SOLVING THE INSOLUBLE WITH DOW

AffiniSo!™

™Trademark of The Dow Chemical Company (“Dow”) or an affiliated company of Dow
Trends in drug characteristics increasingly favor greater degrees of lipophilicity, higher molecular weight, greater physical form complexity and significantly lower aqueous solubility.

Accordingly, it is estimated that 40% of new molecular entities now suffer from poor aqueous solubility.

This presents a huge challenge for therapeutically relevant oral delivery drug products. Indeed, the Active Pharmaceutical Ingredient (API) cannot reach its molecular target if the drug is not dissolved in the gastro-intestinal tract (GIT). Therefore, formulation scientists are increasingly in need of reliable and robust technology solutions to overcome this critical drug delivery issue.
EXCIPIENT & MATERIAL SCIENCE EXPERTISE, STATE OF THE ART TECHNOLOGIES & CAPABILITIES TO ADDRESS PIPELINE CHALLENGES OF POORLY SOLUBLE COMPOUNDS

Dow through its Dow Wolff Cellulosics business unit contributes to solving this unmet pressing need through rigorous science and its AFFINISOL™ range of enabling polymers. Dow fully supports this goal with an array of technologies, including high-throughput synthesis with Active Pharmaceutical Ingredient (API) / polymer screening, laboratory-scale product development, and structure / property optimization, as well as a fully cGMP market-development plant capable of supporting clinical development of optimized solutions.

COLLABORATING WITH A TECHNOLOGY LEADER TO SOLVE CUSTOMER NEEDS

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.

Bend Research has the acknowledged leading competence and intellectual property position in spray-drying, and Dow is a leader in cellulosic polymer innovation and manufacturing. No other option fully integrates the materials and engineering science rationale for the custom polymer through reliable solid dispersion formulation development and scale-up.

ENHANCING DRUG SOLUBILITY AND ACTIVE PHARMACEUTICAL INGREDIENTS (API) BIOAVAILABILITY

- Dow’s AFFINISOL™ product range is uniquely tailored to address the solubilization performance requirements of each API
- Dow leverages its capabilities to analyze and subsequently design distinct polymers to facilitate the required solubilization performance
- Coupled with hypromellose 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 initiative
- The collaboration with Bend Research advantageously couples science leading polymer expertise with Spray-Dried Dispersion (SDD) formulation and scale-up expertise
- New materials to solve poorly water soluble API delivery needs for SDD and Hot Melt Extrusion (HME) are in development
HYDROXYPROLINE ACETATE SUCCINATE (HPMCAS) TAILORED TO ADDRESS DRUG SOLUBILIZATION NEEDS

• Every API is unique. This is why Dow uses a rigorous scientific approach to explore the right AFFINISOL™ HPMCAS product for optimum yet robust performance across both highly crystalline and lipophilic poorly soluble drug classes.

Dow combines a deep understanding of critical polymer properties with small scale synthesis capability to partner with your development team and offer an optimized product that is scientifically designed to address each API’s 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. Dow’s AFFINISOL™ product range goes beyond the current commercial offering, providing more options to maximize solubilization performance.

SUBSTITUTION LEVEL DEPENDENCE

The following APIs were used as model drugs to investigate the dependence of peak drug concentration and sustainment of supersaturated solutions on AFFINISOL™ HPMCAS substitution level in spray dried dispersions (SDDs).

<table>
<thead>
<tr>
<th>DRUG</th>
<th>TM(C)</th>
<th>CLOG P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>286</td>
<td>2.2</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>166</td>
<td>7.1</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>220</td>
<td>2.0</td>
</tr>
<tr>
<td>Danazol</td>
<td>225</td>
<td>4.1</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>172</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Each graph is based on results from internal studies from 2011-2012.
Some APIs, such as nifedipine 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.

Each graph is based on results from internal studies from 2011-2012.
LOW SENSITIVITY TO SUBSTITUTION LEVELS

Not all Active Pharmaceutical Ingredients (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 increase compliance with US FDA Quality by Design (QbD) initiatives and 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 Design of Experiments (DOE) and QbD approach will identify and lock in this range for batch to batch consistency in final product performance.

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

- Based on Dow studies, Hypromellose Acetate Succinate (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 green (7.8% Ac / 12.6% Succ; 8% Ac / 17% Succ and 13.5% Ac / 7% Succ) represent materials that are within the substitution ranges of current commercial products. The sample mapped out in yellow (10.5% Ac / 8.5% 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.

Each graph is based on results from internal studies from 2011-2012.
Dow requests that customers considering use of Dow products in medical applications notify Dow so that appropriate assessments may be conducted. Dow has a Corporate Medical Application Policy in place that guides the use of Dow products in potential new pharmaceutical and medical device uses. Dow reviews all new applications/uses according to this Medical Application Policy to determine if the use is appropriate for Dow materials. Dow does not endorse or claim suitability of its products for specific medical applications. It is the responsibility of the medical device or pharmaceutical manufacturer to determine that the Dow product is safe, lawful, and technically suitable for the intended use. DOW MAKES NO WARRANTIES, EXPRESS OR IMPLIED, CONCERNING THE SUITABILITY OF ANY DOW PRODUCT FOR USE IN MEDICAL APPLICATIONS.

NOTICE: No freedom from infringement of any patent owned by Dow or others is to be inferred. Because use conditions and applicable laws may differ from one location to another and may change with time, Customer is responsible for determining whether products and the information in this document are appropriate for Customer’s use and for ensuring that Customer’s workplace and disposal practices are in compliance with applicable laws and other government enactments. The product shown in this literature may not be available for sale and/or available in all geographies where Dow is represented. The claims made may not have been approved for use in all countries. Dow assumes no obligation or liability for the information in this document. References to “Dow” or the “Company” mean the Dow legal entity selling the products to Customer unless otherwise expressly noted. NO WARRANTIES ARE GIVEN; ALL IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE ARE EXPRESSLY EXCLUDED.