

TECHNICAL INFORMATION 1414

AEROPERL® 300 Pharma

Improving the dissolution
of poorly soluble APIs



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AEROPERL® 

AEROSIL® 

1 AEROPERL® 300 Pharma colloidal silicon dioxide: Our solution to the solubility challenge

Active pharmaceutical ingredients (APIs) in oral dosage forms need to dissolve before they can be absorbed in the intestine to enter the systemic circulation. Therefore, both the dissolution of the APIs, as well as the permeation of the dissolved API through the intestinal membrane into the systemic circulation are important processes to reach the required blood concentration for the API to become effective. A high dissolution rate of the API in the intestinal fluid can positively influence permeation rates.

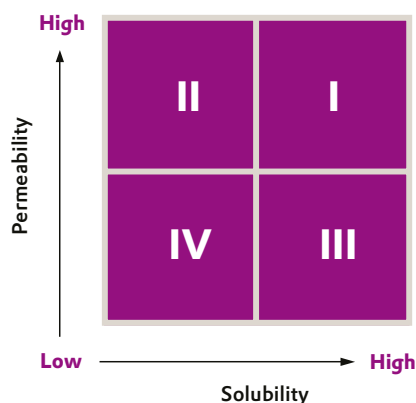
Drugs categorized in class II of the BCS system primarily suffer from poor aqueous solubility, which therefore is the limitation to achieve therapeutically necessary blood concentrations.

Changes in the way new chemical entities are developed and identified have led to a situation where many of the possible API innovations have poor aqueous solubility. Although numbers deviate by source², there is general agreement that many new drug candidates, and even more coming from synthesis³, face aqueous solubility challenges. According to a recent survey, drug solubility and bioavailability are the most important formulation challenges in pharmaceutical development⁴. Insufficient solubility may lead to the abandonment of an otherwise promising new chemical entity.

Unfortunately, no single formulation approach can solve the issue of poor aqueous solubility for all actives and innovative concepts from academia can be hard to implement at a commercial scale. Formulators in the pharmaceutical industry have limited freedom as they need to consider the availability of technical equipment in the plants as well as production costs.

In the previously mentioned survey, several technologies for the improvement of formulations with APIs having low aqueous solubility are listed. Among these, API crystal micronization, solid dispersions and lipid-based drug delivery proved to be more successful.

Figure 1
The Biopharmaceutics Classification System (BCS)



The importance of drug dissolution and permeability is reflected by the Biopharmaceutics Classification System (BCS) originally proposed by Amidon¹, which groups the APIs into four different classes according to their permeability and solubility in aqueous media (see **Figure 1**).

¹ G. L. Amidon, H. Lennernäs, V. P. Shah, J. R. Crison, A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, *Pharm. Res.* 12 (1995) 413–420.

² A study by Lindenberg on the Essential Medicines of the World Health Organization (WHO) identified 27% of the listed APIs to belong to BCS classes II or IV facing some dissolution challenges. See M. Lindenberg, S. Kopp, J.B. Dressman, Classification of orally administered drugs on the World Health Organization model list of essential medicines according to the biopharmaceutics classification system, *Eur. J. Pharm. Biopharm.* 58 (2004) 265–278. Another study on the US-FDA approved generics between 2000 and 2011 finds 20,9% of all drugs to belong to BCS class II. See A.K. Nair, O. Anand, N. Chun, D. P. Conner, M. U. Mehta, D. T. Nhu, J. E. Polli, L. X. Yu, B. M. Davit, Statistics on BCS classification of generic drug products approved between 2000 and 2011 in the USA, *The AAPS Journal* 4 (2012) 664–666.

³ A. C. H. Dubin, Formulation Strategies for poorly soluble drugs, *Drug Delivery Technology* 6, 6 (2006) 34.

⁴ A. Siew, P. van Arnum, Industry Perspectives: achieving solutions for the challenge of poorly water-soluble drugs, *Pharm. Techn.* June 2013.

CRYSTAL MICRONIZATION

Micronization of crystals is a powerful tool to accelerate the dissolution of APIs that are simply dissolving very slowly. By micronization the available surface area exposed to the solvent for dissolution can be greatly increased. The influence of the size of the drug particle has on dissolution is described by the combined Nernst-Bunnauer and Noyes-Whitney equations⁵:

$$\frac{dX}{dt} = \frac{A \times D}{h} \left(C_s - \frac{X_d}{V} \right)$$

in which

dX/dt: dissolution rate

X_d: amount dissolved

A: particle surface

D: diffusion coefficient

C_s: saturation concentration

h: effective boundary layer thickness

V: volume

Micronization can be achieved most elegantly in the crystallization stage of the API production. If this is not possible it may be necessary to lower the particle size of the produced API crystals by milling. No matter whether the micronized API crystals are produced by milling or by targeted crystallization, their small particle size makes them vulnerable to agglomeration⁶. Aggregation very often limits the effect of micronization on the dissolution.

LIPID API PREPARATIONS

APIs with limited solubility in aqueous solutions may be very soluble in oils. In these cases the drug can be dissolved in a liquid matrix and be used as a solution. Typical lipid solvents used in such kind of formulations include natural, synthetic, or semi-synthetic oils⁷. Adding surfactants to such drug solutions can create systems that on contact with water spontaneously form emulsions. Such formulations are typically referred to as self-emulsifying drug delivery systems (SEDDS). Since the API in these formulations is present in a dissolved, and therefore energetically more favorable state, dissolution may be greatly improved. Some lipid based formulations have already been commercialized⁸. However, the approach leads to liquids that need to be filled in suitable capsules to make them available for the patients. This makes processing such formulations in solid dosage challenging and costly.

SOLID DISPERSIONS

Solid dispersions have been widely discussed as a suitable strategy to improve the solubility of poorly soluble APIs⁹. In solid dispersions, the poorly soluble API is finely dispersed in a matrix of another solid. Traditionally, these formulations use organic polymers such as EUDRAGIT^{®10} as the matrix, and are commonly produced by the precipitation of the API on the matrix polymer; for example by spray drying. Another popular way of producing this kind of API formulation is hot melt extrusion in which the API is dispersed in a hot polymer matrix that can even have the drug in molecular form¹¹.

⁵ A. Noyes, W. Whitney, The rate of solution of solid substances in their own solutions, *J. Am. Chem. Soc.* 19 (1897) 930–934. W. Nernst, Theorie der Reaktionsgeschwindigkeit in heterogenen Systemen, *Z. Phys. Chem.* 47 (1) (1904) 52–55. E. Brunner, Reaktionsgeschwindigkeit in heterogenen Systemen, *Z. Phys. Chem.* 47 (1) (1904) 56–102.

⁶ Small particle sizes also imply poor powder flow. How AEROSIL[®] colloidal silicon dioxide can be used to improve the flow of powders is not dealt with here but the topic of TI 1281 “AEROSIL[®] and AEROPERL[®] colloidal silicon dioxide for pharmaceuticals” that can be downloaded from www.aerosil.com.

⁷ D. J. Hauss, Oral lipid formulations, *Adv. Drug Delivery Rev.* 59 (2007) 667–676.

⁸ R. G. Strickley, Solubilizing excipients in oral and injectable formulations, *Pharm. Res.* 2 (2) (2004) 201–230.

⁹ K. Dhirendra, L. Lewis, N. Udupa, K. Atin, Solid dispersions: a review, *J. Pharm. Sci.* 22 (2) (2009) 234–246. S. Janssens, G. van den Mooter, Review: physical chemistry of solid dispersions, *J. Pharm. Pharmacology* 61 (2009) 1571–1586. C. L.-N. Vo, C. Park, B.-J. Lee, Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs, *Eur. J. Pharm. Biopharm.* 85 (2013) 799–813.

¹⁰ EUDRAGIT[®] is a polymethacrylate polymer produced by Evonik Nutrition and Care GmbH, Darmstadt, Germany. For more information please visit <http://eudragit.evonik.com/product/eudragit/en/Pages/default.aspx>.

¹¹ Some authors refer to formulations which contain the API in molecular form in a polymer matrix as solid solution.

Polymer and drug need to be compatible with each other and preferably are able to interact on the molecular level to stabilize the drug. Alternative methods to prepare solid dispersions include melt mixing¹² and the use of supercritical solvents. The selection of the technique used to produce the solid dispersion is largely dependent on the properties of the API and the availability of the necessary equipment. The manufacture of solid dispersions also faces some issues. Spray drying mostly produces low-density powders that are hard to handle and may lead to dusting issues. Hot melt extrusion requires the API to be stable at the high processing temperature required for the process. Stability of the amorphous state of an API is very often hard to maintain over the storage time of a commercial formulation. These challenges have limited the value of this technique, with only a limited number of commercial formulations on the market using this approach¹³.

As pointed out by Butler and Dressman, the insufficient solubility in aqueous media can be attributed either to a slow rate of dissolution (kinetic hindrance, class IIa) or a very low overall solubility (thermodynamic hindrance, class IIb)¹⁴. Properties specific to the individual API require different formulation strategies. If the drug dissolution is kinetically inhibited, then increasing the surface area of the API can help to improve dissolution. For class IIb drugs which have a poor overall solubility in aqueous media high supersaturations can often be realized if the API can be stabilized in an amorphous form or using it dissolved in an oil.

AEROPERL® Pharma colloidal silicon dioxide¹⁵ can help with all of these formulation strategies and support formulators to bring more API innovations to the market, improve patients well-being and generate profitable business.

- **Micronization:**

Active pharmaceutical ingredients can be absorbed in the form of small crystallites on the surface and in the pores of the carrier. Unlike dry milling processes, which lead to API crystallites with a strong tendency to agglomerate, the crystallites absorbed on the carrier are stabilized and separated from each other by carrier-API interactions.

- **Lipid formulations:**

API solutions in suitable oils can be absorbed on the carrier and thereby turned into free flowing powders. Processing of these powders into solid dosage forms is achieved by technologies common in the industry.

- **AEROPERL® 300 Pharma**

can be used as an inorganic carrier for solid dispersions. Due to the small pore size, it is possible to stabilize APIs in the amorphous form.

¹² L. Wang, F. D. Cui, H. Sunada, Preparation and evaluation of solid dispersions of nitrendipine prepared with fine silica particles using the melt-mixing method, *Chem. Pharm. Bull.* 54 (2006) 37–43.

¹³ C. L.-N. Vo, C. Park, B.-J. Lee, Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs, *Eur. J. Pharm. Biopharm.* 85 (2013) 799–813.

¹⁴ J. M. Butler, J. B. Dressman, The developability classification system: application of biopharmaceutics concepts to formulation development, *J. Pharm. Sci.* 99 (12) (2010) 4940.

¹⁵ The term "colloidal silicon dioxide" in this brochure is used in the sense of the USP/NF monograph for silica products produced by flame hydrolysis. Products of this kind are also known as fumed silica in other industries. The products are not to be mistaken for dispersions of spherical silica particles in a fluid which often are named "colloidal silica" or "silica sol".

2 AEROPERL® 300 Pharma: a highly absorptive colloidal silicon dioxide

AEROPERL® 300 Pharma is a member of the AEROSIL® Pharma colloidal silicon dioxide family. AEROPERL® 300 Pharma features all the advantages of the AEROSIL® Pharma silicon dioxides such as:

- Composed of purely amorphous synthetic silicon dioxide
- High purity precursors, therefore extraordinary low elemental contamination levels
- No organic or biogenic material used in production, therefore no contaminations with these kind of material
- Tested against the high quality requirements of monographs "Silica Colloidal Anhydrous" (Ph. Eur.) and "Colloidal Silicon Dioxide" (USP/NF)
- GMP production according to the guideline of IPEC¹⁶
- Production audits available on request according to an annual schedule

However, unlike the fluffy and often dusty AEROSIL® Pharma powders AEROPERL® features a greatly increased density as it consists of round shaped granules in the range of 20–60 µm. **Figure 2** shows the particle shape of the material in a scanning electron microscopy image. In **Figure 3** the difference in density of 8 g of AEROPERL® 300 Pharma compared to the same amount of AEROSIL® 200 Pharma is shown.

Figure 2
Scanning electron microscopy image of
AEROPERL® 300 Pharma

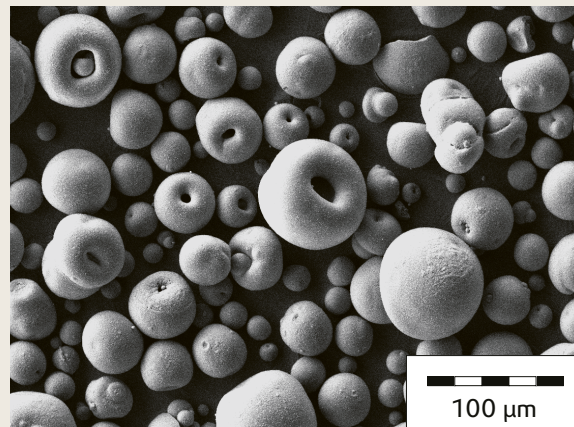


Figure 3
Volume comparison of equal quantities of AEROSIL® 200 Pharma and AEROPERL® 300 Pharma: 8 g of both materials were filled in a graduated cylinder, the one for AEROSIL® 200 Pharma shown on the right and the one for AEROPERL® 300 Pharma on the left.



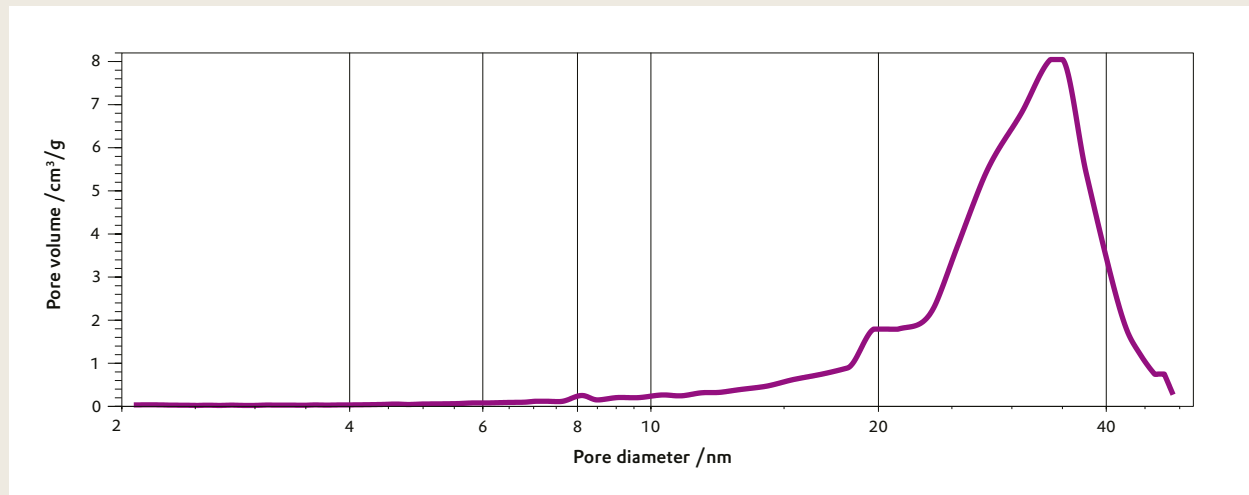
¹⁶ Guideline is available online from [http://ipec-europe.org/UPLOADS/IPEC_PQG_GMP_Guide_2006\(1\).pdf](http://ipec-europe.org/UPLOADS/IPEC_PQG_GMP_Guide_2006(1).pdf)

AEROPERL® 300 Pharma is produced as a highly porous material. As shown in the pore size distribution in **Figure 4** the material features mesopores. The mesopore volume is

in the range of 1.5 to 1.9 ml/g, making the material a highly absorptive silica carrier with pharmaceutical quality.

Figure 4

Pore size distribution of AEROPERL® 300 Pharma



3 Absorption of lipid formulations with AEROPERL® 300 Pharma

AEROPERL® 300 Pharma, due to its porous and highly adsorptive character, can help formulators to transform lipid solutions into powders. As AEROPERL® 300 Pharma features round shaped granules in the d_{50} size range of 20 to 60 μm , the material itself has very favorable powder

flow. Even if the material is used as a carrier and loaded up to 150% of its own weight with an oil, the powder flow behavior of the material remains virtually unchanged, as shown in **Figure 5**.

Figure 5

Study on the powder flow behavior of AEROPERL® 300 Pharma after loading with an oil

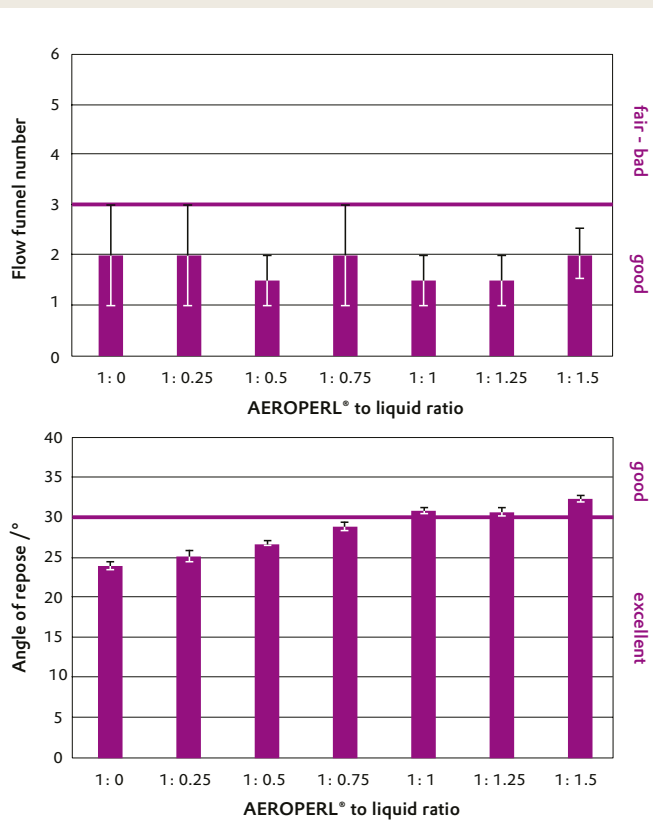
PROCESSING

40 g of AEROPERL® 300 Pharma were filled in the mixing chamber of a Somakon MPL-1 mixer (Somakon Verfahrenstechnik UG, Germany). Different amounts of Dimeticon 100 (Caesar & Loretz GmbH, Germany) ranging from 10 to 60 g were added within 30 s while mixing at 2000 rpm. Several batches were combined to have enough material for the flow tests.

FLOW TESTING

The angle of repose of the material was determined using a modified compendial method¹⁷. The higher the angle of repose value the worse is the powder flowability. Flow funnel tests were performed with glass funnels having orifices with diameters ranging from 2.5 (funnel 1) to 24.0 mm (funnel 6).

The graph records the smallest funnel number through which the material still flows freely without agitation. The higher the funnel number the worse is the powder flow.



Flow testing results

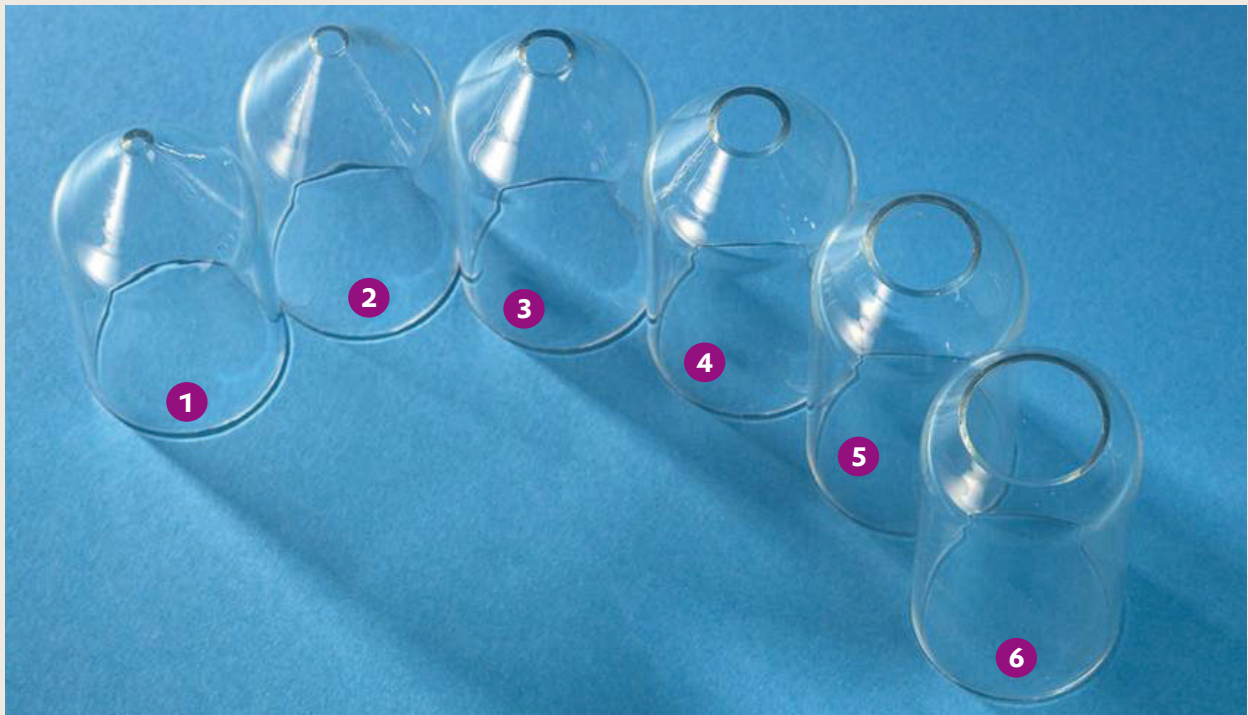
¹⁷ E. g. USP/NF chapter 1174.

Independent of loading level and the analytical method used powders with excellent to good powder flow result are obtained. The reason for the retention of the favorable powder flow lies in the porosity of the material. The narrow pore size of AEROPERL® 300 Pharma leads to high capillary forces that draw the liquid into the pores.

Due to the purely physical nature of the absorption mechanism, the polarity of the liquid does not influence the absorption as long as the liquid has a reasonable viscosity¹⁸.

For indications on suitable technical equipment for the absorption, please refer to technical information TI 1351¹⁹.

Flow funnels used in the experiments



¹⁸ Highly viscous liquids need longer for absorption than those with low viscosity. To facilitate the absorption of very viscous liquids it is advisable to use accelerated temperatures in the absorption process.

¹⁹ TI 1351 Evonik silicas and silicates as flow aids and anticaking agents. Available from <https://www.silica-specialist.com/en>

Having absorbed the liquid formulation on AEROPERL® 300 Pharma, the powder can be easily processed by methods common to the industry. As indicated in **Figure 6** the oil loaded carrier can even be used to directly compress tablets with favorable mechanical stability.

When an oily API formulation is absorbed on AEROPERL® 300 Pharma, the question arises if the API is released after the medication has been swallowed.

This question was addressed using the liquid anticonvulsant and mood stabilizing drug, valproic acid, a liquid with a boiling point of 222 °C. Valproic acid was absorbed on AEROPERL® 300 Pharma, the absorbate, filled in a hard gelatin capsule, and then the capsule was subjected to a compendial release study. The result is shown in **Figure 7**. The favorable result agrees with published studies on the dissolution of lutein²⁰ and steroids²¹ on AEROPERL® and other colloidal silicon dioxide carriers.

Figure 6
Mechanical stability of the tablets

FORMULATIONS

25% AEROPERL® 300 Pharma
25% Dimethicone oil (Silbione® DM 1000, Bluestar)
40% MCC (Avicel® PH 101, FMC Biopolymer)
10% Corn Starch (Caesar & Loretz GmbH)

PROCESSING

Dimethicone oil is absorbed on an equivalent quantity of AEROPERL® 300 Pharma as described in Figure 5. The absorbate is stored overnight and then passed together with the microcrystalline cellulose and the corn starch through a 710 µm sieve. The combined powders are mixed for 10 min at 67 rpm in a tumbling mixer (Turbula T2F, Willy Bachofen GmbH, Germany). The mixture was turned into tablets with a diameter of 12 mm and a weight of appr. 640 mg using a Korsch EK0 single punch press (Korsch AG, Germany). The tablet weight variation is between 2 and 4 mg.

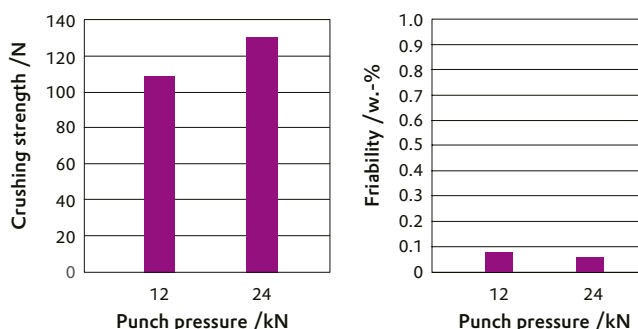
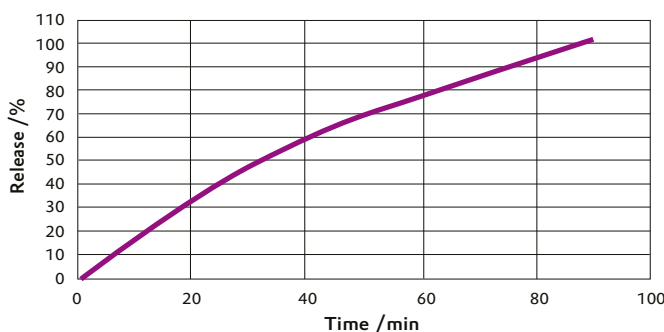


Figure 7
Release of valproic acid adsorbed on AEROPERL® 300 Pharm²²

PROCESSING

1.5 g valproic acid was adsorbed on 1.0 g AEROPERL® 300 Pharma by hand mixing. 250 mg of the adsorbate containing 150 mg valproic acid was filled in a hard gelatin capsule. The release was tested according to USP/NF monograph "valproic acid capsules"



²⁰ S. Shanmugam, R. Baskaran, P. Balakrishnan, P. Thapa, C. S. Yong, B. K. Yoo, Solid self-nanoemulsifying drug delivery system (S-SNEDDS) containing phosphatidylcholine for enhanced bioavailability of highly lipophilic bioactive carotenoid lutein, Eur. J. Pharm. Biopharm. 79 (2011) 250–257.

²¹ WO 2005 087199, Schering AG.

²² Data courtesy of Prof. P. D. Amin, Institute of Chemical Technology, Mumbai, India.

4 Inorganic solid dispersions with AEROPERL® 300 Pharma

Already in 1972 first reports on the positive effect of silica adsorbents on drug dissolution appeared²³. In a recent study the potential of AEROPERL® 300 Pharma to increase the dissolution rate and supersaturation concentration of hesperidin, a bioflavonoid used in the treatment of blood vessel conditions, has been investigated²⁴. The investigation proved that a strong increase in supersaturation concentration and dissolution rate is achieved when the API was adsorbed on the colloidal silicon dioxide carrier. In another study AEROPERL® 300 Pharma proved to be efficient to improve the solubility of bicalutamide, a drug used to treat prostate cancer²⁵.

To take full advantage of AEROPERL® 300 Pharma for the dissolution of BCS class II drugs it might be necessary to follow slightly different approaches dependent on the properties of the API. This is exemplified in case studies using the APIs artemether, itraconazole and celecoxib. **Table 1** shows the medical indication and properties of these drugs.

In a first case study, artemether was adsorbed on AEROPERL® 300 Pharma using different API to carrier ratios. The experimental details and dissolution results of that study are summarized in **Figure 8**.

Artemether adsorbed on AEROPERL® 300 Pharma has significantly higher dissolution rates than the same amount of the API in pure crystalline form. Already at very short contact times, significantly higher dissolution rates are observed for the AEROPERL® based formulation. Over the full time scale of the test, AEROPERL® based formulations have strongly increased dissolution rates. Higher contents of AEROPERL® 300 Pharma in the formulation are favorable for dissolution. The action of AEROPERL® 300 Pharma alone is able to increase the API dissolution rate.

Table 1

Model APIs and their properties

API name	Medical indication	BCS class	Molecular mass	pKa
Artemether	Antimalarial	II	298.37 g/mol	n.n.
Itraconazol	Antifungal	IV	705.63 g/mol	3.7
Celecoxib	Anti-inflammatory	II	381.37 g/mol	11.1

Figure 8

Case study artemether²⁶

FORMULATIONS

Control: 20 mg of pure artemether

Formulation 1: 20 mg of artemether adsorbed on 20 mg AEROPERL® 300 Pharma

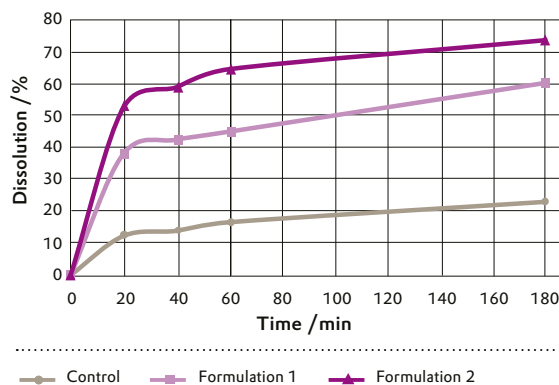
Formulation 2: 20 mg of artemether adsorbed on 60 mg AEROPERL® 300 Pharma

PROCESSING

A solution of 1 g of artemether in 8–10 ml of acetone was prepared. To the solution the necessary amount of AEROPERL® 300 Pharma to produce the respective API to carrier ratio was added. The dispersion was air dried until all solvent was evaporated and the remaining free flowing solid used in the dissolution experiments.

DISSOLUTION TESTING

900 ml of a phosphate buffer solution (pH 7.2) with 1 w.% of added sodium lauryl sulphate as the dissolution medium was used in a USP I apparatus at 37 ± 0.5 °C with a stirrer speed of 100 rpm. Powder samples equivalent to 20 mg of artemether were added to the solution and the dissolved artemether concentration analyzed by photospectrometry at 211 nm.



²³ D. C. Monkhouse, J. L. Lach, Use of adsorbents in enhancement of drug dissolution I, Journal of Pharmaceutical Sciences 61 (9) (1972) 1430–1435.

²⁴ Q. Wie, C. M. Keck, R. H. Müller, CapsMorph® technology for oral delivery – theory, preparation and characterization, Int. J. Pharm. 482 (2015) 11–20.

²⁵ T. Meer, R. Fule, D. Khanna, P. Amin, J. Pharm. Investigation 43 (2013) 279–285.

²⁶ The study was conducted by Prof. P. D. Amin of the Department of Pharmaceutical Sciences of the Institute of Chemical Technology in Mumbai, India.

For improving the dissolution of the very hydrophobic, antifungal itraconazole, the absorption on AEROPERL® 300 Pharma alone is not sufficient. To aid the wetting of itraconazole a surfactant needs to be added to the formulation. The experimental details and dissolution results for the case study on itraconazole are summarized in **Figure 9**.

The pure API clearly has very little solubility and dissolution. The dissolution rate can be increased by a factor of 3 if itraconazole is used in combination with d- α -tocopheryl polyethyleneglycol 1000 succinate (TPGS) as a model surfactant. The dissolution rates, however, are below a level that is sufficient for commercial formulations. Absorbing

both the itraconazole and the TPGS on AEROPERL® 300 Pharma has a very strong impact on the dissolution rate. Already at short contact times of the dissolution medium, a high supersaturation is observed. The dissolution rate is drastically higher than for any of the two comparative formulations and the dissolved API concentration still increases over time. The combination of the carrier and the surfactant is therefore a preferable means to improve the dissolution of itraconazole.

Figure 9

Case study artemether²⁷

FORMULATIONS

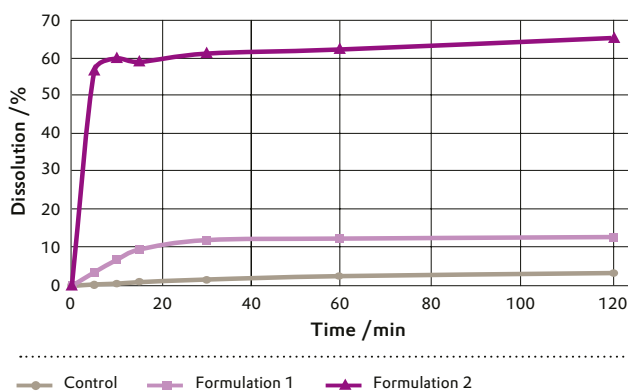
- Control:** pure itraconazole (100 mg)
- Formulation 1:** itraconazole (100 mg) dispersed in TPGS* (100 mg)
- Formulation 2:** itraconazole (100 mg) and TPGS* (100 mg) loaded on AEROPERL® 300 Pharma (2000 mg)

PROCESSING

- Formulation 1:** itraconazole was dispersed in molten TPGS*. The mass is solidified by cooling and powdered.
- Formulation 2:** itraconazole and TPGS* was dissolved in HCl acidified ethanol. AEROPERL® 300 Pharma was added to the solution and the solvent removed at 50°C overnight.

DISSOLUTION TESTING

Dissolution was tested in 500 ml 0.1 N HCl at 37 ± 1°C using a USP II apparatus with a stirrer speed of 75 rpm. The medium was analyzed for dissolved API by HPLC.



*TPGS: D- α -tocopheryl polyethyleneglycol 1000 succinate

²⁷ The study was conducted by Prof. J. B. Dressman of the Institute for Pharmaceutical Technology of the Goethe University of Frankfurt.

The case study with AEROPERL® 300 Pharma adsorbed celecoxib showed just another possible behavior of APIs. **Figure 10** indicates that the dissolution of the drug can be strongly initially improved adsorbing it on AEROPERL® 300 Pharma (formulation 1). The dissolved concentration then drops to the level of the pure API. Thus, the initially achieved strong oversaturation is not stable and the already dissolved API precipitates from the solution.

Hydroxypropyl methylcellulose (HPMC) added to formulation 2 suppresses the precipitation of the API. The very high initial dissolution rates are not observed, but a strong increase of the dissolution rate is observed against the pure drug and the dissolved concentration remains stable over time.

Figure 10
Case study celecoxib²⁸

FORMULATIONS

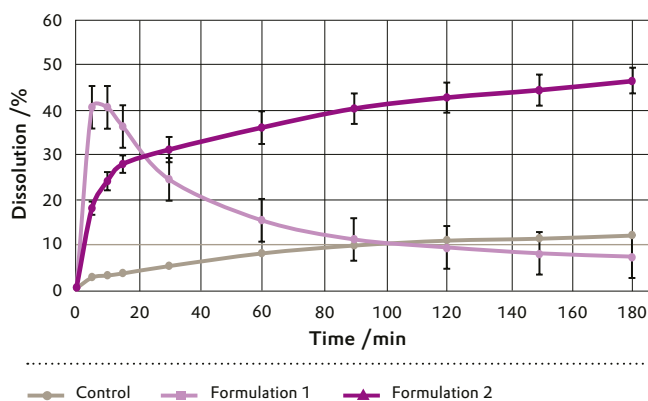
- Control:** pure celecoxib (50 mg)
- Formulation 1:** celecoxib (50 mg) adsorbed on 500 mg AEROPERL® 300 Pharma
- Formulation 2:** same as formulation 1 with the addition of HPMC* (250 mg)

PROCESSING

- Formulation 1:** to a solution of celecoxib in ethanol AEROPERL® 300 Pharma was added and the solvent removed at 50 °C overnight
- Formulation 2:** to a sample of formulation 1 HPMC* was added by physical mixing.

DISSOLUTION TESTING

Dissolution was tested in FASSIF V2 (pH 6.5) at 37 ± 1 °C in a USP II apparatus operated at a stirrer speed of 75 rpm. The solution was analyzed for dissolved API by HPLC.



*HPMC: Hydroxypropyl methylcellulose

²⁸ The study was conducted by Prof. J. B. Dressman of the Institute for Pharmaceutical Technology of the Goethe University of Frankfurt.

5 AEROSIL® and AEROPERL® Pharma colloidal silicon dioxide overview

Colloidal silicon dioxide²⁹ such as the products of the brand AEROSIL® Pharma has been used as a pharmaceutical excipient since the early days of direct compression tableting^{30,31,32}. AEROSIL® 200 Pharma is the traditional glidant, helping to obtain the optimal powder flow required by today's high-speed tablet presses. Since the time of first use of AEROSIL® 200 Pharma as a glidant challenges in formulating solid dosage forms have become more complex. Tablet powders of different average particle size, composition and moisture sensitivity are common in the industry – requiring specialized products to be able to compete in an increasingly cost sensitive health care environment. To support the industry to cope with these challenges Evonik has broadened its AEROSIL® and Pharma portfolio not only to provide optimal glidants for almost any tableting process but also to support the pharmaceutical industry with other formulation challenges such as:

- helping to run granulation processes more efficiently and economically
- incorporating liquids or solutions into solid dosage forms (e. g. liquid or dissolved actives)
- controlling the rheology and helping to stabilize semi-solid dosage forms against thermal degradation
- improving the dissolution of poorly soluble active pharmaceutical ingredients.

Table 2 gives an overview of all AEROSIL® and AEROPERL® Pharma products with their characteristics, physico-chemical properties and their compliance to the different pharmacopeia monographs.

²⁹ This brochure uses the term “colloidal silicon dioxide” in the sense of the USP/NF monograph for silica products produced by flame hydrolysis. Products of this kind are also known as fumed silica in other industries. The products are not to be mistaken as “colloidal silica” or “silica sol” which stands for dispersions of spherical silica particles in a fluid (typically water). For an overview of the different forms of silica please refer to the chapter “Silica” in Ullmann’s Encyclopedia of Industrial Chemistry, Wiley and Sons.”

³⁰ Galenic considerations on AEROSIL® (in German) von Czetsch-Lindenwald, H. Die Pharmazie 12 (12) (1957) 589.

³¹ Galenic considerations on AEROSIL® II (in German) von Czetsch-Leisenwald, H, Die Pharmazie 12 (12) (1957) 810.

³² On direct compression of tablets (in German) Tawashi, R. Pharmazeutische Industrie 26 (1964) 682.

Table 2

Physico-chemical properties of AEROSIL® and AEROPERL® Pharma colloidal silicon dioxide

		AEROSIL® 200 Pharma	AEROSIL® 200 VV Pharma	AEROSIL® 300 Pharma	AEROSIL® R 972 Pharma	AEROPERL® 300 Pharma
Character	Type	Powder	Densified powder	Powder	Powder	Granulate
	Behavior in water	Hydrophilic	Hydrophilic	Hydrophilic	Hydrophobic	Hydrophilic
Typical physico-chemical properties*	Specific surface area (BET, m ² /g)	175–225	175–225	270–330	90–130	260–320
	Tamped density (g/l)	Appr. 50	Appr. 120	Appr. 50	Appr. 50	Appr. 270
	pH	3.5 – 5.5	3.5 – 5.5	3.5 – 5.5	–	3.5 – 5.5
Pharmacopeia compliance	Europe (Ph. Eur.)	Silica, colloidal anhydrous	Silica, colloidal anhydrous	Silica, colloidal anhydrous	Silica, hydrophobic colloidal	Silica, colloidal anhydrous
	India (IP)	Colloidal Silicon Dioxide	–	–	–	–
	USP/NF	Colloidal Silicon Dioxide	Colloidal Silicon Dioxide	Colloidal Silicon Dioxide	Hydrophobic Colloidal Silica	Colloidal Silicon Dioxide
	JP	Light anhydrous silicic acid	–	Light anhydrous silicic acid	–	–

*Typical values for informational purposes only

A detailed description of the different AEROSIL® and AEROPERL® colloidal silicon dioxide products is the topic of “TI 1415 AEROSIL® and AEROPERL® Pharma Colloidal Silicon Dioxide Products” that can be downloaded from

<https://www.silica-specialist.com/en> webpage.

This brochure covers a part of the uses of these products in pharmaceutical preparations.

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The Silica specialists at Evonik – Inside to get it right.