Ashland — focus on drug solubilization

High-quality excipients that improve the solubility of your active pharmaceutical ingredients

ASHLAND®

With good chemistry great things happen.™

Increase Solubility and Enhance Bioavailability

- AquaSolve™ and AquaSolve AS™ hypromellose acetate succinate (HPMCAS)
- Benecel™ methylcellulose and hypromellose (HPMC)
- Cavamax*, Cavitron™ and Cavasol* cyclodextrins
- Klucel™ hydroxypropylcellulose (HPC)
- Pharmasolve™ N-methyl-2-pyrrolidone
- Plasdone™ povidone and copovidone
- Polyplasdone™ crospovidone

* Registered trademark owned by Wacker Chemie AG. Ashland Inc. acts as a worldwide distributor for Wacker.

Ashland Specialty Ingredients offers a variety of excipients and formulation ingredients to meet the needs of the pharmaceutical and nutraceutical industries. We provide cellulosic and vinyl pyrrolidone polymers as well as inclusion complexes with the functionality needed by formulators to create innovative solutions for their drug development programs.

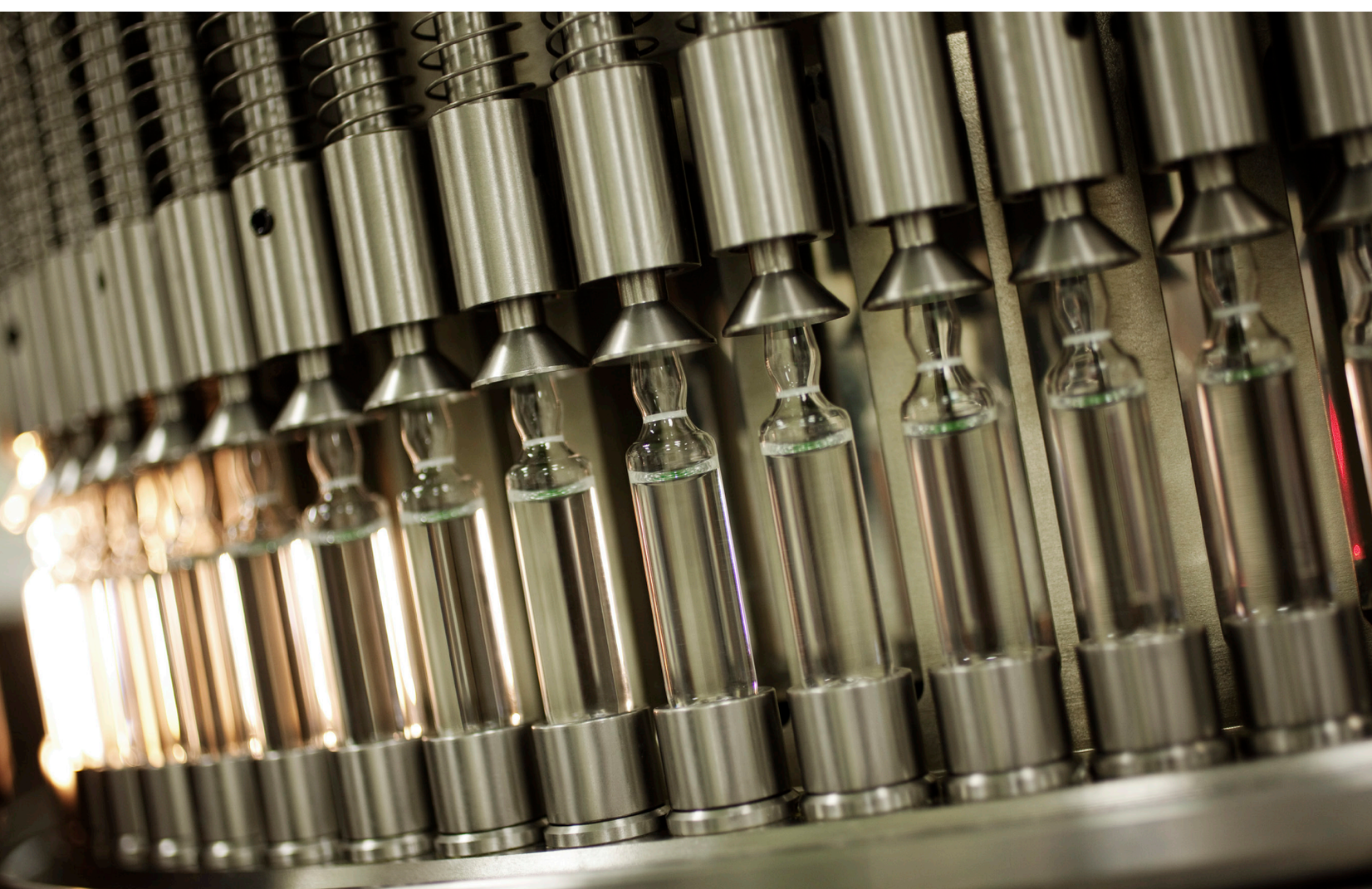
Today's formulation scientists face a new set of challenges as they seek solutions to improve aqueous solubility with the expectation of enhanced bioavailability. Ashland manufactures or markets many common excipients that address solubility issues. Through our contract services business we provide support for formulation and commercialization of poorly soluble active pharmaceutical ingredients (APIs).

Ashland's global manufacturing plants operate under strict cGMP standards, meaning our customers can depend on high-quality products from each of our manufacturing sites. We have over a decade of experience improving the solubility of APIs, and our newest chemistries enable an even wider range of solutions tailored to your unique API needs. When you work with Ashland, you work with one source for a broad range of solubilization excipients and technologies. Ashland adds value to your APIs by improving solubility, enhancing bioavailability and increasing speed to market.

Broad Range of Polymers for Solubilization

Polymers for the improvement of solubilization serve a number of purposes. They can prevent recrystallization, stabilize amorphous APIs, enhance solubility and processability and facilitate dissolution. Ashland's Plasdone povidone and copovidone polymers often have been used to prevent recrystallization of APIs in solutions and water-based pharmaceutical preparations. More recently, these products have found wide utility as polymeric carriers in the formulation of solid dispersions by melt extrusion and spray drying.[1–4] Plasdone povidone is a highly lipophilic polymer; the higher molecular weight grades such as K-29/32 have a high glass transition temperature, which helps to stabilize amorphous APIs. In addition, the carbonyls of the pyrrolidone groups in povidone are capable of accepting hydrogen bonds, and therefore povidone can be an effective solid-dispersion carrier, especially for APIs with hydrogen bond donors. The incorporation of vinyl pyrrolidone and vinyl acetate monomers in a single polymer chain gives Plasdone S-630 copovidone a combination of hydrophilicity and hydrophobicity that makes it a highly effective polymeric carrier and stabilizing agent for use in solid-dispersion applications. Plasdone S-630 copovidone is frequently used to enhance API solubility and bioavailability in both melt-extruded and spray-dried solid dispersions where the API is distributed as amorphous domains or at the molecular level within a polymer matrix. The unique combination of properties found in Plasdone S-630 copovidone stabilizes the API to prevent recrystallization on storage, help facilitate dissolution of the API and inhibit recrystallization i*n vivo*. Furthermore, Plasdone povidone and copovidone have demonstrated excellent processability in both spray drying and melt extrusion. Both povidone and copovidone have been used in marketed solid-dispersion products.

Klucel hydroxypropylcellulose (HPC) is a thermoplastic polymer that is suitable for hot-melt extrusion applications. This family of products is intended for pharmaceutical and food use and can be processed without plasticizers at significantly lower temperatures than other polymers. The thermoplastic property



of Klucel HPC makes it a logical choice in hot-melt extrusion to enhance the processability of polymeric carriers in which the glass transition temperature (T_g) is too high for stand-alone use.[2]

Benecel hypromellose (HPMC) is another valuable polymer for spray-dried dispersions that has been proven to successfully convert and stabilize crystalline APIs to the amorphous form for higher bioavailability. Apart from its high T_g range, HPMC is also a hydrogen bond donor and weak acceptor, and therefore could have molecular interactions with a broad range of APIs. In addition, HPMC is generally regarded as one of the most effective polymeric precipitation inhibitors. HPMC can also be found in many commercially available pharmaceutical products based on solid-dispersion technology.

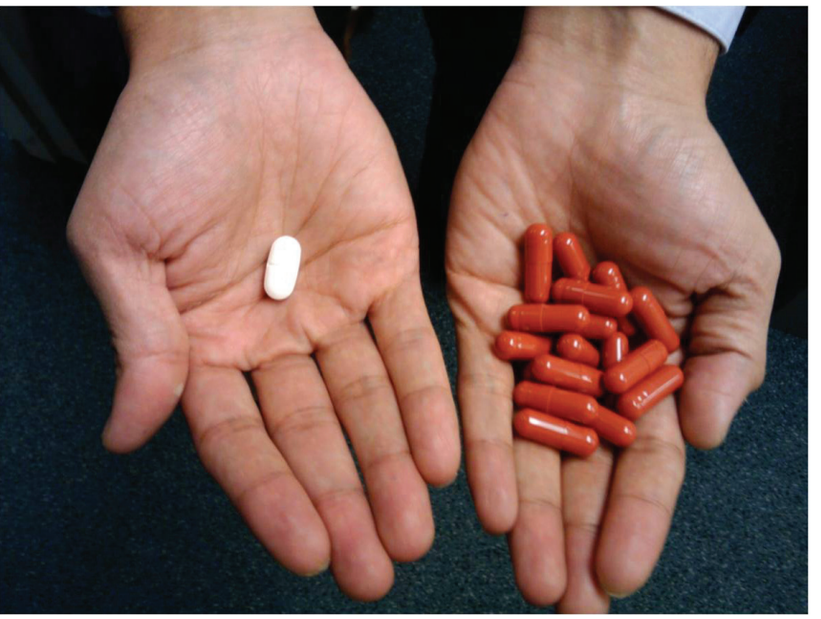
New to our family of polymers is AquaSolve (AquaSolve AS in the United Kingdom) hypromellose acetate succinate (HPMCAS) in L, M and H grades. All three grades have demonstrated interchangeability with competitive products in solubilization applications. HPMCAS is well known for its ability to initiate and maintain supersaturation for drugs with a wide variety of structures and physical properties, and can be found in a number of commercially approved amorphous solid dispersion products. The efficacy advantage of HPMCAS is primarily due to its superiority as a precipitation inhibitor via the formation of colloidal species in aqueous media.[5,6] The most important features of AquaSolve HPMCAS are its amphiphilic nature, high T_g and low viscosity in various organic solvents. It provides an excellent combination of amorphous stability and increased dissolution for many API candidates.

Another up-and-coming technology for improving solubilization involves the formation of inclusion complexes. Ashland markets a line of native cyclodextrins and cyclodextrin derivatives for this purpose that have demonstrated solubilization functionality in many commercial products. Cyclodextrin derivatives are more commonly used in parenteral applications, while native cyclodextrins have more utility in oral dosage forms.

For preformulation studies, Pharmasolve N-methyl-2-pyrrolidone is one of the best solvents on the market. Typically used in early formulation and toxicity studies, Pharmasolve N-methyl-2-pyrrolidone is an excellent choice when seeking the highest drug load possible. It also used in low-dosage levels for certain topical and subcutaneous applications, as well as in injectables for veterinary use.

1. Rahman, M., J.D. Lester, M. Keshtmand, F. El-Saleh, I. Farzana, V. Bi, & T. Dürig. *Comparison of Amorphous Solid Dispersions of Piroxicam in Plasdone™ S-630 Copovidone Prepared by Spray Drying and Hot-melt Extrusion*. Ashland Pharmaceutical Technical Report PTR-093. (2013).
2. Rahman, M., E. Pinto, S. Ozkan, K. Gaughan, A. J. Sosnowik, J.D. Lester, J. Brady, I. Farzana, R. Sulouff, V. Bi, & T. Dürig. *Thermal and Rheological Properties of Klucel™ Hydroxypropylcellulose Polymers for Hot-melt Extrusion Applications*. Ashland Pharmaceutical Technical Report PTR-091. (2013).
3. Yang, J., K. Grey, & J. Doney, "An Improved Kinetics Approach to Describe the Physical Stability of Amorphous Solid Dispersions," *International Journal of Pharmaceutics*, 384, 24–31 (2010).
4. Doney, J., M. Keshtmand, & C. Shores, "Amorphous Spray-dried Formulations to Improve Bioavailability of CoQ10," poster presented at 2008 AAPS Annual Meeting and Exposition, Atlanta, GA, (2008, November).
5. Friesen, D. T., R. Shanker, M. Crew, D. T. Smithey, W. J. Curatolo, & J. A. S. Nightingale, "Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview," *Molecular Pharmaceutics*, 5, 1003–1019 (2008).
6. Curatolo, W., J. A. Nightingale, & S. M. Herbig, "Utility of hydroxypropylmethylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu," *Pharmaceutical Research*, 26, 1419–1431 (2009).

Enabling Technologies for Drug Solubilization



Over the last several decades, medicinal chemists have succeeded in their quest to develop new APIs with more specificity and therapeutic value. Their success has lead to an increase in compounds with low aqueous solubility and, hence, poor bioavailability. Traditionally, formulation scientists addressed solubility issues by particle-size reduction, salt formation or formulating with surfactants; now formulators often need to investigate enabling technologies to overcome poor solubility.

Amorphous solid dispersions are becoming the go-to technology for solubilization. Although developed more than 50 years ago, amorphous solid-dispersion technology didn't catch on until the start of the 21st century. More than a dozen commercial pharmaceuticals formulated as amorphous solid dispersions are on the market today, which have contributed to acceptance of and excitement around this technology as a viable solubilization process. Ashland provides many of the more commonly used and value-added polymers in amorphous solid-dispersion technology. Additionally, Ashland has been a pioneer in the development, evaluation and manufacture of amorphous solid dispersions, through our contract services business.

In addition to amorphous solid dispersions, Ashland markets a variety of other products that support solubilization technologies for preformulation, liquid and veterinary parenteral applications.

Solid-dispersion Technologies

Poorly soluble APIs pose development challenges, and common techniques for improving API solubility, such as salt formation and particle-size reduction, do not always result in sufficient bioavailability required for therapeutic efficacy. As a result, there is increasing interest in the use of amorphous solid-dispersion technology to improve the aqueous solubility and enhance the bioavailability of poorly soluble APIs. Multiple methods for preparing solid dispersions have been reported. Currently, the methods of most interest are hot-melt extrusion and spray drying.

Solid dispersions are molecular (thermodynamically stable solid solutions) and/or amorphous colloidal (kinetically stable solid suspensions) dispersions of an API dispersed in a polymeric carrier that enhance the solubility and bioavailability of poorly soluble compounds. Amorphous solid dispersions are particularly attractive for many poorly soluble drug candidates because they can increase both solubility and dissolution rates.[7,8] Recent research on amorphous solid-dispersion formulations has indicated a concomitant increase in drug flux through the intestinal membrane, in addition to the significant solubilization enhancement effect.[9] As a result, bioavailability of poorly soluble APIs is significantly enhanced. Research in the past decade in solid-dispersion formulation and process technologies has established that stable amorphous solid dispersions with high bioavailability can be prepared at commercial scale by spray drying or melt extrusion.

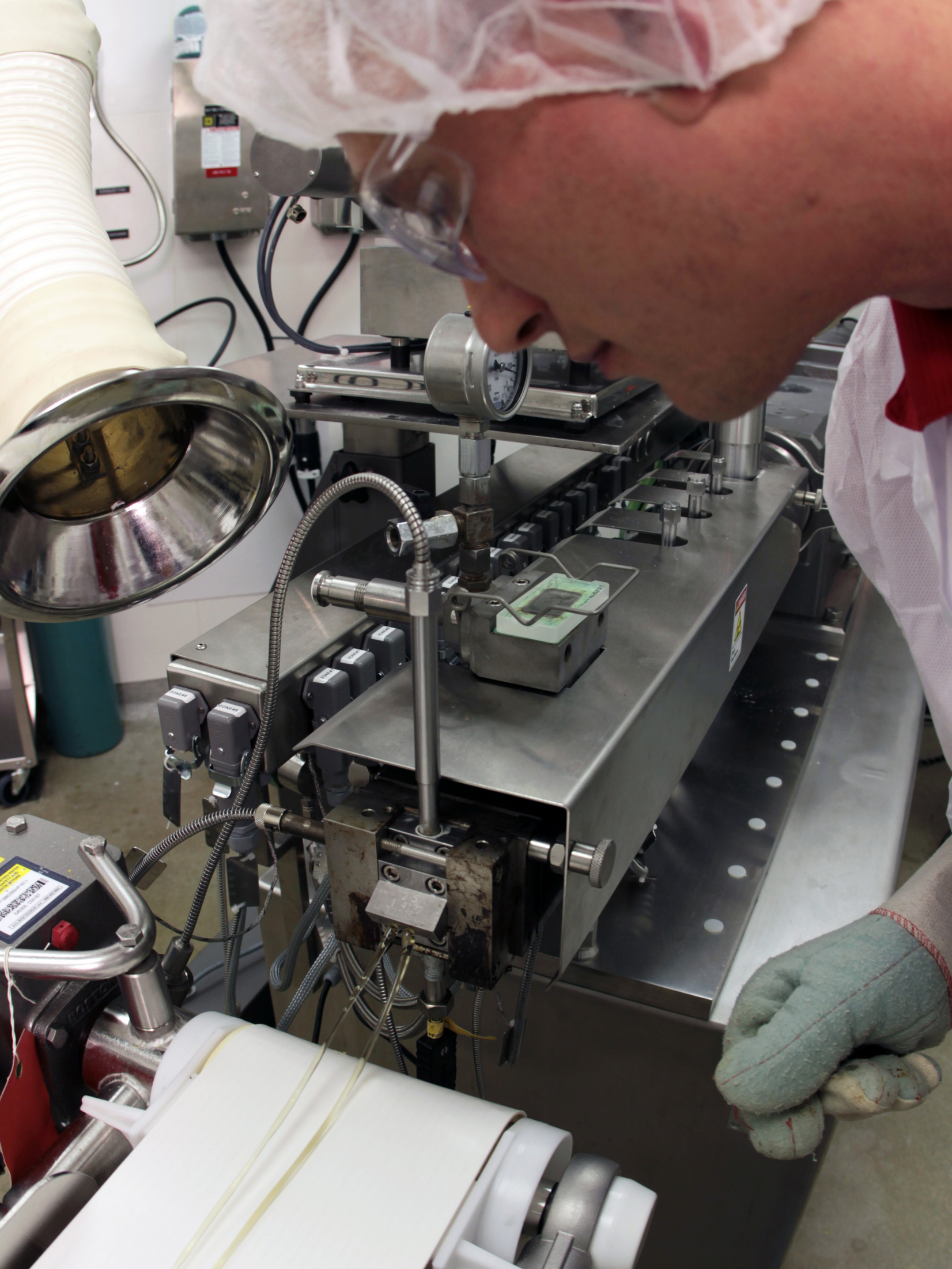
Ashland has over a decade of experience with solid-dispersion technology through its contract services offering and a high level of expertise in the development and scale-up of solid dispersion manufacturing processes by spray drying and, to a lesser extent, by hot-melt extrusion (HME). Selection of one process over the other is typically based on API characteristics such as melting point, T_g, thermal stability, and solvent solubility. Other factors often come into consideration, such as API and equipment availability, development timeline and budget.

Advantages of spray drying over other processes include continuous processing efficiencies, improved product uniformity, reduced thermal exposure and enhanced solubility due to molecular dispersion of the API. Spray-dried dispersions can be formulated into tablets or capsules. To do this, an API and polymeric carrier are dissolved in a common solvent and pumped through an atomizer at the top of the spray-drying chamber. Solvent is rapidly evaporated, resulting in a powder that is collected in the cyclone located at the bottom of the chamber.

Advantages of HME over other processes include efficiencies such as high throughput, lower cost, elimination of solvents or water; improved product uniformity and enhanced solubility due to molecular dispersion of the API. HME can be used to make granules that are then made into tablets or alternative dosage forms, such as thin films.

In this application, molten thermoplastic polymers function as thermal binders during extrusion and upon cooling and solidification. Because many drugs are thermally sensitive, it is important that the polymer is processable at a relatively low temperature.

7. Leuner, C., & J. Dressman. "Improving Drug Solubility for Oral Delivery Using Solid Dispersions," *European Journal of Pharmaceutics and Biopharmaceutics*, 50, 47–60 (2000).
8. Craig, D.Q.M. "The Mechanisms of Drug Release from Solid Dispersions in Water-soluble Polymers," *International Journal of Pharmaceutics*, 231, 131–144 (2002).
9. Dahan, A., A. Beig, V. Ioffe-Dahan, 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," *AAPS Journal*, 15, 347–353 (2013).



Technology Development and Contract Services

In addition to our broad range of polymer chemistries Ashland has over a decade of hands-on experience with solid-dispersion technologies. This experience and extensive practical know-how has been gained from the numerous technology development and contract manufacturing projects we have completed for our customers since 1999. Starting with proof-of-concept studies, Ashland's team of solid-dispersion experts will design a program to screen API solid-dispersion prototypes for fit and performance to identify the formulation with the best combination of solubility improvement and stability. Once a prototype has been identified, Ashland will develop a process suitable for manufacturing and secondary formulation development. The project is then finalized with a GMP manufacturing campaign to provide material for human testing—the ultimate determination of enhanced bioavailability. When evaluating enabling technologies for poorly soluble drugs, it is important to know which excipients will enhance drug solubility and dissolution. A deep understanding of solid-dispersion manufacturing technology is also essential because the process can affect product performance. Backed by this hands-on experience and extensive excipient knowledge, Ashland is an excellent resource when exploring the possibilities of solid-dispersion technology.

Technology Development and Contract Manufacturing Services Capabilities

- Proof-of-concept studies
- Solid-dispersion process development
- Secondary dosage formulation development
- cGMP manufacturing for clinical trial support
- Method development and validation
- Stability studies

Solid-dispersion Manufacturing Equipment

- Niro SD-Micro* spray dryer (R&D)
- Niro PSD-1 spray dryer (R&D)
- Niro PSD-1 spray dryer (GMP)
- Dynisco laboratory mixing extruder
- Leistritz 18mm twin-screw hot-melt extruder
- Niro MP4/5 fluid bed dryer
- Hata 38-station tablet press

* Trademark owned by a third party

Additional Non-contract Global Technical Capabilities

Ashland offers a formidable variety of non-contract technical capabilities to meet the needs of the pharmaceutical and nutraceutical industries. Through our global network of technical service laboratories we offer assistance with formulation development, problem solving and analytical support. Our facilities are located in Wilmington, Del., USA; Buenos Aires, Argentina; São Paulo, Brazil; Shanghai, China; Düsseldorf, Germany; Hyderabad, India; Mexico City, Mexico and Istanbul, Turkey.

Our experts around the world can provide access to granulation (fluid bed, high shear, twin-screw continuous extrusion) and controlled-release technologies (release-profile prediction and simulation, twin-screw continuous extrusion, particle and pellet coating, drug layering, matrix tablets). Additional capabilities include compaction simulation, tablet production and coating and stability studies. Ashland also has considerable expertise in characterization of powder properties (e.g., flow, particle size, surface area, morphology). Our scientists possess extensive analytical and testing capabilities, including the following:

Analytical Capabilities

- Advanced powder-flow and segregation testing
- Dissolution USP I, II and III
- Differential scanning calorimetry and thermogravimetric analysis
- Melt rheology
- Microscopy—scanning electron, polarized light and high-resolution digital
- Advanced mechanical testing
- Size-exclusion chromatography
- Nuclear magnetic resonance
- High-performance liquid chromatography and gas chromatography
- Infrared spectroscopy
- X-ray powder diffraction

Value-added Benefits from Ashland

At Ashland, we are very involved in regulatory advocacy activities and trade associations. Among other areas of participation, Ashland has been an active member of the International Pharmaceutical Excipients Council (IPEC) Americas for many years and participates on all committees, including the IPEC Americas Executive Committee, Compendial Review, Excipient Qualification, Regulatory Affairs and Excipient Composition. We are also active participants in IPEC Europe and IPEC Japan and founding members of IPEC China. In addition, we are active in the ASTM International D01.36 Cellulose subcommittee.

Global Headquarters

Ashland Inc.
50 East RiverCenter Blvd.
P.O. Box 391
Covington, KY 41012-0391 U.S.A.
Tel: +1 859 815 3333

Ashland Specialty Ingredients
8145 Blazer Drive
Wilmington, DE 19808 U.S.A.
Tel: +1 877 546 2782

Regional Centers
Europe — Switzerland
Tel: +41 52 560 55 00
Fax: +41 52 560 55 99

India — Maharashtra
Tel: +91 22 61489696
Fax: +91 22 61712514

Asia Pacific — Singapore
Tel.: +65 6775 5366
Fax: +65 6776 9690

Latin America — Mexico
Tel.: +5255 5211 0111
Fax: +5255 5212 0883

pharmaceutical@ashland.com

ashland.com/pharmaceutical

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