FORMULATION FLEXIBILITY WITH NEW ERA HPMC CAPSULES

In this article, Sanjay Powale, Head – Research & Development; Anita Solanki, Lead – White Papers and Publications; and Dorene Almeida, Lead – Application Lab, all of ACG, discuss the benefits of HPMC capsules in overcoming challenges faced by traditional gelatin capsules.

The two-piece hard capsule has evolved significantly since its inception around 170 years ago.[1] One of the most versatile dosage forms used for formulating pharmaceutical products, today's hard capsules have opened avenues for innovation by offering a high degree of flexibility in terms of what they can contain – from powders and pellets to semisolids and even liquids. Additionally, capsules can also be used to deliver more than one active ingredient with the added advantage of masking unpleasant taste and odour.

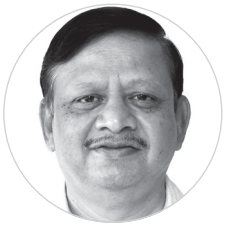
Traditionally, capsules have been made from gelatin which is obtained from animal sources. Owing to the high suitability of gelatin capsules in pharmaceutical formulations, they achieved significant success quickly. They are non-toxic, robust and easy to handle on high speed machines. Gelatin capsules disintegrate within 5–10 minutes in biological media. They also show rapid *in vitro* dissolution of immediate-release (IR) solid oral dosage forms which is desirable and is also an indication of satisfactory *in vivo* performance. Therefore, gelatin capsules are preferred by pharmaceutical manufacturers for producing IR formulations. Gelatin, due to its excellent gelling properties, forms robust films and has remained a popular choice among empty capsule manufacturers.

However, although nearly ideal, gelatin capsules are associated with challenges such as high inherent moisture content, which often leads to incompatibility issues when filled with moisture-sensitive ingredients; high susceptibility to adverse interactions with ingredients containing aldehydic functional group; and transmissible spongiform encephalopathies (TSE) and bovine spongiform encephalopathy (BSE) related concerns. These limitations have necessitated the introduction of newer polymers to advance into more sophisticated materials for manufacturing capsule shells.

> "HPMC capsules have inherently low moisture content which allows for the encapsulation of ingredients that are sensitive to moisture and are hygroscopic in nature."

HYDROXYPROPYL METHYLCELLULOSE (HPMC)

Hydroxypropyl methylcellulose (HPMC), a cellulose-based polymer (derived from plant sources), which has been used in pharmaceutical products for many years as an excipient in various formulations and coating applications, successfully addresses most of the limitations of gelatin when used as capsule shell material.[2] HPMC complies with global pharmaceutical regulatory norms and it is acceptable as an additive for human consumption in accordance with



Sanjay Powale
Head – Research & Development
T: +91 22 7194 8411
E: sc.powale@acg-world.com

Anita Solanki
Lead – White Papers & Publications
T: +91 22 7194 8419
E: anita.solanki@acg-world.com

Dorene Almeida
Lead – Application Lab
T: +91 22 7194 8416
E: dorene.almeida@acg-world.com

ACG Capsules
Plot 131
Kandivali Industrial Estate
Kandivali West
Mumbai – 400 067
India

www.acg-world.com

US Code of Federal Regulations Title 21 Section 172.874 and EU Regulation (EC) No. 1333/2008. It is also listed in the US FDA Inactive Ingredient Database.[3]

HPMC CAPSULES

Two-piece HPMC capsules were first developed in 1989 as a vegetarian alternative to hard gelatin capsules. HPMC capsules is certified by Vegan USA, and the UK Vegetarian Society. It is also certified by various Kosher and Halal certifying bodies.

HPMC capsules have inherently low moisture content which allows for the encapsulation of ingredients that are sensitive to moisture and are hygroscopic in nature. This has greatly broadened the scope of capsules in drug delivery. Due to their manifold advantages, HPMC capsules are gradually gaining popularity among pharmaceutical and nutraceutical manufacturers.

HPMC CAPSULE MANUFACTURING PROCESS

The method used for manufacturing HPMC capsules conventionally has been adapted from the gelatin capsule making process. The process involves dipping cold pin moulds into a hot solution of HPMC followed by gelation at low temperature and then drying to obtain the capsules. This method is perfectly suitable for gelatin because it gels on its own at cold temperatures, unlike HPMC. So, to manufacture HPMC capsules by this method, the incorporation of a gelling system is required. The gelling system usually includes a gelling agent such as carrageenan,[4] gellan gum, pectin and gel promoters such as potassium ions, calcium ions and sodium ions, which help in forming the capsule shell.

Dissolution testing is a very important parameter for predicting a product's efficacy. Achieving the desired dissolution criterion with regular HPMC capsules can sometimes be challenging. To address this lacuna, ACG Capsules has specially formulated ACGcaps™ H+ and ACGcaps™ HA. These newer variants of HPMC capsules not only exhibit gelatin-like dissolution performance but also possess several other additional advantages. The *in vivo* and *in vitro* performances of HPMC capsules largely depend on the capsule shell composition and manufacturing process. Hence, by employing a novel technology that eliminates or limits the use of gelling system, ACG Capsules has been able to produce HPMC capsules that are capable of superior dissolution. The advanced technology used to manufacture ACGcaps™ H+ is called thermo-gelation. This process is ideal for polymers such as HPMC which exhibit gelling capabilities at high temperatures. HPMC is liquid at lower temperatures and completely soluble in water. This procedure of manufacturing capsules involves dipping hot pin moulds in a cold solution of HPMC and achieving gelling under hot conditions. This does not require the use of any gelling system due to the temperature-dependent rheological behaviour of the HPMC polymer.

> "ACG is the first and only capsule manufacturer in the world to be certified by the Clean Label Project for ACGcaps™ H+. This certification confirms that ACGcaps™ H+ capsules are clean, safe, healthy and contaminant-free."

ACGcaps™ H+

Since there are no gelling agents or promoter, ACGcaps™ H+ only contains HPMC as the film forming polymer of the capsule. It shows superior dissolution performance compared with regular HPMC capsules, releasing its contents independently of pH and ionic strength of the dissolution media that is comparable to gelatin capsules. These capsules are suitable for filling ingredients that are hygroscopic and/or sensitive to moisture. Additionally, the absence of gelling agents eliminates the chance of any possible interaction with the dissolution media. Due to its vegetarian source, this capsule supports the claims of Vegan society and meets global dietary needs and preferences. ACG is the first and only capsule manufacturer in the world to be certified by the Clean Label Project for ACGcaps™ H+. This certification confirms that ACGcaps™ H+ capsules are clean, safe, healthy and contaminant-free.

> "Regular HPMC capsules made using carrageenan as a gelling agent show variable drug release patterns in certain dissolution media. However, this does not hold true for ACG's ACGcaps™ HA."

DISSOLUTION PROFILE: PH INDEPENDENT DRUG RELEASE

Regular HPMC capsules exhibit differences in dissolution at different pH levels. At certain pH levels, the dissolution profile may not meet the desired criteria. However, ACGcaps H+ does not show a pH-dependent dissolution profile. This has been further demonstrated with a study conducted using ACGcaps™ H+. An *in vitro* dissolution study of ACGcaps™ H+ containing acetaminophen was conducted in five different dissolution media of varying pH and ionic strengths. The capsules showed pH independent release. The result of this dissolution study is represented in Figure 1.

The dissolution study that was conducted on ACGcaps™ H+ confirms its pH-independent drug release profile in all five dissolution media.

KEY BENEFITS OF ACGcaps™ H+

- Dissolution is independent of pH and ionic strengths
- Consistent dissolution performance across all biological pHs
- Possesses disintegration characteristics that are comparable to gelatin capsules
- Made primarily with HPMC and water, without processing aids such as gelling agents
- Clean, inert and robust capsules for pharmaceutical and nutraceutical applications
- Remain stable and robust on storage across a broad temperature range.

ACGcaps™ HA

Regular HPMC capsules made using carrageenan as a gelling agent show variable drug release patterns in certain dissolution media. However, this does not hold true for

ACGcaps™ HA, which contain carrageenan as a gelling agent and employs a modified manufacturing process. It is an inert and high performing HPMC capsule that is intended for pharmaceutical applications. These capsules are suitable for molecules that need to meet the required dissolution criterion in 0.01N HCl. They are also suitable for hygroscopic and moisture sensitive ingredients.

ACGcaps™ HA is specially designed for molecules such as dabigatran etexilate mesylate whose dissolution medium assigned by the FDA's Office of Generic Drugs is 0.01N HCl.

In order to examine the dissolution performance of these capsules, a study was performed with dabigatran etexilate mesylate capsules. The innovator product contained the drug in the form of pellets that were filled into capsules. Dissolution of ACGcaps™ HA (containing dabigatran etexilate mesylate pellets) and the innovator product was carried out using the method described in Table 1.

CHALLENGES WITH OTHER CAPSULES

Inconsistent dissolution profile and variation in drug release in 0.01N HCl was observed. However, with ACGcaps™ HA capsules, desired dissolution performance in 0.01N HCl was observed which was in-line with the innovator product. The results have been presented graphically in Figure 2.

This dissolution of ACGcaps™ HA confirms its desirable dissolution properties for dabigatran.

KEY BENEFITS OF ACGcaps™ HA

- Suitability for molecules that need to achieve the desired dissolution performance in 0.01N HCl (pH 2.0)
- Modified capsule shell composition for better dissolution performance
- Less susceptible to cross linking
- Consistent quality and machine performance

CONCLUSION

HPMC capsules are now being extensively used by many leading pharmaceutical manufacturers globally. In 2019, five new capsule products were launched in different HPMC capsule variants by prominent pharmaceutical companies. Today, the commercially available HPMC capsules range from conventional powder-fill to liquid-fill capsules, sprinkle capsules, dry powder inhalation capsules and much more, offering greater formulation flexibility for product development.

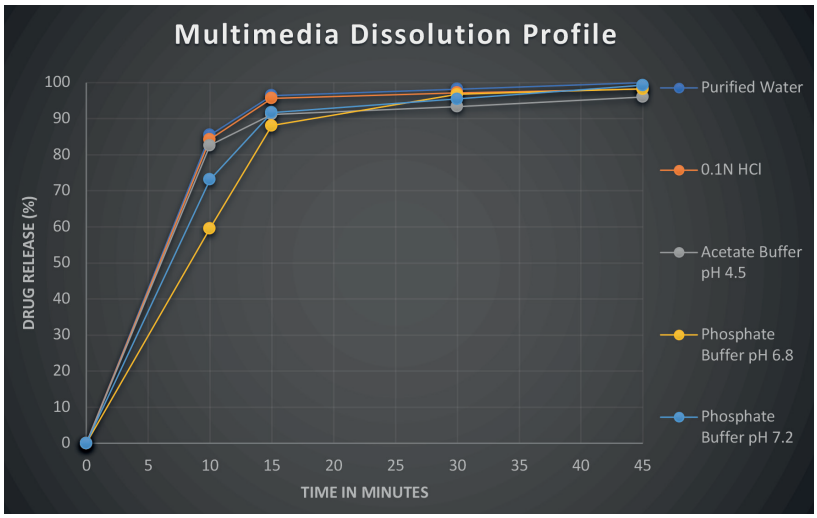


Figure 1: Dissolution profile of acetaminophen in ACGcaps™ H+. (Apparatus used: USP Type 2; Volume: 900 mL; Speed: 50 rpm; Time interval: 10, 15, 30 and 45 minutes.)

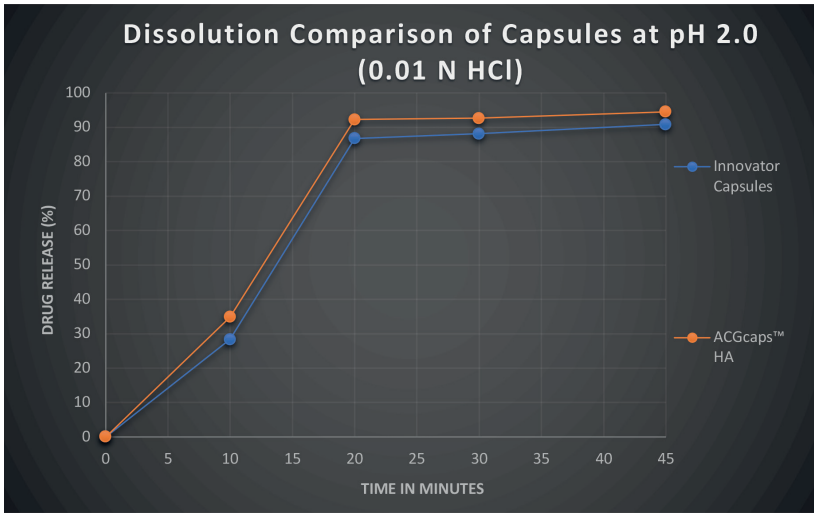


Figure 2: Dissolution profile of ACGcaps™ HA versus innovator capsules containing dabigatran etexilate mesylate pellets. (Apparatus: Modified Basket; Capsule size: 0; Speed: 100 rpm.)

USP Apparatus	Speed (RPM)	Medium	Volume (mL)	Sampling Time Points (minutes)
I (Basket) for 75 mg I (Basket with modified diameter of 24.5 mm) for 150 mg	100	0.01N HCl (pH 2.0)	900	10, 20, 30 & 45

Table 1: FDA-recommended dissolution method for dabigatran etexilate mesylate.

"...the commercially available HPMC capsules range from conventional powder-fill to liquid-fill capsules, sprinkle capsules, dry powder inhalation capsules and much more, offering greater formulation flexibility for product development."

With a strong focus centred around innovative therapy, ACG Capsules has been able to devise new era products to provide pharmaceutical manufacturers with

better drug delivery. The thermally gelled capsule, ACGcaps™ H+, not only delivers the clean label promise but also significantly aids the achievement of desired dissolution characteristics across all biological media and helps formulate stable products. This variant can be used for pharmaceutical and nutraceutical products. For specific pharmaceutical products faced with dissolution hurdles, ACGcaps™ HA is the optimal choice.

ABOUT THE COMPANY

ACG has been serving the pharmaceutical industry for more than five decades. It is one of the largest manufacturers of empty hard capsules in the world. The company's integrated pharmaceutical manufacturing solutions encompass a varied portfolio of not only capsules, but also packaging films and foils and extends further to tablet manufacturing, encapsulation, end-to-end packaging and inspection machines, all of which operate with the synergy of delivering the One ACG experience. ACG has a presence in over 100 countries and a strong team of nearly 3,200 associates that collaborate to provide world-class technologies across multiple domains.

REFERENCES

1. *Kendall RA, Basit AW, "The Role of Polymers in Solid Oral Dosage Forms". Polymers in Drug Delivery, 2006, Edition 1, pp 35–48.*
2. *Moawia MA, "HPMC Capsules: Current Status and Future Prospects". J Pharm Pharm Sci, 2010, Vol 13(3), pp 428–442.*
3. *Majee SB, Avlani D, Biswas GR, "HPMC as Capsule Shell Material: Physicochemical, Pharmaceutical and Biopharmaceutical Properties". Int J Pharm Pharm Sci, 2017, Vol 9(10), pp 1–12.*
4. *Patil D, Kalafat J, Bhat J, Powale S, Giripunje A, Diez F, HPMC Capsules in DPIs: Evaluation of the Puncturing Force using Capsules Prepared by Different Manufacturing Methods and having Different Compositions. Drug Delivery to Lungs, 2018.*

ABOUT THE AUTHORS

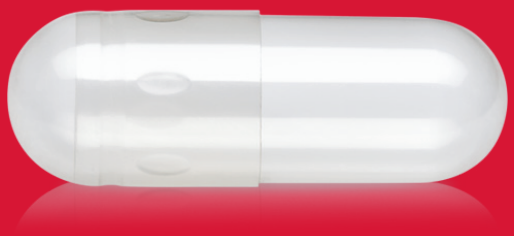
Sanjay Powale is Head of Research & Development at ACG Capsules. He leads the innovation teams and is responsible for building a pipeline of new products, for the material sciences division and for formulation, which ensures parity or differentiation with competition. Mr Powale keeps a close watch on emerging technologies and science to be incorporated to build cutting edge technology for manufacturing of hard capsules. For protection of business interest, he also drives publications of white papers, application notes and patents.

Anita Solanki, Lead – White Paper & Publications, team of ACG Capsules for over two years. She had been involved in the Research & Development department with a cumulative experience of about four years. Her primary responsibility includes creating, writing and publishing scientific literature, involvement in segmented solutions for customers and preparing research articles. Ms Solanki also leads all the industry-institute collaborative projects and research activities to support ACG branding initiatives.

Dorene Almeida, Lead – Application Lab, is a key member of the Research & Development department at ACG Capsules with a total experience of five years. Ms Almeida is involved in all activities in the Application Lab (Pharma), where her primary responsibility is to help customers resolve their capsule formulation challenges. Along with this, she is also a lead in performing scientific studies on capsules which provide solutions for numerous capsule-based formulations. She also works closely with new polymer development laboratories and the scientific business development team for new products.

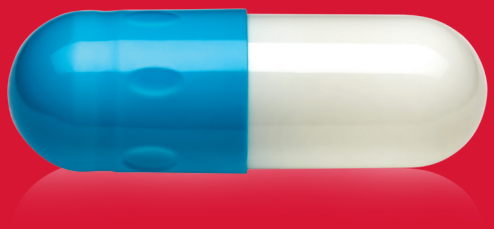
IS MEETING THE DESIRED DISSOLUTION CRITERION GETTING INCREASINGLY CHALLENGING?

Not anymore! ACGcaps™ H+ and ACGcaps™ HA are here to make it easy



ACGcaps™ H+
HPMC Plus Capsules

Made with HPMC and water, these capsules are ideal for immediate-release products. They exhibit excellent dissolution performance releasing all contents independent of pH and ionic strength.



ACGcaps™ HA
Platinum Standard in HPMC Capsules

These capsules possess superior dissolution characteristics and are a perfect fit for drugs which need to meet the dissolution criterion in 0.01N HCl. They are suitable for moisture-sensitive ingredients.

Making the world healthier, together.

Scan the code to get in touch with us and know more about our new age HPMC capsules

ACG CAPSULES