UNIQUE TOGETHER

CONTROLLED RELEASE ALLIANCE

AFFINISOL™ HPMCAS for Spray-Dried Dispersion (SDD)

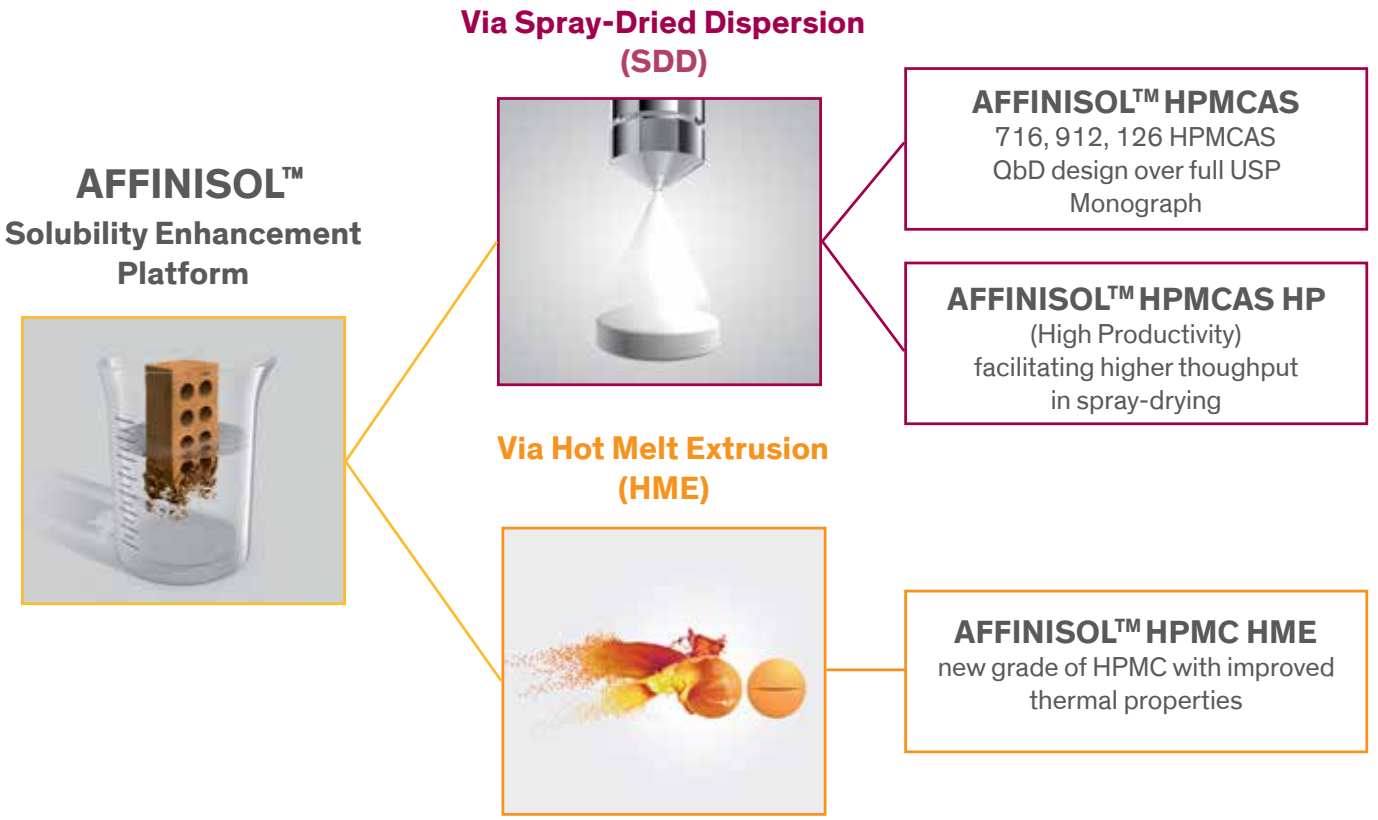
Solving the Insoluble

This document is valid at the time of distribution. Distributed 14-Nov-2018 (UTC)

At Dow Pharma 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 help you solve the insoluble. Our AFFINISOL™ polymers are uniquely 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).

AFFINISOL™ Hypromellose Acetate Succinate (HPMCAS) is an excellent polymer for the formation of solid dispersions with active pharmaceutical ingredients (APIs). HPMCAS is a soluble polymer that can help maintain stable solid dispersions and inhibit API crystallization in solution promoting supersaturation of the drug. In addition, AFFINISOL™ HPMCAS offers flexibility in acetate and succinate substitution levels helping for optimization of both solubility enhancement and material processing. These combined properties make AFFINISOL™ HPMCAS an excellent choice for formulating 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 an excellent product that is scientifically designed to address your API's unique needs. AFFINISOL™ HPMCAS goes beyond the products commercially available today, offering more options to help maximize solubilization performance.



Hyrdroxypropyl Methylcellulose Acetate Succinate (HPMCAS)

Dow has created AFFINISOL™ HPMCAS, building on over half a century of cellulosic expertise. AFFINISOL™ HPMCAS is hydroxypropyl methylcellulose (HPMC) functionalized with a mixture of monosuccinic acid and acetic acid esters (Figure 1). AFFINISOL™ HPMCAS has been developed to create stable amorphous solid dispersions (ASDs) with poorly soluble active pharmaceutical ingredients (APIs). The ability of AFFINISOL™ HPMCAS to form stable ASDs can result in solubility enhancement and a subsequent increase in bioavailability.

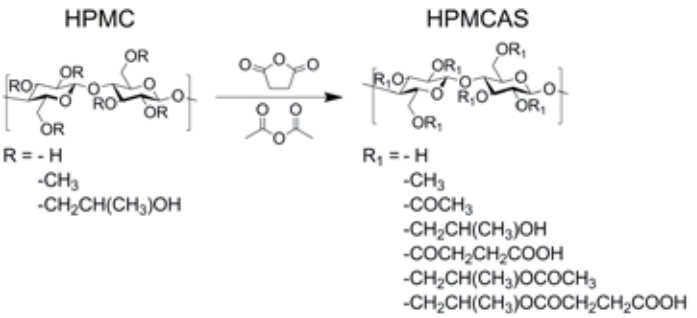


Figure 1. The reaction scheme to convert HPMC to HPMCAS.

AFFINISOL™ HPMCAS

AFFINSIOL™ HPMCAS is available in three standard commercial cGMP granular grades: HPMCAS 716, HPMCAS 912, and HPMCAS 126 (Figure 2). These three grades are differentiated by the ratio of succinyl and acetyl substituents on the HPMC backbone (Table 1). AFFINISOL™ HPMCAS meets the requirements of the United States Pharmacopeia National Formulary (USP-NF) and the Japanese Pharmaceutical Excipients (JPE), depicted by the region in Figure 2. AFFINISOL™ HPMCAS is a white to off-white powder with a faint acetic acid odor.

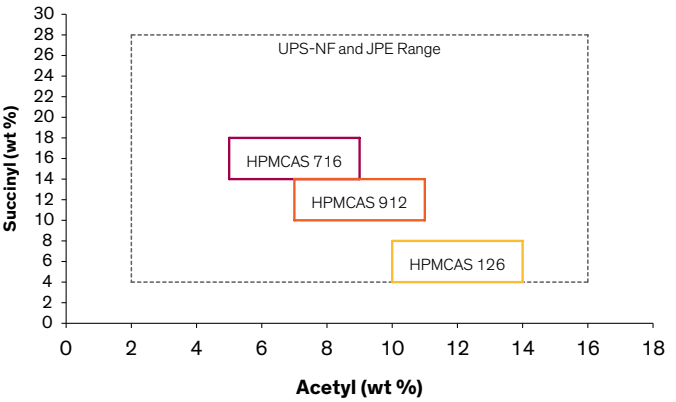


Figure 2. The USP-NF monograph substitution space for HPMCAS and the standard AFFINISOL™ HPMCAS 716, HPMCAS 912 and HPMCAS 126 substitution ranges.

Table 1. Specifications of AFFINISOL HPMCAS

AFFINISOL™ HPMCAS			
	716	912	126
Hydroxypropyl	5.0 – 9.0 %	5.0 – 9.0 %	6.0 – 10.0 %
Methoxyl	20.0 – 24.0 %	21.0 -25.0 %	22.0 – 26.0 %
Viscosity*	2.4 – 3.6 cP	2.4 – 3.6 cP	2.4 – 3.6 cP
Residue on Ignition	< 0.20 %	< 0.20 %	< 0.20 %
Loss on Drying	< 5.0 %	< 5.0 %	< 5.0 %
Free Acids	< 1.0 %	< 1.0 %	< 1.0 %
Acetate Substitution	5.0-9.0 %	7.0 – 11.0 %	10.0 – 14.0 %
Succinate Substitution	14.0-18.0 %	10.0 – 14.0 %	4.0 – 8.0 %
Acetic Acid	0.5 %	0.5 %	0.5 %

* Viscosity determined as a 2 % solution in NaOH solution

The physical properties of AFFINISOL™ HPMCAS make it a desirable excipient for spray drying with poorly water soluble APIs. AFFINISOL™ HPMCAS is soluble in a wide range of organic solvents (Table 2) which makes it compatible with a range of APIs. Additionally, AFFINISOL™ HPMCAS has a pH dependent solubility in aqueous media, allowing for targeted delivery of an active. The Hansen Solubility Parameters have been determined for each grade to aid in determining compatibility with an API (Table 3).

Table 2. Solubility of AFFINISOL™ HPMCAS in Solvents Typically Used for Spray Drying

Solvent	HPMCAS 716	HPMCAS 912	HPMCAS 126
DI – Water	I	I	I
Methanol	S	S	S
Methanol/Dichloromethane (1:2)	S	S	S
Ethanol	I	I	P
Ethanol/Water (4:1)	S	S	S
Ethanol/Dichloromethane (1:1)	S	S	S
Acetone	S	S	S
Tetrahydrofuran	S	S	S
Methylene Chloride	S	S	S
S = Soluble; P = Partially Soluble; I = Insoluble			

Table 3. Hansen Solubility Parameters for AFFINISOL™ HPMCAS

	Interaction Radius $(J/cc)^{0.5}$	Polar $(J/cc)^{0.5}$	Hydrogen Bonding $(J/cc)^{0.5}$	Dispersive $(J/cc)^{0.5}$
HPMCAS 716	10.06	11.87	10.19	17.77
HPMCAS 912	10.76	12.37	10.33	16.73
HPMCAS 126	9.85	12.76	9.67	18.09

AFFINISOL™ HPMCAS viscosity is dependent on the concentration and solvent system used. This is demonstrated in Figure 3A in which the rheology of all three grades of AFFINISOL™ HPMCAS are shown as 20 wt% solutions in acetone. Additionally, Figure 3B shows the rheology of AFFINISOL™ HPMCAS 716 compared at several polymer concentrations in two separate solvent systems. The viscosity of a solution for spray-drying is a critical factor in achieving an ideal formulation. The ability of AFFINISOL™ HPMCAS to be dissolved in multiple organic solvents and solvent systems allows flexibility in production of a spray-dried dispersion.

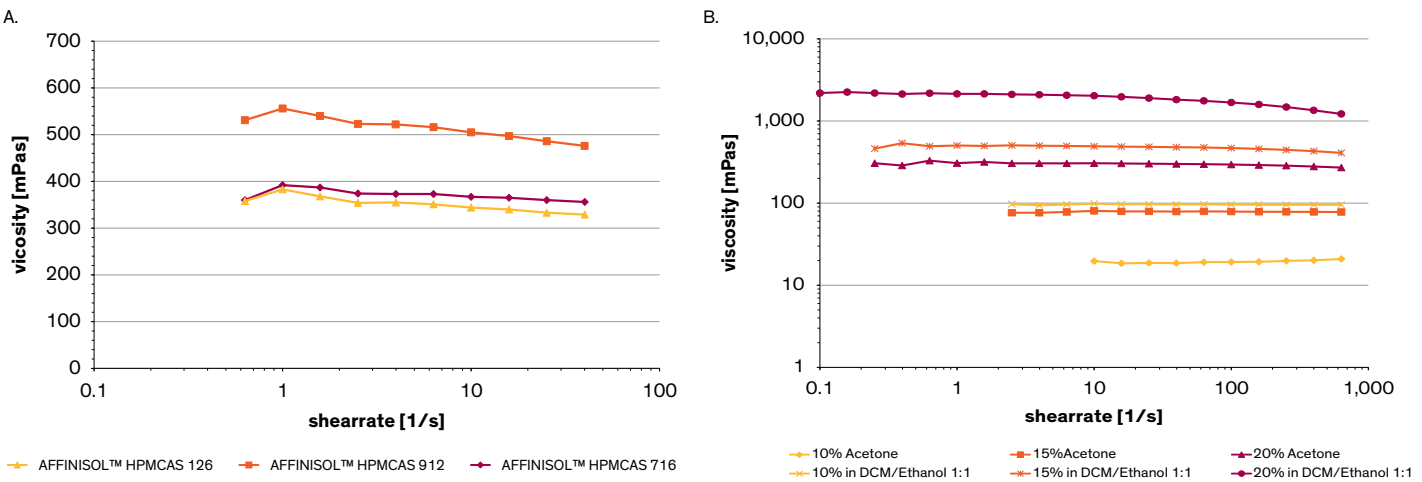


Figure 3. A. Rheology of AFFINISOL™ HPMCAS 716, 912, and 126 as a 20 wt % solution in acetone at 20 °C. B. Rheology of AFFINISOL™ HPMCAS 716 as 10 wt %, 15 wt % and 20 wt % solutions in acetone and a 1:1 dichloromethane (DCM) – ethanol solvent mixture at 20 °C.

Moisture Absorption

AFFINISOL™ HPMCAS absorbs moisture from the air. The amount of moisture absorbed depends on several factors including the starting moisture level, temperature and substitution levels of the polymer. The moisture sorption of AFFINISOL™ HPMCAS is demonstrated in Figure 4.

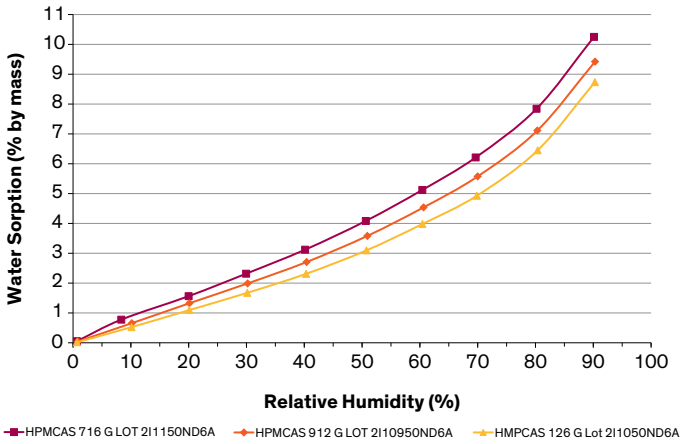


Figure 4. Moisture sorption of AFFINISOL™ HPMCAS as a function of relative humidity

Thermal Properties

AFFINISOL™ HPMCAS is a robust polymer with a degradation onset temperature near 200°C (Figure 5) providing a broad processing window for API formulation. In addition, AFFINISOL™ HPMCAS has a high glass transition temperature (Tg) to provide excellent stability to amorphous solid dispersions of an API in the polymer. As demonstrated in Figure 6, the Tg of AFFINISOL™ HPMCAS varies with the acetate and succinate substitution levels as well as with absorbed moisture content.

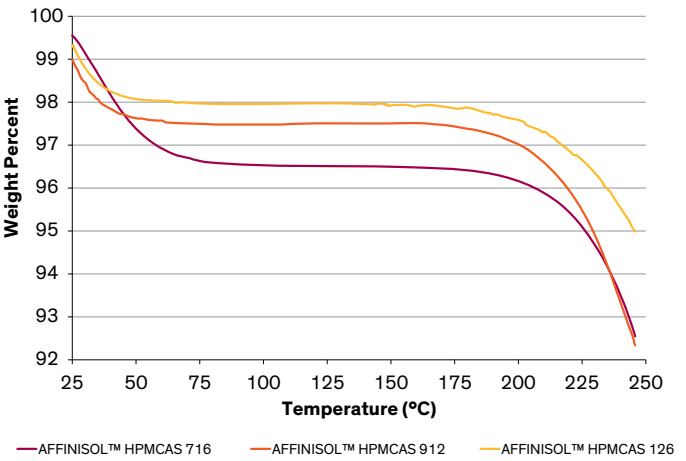


Figure 5. Thermal gravimetric analysis of AFFFINISOL HPMCAS

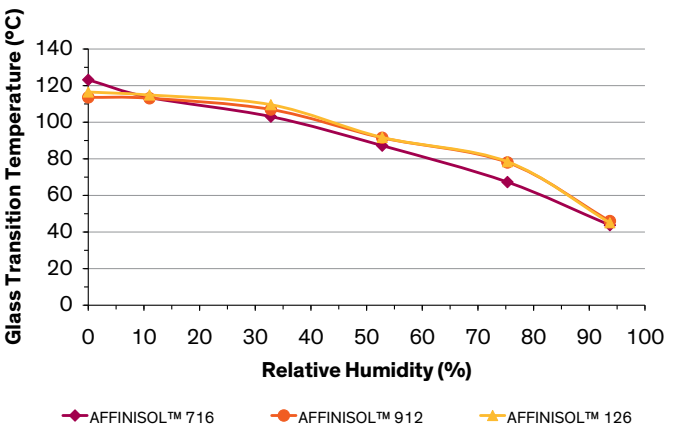


Figure 6. The Tg of AFFINISOL™ HPMCAS as a function of relative humidity.

AFFINISOL™ HPMCAS for Spray-Dried Dispersion (SDD)

HPMCAS has demonstrated utility in forming amorphous solid dispersions with poorly soluble APIs that result in an apparent solubility enhancement through its ability to achieve and sustain a supersaturated solution of the API.[1, 2] In addition, the formation of an amorphous solid dispersion with HPMCAS has been shown to have little or no impact on the permeability of the API.[3] The extent of solubility enhancement and sustainment is dependent on acetate and succinate content of the polymer, and the optimum ratio varies for each API. This is demonstrated in Figure 8 where the solubility of phenytoin and itraconazole amorphous solid dispersions with all AFFINISOL™ HPMCAS grades were evaluated.

The SDDs were created by dissolving phenytoin in acetone or itraconazole in tetrahydrofuran and adding the AFFINISOL™ HPMCAS to the solution to give a clear to slightly opaque final solution with 25 wt% API to 75 wt% AFFINISOL™ HPMCAS ratio. The solutions were spray dried on a Bend miniSD spray drying unit and the resulting samples were dried at 25 °C under reduced pressure. The dispersions were analyzed by DSC and PXRD to confirm amorphous dispersions were created.

Drug release from the isolated powder was evaluated by transferring 7.2 mg of the SDD into a microcentrifuge tube. The powder was diluted with 1.8 mL fasted simulated intestinal fluid at pH 6.5. At each sample time, the samples were centrifuged for 1 min at 13,000 x g. Fifty microliters of the supernate was removed and diluted with 250 µL of MeOH. The amount of dissolved drug was detected by HPLC-UV. All sample preparation steps were completed in a 37°C constant temperature box.[1]

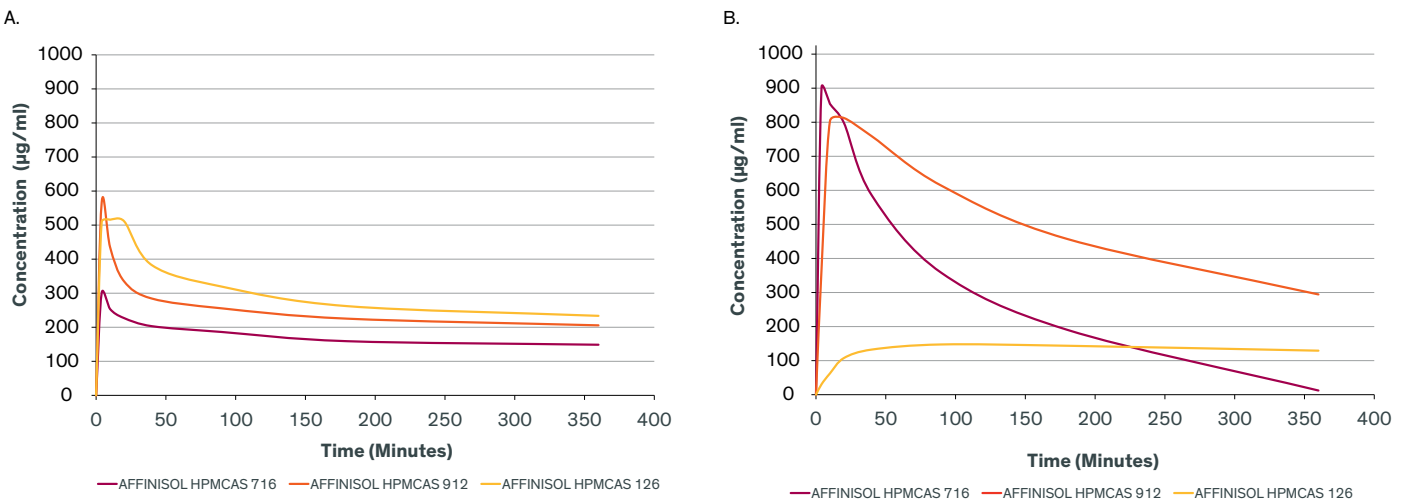


Figure 7. Dissolution profiles for 25 wt % amorphous solid dispersions formed with (A.) phenytoin and (B.) itraconazole in AFFINISOL HPMCAS demonstrating the solubility enhancement dependence on acetate and succinate substitution levels.

Performance by Design (PbD) Formulation with AFFINISOL™ HPMCAS

The solubility enhancement performance of amorphous solid dispersions formed with HPMCAS has a strong dependence on the acetate and succinate substitution levels. AFFINISOL™ HPMCAS 716, HPMCAS 912, and HPMCAS 126 represent only a small portion of the substitution space that is approved for use by the USP-NF and the JPE. A formulation with HPMCAS 716, 912, and 126 may provide enhanced solubility, however that formulation may not be robust to lot to lot variation in acetate and succinate substitution. Dow Pharma and Food Solutions has the capability to perform high throughput synthesis of HPMCAS polymers allowing the complete exploration of the acetate and succinate space. Figure 8 demonstrates a set of high throughput experiments to explore the acetate and succinate substitution space. In addition Dow has high throughput screening techniques to rapidly test polymers with APIs to identify good excipient candidates.

With a complete understanding of the synthetically viable acetate and succinate substitution levels and the levels that provide good organic solubility, the ideal polymer substitution range can be identified. Dow's Six Sigma Black Belts used Design of Experiment (DoE) principals to create a partial factorial sample set with linear constraints for the acetate and succinate substitution range (Figure 9). This sample set also includes samples of the standard AFFINISOL™ HPMCAS grades to provide a complete study of formulation robustness with HPMCAS. Utilizing this sample set provides a Performance by Design (PbD) approach to formulation to faciliate the most robust drug product possible.

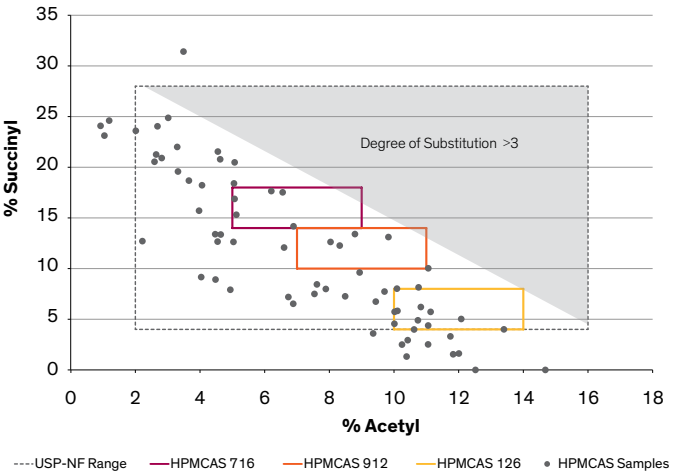


Figure 8. Demonstration of a high throughput synthesis exploration of the acetate and succinate substitution space. For cellulosic polymers a degree of substitution greater than 3 is not possible.

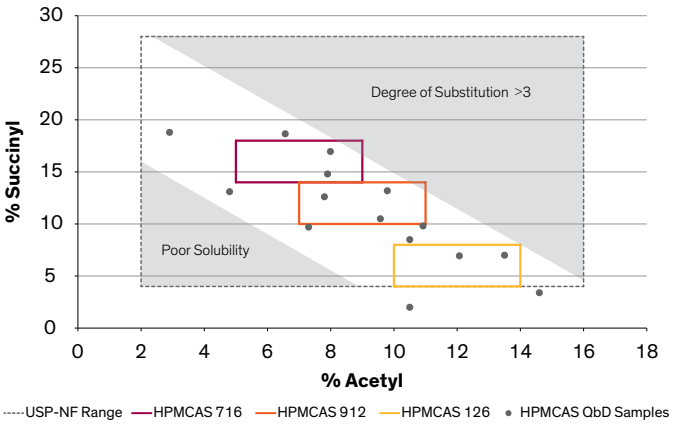


Figure 9. DoE sample set of AFFINISOL™ HPMCAS with AFFINISOL™ HPMCAS 716 (maroon), AFFINISOL™ HPMCAS 912 (orange) and AFFINISOL™ HPMCAS 126 (yellow) included. This sample set provides a QbD approach to understanding the robustness of a formulation.

To demonstrate the need for PbD studies of the acetate and succinate substitution levels, four model poorly soluble APIs, itraconazole, griseofulvin, danazol, and phenytoin, with a range of physical properties were studied (Table 4) with the DoE sample set. Spray dried dispersions and solubility studies were performed as described previously. Performance maps for the solubility enhancement capability of each HPMCAS polymer in the set were created using the area under the curve (AUC) to the 90 minute time point (Figure 10). [4] These model studies demonstrate how each API is unique and requires in-depth study to formulate with HPMCAS. For example, itraconazole forms a robust formulation with HPMCAS polymers having between 5 and 10 weight percent acetate and 10 to 18 weight percent succinate. In contrast, griseofulvin displays the maximum solubility enhancement with the AFFINSIOL™ HPMCAS 126 grade. However, as the acetate and succinate levels change only slightly, the solubility enhancement performance rapidly decreases.

AFFINISOL™ HPMCAS PbD sample sets can be customized to your formulation need and are available from our lab and cGMP Market Development Plant. Identifying the best HPMCAS composition for robust drug performance and being able to support scale-up to commercialization are key differentiators of the Dow custom and PbD offering for AFFINISOL™ HPMCAS.

TABLE 4. Model compounds and physical properties of APIs used with AFFINISOL™ HPMCAS PbD sample set.

Model API	T (°C)	T (°C)	clogP
Phenytoin	71	286	2.2
Itraconazole	60	166	7.1
Griseofulvin	89	220	2
Danazol	88	225	4.1

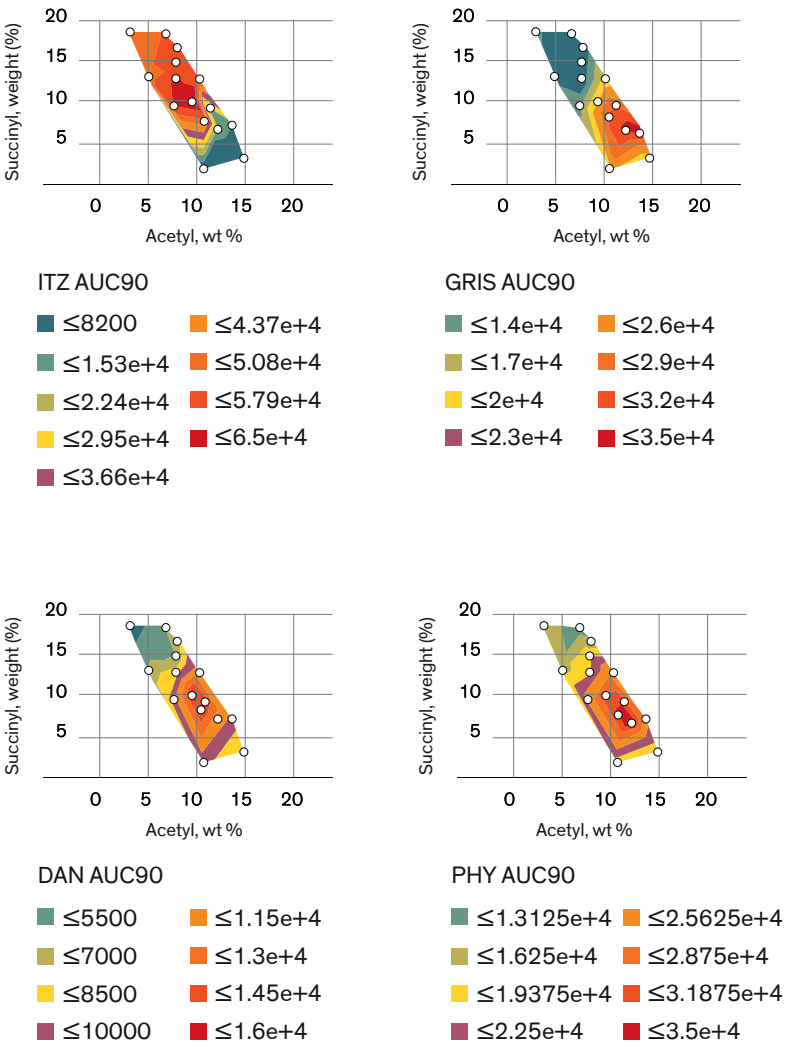


Figure 10. Performance maps (red is highest solubility; blue is lowest solubility) with the AFFINISOL™ HPMCAS PbD sample set with model compounds Itraconazole, Griseofulvin, Danazol, and Phenytoin.[4] The performance maps demonstrate the need to have a full understanding of the allowable HPMCAS substitution space and how minor changes in acetate and succinate substitution can have a substantial impact on solubility enhancement.

References

1. Curatolo, W., J. Nightingale, and S. Herbig, Utility of Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS) for Initiation and Maintenance of Drug Supersaturation in the GI Milieu. Pharmaceutical Research, 2009. 26(6): p. 1419-1431.
2. Friesen, D.T., et al., Hydroxypropyl Methylcellulose Acetate Succinate-Based Spray-Dried Dispersions: An Overview. Molecular Pharmaceutics, 2008. 5(6): p. 1003-1019.
3. Dahan, A., et al., The Twofold Advantage of the Amorphous Form as an Oral Drug Delivery Practice for Lipophilic Compounds: Increased Apparent Solubility and Drug Flux Through the Intestinal Membrane. The AAPS Journal, 2013. 15(2): p. 347-353.
4. Porter III, W.W., et al. Effect of Acetate and Succinate Substitution Levels On Spray Dried Dispersions of Hypromellose Acetate Succinate – A Quality by Design Approach. in 2012 AIChE Annual Meeting. 2012. Pittsburgh, PA USA.
5. Hoshi, N., et al., EFFECTS ON OFFSPRING INDUCED BY ORAL ADMINISTRATION OF HYDROXYPROPYLMETHYLCELLULOSE ACETATE SUCCINATE TO THE FEMALE RATS IN PERI-AND POST-NATAL PERIODS. The Journal of Toxicological Sciences, 1985. 10(SupplementII): p. 235-255.
6. Hoshi, N., et al., TERATOLOGICAL STUDY OF HYDROXYPROPYLMETHYLCELLULOSE ACETATE SUCCINATE IN RABBITS. The Journal of Toxicological Sciences, 1985. 10(SupplementII): p. 227-234.
7. Hoshi, N., et al., TERATOLOGICAL STUDIES OF HYDROXYPROPYLMETHYLCELLULOSE ACETATE SUCCINATE IN RATS. The Journal of Toxicological Sciences, 1985. 10(SupplementII): p. 203-226.
8. Hoshi, N., et al., STUDIES OF HYDROXYPROPYLMETHYLCELLULOSE ACETATE SUCCINATE ON FERTILITY IN RATS. The Journal of Toxicological Sciences, 1985. 10(SupplementII): p. 187-201.
9. Hoshi, N., et al., GENERAL PHARMACOLOGICAL STUDIES OF HYDROXYPROPYLMETHYLCELLULOSE ACETATE SUCCINATE IN EXPERIMENTAL ANIMALS. The Journal of Toxicological Sciences, 1985. 10(SupplementII): p. 129-146.
10. Hoshi, N., et al., TOXICOLOGICAL STUDIES OF HYDROXYPROPYLMETHYLCELLULOSE ACETATE SUCCINATE : ACUTE TOXICITY IN RATS AND RABBITS, AND SUBCHRONIC AND CHRONIC TOXICITIES IN RATS. The Journal of Toxicological Sciences, 1985. 10(SupplementII): p. 147-185.

UNIQUE TOGETHER

CONTROLLED RELEASE ALLIANCE

Contact your Dow representative or call:

North America	+1 800 447 4369
Europe, Middle East, Africa	+31 11 567 2626
Pacific	+60 3 7965 5392
Latin America	+55 11 5184 8722

www.dowpharmasolutions.com

Contact your Colorcon representative or call:

North America	+1-215-699-7733
Europe, Middle East, Africa	+44-(0)-1322-293000
Latin America	+54-11-5556-7700
India	+91-832-6727373
China	+86-21-61982300

www.colorcon.com

This document is valid at the time of distribution. Distributed 14-Nov-2018 (UTC)