EVONIK INDUSTRIES

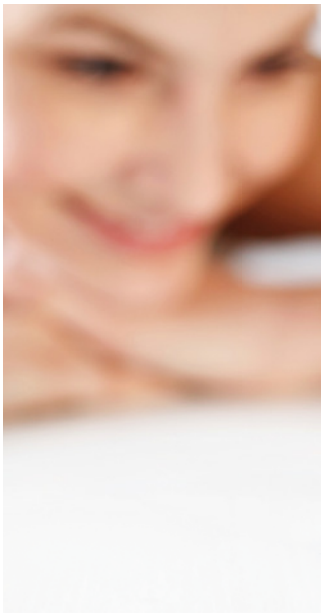
One contact, many experts.

Solubility enhancement is our business.

Evonik. Power to create.

Smart solubility.

What new active pharmaceutical ingredients promise in theory depends entirely on bioavailability in practice. Evonik combines decades of expertise in all the areas that touch on solubility enhancement to meet your challenge – and deliver a solution tailored to your needs.



New chemical entities, more challenges

Poor solubility and permeability is what keeps many drugs from delivering on their promise. Active pharmaceutical ingredients (APIs) must be dissolved before they can become bioavailable and unfold their full potential. The majority of newly developed APIs are more hydrophobic than traditional drugs, however, and don't readily dissolve. As highly potent as they may be, they never make it to market because they can't be converted into a drug with sufficient bioavailability. Ensuring API solubility in the gastrointestinal fluids and/or permeability of the dissolved drug through membranes into the bloodstream is key.

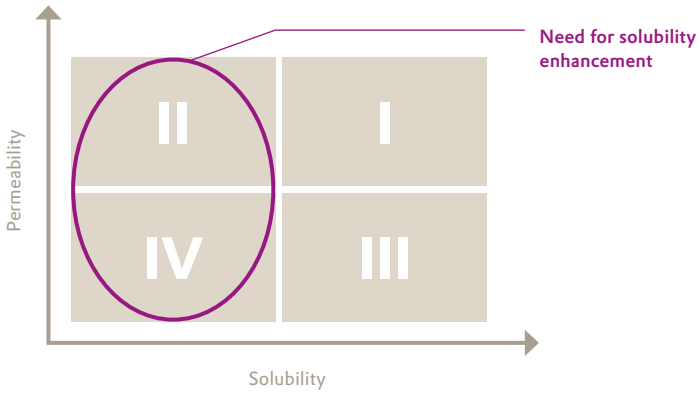
Evonik offers formulators a broad spectrum of options for enhancing drug solubility and ultimately efficacy.

Not just answers, but solutions

As a leading specialty chemicals company, Evonik unites all the major capabilities involved in solubility enhancement. Cutting edge expertise in API synthesis, functional excipients and formulation technologies – you get everything that impacts effective solubility enhancement from one source.

Add to this a global technical network with experienced and dedicated specialists for rapid and competent response, and you have the ingredients for a strong partnership in meeting your bioavailability challenges.

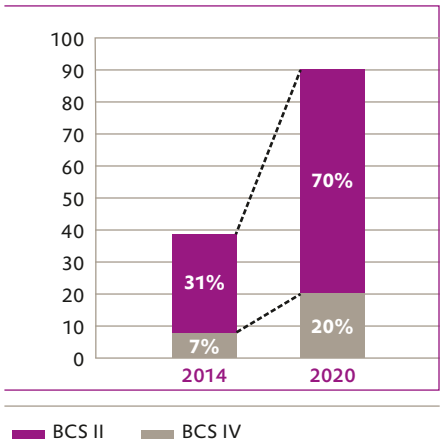
Biopharmaceutical Classification System (BCS)



Solubility enhancement is more and more a must

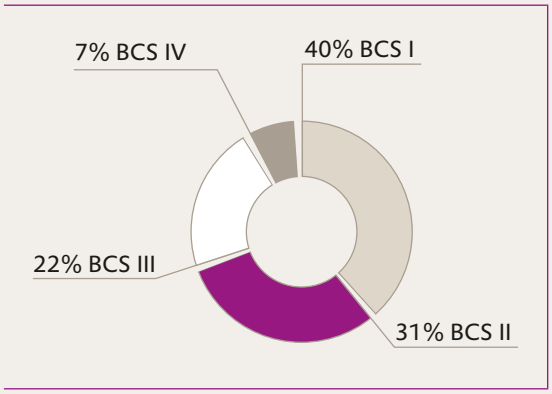
Many drugs already on the market still show a lot of potential for improvement in the two areas critical to bioavailability: solubility and permeability. Our development platforms, dedicated to drugs in BCS classes II and IV, combine all the prerequisites for realizing that potential. And besides making it possible to quickly and cost-effectively improve the bioavailability of existing molecules, they also open new possibilities for formulation development.

Predicted Development in Market Share of BCS II and IV Drugs until 2020



Source: EVALUSERVE 2015

Marketed Drugs



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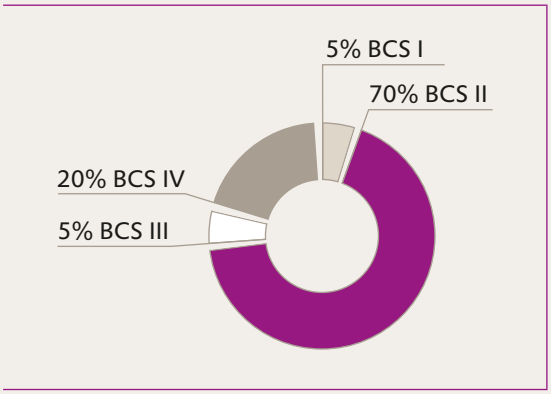
Recently Developed Drugs



Source: EVALUSERVE 2015

Drug particle engineering accurate to your needs.

Conventional particle size reduction techniques only go so far to increase surface area. We cut through the solubility knot with superior drug particle engineering.

Improving the dissolution behavior of a drug substance comes down to engineering the particles that make up the API in such way as to increase surface area, alter crystalline structure, or allow for the amorphous state.

There are several methods for achieving this by influencing particle size, shape or crystalline structure, and they can be combined. Evonik's capabilities, developed over decades of experience, cover the full spectrum of approaches to enhancing solubility.

Our deep knowledge of the molecular properties of drug substances and extensive experience with crystallization processes enable us to respond even more effectively to the solubility issues of an ever-increasing number of new chemical entities, including highly potent APIs.

Crystal engineering

Impinging jet crystallization is just one bottom-up size reduction method in our competency portfolio – we are just as comfortable with top-down processes. Evonik's engineering platform for achieving your target dissolution characteristics offers state-of-the-art expertise and equipment for the following solubility enhancement methods:

- Isolation into specific salts to form ionized species
- Polymorph control
- Nucleation and crystal growth control to build on shape and/or size-specific possibilities for enhancing solubility
- Cocrystal formation (via cocrystallization or cogrinding)
- Amorphization

Based on your API requirements, we can combine this expertise with pharma-grade polymer and supercritical CO_2 applications know-how to deliver nano-crystals using various bottom-up methods:

- Impinging jet crystallization
- Super critical CO_2 precipitation
- High pressure homogenization

Particle size reduction

Our dry milling capabilities for breaking down APIs into micro-scale particles include:

- Hammer milling
- Pin milling
- Jet milling (micronization)
- Wet milling (bead & rotor-stator)

Designed for APIs that are not prone to thermal or chemical degradation as a result of the energy involved in these processes, our methods and hardware ensure effective containment and mitigate typical issues like loss of material and dust build-up.

Evonik's capabilities for ensuring efficient and cost-effective development

- Dedicated experts with in-depth knowledge of crystallization, thermodynamics of heterogeneous equilibria and solid-state characterization
- Parallel crystallization devices for rapid screening
- PAT (process analytical technology) for rapidly gaining a thorough understanding of the crystallization mechanism – and developing and controlling crystallization
- High energy milling for co-crystal screening
- DOE (design of experiments)

Customized capabilities

Our technical resources and process expertise are all about tailoring drug substance particles to exact specifications – and ensuring they deliver on your promise.

Solid solutions. And they're robust, too.

Where oral delivery is the preferred route for drug administration, solid dispersions are a sure path to enhanced solubility. Evonik's polymer expertise points the way.

The key to maximizing bioavailability is ensuring the API gets dissolved in the gastrointestinal tract. Evonik, building on extensive expertise in pharmaceutical polymers and on deep formulation know-how, achieves just that: by intertwining a poorly soluble API with an amorphous polymer carrier. The Eudragit® family of pharmaceutical-grade polymers offers a range of properties and functionalities that opens an even broader spectrum of formulation possibilities. Different polymer combinations, powders, granulates and dispersions – Evonik brings the diversity of its expertise into focus on your specific solubility challenge.

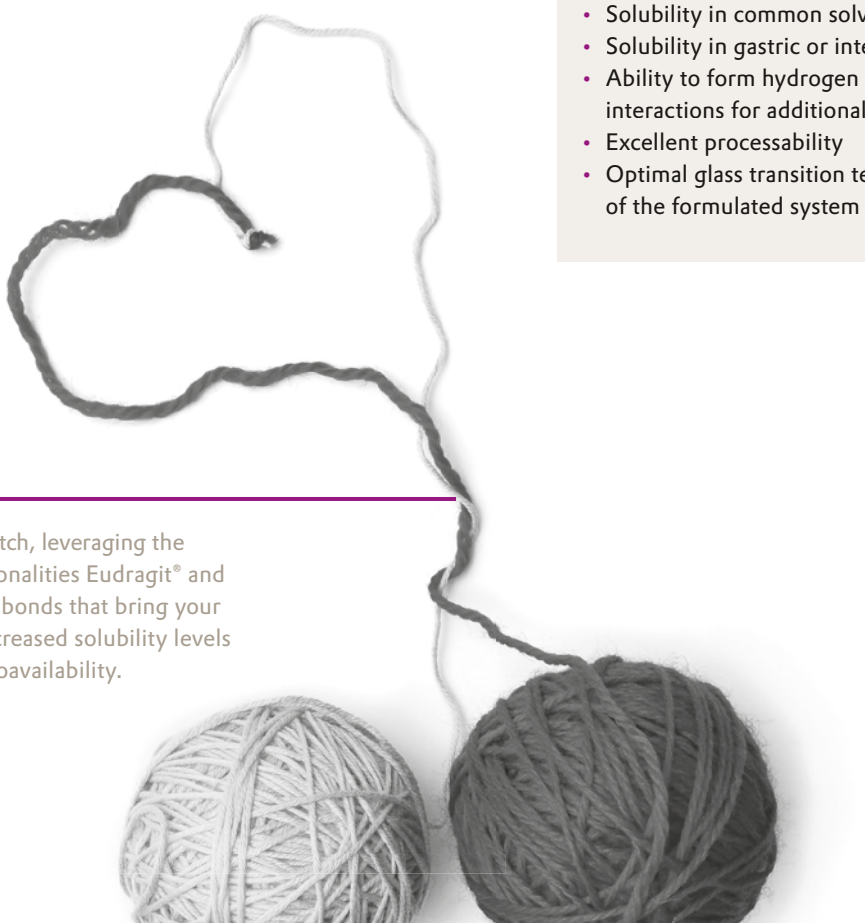
Safe. Versatile. Proven.

Eudragit® polymers have been proving their value in high quality pharmaceutical applications for over 60 years. They also come with comprehensive regulatory documentation and safety data packages. And they meet all the key prerequisites for enhancing solubility:

- Excellent thermoplastic properties and high thermostability
- High miscibility with APIs and other excipients
- Excellent powder flow and mechanical properties
- Superior moisture protection
- Reliable batch-to-batch consistency as fully synthetic polymers
- Solubility in common solvents
- Solubility in gastric or intestinal conditions
- Ability to form hydrogen bonds and/or ionic interactions for additional tailored effects
- Excellent processability
- Optimal glass transition temperature (Tg) of the formulated system

A lasting bond

More than a perfect match, leveraging the specific polymer functionalities Eudragit® and your API form physical bonds that bring your drug to significantly increased solubility levels and thus enhance its bioavailability.



Melt extrusion – embedded quality

With Evonik, you can be sure that all the details which make up the big picture get sorted, too. In addition to the core dosing and extrusion processes, we offer the most common downstreaming options:

- Strand granulation
- Micropelletization

Our melt extrusion capabilities:

- Small scale batches from 10 g up to 5 kg/h
- Liquid feeding to introduce e. g. polymer dispersions, plasticizers or surfactants
- GMP clinical supply manufacture, including HPAPIs

Spray drying – for more options

In line with our one-stop shop philosophy, all our labs offer both aqueous and organic processing. Also, our capabilities enable us to leverage both the inherent characteristics and the various grades of Eudragit® polymers to meet your requirements. Onward processing to the final dosage form is part of our standard formulation service offering as well.

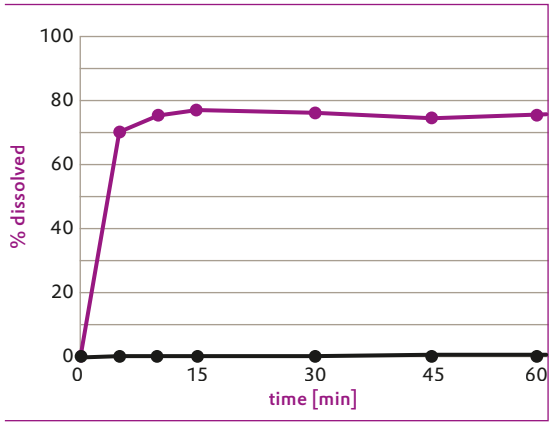
Spray drying with Eudragit® polymers keeps options open where thermosensitive APIs set clear limits:

- Excellent compressibility
- Easy dissolution in common solvents

Our spray drying capabilities:

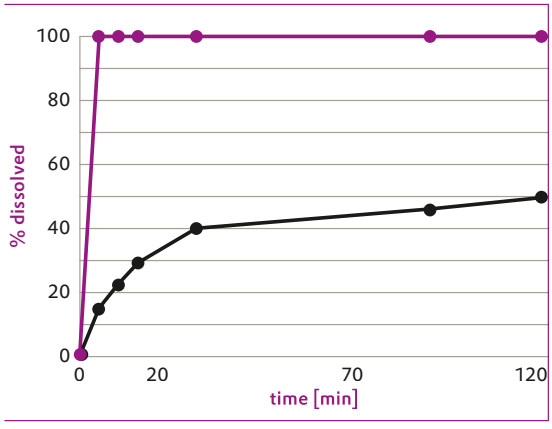
- Büchi Nano Spray Dryer B-90 (Germany)
- Büchi Mini Spray Dryer B-290 (India, Japan)
- ProCepT Spray dryer (USA)

HME: Case study Felodipine



Melt extrudate with 10% drug content — Pure drug

Spray Drying: Case study Carbamazepine



Spray dried sample with 10% drug content — Pure drug

A powerful answer to poor solubility: fix it.

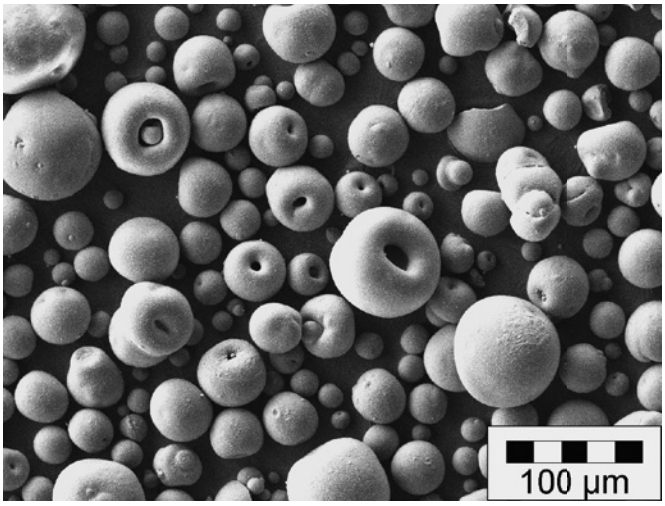
Evonik technology opens new options for improving bioavailability by combining poorly soluble APIs with the AEROPERL® inert carrier.

Enhancing the solubility of APIs by micronization or generation of amorphous forms are accepted strategies to increase the solubility of APIs. Both can be achieved by adsorbing the active on AEROPERL® 300 Pharma, a mesoporous silica granulate developed by Evonik. Keeping temperatures above the API's melting point prevents drug crystallization in the pores. The resulting highly dispersed API now has a significantly higher surface area and increased dissolution speed.

AEROPERL® 300 Pharma – a fresh new talent in the colloidal silicon dioxide family

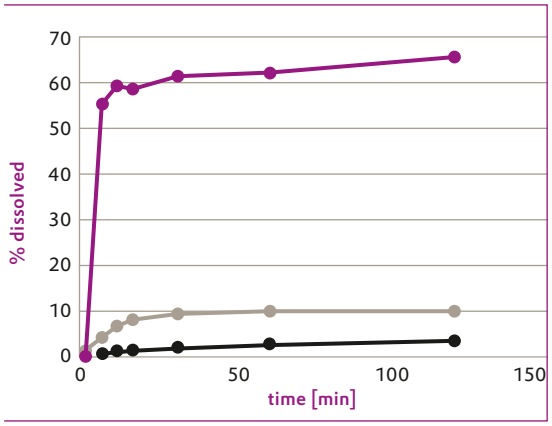
AEROPERL® 300 Pharma is an inert and highly adsorptive carrier, a granulated form of a colloidal silicon dioxide consisting of particles with a mean diameter of approximately 30 µm. The high tamped density of AEROPERL® 300 Pharma and its spherical particle shape ensure straightforward processing with favorable powder flow and low dust formation.

AEROPERL® 300 Pharma can also be used to absorb liquid formulations and turn them into free-flowing powders than can easily be used for direct tableting processes. Readily available in commercial quantities, AEROPERL® 300 Pharma is the pivotal component of an innovative, cost effective and reliable formulation strategy.



AEROPERL® 300 Pharma particles

AEROPERL® 300 Pharma



- Pure itraconazole
- Formulation 2: Itraconazole formulated with d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) as surfactant
- Formulation 3: Formulation 2 adsorbed by AEROPERL® 300 Pharma

Reliable accommodation for your API

Adsorbing the actives in a fine distribution on our inert carrier enables amorphous states with higher dissolution rates. AEROPERL® 300 Pharma: just one example of how Evonik's extensive experience in all aspects of solubility enhancement translates into solutions for the evolving challenges formulators face.

Partnership paired with performance.

Beyond APIs and excipients, Evonik delivers the advanced development services that enable your drug to unfold its full potential faster and more effectively. As your strategic resource, we translate a unique set of formulation skills into greater speed to market.

Evonik's capabilities and processes have progressed and improved over decades of development, manufacturing and logistics on the basis of collaborating with our customers in a partnership spirit.

We believe in offering a global presence just as strongly as we do in ensuring local proximity. That makes us even more effective in understanding where you are coming from – and faster in translating your needs into solutions. It ties in with Evonik's focus on providing stability and reliability for the long term.

In our pursuit of constant innovation, we bring together state-of-the-art technical capabilities with highly qualified teams to meet your solubility challenges and build a lasting relationship.

Hot melt extrusion with highly potent APIs

You can count on:

- Efficiency gains in R&D processes
- Access to innovative and powerful drug delivery technologies
- Shorter time-to-market
- Professional product lifecycle management
- Reliable large scale manufacturing processes
- Collaborative development of enabling technologies and proprietary solutions

All the necessary certifications and permits for handling controlled substances and highly potent APIs.

MemFis™ – in silico modeling for solid dispersions

MemFis™ (Melt extrusion modeling and Formulation information system) is an Evonik proprietary system for enabling formulators to systematically screen formulations and processing conditions at the earliest development stage. Based on established solubility parameters and decades of process know-how,

MemFis™

- provides estimations for formulation processes, including scale-up and tech transfer
- combines Evonik's information technology with melt extrusion expertise
- reduces the number of experiments to save time and costs
- enables development with small API quantities
- supports the right choice of API for life cycle management (generics / originators)
- applies to all solid dispersion process technologies, including spray drying

Design quality– with robust analytics

Because quality means accountability, our comprehensive formulation services go hand in hand with thorough analytical testing. We can identify any hurdles early on and ensure dependable quality throughout the process – right after preparation and during stability testing.

Our quality assurance portfolio extends far beyond compendial methods to include analytical capabilities alongside the development path, such as physico-chemical characterization of drug molecules, intermediates and final formulations. Able to develop new analytical methods to suit your needs, our experts are at home with the state-of-the-art in analytical tools:

- Thermal properties (DSC, TGA)
- X-ray powder diffraction
- Microscopy (SEM with edx feature)
- Spectroscopy (FTIR, ^{1}H-NMR, UV-VIS, Fluorescence, Raman)
- Dissolution Testing USP I - IV and biorelevant media
- Chromatography (HPLC, NMR, LC-MS, GC)
- Rheology & viscosity
- Particle size analysis (laser diffraction, dynamic light scattering)
- Zeta-potential determination

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