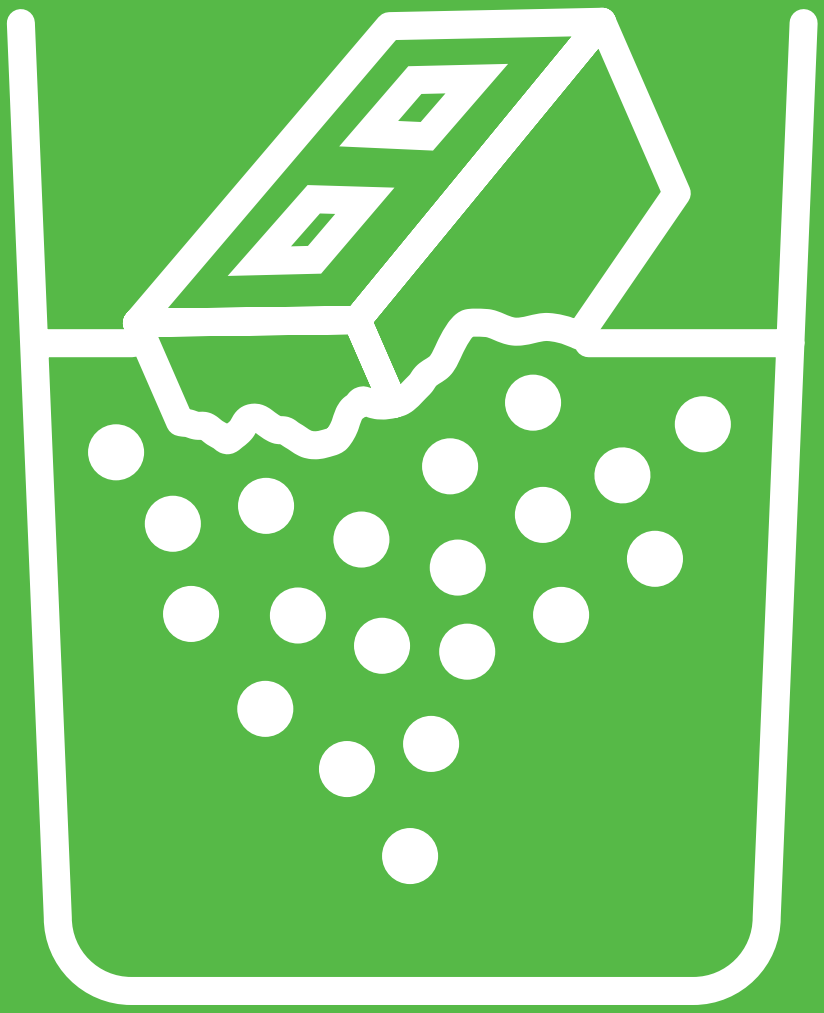
Nutrition & Biosciences

DUPONT

Pharma Solutions

AFFINISOL™ HPMC HME

For Hot Melt Extrusion



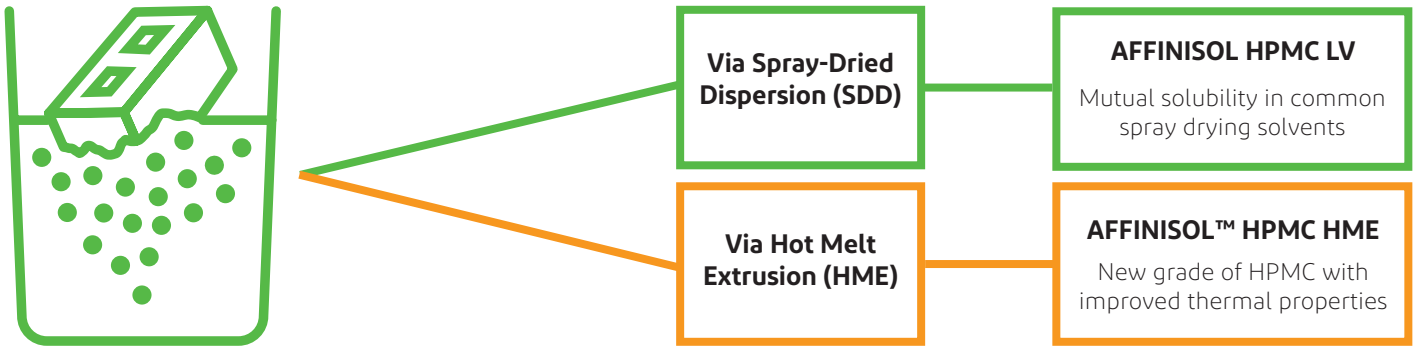
AFFINISOL™ HPMC HME

At DuPont, we appreciate that solubilization of a pipeline of poorly soluble drug candidates is the leading challenge facing the pharmaceutical industry. Thus, we designed AFFINISOL™, our solubilization polymer portfolio, to provide a range of options to solve the insoluble. Our AFFINISOL™ polymers are specifically tailored to address the solubilization performance requirements of your active pharmaceutical ingredient (API), whether you have chosen to formulate via Spray-Dried Dispersion (SDD) or Hot Melt Extrusion (HME).

Hypromellose (HPMC) is an excellent polymer for the formation of solid dispersions with APIs. HPMC is a water soluble polymer that can help maintain stable solid dispersions and inhibit API crystallization in solution promoting supersaturation of the drug. Affinisol HPMC HME builds upon these beneficial properties of HPMC by expanding the thermal processing window and increasing solubility in organic solvents. The polymer's added organosolubility further creates advantages for employing HPMC in solvent spray drying applications. These combined properties make AFFINISOL™ HPMC HME an excellent choice for formulating poorly soluble drugs such as Biopharmaceutical Classification System (BCS) Class II and Class IV compounds.

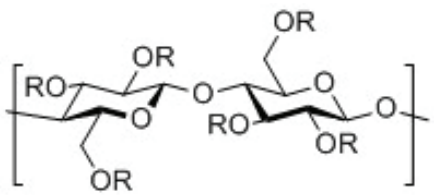
Through its leadership in cellulosic chemistry and pharmaceutical formulation knowledge, DuPont helps provide proven and innovative polymers for solubility enhancement. DuPont combines a deep understanding of critical polymer properties with small scale synthesis capability to partner with your development team and offer a product that is scientifically designed to address your API's unique needs. AFFINISOL™ HPMC HME provides a critical tool for resolving solubility challenges through a variety of processing techniques.

AFFINISOL™ Solubility Enhancement Platform



DuPont developed AFFINISOL™ HPMC HME, building on over half a century of cellulosic expertise. AFFINISOL™ HPMC HME is hydroxypropyl methylcellulose (Figure 1) designed with a polymer substitution architecture that enables thermal processability. Thus, AFFINISOL™ HME has excellent utility in manufacturing methods such as HME to create stable amorphous solid dispersions (ASDs) with poorly soluble APIs. HME is a solvent free, continuous manufacturing process with proven applicability to the pharmaceutical industry for solubility enhancement. AFFINISOL™ HPMC HME is uniquely suited to form stable ASDs which can result in solubility enhancement and a subsequent increase in bioavailability for both immediate release formulations and controlled release formulations.

Figure 1. Chemical structure of HPMC.



R = - H
-CH3
-CH2CH(CH3)OH

AFFINISOL™ HPMC HME

AFFINISOL™ HPMC HME is a water soluble amorphous polymer provided as a white to off-white powder currently available in 3 grades: HPMC HME 15 LV, HPMC HME 100 LV and HPMC HME 4M. These grades differ in regards to their molecular weight (Figure 2) and depending on formulation needs, the appropriate material can be selected to properly balance the degree of solubility enhancement with the desired drug release profile. Additional properties of AFFINISOL™ HPMC HME can be found in Tables 1-3.

Figure 2. Molecular weight of commercial grades of AFFINISOL™ HPMC HME.

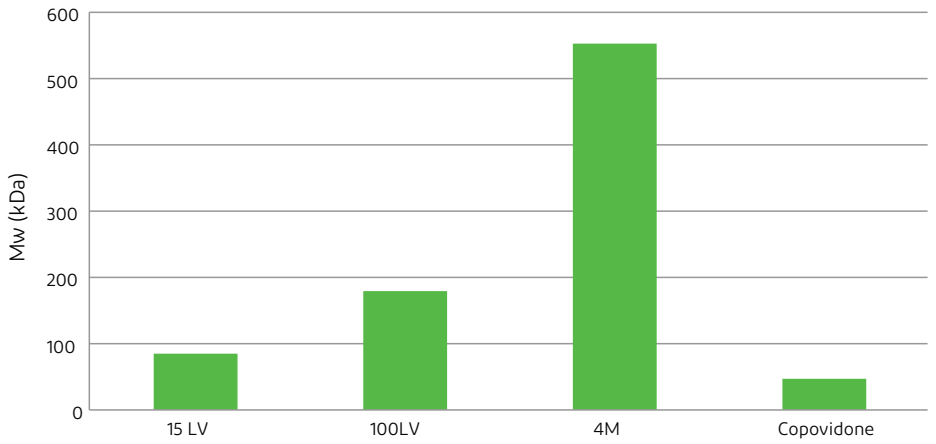


Table 1

Physical properties of AFFINISOL HPMC HME	
Bulk Density (g/cc)	0.42
Tapped Density (g/cc)	0.55
True Density (g/cc)	1.2
Cloud Point (°C)	46
Loss on Drying (%)	1-3
Angle of Repose (°)	32
CARR Index	23.64

Table 2. Particle size determined on Malvern Mastersizer 2000 (microns)

	D(0.1)	D(0.5)	D(0.9)
15 LV	54.35	104.49	207.068
100 LV	52.75	102.63	208.87
4M	53.17	107.92	237.12

Table 3. Hansen Solubility Parameters

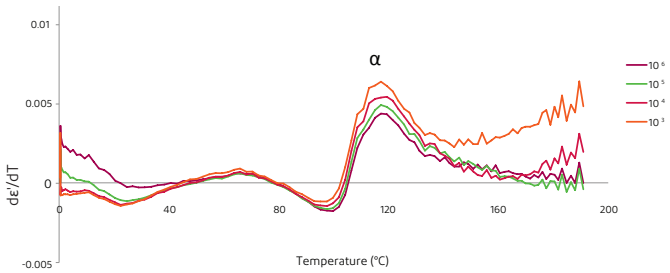
	Dispersion $(J/cc)^{1/2}$	Polar $(J/cc)^{1/2}$	Hydrogen Bonding $(J/cc)^{1/2}$	R $(J/cc)^{1/2}$
15 LV	18.0	11.9	12.3	10.9
100 LV	17.9	12.5	12.7	10.6
4M	17.8	11.4	12.7	9.8

(1)The properties shown are typical but not to be construed as specifications, data is based on results from internal studies

Thermal Properties

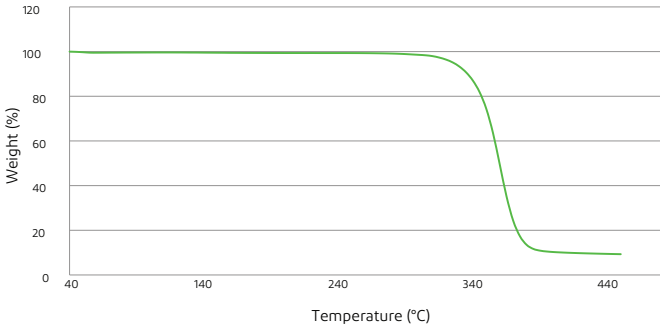
AFFINISOL™ HPMC HME has a glass transition temperature (Tg) of approximately 115°C[1] (Figure 3) while remaining stable against thermal degradation to temperatures above 250 °C (Figure 4). This lower Tg is sufficient to significantly open the processing window for this polymer while also being adequately high to promote solid state stability of ASDs. Additionally, the polymer is resistant to color change at elevated temperature preventing the characteristic charring observed with other grades of HPMC.

Figure 3



Glass transition temperature of AFFINISOL™ HPMC HME 100 LV determined by dielectric spectroscopy. The T_g manifests as the alpha transition, denoted by α.

Figure 4



Thermogravimetric Analysis of AFFINISOL™ HPMC HME 4M – All viscosity grades exhibit identical results..

These improved thermal properties in conjunction with a lower melt viscosity enable AFFINISOL™ HPMC HME to be processed by HME without plasticizers; a feature which reduces formulation requirements, can improve physical stability, and may reduce toxicity. This property is maintained for all three grades enabling adjustments of the dissolution profile by selection of the appropriate polymer viscosity.

While the polymer is thermally stable over a broad temperature range, it is recommended to extrude AFFINISOL™ HPMC HME at temperatures below 200°C to minimize color change and prevent molecular weight degradation. Table 4 displays the recommended highest and lowest temperatures for extruding pure AFFINISOL™ HPMC HME to ensure adequate processing with minimal color formation. Formulated systems can be extruded above and below these temperatures depending upon the materials present with minor modifications to the process.

Table 4. Recommended processing conditions for pure AFFINISOL™ HPMC HME

Grade	Recommended Lowest Processing Temperature of Neat Polymer	Recommended Highest Processing Temperature of Neat Polymer
AFFINISOL™ HPMC HME 15LV	135°C	190°C
AFFINISOL™ HPMC HME 100LV	145°C	195°C
AFFINISOL™ HPMC HME 4M	155°C	200°C

Moisture Sorption

The uptake of atmospheric moisture can greatly impact the performance and physical stability of a finished drug product. AFFINISOL™ HPMC HME displays reduced moisture uptake compared to other grades of HPMC as well as non-cellulosic materials commonly used in HME (Figure 5) – which significantly decreases the possible impact to performance and physical stability of the finished product. This advantageous property is not dependent upon the molecular weight of the polymer.

Low moisture sorption is crucial for ASDs where the presence of water may plasticize the formulation, resulting in a reduction in the Tg and increasing the risk of physical instability[2]. AFFINISOL™ HPMC HME exhibits this anticipated change in Tg to a lesser extent as moisture content increases (Figure 6) compared to many other common HME polymers minimizing the impact of water on product performance.

Figure 5. Dynamic Vapor Sorption. at 25° C

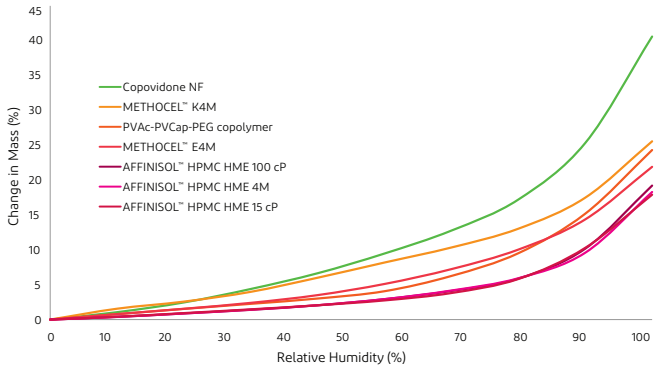
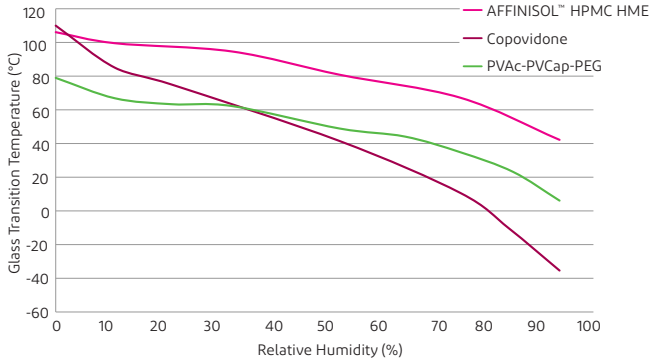


Figure 6. Reduction in the Tg of HME polymers upon moisture uptake.



Solubility

In addition to the above properties ideal for extrusion, AFFINISOL™ HPMC HME is soluble in many organic solvents and solvent blends allowing easier formulation in aqueous free systems for preformulation studies, or solvent based applications such as spray drying or film casting. The primary recommended solvents and solvent blends are shown in Table 5. Degree of solubility is dependent on the AFFINISOL™ HPMC HME grade and solvent. As spray processes are typically viscosity limited it is recommended to start with AFFINISOL™ HPMC HME 15LV in order to maximize solids load.

Down Stream Processing

AFFINISOL™ HPMC HME is amenable to many downstream processing technologies, however, the most commonly applied process is milling. While milling conditions will change based on the formulation being processed, in order to generate a fine powder from a pelletized extrudate of AFFINISOL™ HPMC HME, it is recommended to use an impact mill such as a Fitz Mill or Alpine Impact Mill. A mill screen with a larger diameter will prevent the formation of a fibrous product; a 0.5 - 1 mm screen is recommended.

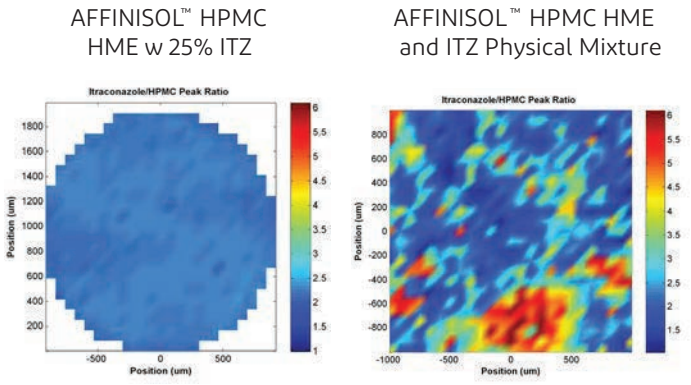
Solvent A	Solvent B
Acetone	NA
Tetrahydrofuran	NA
Methanol	NA
Ethanol	NA
Methylene Chloride	NA
Acetone	Ethanol
Acetone	Acetone
Acetone	Methanol
Acetonitrile	Ethanol
Acetonitrile	Isopropanol
Acetonitrile	Methanol
Ethanol	Tetrahydrofuran
Ethyl Acetate	Ethanol
Ethyl Acetate	Methanol
Ethyl Acetate	Tetrahydrofuran
Methanol	Tetrahydrofuran

Examples

Example 1: BCS Class II API Itraconazole (ITZ)

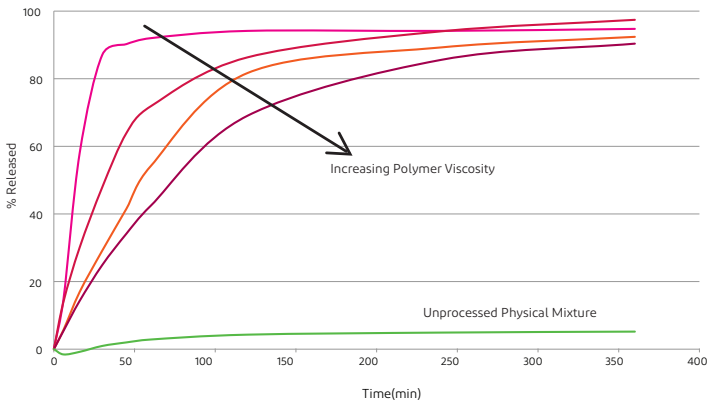
- Drug load of 10, 25 and 40% (w/w) regardless of polymer viscosity results in translucent strands demonstrating excellent drug loading capability
- All extrudates confirmed amorphous via x-ray diffraction, DSC and Raman Spectroscopy
- Raman mapping demonstrates extrudates are homogeneous (Figure 7) • All extrudates provide significant improvement in ITZ solubility
- Increasing polymer viscosity allows for modified release with solubility enhancement (Figure 8; 25% API extrudates shown)

Figure 7



Raman mapping of ITZ extrudate vs pressed physical mixture.

Figure 8

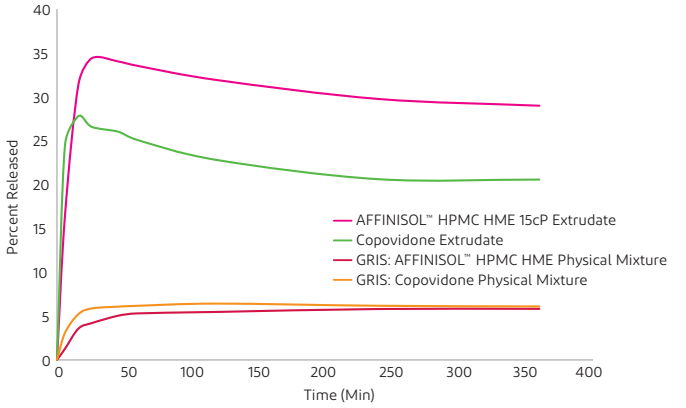


Itraconazole release from milled extrudates in 0.1 N HCl. Drug quantified by HPLC.

Example 2: High Melting Point BSC Class II API Griseofulvin (GRIS)

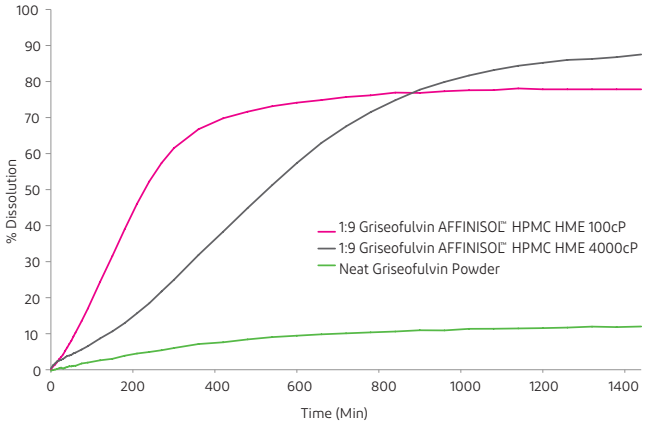
- Operating temperature of 180 °C; 40 °C below melting point of API
- Translucent extrudates obtained at drug load up to 25% with all 3 grades of AFFINISOL™ HPMC HME
- Physical characterization demonstrates all extrudates are amorphous
- Dissolution analysis demonstrates ability to provide immediate or controlled release of amorphous poorly soluble API by selecting appropriate molecular weight grade (Figures 9-10)

Figure 9



Immediate release from milled extrudates containing 25wt% griseofulvin

Figure 10



Immediate release from milled extrudates containing 25wt% griseofulvin

Toxicity

AFFINISOL™ HPMC HME is pure hydroxypropyl methylcellulose. It does not contain any plasticizers or additives to give it functionality. AFFINISOL™ HPMC HME has hydroxypropyl and methoxy substitution ranges which fall withing the extended substitution pattern (ESP) grades presented to the U.S. FDA in GRAS Notice 000213 (2006). It was concluded through the GRAS notification process that HPMC ESP grades are generally recognized as safe according to scientific procedures for general use in food at intake levels up to 20 grams/person/day.

While AFFINISOL™ HPMC HME does not currently fall within any of the four hydroxypropyl and methoxy substitution ranges as defined by the USP/EP/JP, subchronic testing conducted specifically on AFFINISOL™ HPMC HME confirms that this polymer has a consistent toxicology profile to current compendial grades with the same maximum daily intake.

Below is a summary of the toxicity testing and findings. A detailed toxicity summary is available upon request.

28 Day repeated dose study in Crl:CD rats

- Doses of 0, 500, 1000 or 2000 mg/kg/day by oral gavage as a solution

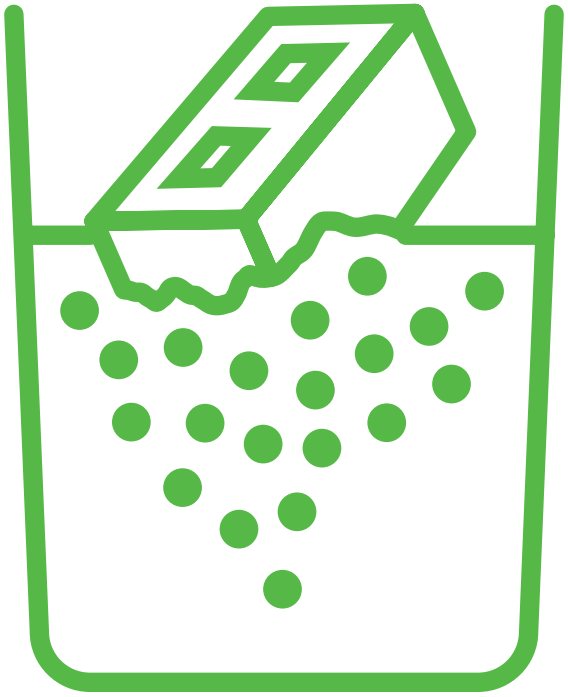
Results

Consistent with historical data of HPMC

- No treatment-related effects in clinical signs, feed consumption, ophthalmic examinations, hematology, prothrombin time, or urinalysis parameters.
- No treatment-related organ weight effects, gross or histopathologic observations.
- There were no statistically significant body weight changes in males or females throughout the study at any dose level as compared to the controls.
- However, the mean body weight gains relative to test day 1 of males and females given 1000 or 2000 mg/kg/day weredecreased as compared to the respective controls throughout most of the study; a common observation in other rat studies fed high concentrations of HPMC
- Increase in serum bile acids; No treatment-related liver histopathology nor any increase in serum enzymes associated with liver injury.
- A slight but significant reduction in mean serum glucose levels in males given 1000 or 2000 mg/kg/day; This has been observed with other grades of HPMC and previously explored for benefits towards glucose level control.

Request a Sample

Samples of AFFINISOL™ HPMC HME are currently available upon request for lab scale (0.5-2 kg) work or large scale (25+ kg) in both cGMP and non-cGMP grades



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