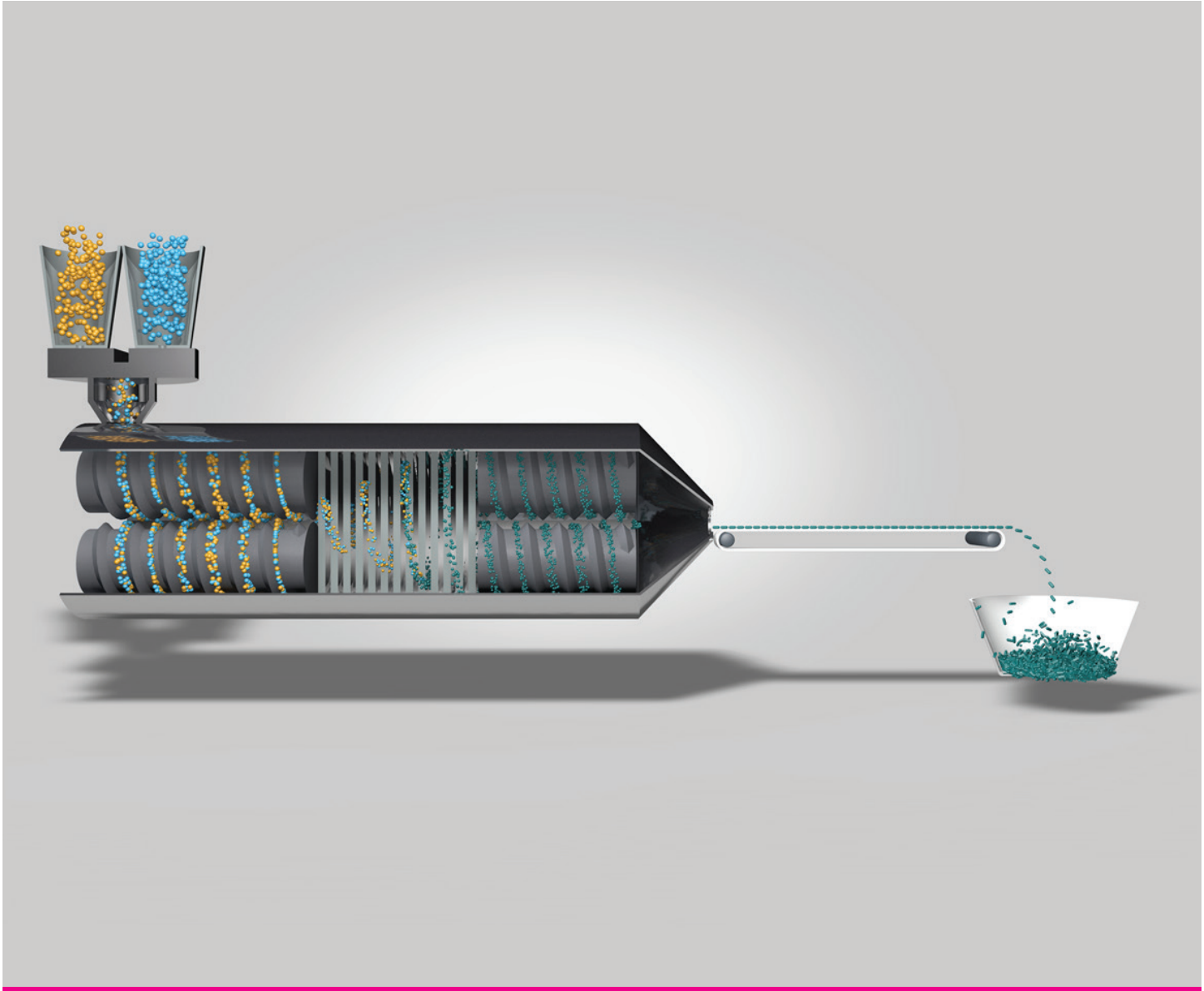
Dow Pharma & Food Solutions

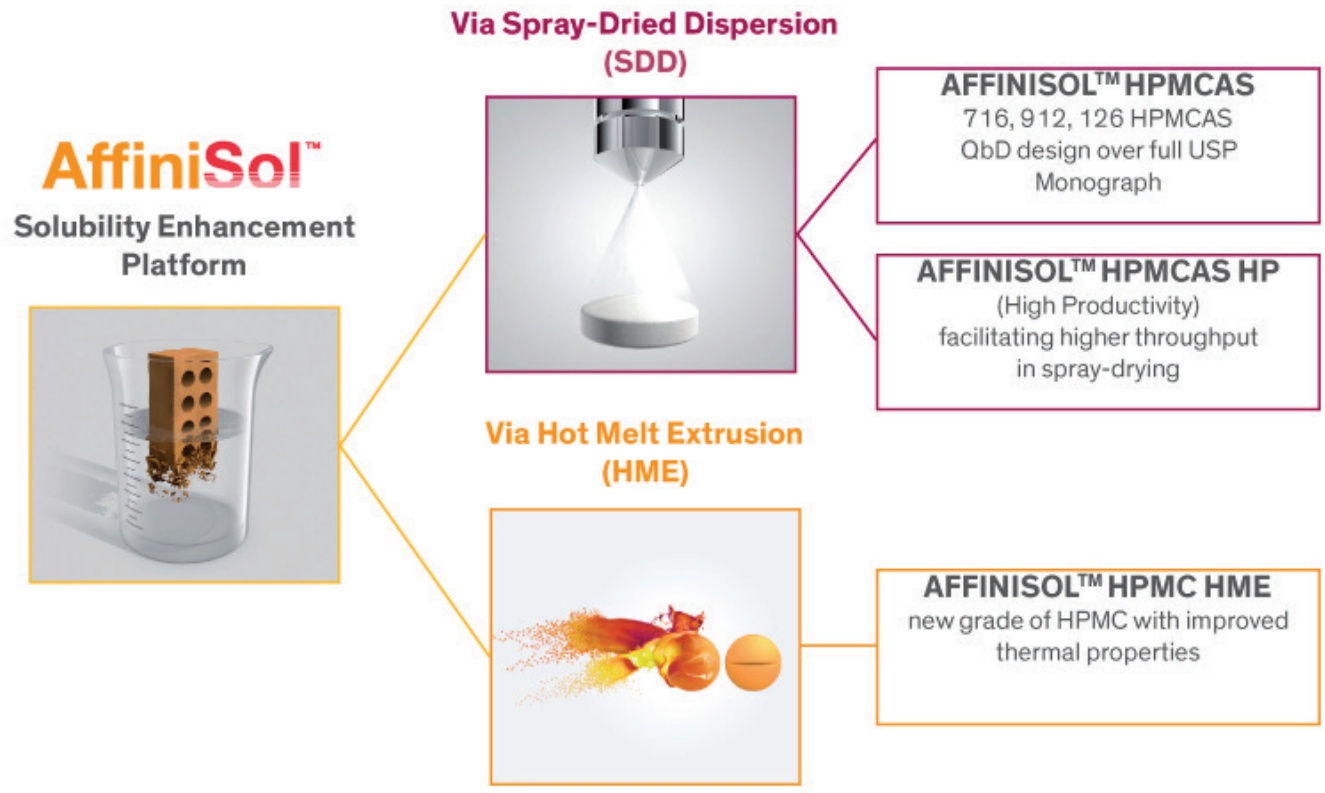
AFFINISOL™ HPMC HME for Hot Melt Extrusion



At Dow Pharma & Food Solutions, 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 options to solve the insoluble. Our AFFINISOL™ polymers are specifically tailored to address the solubilization performance requirements of your APIs, 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 active pharmaceutical ingredients (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. Now with thermal processing utility, AFFINISOL™ HPMC HME offers new HME process flexibility in choosing a polymer viscosity for optimization of both solubility enhancement and drug release profiles. 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 investments in infrastructure and R&D capabilities, Dow helps provide proven and innovative polymers for solubility enhancement. Dow 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 goes beyond the products commercially available today, offering process and formulation flexibility to help maximize solubilization performance.



Dow 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.

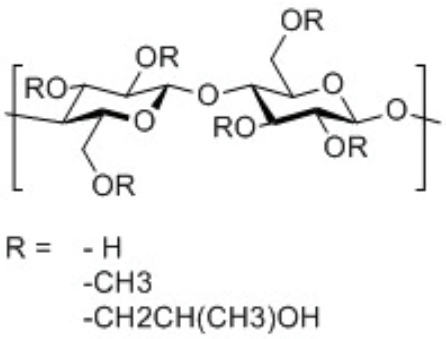


Figure 1. Chemical structure of HPMC.

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 cP, HPMC HME 100 cP 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.

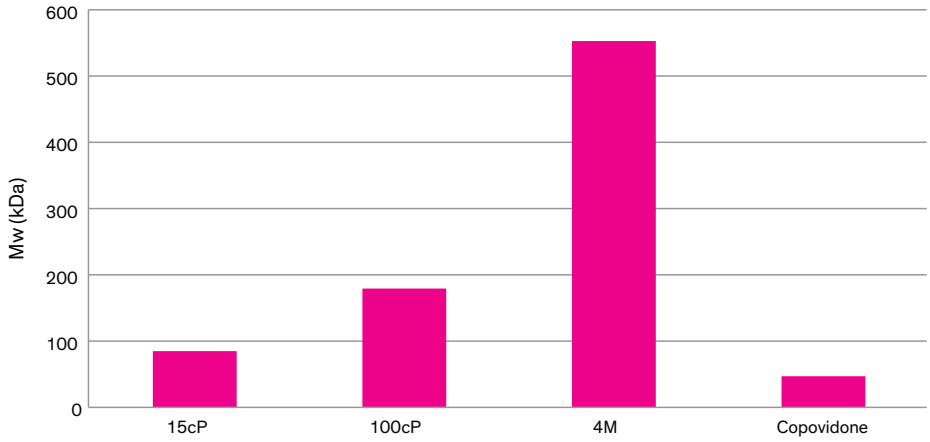


Figure 2. Molecular weight of commercial grades of AFFINISOL™ HPMC HME.

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	16.2

These are typical properties not be construed as specifications.

Table 2. Particle size determined on Malvern Mastersizer 2000			
	D(0.1)	D(0.5)	D(0.9)
15 cP	54.35	104.49	207.068
100 cP	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 cP	18.0	11.9	12.3	10.9
100 cP	17.9	12.5	12.7	10.6
4M	17.8	11.4	12.7	9. 8

Thermal Properties

AFFINISOL™ HPMC HME has a glass transition temperature (T_g) of approximately 115 °C[1] (Figure 3) while remaining stable against thermal degradation to temperatures above 250 °C (Figure 4). This lower T_g 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 further broadening available processing conditions.

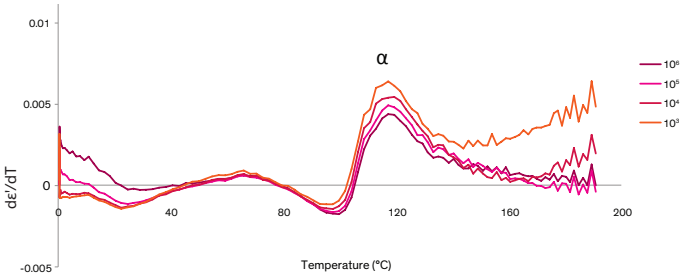


Figure 3. Glass transition temperature of AFFINISOL™ HPMC HME 100 cP determined by dielectric spectroscopy. The T_g manifests as the alpha transition, denoted by α.

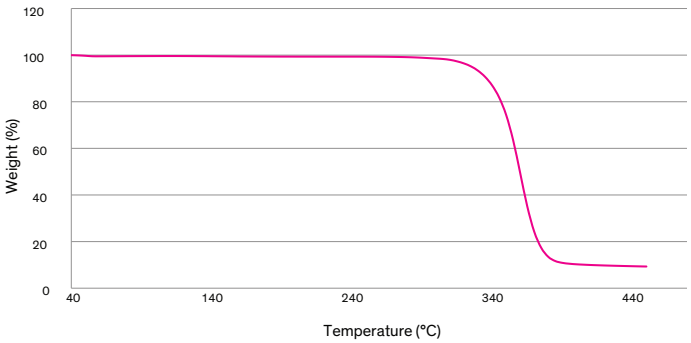


Figure 4. Thermogravimetric Analysis of AFFINISOL™ HPMC HME 4M – All viscosity grades exhibit identical results.

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 ability 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. 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 T_g increasing the risk of physical instability[2]. AFFINISOL™ HPMC HME exhibits this anticipated change in T_g 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.

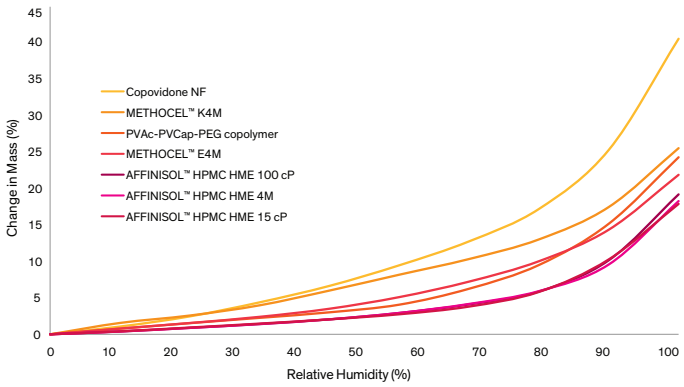


Figure 5. Dynamic Vapor Sorption. at 25° C

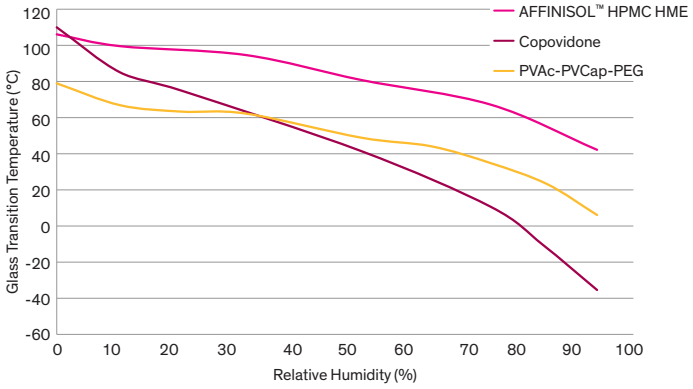


Figure 6. Reduction in the T_g of HME polymers upon moisture uptake.

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.

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.

Table 5. Recommended Solvents

Solvent A	Solvent B
Acetone	NA
Tetrahydrofuran	NA
Methanol	NA
Ethanol	NA
Methylene Chloride	NA
Acetone	Ethanol
Acetone	Isopropanol
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 controlled release with solubility enhancement (Figure 8; 25% API extrudates shown)

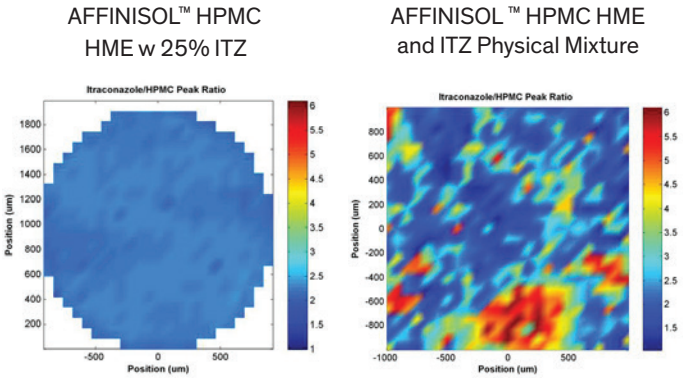


Figure 7. Raman mapping of ITZ extrudate (top) vs pressed physical mixture (bottom).

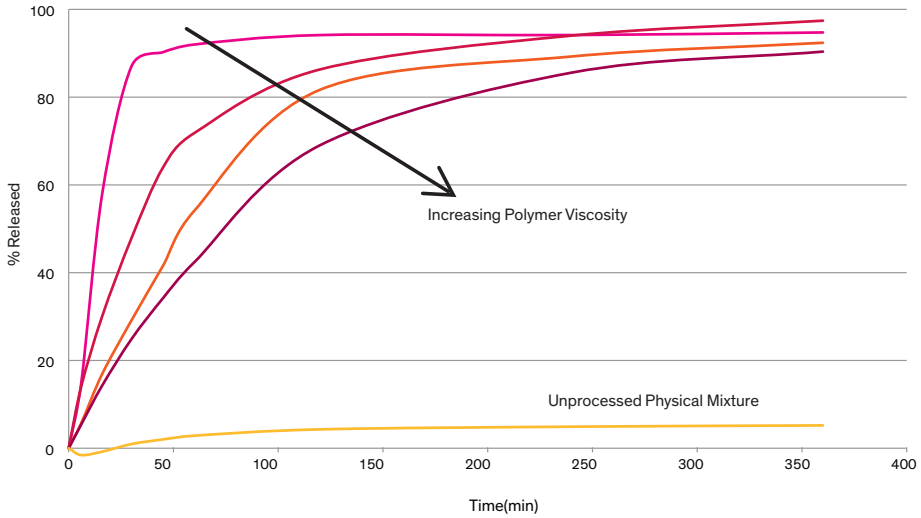
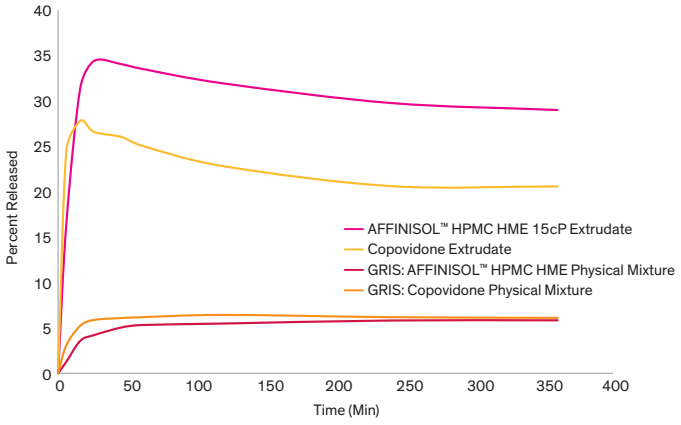


Figure 8. Itraconazole release from milled extrudates in 0.1 N HCl. Drug quantified by HPLC.

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)



Figures 9. Immediate release from milled extrudates containing 25wt% griseofulvin.

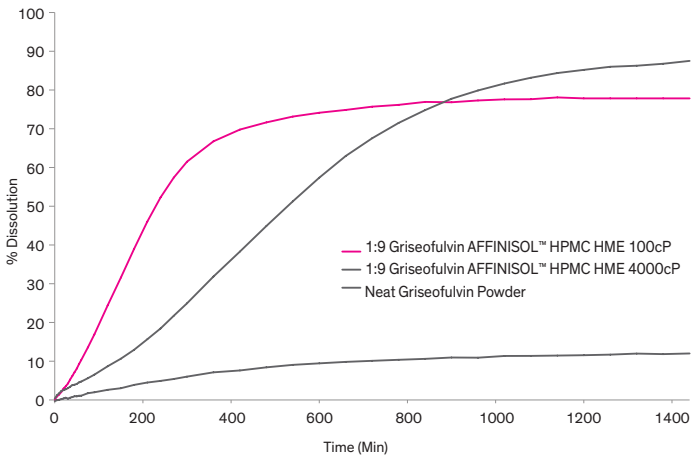


Figure 10. Controlled release from pelletized extrudates containing 10wt% griseofulvin.

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 were decreased 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

References

1. O'Donnell, K.P. and W.H.H. Woodward, Dielectric spectroscopy for the determination of the glass transition temperature of pharmaceutical solid dispersions. Drug Development and Industrial Pharmacy, 2014: p. 1-10.
2. Lakshman, J.P., Cao, Y., Kowalski, J., Serajuddin, A.T.M., Application of Melt Extrusion in the Development of a Physically and Chemically Stable High-Energy Amorphous Solid Dispersion of a Poorly Water-Soluble Drug. Molecular Pharmaceutics, 2008. 5(6): p. 994-1002.

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