Introducing METHOCEL™ K200M Premium and Premium CR

The Dow-Colorcon Controlled Release Alliance has expanded the product line of METHOCEL™ Premium Cellulose Ethers to include METHOCEL K200M Premium and K200M Premium CR for use in extended release matrix formulations. These new offerings provide formulators with additional tools to meet their needs for extended release matrix formulations.

Properties of METHOCEL K100M Compared to METHOCEL K200M

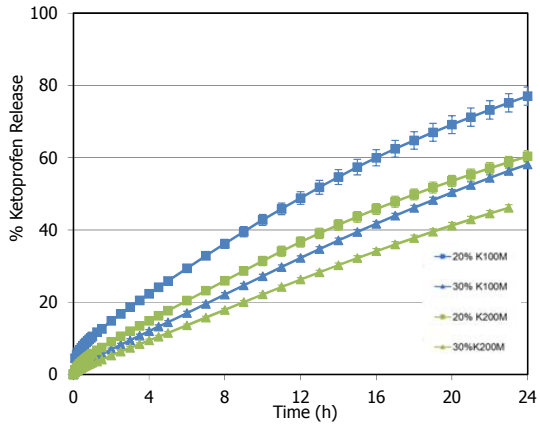
METHOCEL K200M offers the same quality control of critical material attributes (CMA) associated with the established high viscosity METHOCEL range of polymers, available through the CR Alliance.

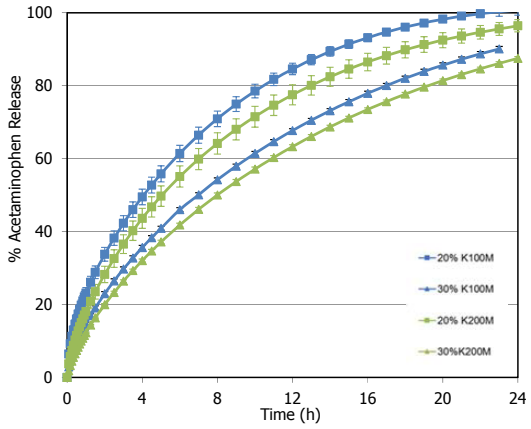
Polymer Attribute	K100M Premium	K100M Premium CR	K200M Premium	K200M Premium CR
Viscosity (cP)	75,000 - 140,000	75,000 - 140,000	150,000 - 280,000	150,000 - 280,000
Hydroxypropoxyl (HP) substitution (%)	7.0 - 12.0	9.5 - 11.5	7.0 -12.0	9.5 -11.5
Methoxyl (MeO) substitution (%)	19.0 - 24.0	22.0 - 24.0	19.0 - 24.0	22.0 - 24.0
Particle Size through 100 mesh	Min 90%	Min 90%	Min 90%	Min 90%
Particle Size through 230 mesh	N/A	50 - 80%	N/A	50 - 80%

Case Study 1: Extended Release of Two Model Drugs of Varying Solubility

METHOCEL usage level and viscosity can significantly affect drug release. Two model drugs of varying solubility: ketoprofen (BCS Class II, 0.05 mg/ml) and acetaminophen (BCS Class III, 14 mg/ml), were each formulated with METHOCEL as 400 mg matrix tablets, and dissolution profiles evaluated.

Extended Drug Release is Affected by Both Usage Level and Molecular Weight



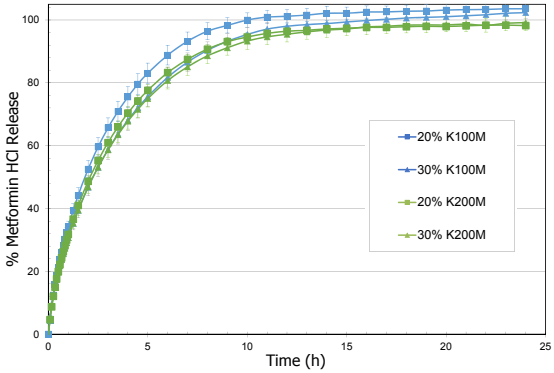


Increasing molecular weight, from METHOCEL K100M to K200M, resulted in further extended release at equivalent use level.

Case Study 2: High Dose Formulation - Metformin HCl

Overall tablet weight is a primary formulation concern for high dose actives, such as metformin HCl (BCS Class III, >300 mg/ml solubility in water), which leave little room for excipients. Three metformin HCl formulations were produced using either METHOCEL K100M or K200M at varying polymer usage level to achieve a total tablet weight of 1000 mg.

Effects of METHOCEL Viscosity are Highly Dependent on the Drug



- Both metformin HCl formulations using 30% w/w METHOCEL K100M and K200M achieved equivalent release profiles
- Reduction of METHOCEL K200M to 20% w/w provided release of metformin HCl equivalent to 30% w/w, thus providing formulators the potential to reduce the overall tablet weight and size

- As best practice for hydrophilic matrices, 30% w/w polymer is used (which is above critical percolation threshold) to reduce potential sensitivity of the formulation to CMAs [1]
- Lower usage levels of polymer may result in an increased tablet-to-tablet and batch-to-batch variability

Dow-Colorcon Controlled Release Alliance – UNIQUE TOGETHER

- Provides formulators with a full range of high viscosity hypromellose from METHOCEL K100LV Premium CR to K200M Premium CR
- Global network of customer service and distribution facilities for local supply
- Combines Dow's world class polymer and material science expertise together with Colorcon's extensive formulation experience and technical support for unsurpassed customer service

Additional Considerations for Formulation Development

- HyperStart® oral solid dose starting formulation service, provides recommendations to accelerate your product development
- Use of Starch 1500® partially pregelatinized maize starch, in combination with METHOCEL can further slow drug release in extended release matrices[2]
- An immediate release coating, such as Opadry® complete film coating system, is recommended to enhance mechanical robustness of the tablet, improve ease of swallowing and help to reduce medication error through use of color[3-5]

REFERENCES

1. H. Deng, S. Vass, S. Tiwari, T. Farrell, A. Faham, T. Cabelka & A. Rajabi-Siahboomi, "Application of Quality by Design (QbD) Principles to the Formulation of Extended Release Propranolol Hydrochloride Hydrophilic Matrix Tablets," American Association of Pharmaceutical Scientists (AAPS), San Francisco, CA, 2010.
2. M. Levina and A. Rajabi-Siahboomi, "Influence of Excipients on Drug Release from Hydroxypropyl Methylcellulose Matrices," *J. Pharm. Sci.*, Vol. 93, No. 11, Nov 2004: 2746-2754.
3. C. Wilson, B. O'Mahony, T. Farrell, B. Friend & D. Taylor, "Modern Tablet Film Coatings and Influence on Ease of Swallowing," AAPS, Salt Lake City, UT, 2003.
4. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), "Safety Considerations for Product Design to Minimize Medication Errors," Draft Guidance for Industry, December 2012.
5. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), "Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules," Guidance for Industry, June 2015.

* Data shown generated by Dow Pharmaceutical and Food Solutions, Midland, MI, USA (2013-14).

METHOCEL™ PREMIUM CELLULOSE ETHERS

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