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TAKE CONTROL OF YOUR FORMULATIONS

An essential guide for selecting METHOCEL™ hydroxypropyl methylcellulose excipients

SYNOPSIS

Controlled release (CR) formulations are revolutionizing drug delivery across the pharmaceutical landscape. Offering advantages like enhanced therapeutic outcomes and patient convenience, this innovative drug formulation is experiencing rapid global growth. The popularity of CR formulations is particularly notable in epilepsy, diabetes, hypertension and chronic pain management, where safe, long-term treatment is needed.

However, as the market progresses to address the ever evolving and unique needs of patients, CR formulations are becoming more complex. To keep pace, the next generation of cutting-edge CR delivery systems demand even more from functional excipients.

Polymeric excipient solutions, like METHOCEL™ hydroxypropyl methylcellulose (HPMC), serve as a foundation for CR performance – essential for facilitating the gradual release of active ingredients over an extended period of time. Without them, CR mechanisms wouldn't be possible. But do you know exactly how excipient properties impact CR performance?

Understanding this is pivotal for achieving tailored release profiles with differentiated performance – and staying one step ahead in the CR landscape with advanced formulations.

Ready to take control of your formulation?

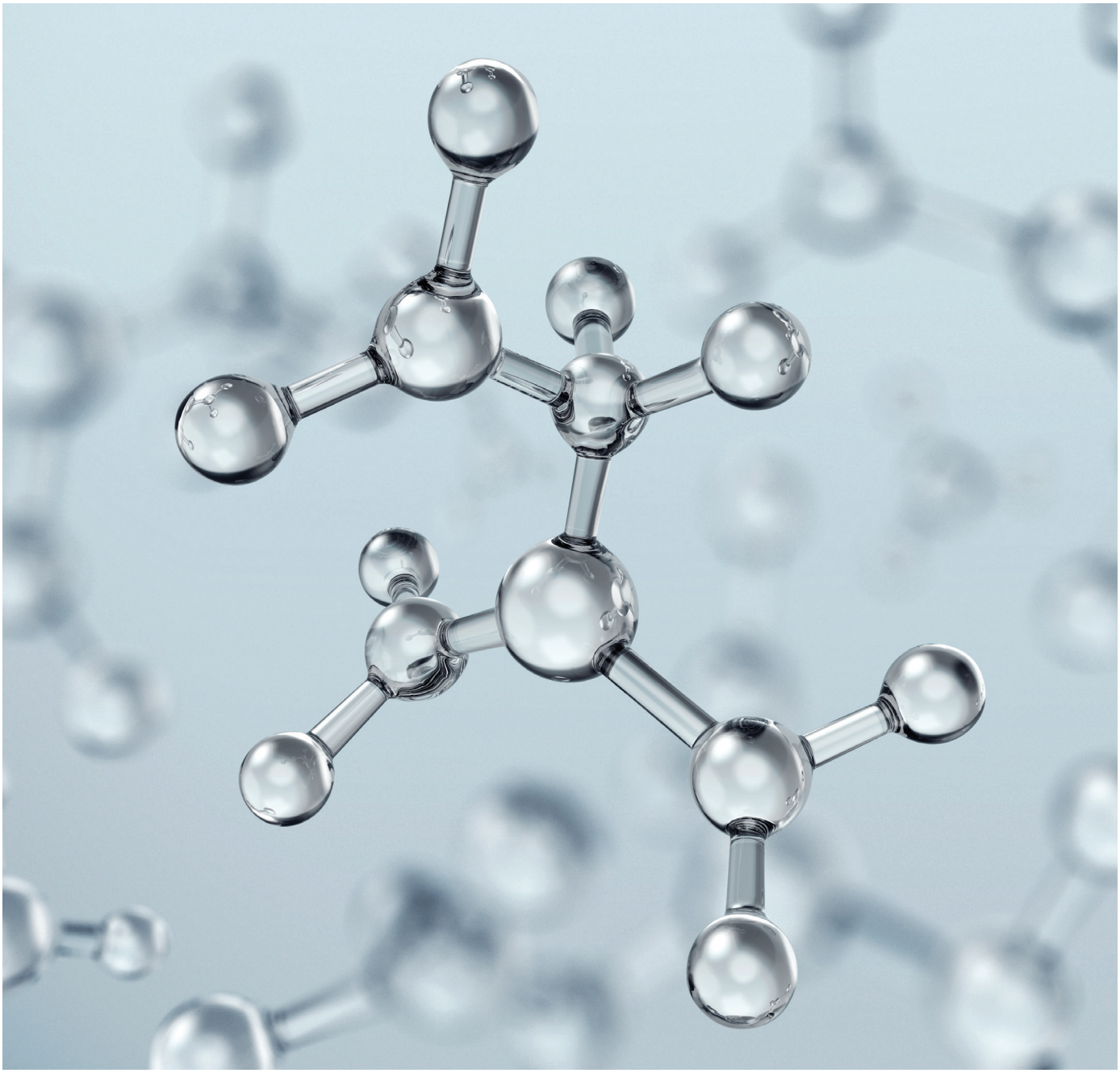
Learn why excipient choice matters – using METHOCEL™ HPMC as an example – and unlock four considerations for mastering robust CR delivery performance.

WHY METHOCEL™ HPMC CHOICE MATTERS

Patients prefer solid oral dosage forms. And hydrophilic matrix systems are among the most widely used means for controlled drug delivery in solid oral dosage.

Functional excipients are essential in CR formulations as they help to control the release of the active ingredient over a specified time period; supporting therapeutic efficacy and patient compliance. Many innovative CR formulations, including hydrophilic matrix tablets, utilize high molecular weight, water-soluble cellulose ethers, like HPMC, to achieve desired CR performance. However, with an array of HPMC solutions (and other excipients) available – all with different molecular weights, degrees of substitution and viscosity – formulators face the challenge of selecting the most suitable HPMC type or grade to meet their specific release performance targets.

The first step in choosing the right excipient requires comprehensive knowledge of how the molecule's specific properties influence drug release. To support formulators in leveraging the best excipient for their unique CR needs, we have outlined four things every CR drug manufacturer should know about HPMC chemistry.



1. Cellulose ether chemistry

The CR mechanism of a hydrophilic matrix tablet is achieved through the formation of a robust and continuous hydrogel layer around the matrix tablet. It forms when the tablet contacts an aqueous media – like fluid in the gastrointestinal tract – and HPMC particles near the tablet surface hydrate, swell, and coalesce; creating a swollen gel layer around the matrix core.

This gel later acts as a barrier, controlling the release of active ingredients from the dosage form and thereby regulating its release rate. At first glance, the excipient's gel strength may appear essential for achieving the hydrogel layer. However, there are other factors at play.

Don't forget powder dissolution temperature (PDT)
Take methylcellulose (MC) and HPMC excipients as an example. Both produce clear and viscous solutions when dissolved at low temperatures, but MC forms a strong gel and HPMC forms a weak gel upon heating (Figure 1). , If gel strength is strongly linked to the development of the swollen hydrogel layer, this suggests that MC would outperform HPMC in CR applications. However, it does not.

HPMC excipients emerge as superior for CR functionality – despite forming weaker gels. The reason for this is because powder dissolution temperature (PDT) is a key factor to consider (Figure 2). Excipients are present as dry particles (and not as dissolved solutions) in CR matrix tablets, and they must first hydrate from dry state, swell and combine with other particles nearby to form the hydrogel layer. This suggests that the temperature at which the polymeric powder dissolves is a more important parameter for CR performance.

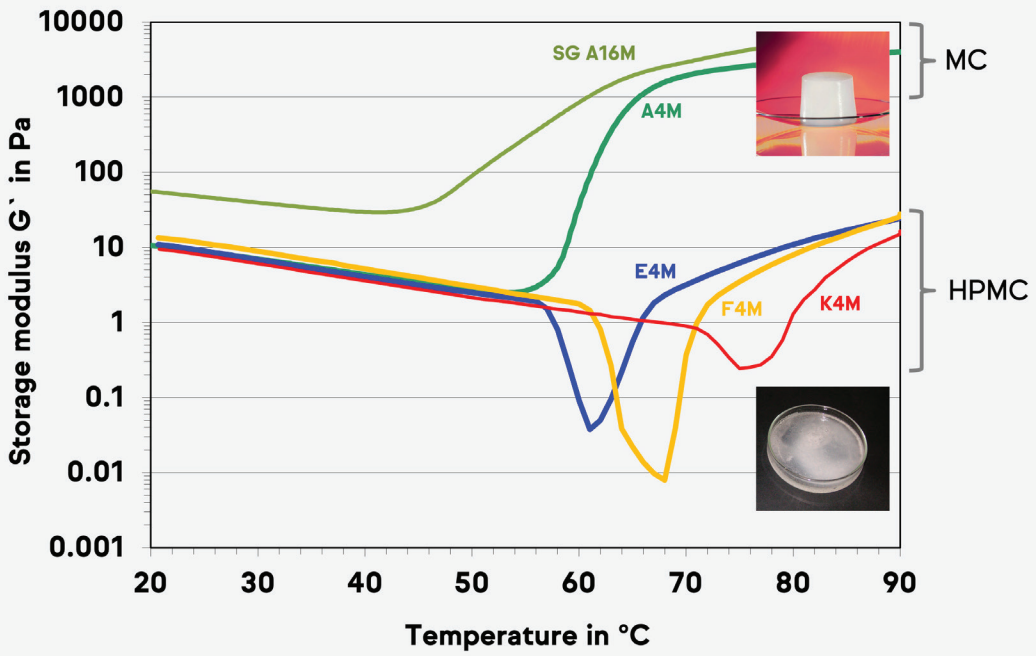


Figure 1: Gelation and precipitation of MC versus HPMC solutions based on rheological temperature-sweep measurements. When dissolved (at a concentration c = 2%) and heated to temperatures exceeding 60 °C, MC and HPMC performed differently – MC forms a gel and HPMC undergoes precipitation, followed by weak gel formation.

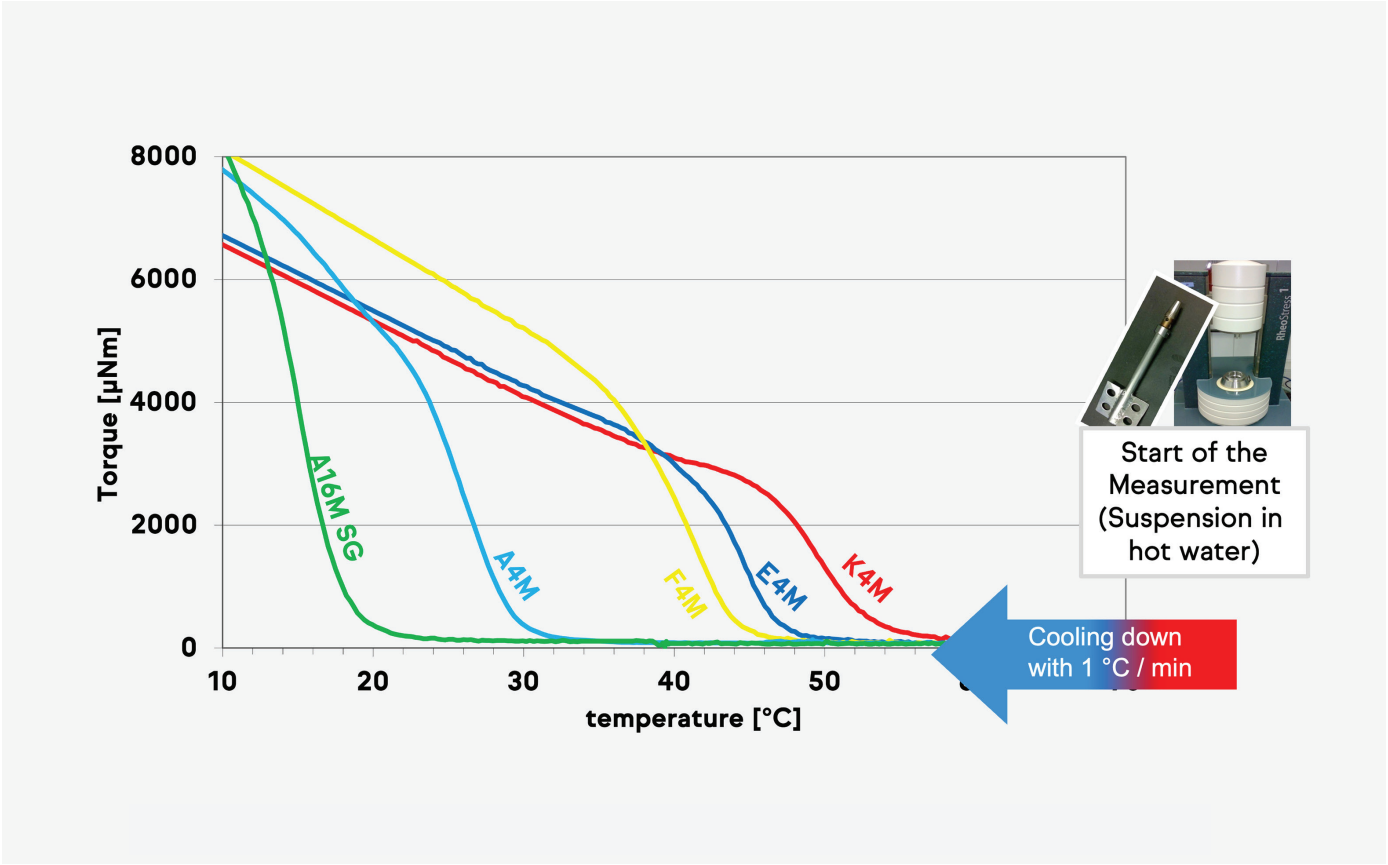


Figure 2: Comparison of the powder dissolution temperature (PDT) measurements between MC (A16MSG and A4M) and HPMC (F4M, E4M and K4M) polymeric excipients.3 HPMC grades demonstrate higher PDTs than MC. The K-Chemistry HPMC (K4M) has the highest PDT, at a temperature above 50 °C. On the other hand, the A-Chemistry MC grades had notably lower PDTs, in the range of 30 °C and below.

Key takeaway for formulators?

Polymer chemistry – whether it is MC or HPMC – impacts temperature-dependent hydration of the excipient particles (or PDT) in a matrix tablet. HPMC excipients – especially K-Chemistry grades – exhibit the highest PDTs (above body temperature), meaning they can more readily hydrate at physiological temperature to form a hydrogel layer around the matrix tablet.

2. Particle size

Another key factor for attaining a strong and uniform hydrogel layer – and facilitating reliable CR performance – is achieving a percolating network of HPMC particles throughout the matrix tablet. This is a continuous lattice of equally distributed HPMC particles, close enough to hydrate and coalesce and form the hydrogel layer.

The size of HPMC particles affects how well this network forms throughout the tablet. For example, smaller HPMC particles (45-125 µm) form a robust, contiguous hydrogel layer with low porosity upon hydration – reducing API release rates. However, larger HPMC particles (125–355 µm) form less contiguous swollen hydrogels with greater pore sizes, leading to faster API release rates.

Key takeaway for formulators?

The particle size of HPMC affects the ability of the excipient to form a percolating network of particles throughout the matrix tablet. If HPMC particles are larger, a higher concentration of HPMC will be needed to achieve this connected grid and slower release profiles.

3. Molecular weight

The duration of CR typically spans from 6 to 24 hours, depending on the characteristics of the active ingredient, its physicochemical properties and pharmacokinetics (PK) – and the molecular weight (or viscosity grade) of the HPMC. HPMC viscosity grade plays a critical role in determining the release duration of a CR system as it affects the turnover of the hydrogel at the erosion front of the swollen matrix layer.

For example, a higher molecular weight of HPMC leads to a slower turnover of the hydrogel at the erosion front, resulting in a prolonged release duration. In general, poorly water-soluble actives, like acetaminophen, rely on erosion-dominated release through the hydrogel layer. This is achieved with lower viscosity grades of HPMC, which allow quicker turnover of the hydrogel. Conversely, more water-soluble actives, such as metformin, depend on diffusion-dominated release. They therefore require HPMC excipients with a higher viscosity.

Key takeaway for formulators?
Higher viscosity HPMC grades are best suited for water-soluble drugs, whereas lower viscosity HPMC grades are better for poorly water-soluble actives.

4. Hydroxypropyl (HP) substitution

Need a more customized release profile? Polymer substitution can help to fine-tune drug release to meet specific performance needs. However, it is often overlooked by formulators. Here is how it works:

- Changing hydroxypropyl (HP) substitution of HPMC impacts its hydrophilicity
- For instance, increasing HP substitution (i.e. adding HP content to the HPMC excipient) boosts HPMC hydrophilicity and PDT
- This equals faster hydrogel formation around the matrix tablet and erosion kinetics

Understanding how HP substitution influences hydrogel formation and erosion kinetics is essential to taking a more tailored approach to CR development and achieving unique performance functions. This expertise could be especially beneficial for challenging actives, like gliclazide – a poorly soluble drug used to treat type 2 diabetes. Figure 3 demonstrates why.

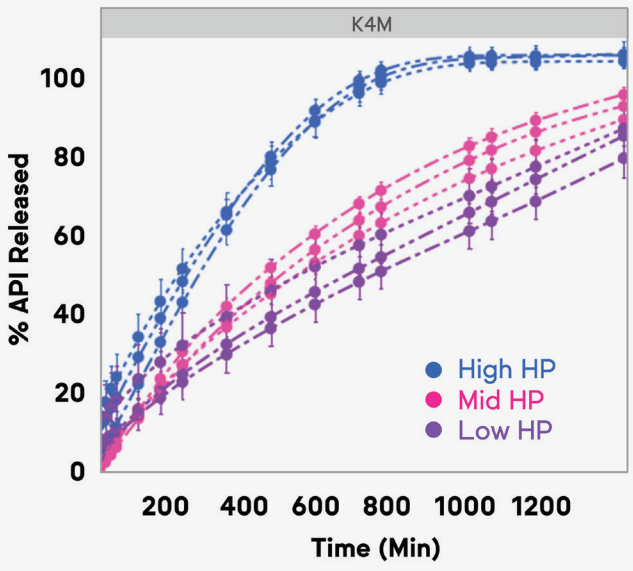


Figure 3: Our data reveals that gliclazide matrix tablets containing HPMC with higher HP content (and therefore higher PDT) deliver the desired release kinetics over the required duration.

Key takeaway for formulators?

Formulators who want to achieve more specialized CR performance should explore the power of HP substitution.

YOUR TRUSTED EXCIPIENT PARTNER

Maximize the success of your tablet dosage form with an expert in advanced excipients.

As a solutions-focused partner to the pharmaceutical industry, IFF combines decades of polymer expertise and deep market understanding to help manufacturers solve challenges beyond imagination. Discover a world of possibilities with our cutting-edge excipient products for CR pharmaceuticals.

METHOCEL™
A premium family of water-soluble cellulose ethers, including varying grades of MC and HPMC polymers to suit your CR needs.

ETHOCEL™
These premium ethylcellulose resins are water-insoluble polymers for modified-release matrix tablets. We offer several viscosity grades with high purity, making ETHOCEL™ an excellent option for a variety of unique formulation and processing needs.

POLYOX™
Our POLYOX™ polyethylene oxide water-soluble resins possess a unique set of properties to facilitate the development of distinctive drug delivery solutions, making them ideal for specialty matrices requiring unique functions.

Partner with our experts to fine-tune HPMC parameters in your drug formulations to achieve the ultimate CR performance.

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