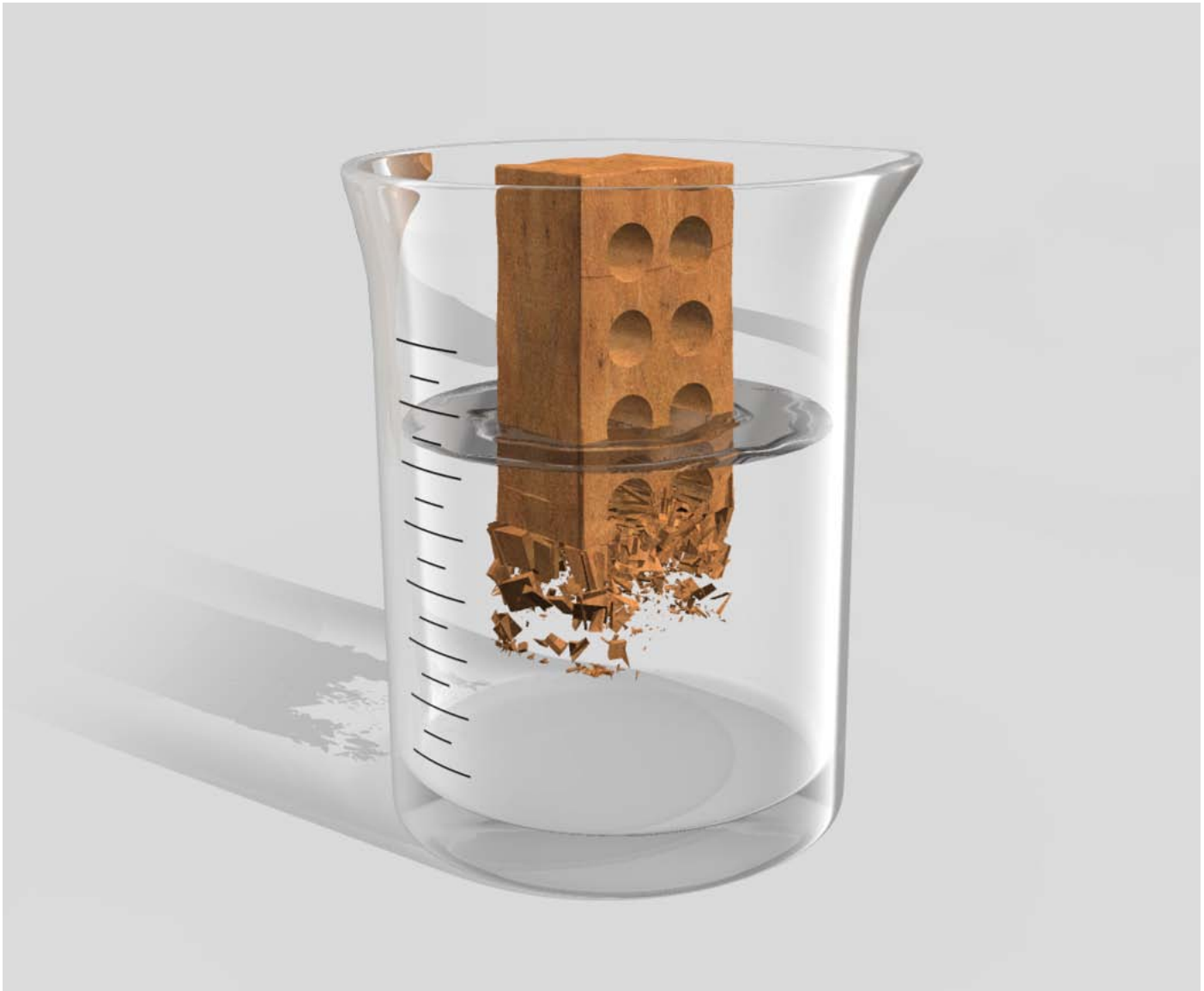
DOW®

AffiniSol™

Pharma & Food Solutions

AFFINISOL™

Solving the Insoluble with Dow



Solving the Insoluble
With DOW

High throughput screening methods are frequently identifying physically complex new chemical entities (NCEs) that are lipophilic with higher molecular weights. This has resulted in approximately 40% of NCEs in drug development pipelines having poor water solubility. More recent reports indicate this number has grown substantially to nearly 90%*. Many of these Active Pharmaceutical Ingredients (APIs) fall into the Biopharmaceutics Classification System (BCS) Class II displaying low solubility but having high biological permeability.

For such APIs the low aqueous solubility severely limits the compound's oral bioavailability and thus commercial viability. Therefore, formulation scientists are consistently in need of functional excipients and enabling technologies capable of increasing the API solubility in order to achieve therapeutically relevant and reproducible concentrations within the blood and thus a successful drug product.

* Stokbroekx Sigrid: Formulation Effects on Drug Absorption. Bioavailability and Bioequivalence: Focus on Physiological Factors and Variability. EUFEPS and COST B25 Conference; 2007

Excipient & Material Science Expertise Combined with State of the Art Technologies

Dow, through its Dow Pharma & Food Solutions (DP&FS) business unit, is committed to addressing the pipeline challenges associated with poorly soluble drug compounds.
To meet the industry needs, DP&FS utilizes an array of technologies including high-throughput polymer synthesis, API polymer performance screening, laboratory-scale product development, and structure-property optimization to match the polymer with the API for exceptional performance.
In addition, DP&FS operates a cGMP (Current Good Manufacturing Practices) market-development production plant to support clinical development of optimized polymers.

Collaborating with a Technology Leader to Solve Customer Needs

Bend Research is the industry leader in spray-drying and formulation development for drug compounds with poor aqueous solubility.

DP&FS is an industry leader in cellulosic polymer chemistry, innovation, and manufacturing.

Dow has an exclusive collaboration with Bend Research to provide rigorous science-based spray-dried dispersion solutions and a selection of enabling cellulosics polymers to address the challenge of formulating poorly soluble drugs.

Enhancing Drug Solubility

- Our AFFINISOL™ product range is tailored to address the solubilization performance requirements of each API
- Dow utilizes structure-property relationships to design distinct polymers to facilitate the required solubilization performance of an API
- Coupled with hydroxypropyl methoxycellulose products, AFFINISOL™ Hypromellose Acetate Succinate (HPMCAS) goes beyond the products commercially available today
- Dow offers sample sets which can be used to facilitate compliance with US FDA's Quality by Design (QbD) initiative
- The collaboration with Bend Research leverages polymer expertise with spray-dried dispersion (SDD) formulation and scale-up expertise
- New materials to enhance aqueous solubility of APIs through SDDs and Hot Melt Extrusi on (HME) are in development

Hypromellose Acetate Succinate Tailored to Address Drug Solubilization Needs

Every API is unique. This is why Dow utilizes a Design of Experiment (DOE) approach to explore substituent space to offer optimized and robust performance for poorly soluble drug compounds.

Dow combines polymer structure-property relationships with small scale synthesis capability to offer an excellent product that is designed to address each APIs unique needs.

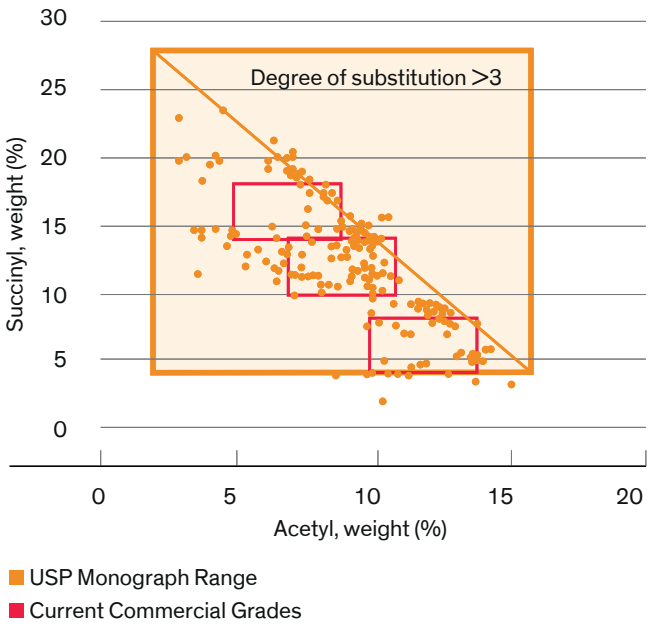
Many Substitution Options Available

Not all APIs can achieve a desirable balance between peak drug concentration and sustainment of supersaturated drug concentration using commercially available HPMCAS grades. Our AFFINISOL™ product range goes beyond the current commercial offering, providing more options to enhance solubilization performance.

Substitution Level Dependence

The APIs listed in the table on the right were used as model drugs to investigate the dependence of peak drug concentration and sustainment of supersaturated solutions on AFFINISOL™ HPMCAS substitution level in SDDs.

DRUG	TM(C)	CLOG P
Phenytoin	286	2.2
Itraconazole	166	7.1
Griseofulvin	220	2.0
Danazol	225	4.1

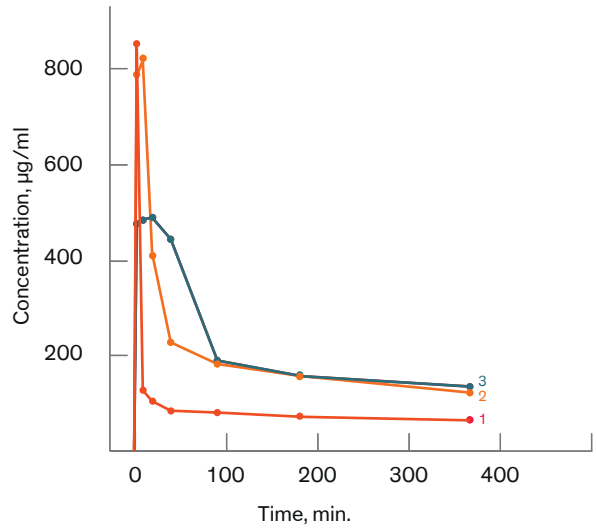


Each graph is based on results from internal studies from 2011-2012.

Strong Dependence on Substitution Levels

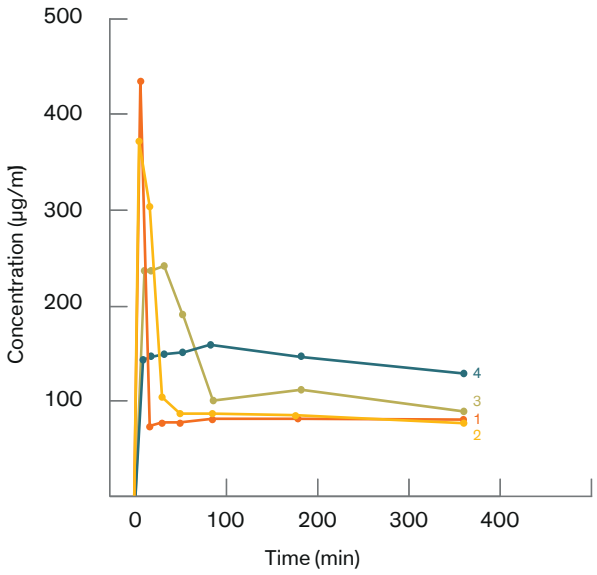
Some APIs, such as griseofulvin and danazol showed a strong dependence on acetyl and succinyl substitution levels. Partnering with Dow to explore the entire substitution space will be beneficial for these types of APIs to find the optimum point for best performance.

25% Griseofulvin / HPMCAS SDD

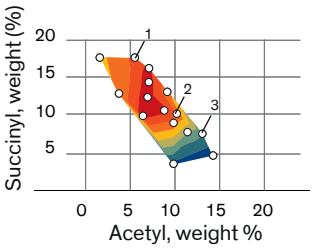


6.6% Ac/18.7% Succ
13.5% Ac/7% Succ
10.9% Ac/9.8% Succ

25% Danazol / HPMCAS SDD

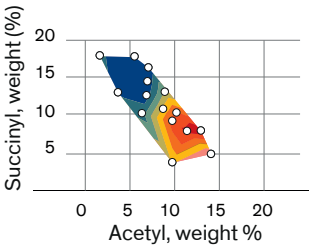


4.8% Ac / 13.1% Succ
9.6% Ac / 10.5% Succ
7.8% Ac / 12.6% Succ
12.1% Ac / 6.9% Succ



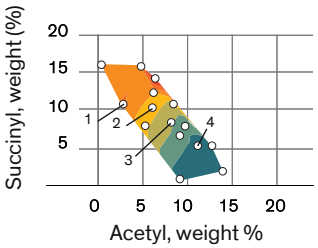
GRIS Cmax

≤387 500
≤475 000
≤562 500
≤650 000
≤737 500
≤825 000
≤912 500
≤1 000 000



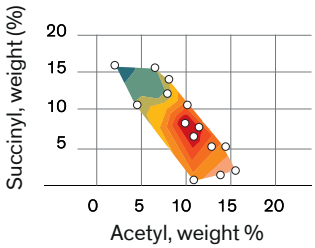
GRIS AUC90

≤1.4e+4
≤1.7e+4
≤2e+4
≤2.3e+4
≤2.6e+4
≤2.9e+4
≤3.2e+4
≤3.5e+4



DAN Cmax

≤175
≤250
≤325
≤400
≤475
≤550
≤625
≤700



DAN AUC90

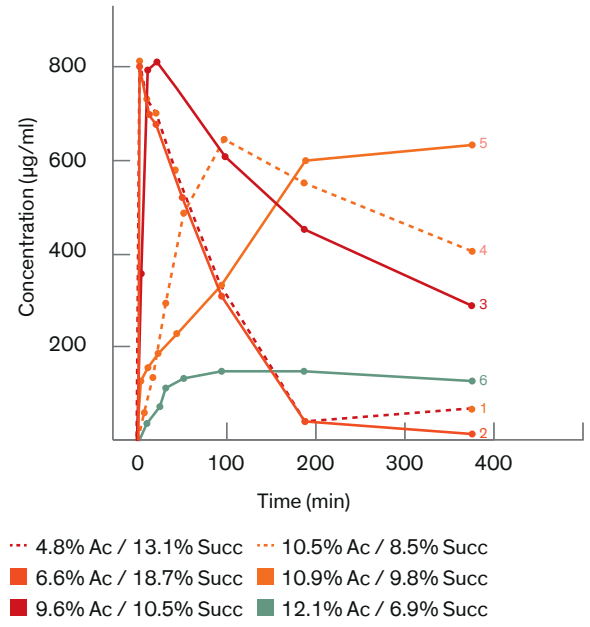
≤5500
≤7000
≤8500
≤10000
≤1.15e+4
≤1.3e+4
≤1.45e+4
≤1.6e+4

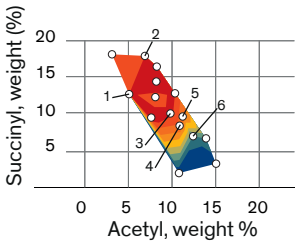
Each graph is based on results from internal studies from 2011-2012.

Low Sensitivity to Substitution Levels

Not all APIs are highly sensitive to acetyl and succinyl substitution levels. Partnering with Dow to demonstrate similar drug release performance across a wide range of substitution levels can help increase compliance with US FDA's QbD initiatives and potentially lead to better, more robust formulations. The itraconazole formulation on the right shows similar drug release behavior across a range of substitution levels. Dow's DOE approach to exploring HPMCAS substitution space will identify and lock in this range for batch to batch consistency in final product performance.

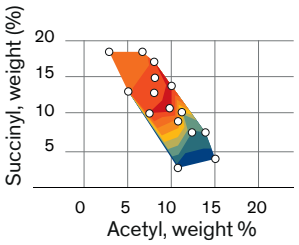
25% Itraconazole / HPMCAS SDD





ITZ Cmax

- ≤100
- ≤200
- ≤300
- ≤400
- ≤500
- ≤600
- ≤700
- ≤800
- ≤900



ITZ AUC90

- ≤5000
- ≤1.25e+4
- ≤2e+4
- ≤2.75e+4
- ≤3.5e+4
- ≤4.25e+4
- ≤5e+4
- ≤5.75e+4
- ≤6.5e+4

Each graph is based on results from internal studies from 2011-2012.

Solubilization API Trends

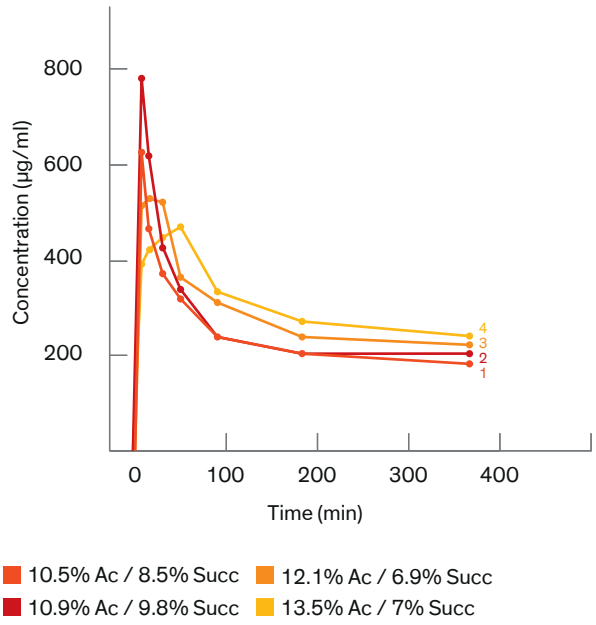
- Based on Dow studies, HPMCAS materials with higher acetyl substitution and lower succinyl substitution are best for crystallization inhibition.
  On the other hand, materials with low acetyl and high succinyl substitution are best for lipophilic compounds.

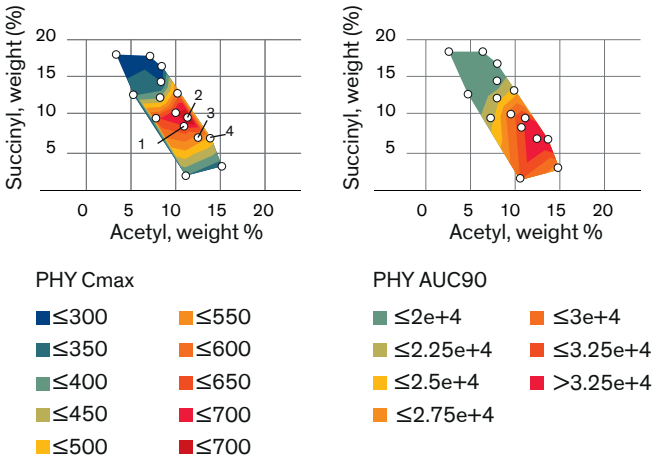
- The substitution level of HPMCAS providing the best balance of peak drug concentration and sustainment of supersaturation may not always be a current commercially available product.
  In the example shown on the right, the samples plotted in dark orange, orange and yellow (10.5% Ac / 8.5% Succ; 12.1 Ac/ 6.9% Succ and 13.5% Ac / 7% Succ) represent materials that are within the substitution ranges of current commercial products. The sample mapped out in dark red (10.9% Ac / 9.8% Succ) provides a higher peak drug concentration and better maintenance of elevated concentration for extended periods of time compared to any of the materials with substitution levels within current grades.

Innovative Solutions in the Making

Dow continues to invest in developing expanded AFFINISOL™ polymer solutions, both cellulosics and non-cellulosics-based, to address poorly soluble drug challenges and improvements to the solid dispersion as well as hot melt extrusion manufacturing processes.

25% Phenytoin / HPMCAS SDD





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