin. **Figures 15** and **16** present the dissolution performances of all four drugs.

Drug sustainment as a function of drug concentration was also studied for the four weakly drugs, as this can have an effect on the crystallization precipitation kinetics. It was determined that sustainment depends on the drug concentration and is better with pre-dissolved HPMC (**Figure 17**).

A fair question would be whether these differences in sustainment observed *in vitro* are manifested *in vivo*. When dosed in HPMC-based capsules *in-vitro*, the HPMC inhibits crystallization of the free base leading to higher transient drug concentration (**Figure 18**). It is believed that HPMC-based

Figure 13: Modeling of Acetaminophen PK Profiles.

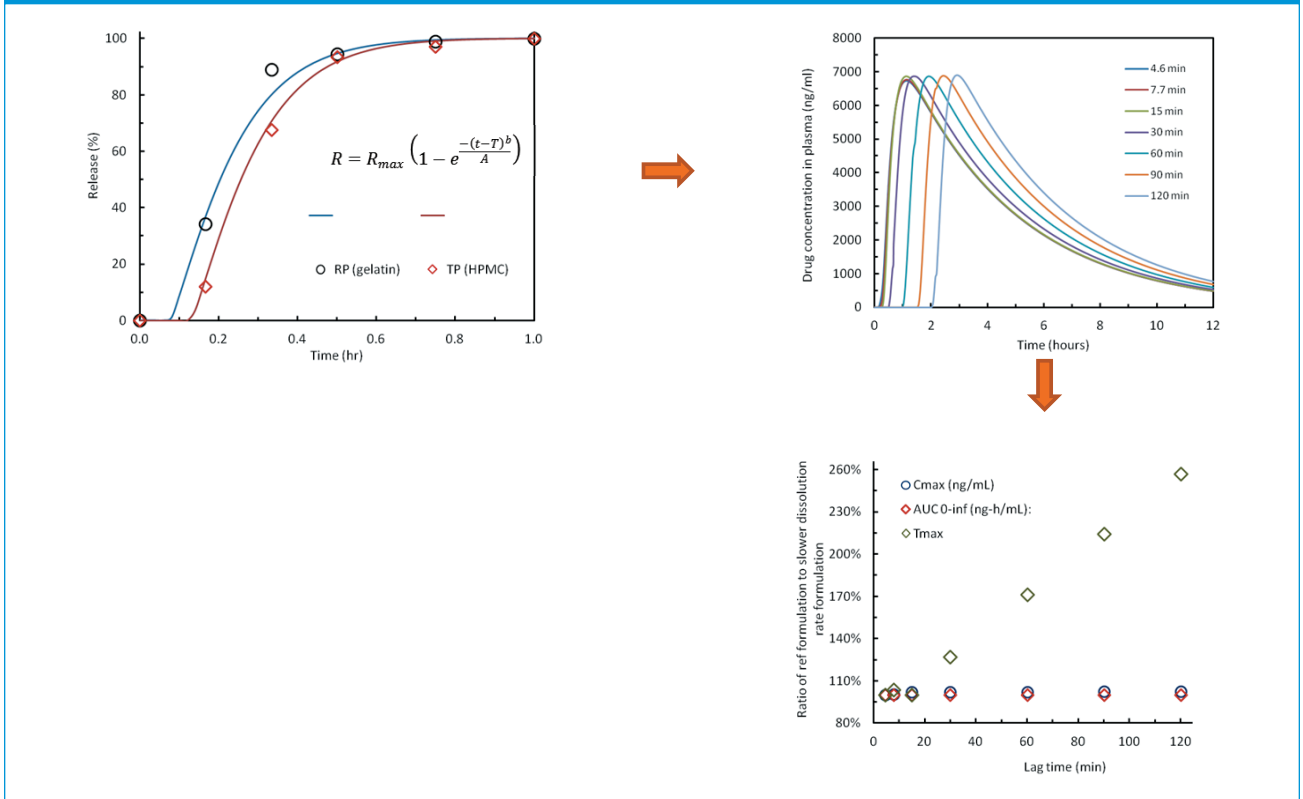


Figure 14: Modeling the effect of dissolution rate on PK Profile.

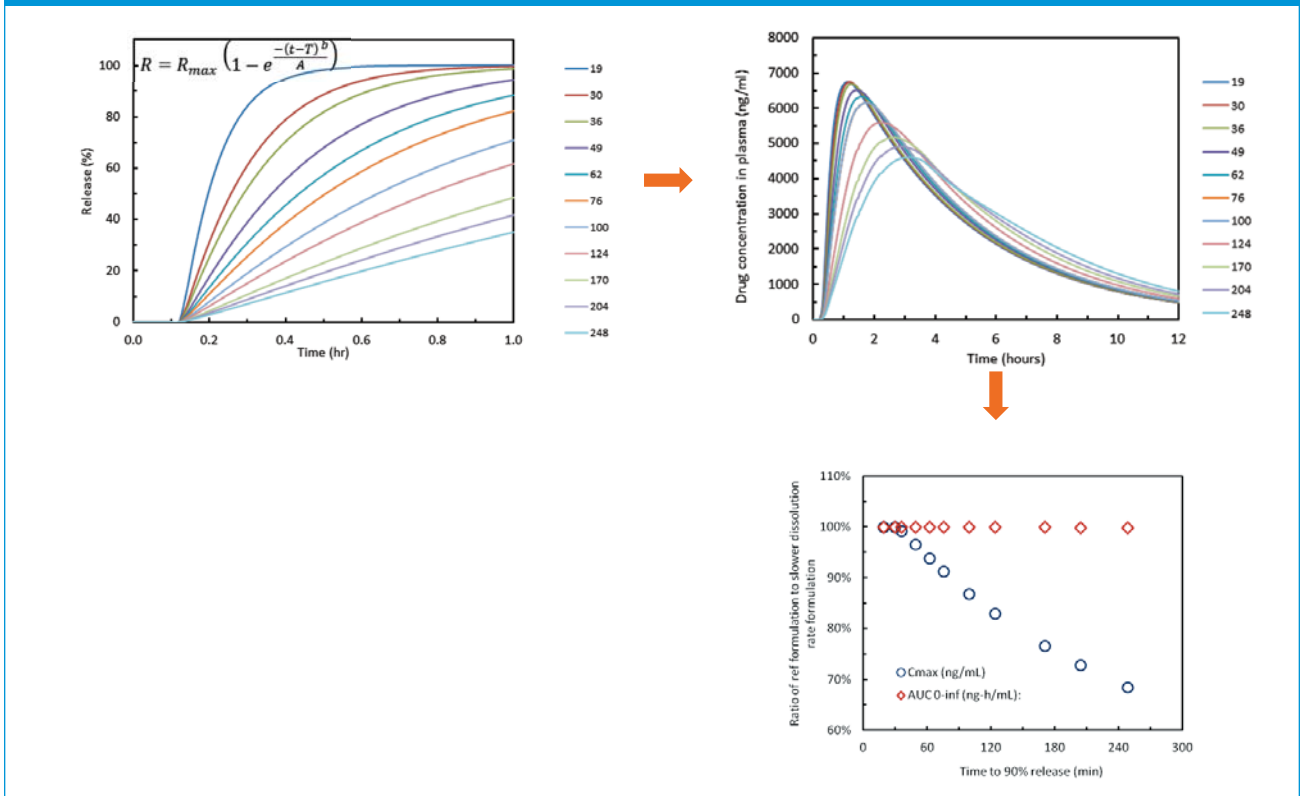


Figure 15: Weakly basic API in capsule dissolution performance.

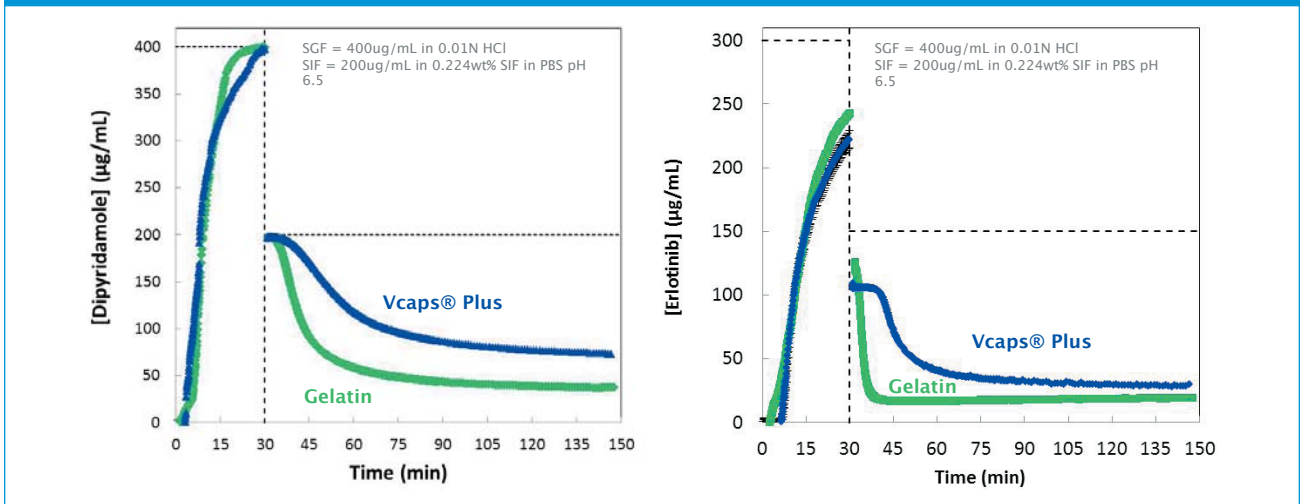


Figure 16: Weakly basic API in capsule dissolution performance.

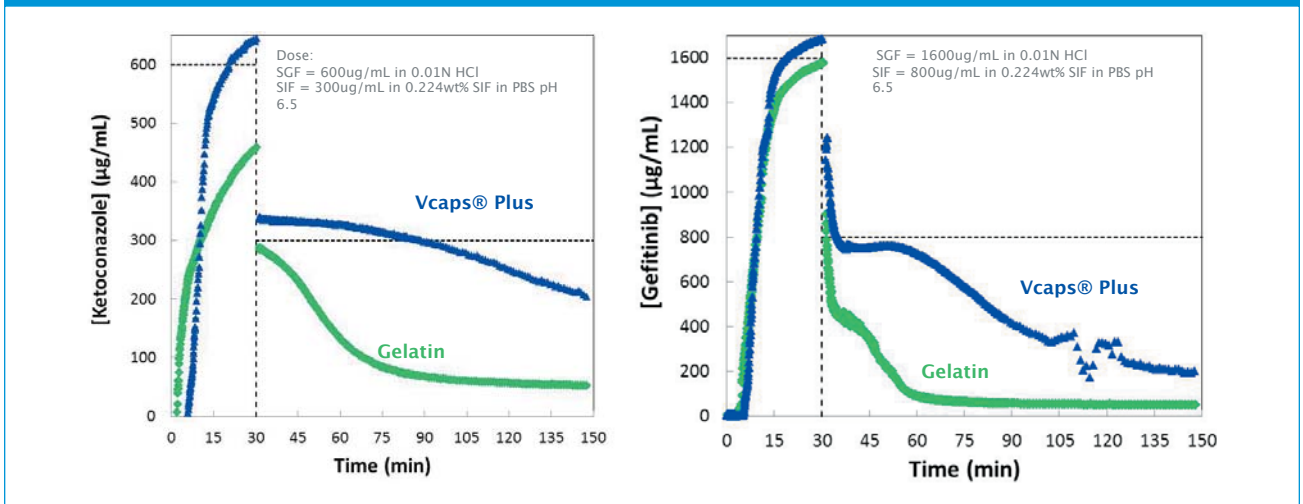


Figure 17: Sustainment of Erlotinib vs. dose after transfer from pH 2 to FaSSiF.

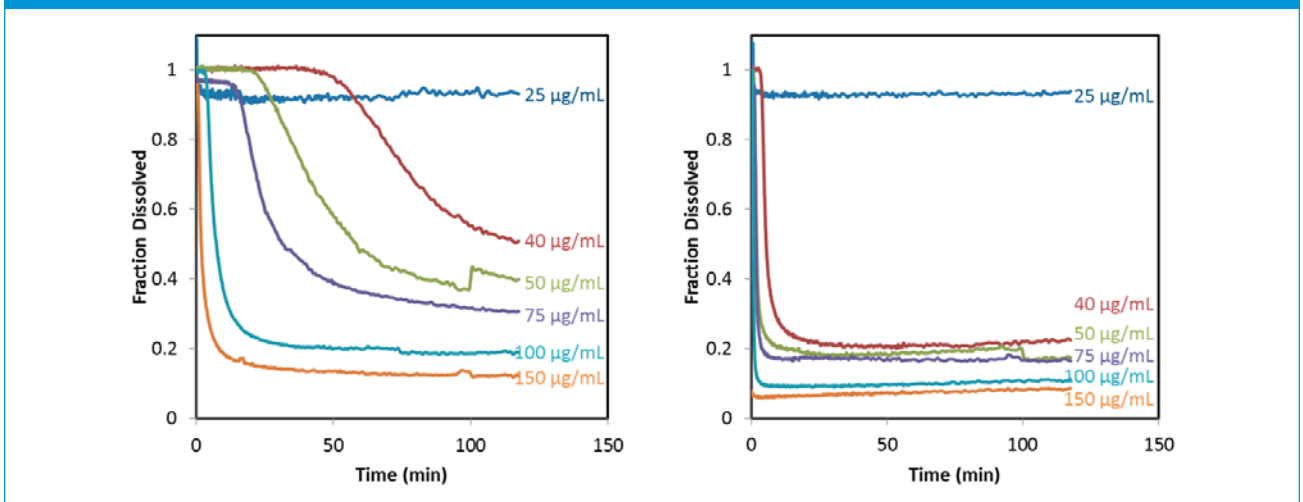
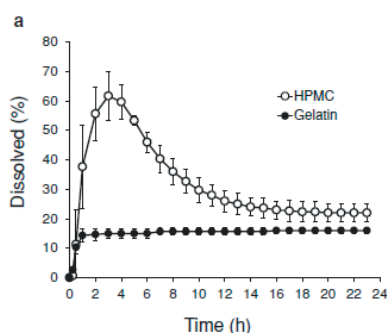
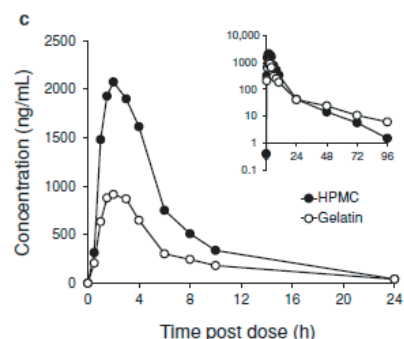


Figure 18: Literature example of increased *in-vivo* AUC for a drug encapsulated in HPMC vs. in Gelatin Capsules.

Effects of Particle Size, Food, and Capsule Shell Composition on the Oral Bioavailability of Dabrafenib, a BRAF inhibitor, in Patients with BRAF Mutation-Positive Tumors

DANIELE OUELLET,¹ KENNETH F. GROSSMANN,² GISELLE LIMENTANI,¹ NOELIA NEBOT,¹ KEVIN LAN,¹ LARA KNOWLES,¹ MICHAEL S. GORDON,³ SUNIL SHARMA,² JEFFREY R. INFANTE,⁴ PATRICIA M. LORUSSO,² GIRISH PANDE,¹ ELIZABETH C. KRACHEY,¹ SAMUEL C. BLACKMAN,¹ STANLEY W. CARSON⁵

¹GlaxoSmithKline, Research Triangle Park, North Carolina

²Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah

³Pinnacle Oncology, Scottsdale, Arizona

⁴Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, Tennessee

⁵Karmanos Cancer Institute, Detroit, Michigan

Received 7 November 2012; revised 1 March 2013; accepted 4 March 2013

JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 102, NO. 9, SEPTEMBER 2013

Dabrafenib mesylate dissolves to a super-saturated concentration (relative to the free base solubility at intestinal pH).

When dosed in HPMC-based capsules *in-vitro*, the HPMC inhibits crystallization of the free base leading to higher transient drug concentration (see figure).

It is believed that HPMC-based capsules also inhibit crystallization of dabrafenib free base *in-vivo* – leading to a higher dissolved drug concentration in the intestine, and higher AUC.

capsules also inhibit crystallization of dabrafenib free base *in vivo*, leading to a higher dissolved drug concentration in the intestine, and higher AUC.

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 to inhibit crystallization and help sustain the concentration of super-saturated drugs in the GI tract. Using HPMC as the capsule shell serves the dual role of encapsulating the formulation and providing a drug concentration sustaining excipient without having to incorporate the HPMC directly into the formulation itself. This could potentially simplify the formulation composition and processing, leaving more space in the dosage form to increase API load or other necessary excipients.

The Opportunity Space

The portfolio of molecules formulated at Bend showed that approximately 40% of them are weakly basic, that is, having

a basic pKa between 2 and 7. And almost all of these compounds are poorly water soluble. So there are quite a few compounds that potentially can benefit from HPMC-based capsules. And the opportunity space is larger than that because many non-basic drug compounds have low solubility and are therefore formulated as a high-energy form, such as an amorphous dispersion or a high-energy salt. These forms can super-saturate in the GI tract and potentially benefit from crystallization inhibition.

Summary

Gelatin and Vcaps® Plus capsules are likely to give similar performance for a broad range of applications where the API is relatively soluble and rapidly absorbed. For certain applications, such as for weakly basic crystalline APIs or for amorphous forms or low solubility APIs, Vcaps® Plus capsules may improve solubilization and precipitation inhibition.

Capsugel is a global leader in delivering high-quality, innovative dosage forms and solutions to healthcare companies around the world. Our customers turn to us for the science and engineering expertise they need to bring better medicines and nutritionals to market. As the world's leading provider of empty, two-piece hard capsules and an innovator of drug delivery systems, we continue to build on our decades-long track record of quality, reliability, innovation and value creation.

See more at: <http://www.capsugel.com/about/about-us#sthash.Oq1dErVb.dpuf>