CAPSUGEL®

Dominique Cadé

Vcaps® Plus Capsules

A New HPMC Capsule for Optimum Formulation of Pharmaceutical Dosage Forms

ABSTRACT

Hypromellose (HPMC) capsules were originally formulated with a secondary gelling agent. This agent can delay dissolution in some circumstances and lead to unwanted issues during product development.

In this article, we discuss the rationale for developing Capsugel's Vcaps® Plus capsules without a gelling agent. We also describe how these capsules – now in use at many major pharmaceutical companies to encapsulate their existing over-the-counter [OTC] products and New Chemical Entities [NCEs] – can optimize product performance and improve product stability, as well as reduce development timelines.

Figure 1: Gelatin capsule dipping

Rationale for HPMC capsules

Traditionally, hard capsule manufacturing by dip molding is based on the unique melting and solidifying properties of gelatin. By dipping stainless steel mold pins at room temperature into a hot liquid gelatin solution, a film of controlled dimensions is formed on the mold *(Figure 1)*. After drying, this results in capsule halves with shell wall thickness of 0.1 mm, as well as good flexibility and dissolution properties.

However, for some drug products, gelatin capsules may not provide sufficient protection against moisture (leading to drug degradation) or may become brittle (leading to capsule breakage)[1-4]. In addition, some patients and consumers prefer to take medication that does not contain any animal ingredients such as gelatin. Therefore, vegetarian capsules made of plant derived cellulose such as Hypromellose (HPMC) capsules were developed and have been used in pharmaceutical applications since 1998[5].

HPMC is a methyl and hydroxypropyl mixed ether of cellulose *(Figure 2)*. It contains, calculated on a dried basis, methoxy ($-OCH_3$: 31.03) and hydroxypropoxy ($-OC_3H_6OH$: 75.09) groups conforming to the limits for the types of HPMC shown in Table 1 at right.

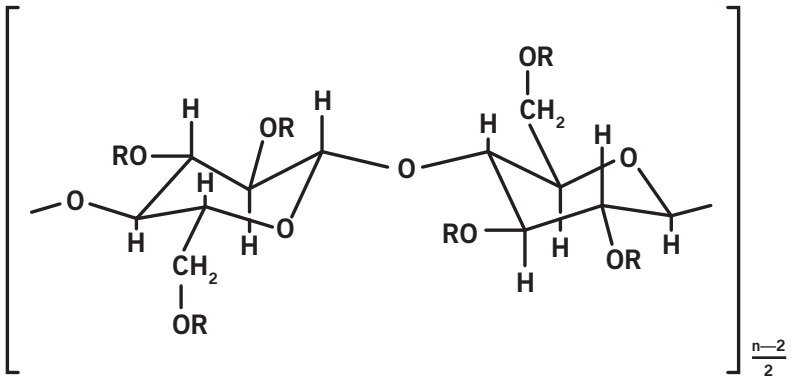


Figure 2: HPMC structural formula

	Methoxy (%)		Hydroxypropoxy (%)	
Substitution Type	**Min.**	**Max.**	**Min.**	**Max.**
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

Table 1: HPMC substitution types

The HPMC polymer has reasonable flexibility properties and with the use of secondary gelling agents, capsule manufacturers can generate quick setting HPMC, which promotes homogeneous film distribution on the molding pins *(Figure 3)*.

An issue with the use of secondary gelling systems is that they can interact with dissolution media causing delayed drug release that may be undesirable during product development. It is well established that the gelling of kappa-carrageenan is strongly enhanced by some cations, notably potassium and calcium. Within the stomach, the presence of foods containing potassium or calcium would cause an interaction that would delay or change the product release, something which is unacceptable for many drug products where rapid relief is required.

An *in vitro* dissolution test shows that in pH 1.2 USP medium, the switch from 2 g NaCl/L to 2 g KCl/L causes a significant delay in dissolution of capsules with kappa-carrageenan. The same occurs with the simulated milk fluid (*Figure 4*). Both of these show the influence of ionic media on HPMC capsules containing a gelling agent. This is comparable with data generated in an independent study[6] where drug release for two of three compounds tested was hindered in dissolution at pH 1.0 and attributed to the use of the gelling agent carrageenan in the capsules used. The study also reported a significant difference in behavior when switching from sodium to potassium phosphate buffer where potassium, the gelling promoter, caused delay in capsule opening and substantial increase in variability of dissolution.

Influence of gelling systems on HPMC capsules in dissolution testing

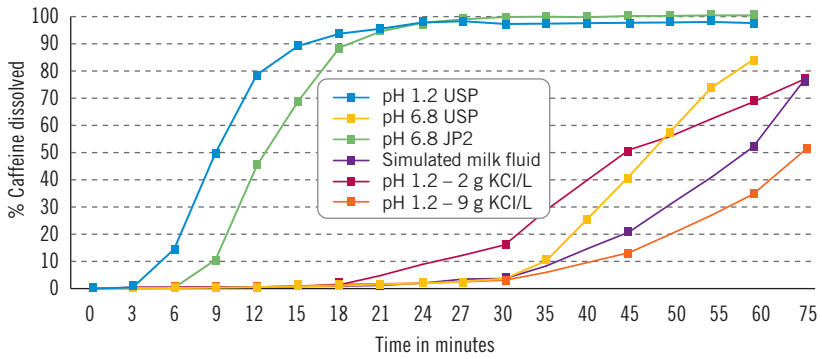
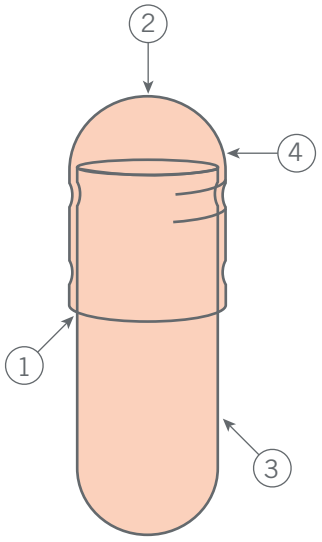


Figure 4: In vitro dissolution of caffeine filled in hypromellose capsules produced with gelling systems

Optimal hard capsule dimensions



1 - Gap between body and cap > 0.05 mm
2 - Top wall thickness > 0.12 mm
3 - Side wall thickness 0.1 mm
4 - Shoulder thickness > 0.07 mm

Figure 3: Hard capsule film distribution

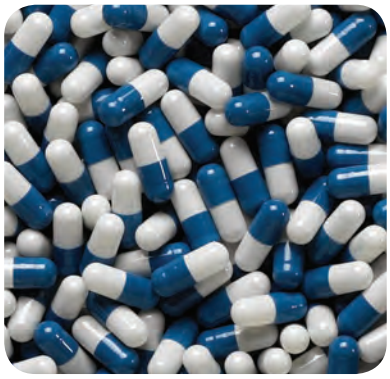


Figure 5: Transparent Vcaps® Plus capsules (top) and colored Vcaps® Plus capsules (bottom)

Development of HPMC capsules without gelling agents

To develop an HPMC capsule without using a gelling agent, Capsugel scientists assessed the impact of the mold pin temperature and conditions to achieve optimal capsule drying. From these studies, a thermal gelling process was selected that eliminated the need to use a gelling agent and salts as co-gelling agents. The resulting capsules are known as Vcaps® Plus capsules.

The manufacturing process was defined to ensure the highest levels of capsule performance and the capsules were tested to ensure reproducibility of their weight, dimensions, absence of defects and performance on filling machines. The resulting Vcaps® Plus capsules that were developed have a smooth surface that facilitates easy capsule handling. They can be transparent or colored opaque capsules *(Figure 5)*, which means they offer flexible dosage formats and are suitable for encapsulating OTC, NCE and off-patent products.

Properties of Vcaps® Plus capsules for optimizing product performance

To optimize the performance of an encapsulated drug, the capsules must disintegrate, as well as release their contents rapidly.

Disintegration and dissolution

A Capsugel in-house study utilizing a Sotax® disintegration test with an automated end point compared the disintegration times of Vcaps® Plus capsules with gelatin capsules *(Figure 6)*. The test shows that Vcaps® Plus capsules have a similar disintegration time to gelatin capsules and will disintegrate in less than 10 minutes.

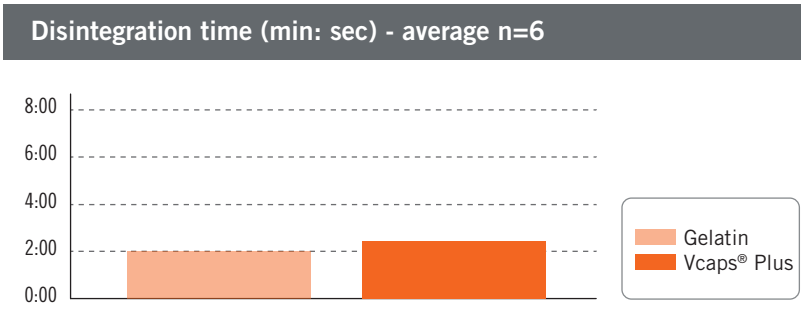


Figure 6: Disintegration time of Vcaps® Plus capsules compared to gelatin capsules

Dissolution of Vcaps® Plus capsules was tested with a variety of dissolution media at pH 1.2, pH 6.8 and in simulated milk fluid (*Figure 7*). The test demonstrated that Vcaps® Plus capsules exhibited independent dissolution from both pH affects and/or ionic media. These results are confirmed in an independent study[6] which compared HPMC capsules with and without a gelling system. The study reported capsules with gelling systems demonstrated both a retardation of dissolution at pH 1.0 and variability in dissolution using pH 6.8 phosphate buffer systems. Neither effect was evidenced with Vcaps® Plus capsules, which require neither a gelling agent nor a promoter.

Capsugel in-house tests[7] also demonstrate that dissolution time is independent of Vcaps® Plus capsule size *(Figure 8)*. These dissolution results demonstrate that Vcaps® Plus capsules provide a consistent and pH independent release of products. This means they offer a more effective alternative to HPMC capsules containing gelling systems for pharmaceutical manufacturers that want to optimize product performance.

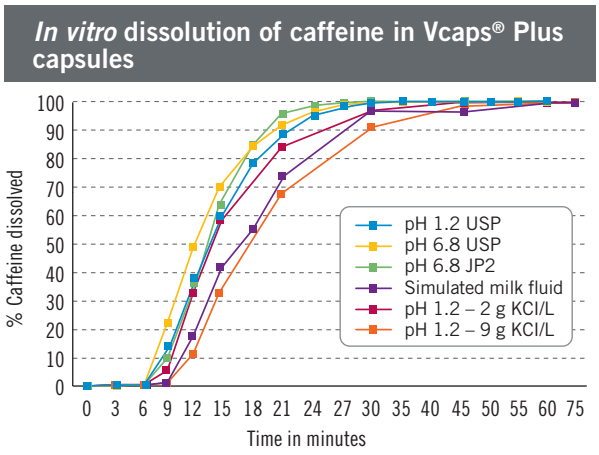


Figure 7: Caffeine in vitro dissolution with various dissolution media exhibit pH independence with Vcaps® Plus capsules

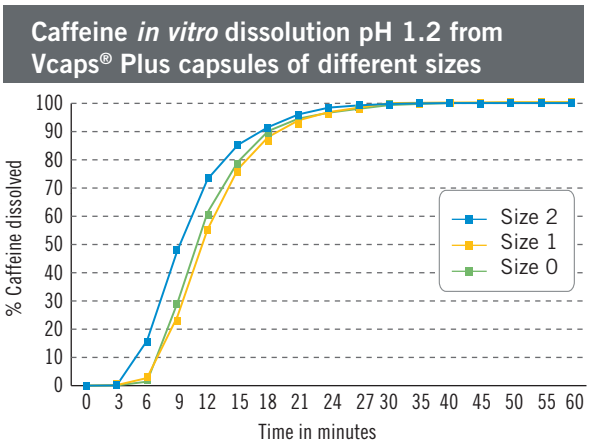


Figure 8: Caffeine in vitro dissolution pH 1.2 in Vcaps® Plus capsules of different sizes

Properties of Vcaps® Plus capsules for improving product stability

To ensure product stability, it is essential that Vcaps® Plus capsules protect the contents from degradation or product changes due to temperature fluctuations or exposure to moisture.

Temperature stability

In a Capsugel study, empty Vcaps® Plus capsules in closed HDPE bottles subjected to low temperature storage (4°C and -18°C) for up to one week did not show any changes in color, transparency, loss on drying (LOD), disintegration, dissolution or filling performance. In a second in-house study, empty Vcaps® Plus capsules stored in fully filled closed glass bottles and heated at different temperatures (40°C, 50°C and 60°C) for 24 hours in an oven, followed by five days storage at room temperature did not show any changes in disintegration, dissolution or mechanical performance. A short-term high temperature study of Vcaps® Plus capsules carried out at Wyeth[8] also indicated Vcaps® Plus capsules had greater resistance and less discoloration than hard gelatin capsules. These results demonstrate that Vcaps® Plus capsules have a stable formulation and exposing Vcaps® Plus capsules to high or low temperatures for short periods will not affect their physical or mechanical properties.

Long-term storage stability

In a Capsugel study, empty Vcaps® Plus capsules in closed HDPE bottles subjected to a range of storage temperature and relative humidity (RH) conditions (6 months at 40°C - 75% RH, 2 years at 25°C - 65% RH, 2 years at 30°C - 70% RH) did not show any changes in physical performance *(Table 2 showing 6 month data)*.

Capsule	Time point	Disintegration	Dissolution	Microbiology (as per TRF*)
Vcaps® Plus lot 90051731	Initial	4.0 minutes	96.50%	Pass
Nat. Transparent	6 months	4.1 minutes	95.90%	Pass
Vcaps® Plus lot 90053161	Initial	3.8 minutes	91.00%	Pass
Colored	6 months	4.5 minutes	94.00%	Pass

*TRF - Technical Reference File

Table 2: Performance of Vcaps® Plus capsules after 6 months storage (40˚C, 75% RH)

Effects of moisture

In the Wyeth study[8] empty Vcaps® Plus capsules stored at room temperature for one week in different RH conditions (2.5% – 6.5% RH) showed that Vcaps® Plus capsules have three-fold lower average moisture content than gelatin capsules and are less hygroscopic than gelatin. An in-house Capsugel study of Vcaps® Plus capsules and gelatin capsules stored in a range of RH conditions, also reported that there were fewer broken Vcaps® Plus capsules, showing the mechanical properties of Vcaps® Plus capsules are less affected by moisture changes than gelatin *(Figure 9)*.

These results indicate that as a consequence of being less hygroscopic, moisture transfer from a Vcaps® Plus capsule to the encapsulated product could potentially be reduced, helping to maintain product stability. Also, as water does not act as a plasticizer for Vcaps® Plus, the capsules are less likely to break even in dry conditions, again helping to maintain stability of products inside the capsule.

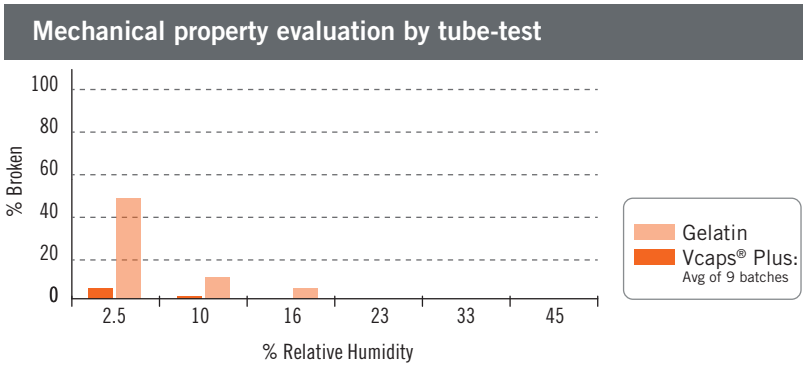


Figure 9: Mechanical properties of Vcaps® Plus capsules and gelatin capsules evaluated by the tube-test method. Tube Test: 100g weight dropped onto a capsule from a height of 8 cm

One example of how using less hygroscopic Vcaps® Plus capsules improves product stability and also effectiveness is the use of Vcaps® Plus capsules in Dry Powder Inhalers (DPIs). In a Capsugel study[9] when Vcaps® Plus capsules were tested in DPIs they exhibited a clean puncture *(Figure 10)* and kept active pharmaceutical ingredients (API) in the capsule drier, which produced better particle dispersion of the API. Therefore, as Vcaps® Plus capsules are less hygroscopic, this makes them ideally suited for rapid development of stable capsule formulations for use in DPIs.

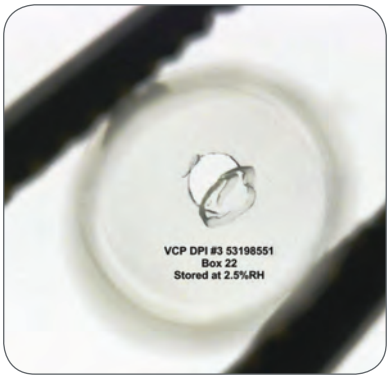


Figure 10: Vcaps® Plus capsule dome after puncturing in a DPI

Figure 11: Fused zone of sealed capsule: Microscope image of the microtome cup of a sealed Vcaps® Plus capsule

Properties of Vcaps® Plus capsules for reducing development timelines

For fast development of capsule based formulations in Vcaps® Plus, the products are easily integrated into existing capsule filling, sealing and coating operations and enable regulatory approval worldwide.

Filling and sealing performance

Performance trials on many common high-speed capsule filling machines (CFMs)[8] indicate that Vcaps® Plus capsules with their smooth and shiny finish show better performance than HPMC capsules containing gelling agents, in terms of filling and rejection rate, and have a similar performance to gelatin capsules. Therefore, development timelines can potentially be reduced if a formulation is being changed from a traditional HPMC and being encapsulated in Vcaps® Plus capsules.

Vcaps® Plus capsules are fully compatible with Capsugel's hard capsule Fusion process, for making one-piece hermetically sealed liquid-filled capsule. This involves application of a hydro-alcoholic sealing fluid followed by gentle heat to fuse the two capsule halves. Using this process, Vcaps® Plus capsules have a tight and reliable capsule seal *(Figure 11)*, making them a suitable capsule format to use for development or commercial manufacture of liquid formulations *(Figure 12)*.

Figure 12: Liquid filled Vcaps® Plus capsules sealed with Capsugel's Fusion® technology

Coating

Vcaps® Plus capsules coated to achieve enteric properties using the technique described by Cole et al[10] demonstrated good dissolution profiles *(Figure 13)* reported in in-house studies at Capsugel. This indicates Vcaps® Plus capsules can be used with common coating techniques and still maintain good physical performance properties.

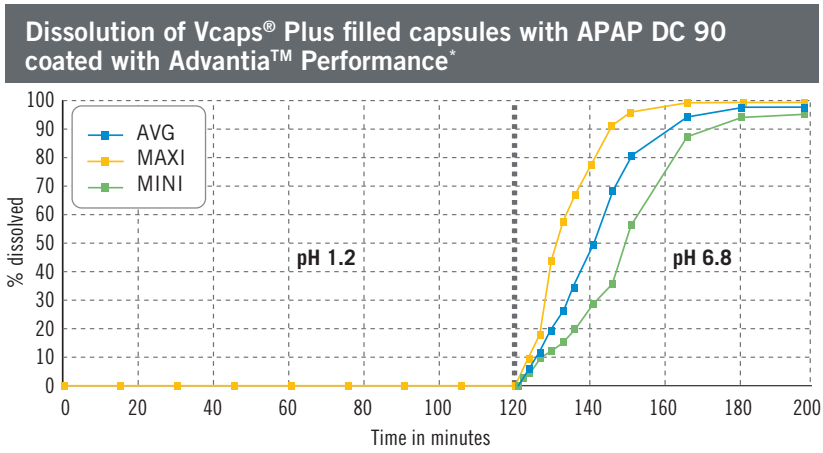


Figure 13: In vitro dissolution of APAP from enteric coated Vcaps® Plus capsules
**Advantia™ ISP Pharmaceuticals*

Regulatory environment

All primary components of Vcaps® Plus capsules are acceptable for use in pharmaceutical and dietary supplement oral dosage applications in major markets of the US, Canada, EU, Japan, and Australia. In addition, Vcaps® Plus capsules are certified Kosher by Ko, approved for vegetarians by the Vegetarian Society, and Halal by IFANCA. This is because Vcaps® Plus capsules are manufactured in accordance with IPEC's (International Pharmaceutical Excipient Council) Good Manufacturing Practice (GMP) Guide for Bulk Pharmaceutical Excipients, in facilities which are ISO 9001 certified. Additionally, post-capsule manufacturing treatments, such as lubricants, inks, packaging materials are available to meet individual country regulatory requirements. This means that use of the Vcaps® Plus capsule is a well established dosage form and can be used in product development programs and commercial manufacturing processes.

Conclusions

Vcaps® Plus capsules developed without gelling agents provide HPMC capsules with improved physical and operational features to match the needs of the pharmaceutical industry. Numerous studies have shown that Vcaps® Plus capsules have both good and consistent disintegration and dissolution properties, allowing quick release and optimizing product performance. Vcaps® Plus capsules are tolerant of high temperatures and are less hygroscopic than gelatin, making them well suited for encapsulating hygroscopic compounds, as well as formulations that include materials that are moisture sensitive or chemically unstable. They are also more resistant to breaking at low humidity, which can safeguard the encapsulated products during long-term storage. Vcaps® Plus capsules are acceptable for use in a GMP environment and can be used on many common capsule filling machines, where they show a better filling and rejection rate profile than traditional HPMC capsules, so they have the potential to reduce drug development timelines.

In summary, the proven properties of Vcaps® Plus capsules means they are an excellent alternative to gelatin or traditional HPMC for optimizing delivery, performance and stability of OTC, NCEs and off-patent products.

References

1. Rowe, R.C., Sheskey, P.S., Weller, P.J., Handbook of Pharmaceutical Excipients, 5th ed. Pharmaceutical Press (London, UK) and the American Pharmacists Association (Washington DC, USA), 2003.

2. Cole, S.K., Story, M.J., Attwood, D., Laudanski, T., Robertson, J., Barnwell, S.G., Studies using a non-ionic surfactant-containing drug delivery system designed for hard gelatin capsule compatibility. Int. J. Pharm. Vol. 88, 211–220, 1992.

3. Liebowitz, S.M., Vadino, W.A., Ambrosio, T.J., Determination of hard gelatin capsule brittleness using a motorized compression test stand. Drug Dev. Ind. Pharm. Vol. 16, 995–1010, 1990.

4. Brown, J., Madit, N., Cole, E.T., Wilding, I.R., Cadé, D., Effect of cross-linking on the *in vivo* disintegration of hard gelatin capsules. Pharm. Res. Vol. 15, 1026–1030, 1998.

5. Ogura, T., Furuya, Y., Matuura, S., HPMC capsules: an alternative to gelatin. Pharm. Tech. Europe. Vol. 10(11):32-42, 1998.

6. Ku, M.S., Lu, Q., Li, W., Chen, Y., Performance qualification of a new hypromellose capsule: Part II. Disintegration and dissolution comparison between two types of hypromellose capsules. Int. J. Pharm. Vol. 15; 416(1):16-24, 2011.

7. Groshens, E., He, X., Cadé, D., Hypromellose Hard Capsules – Reproducibility of the In Vitro Dissolution Performance in USP SGF Media. Poster presented at the 2009 Annual Meeting and Exposition of the American Association of Pharmaceutical Scientists http://capsugel.com/media/library/hypromellose-hard-capsules-reproducibility-of-the-in-vitro-dissolution-performance-in-usp-sgf-media.pdf.

8. Ku, S.M., Li W., Dulin, W., Donahue, F., Cadé, D., Benameur, H., Hutchison, K., Performance qualification of a new hypromellose capsule: Part I. Comparative evaluation of physical, mechanical and processability quality attributes of Vcaps® Plus, Quali-V and gelatin capsules. Int. J. Pharm. Vol. 15; 386(1-2):30-41, 2010.

9. Cadé, D., In Vitro Performance Testing and Capsule Optimization to Increase Fine Particle Fraction Delivered to the Lung presentation at 2nd Open Forum Pharmaceutics and Biopharmaceutics Istanbul 2012.

10. Cole, E.T., Scott, R.A., Connor, A.L., Wilding, I.R., Petereit, H.U., Schminke, C., Beckert, T., Cadé, D., Enteric coated HPMC capsules designed to achieve intestinal targeting. Int. Journal of Pharmaceutics Vol. 231 83–95, 2002.

For more information contact us at **marketing.amer@capsugel.com** or call **888-783-6361**.

capsugel.com