

# Pharma Silica Insights

A newsletter for silica excipients for pharmaceutical formulations

Issue 1 | 2012

## What about silica?

AEROSIL® colloidal silicon dioxide is a well known excipient that helps to make pharmaceutical manufacturing processes more efficient. It has been known to act as a glidant to improve the flow and processing of powder for direct compression of tablets for 70 years. Evonik Industries AEROSIL® Pharma products have gained acceptance and recognition as pharmaceutical excipients through their excellent performance.

The pharmaceutical industry is constantly looking for (new) technologies and concepts that will allow them to improve efficiency, reduce costs as well as to bring their newly developed active

pharmaceutical ingredients (APIs) into therapeutically active dosage forms.

We at Evonik strongly believe that AEROSIL® Pharma and AEROPERL® Pharma products can help to overcome many of the most pressing challenges of today.

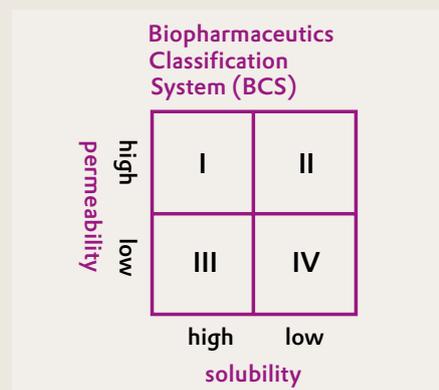
This newsletter is to inform pharmaceutical formulators, manufacturers and other interested people of new developments relating to the use of colloidal silicon dioxide in pharmaceutical formulations.

Enjoy your reading!

## AEROPERL® 300 Pharma: a solution to tackle the low solubility challenge

The majority of newly developed active pharmaceutical ingredients (APIs) are more hydrophobic than traditional drugs and so formulating them into therapeutically active dosage forms can become a challenge. Some APIs although being highly potent drugs never make it to the market as it is impossible to convert them into a drug form with suitable bioavailability. Bio-availability can be hampered either by an insufficient solubility of the API in the gastrointestinal fluids or limited permeability of the dissolved drug through the membranes into the blood stream. The different behaviors of APIs are reflected by the biopharmaceutics classification system (BCS) as exemplified in Figure 1.

APIs of class II have low solubility but good permeability in the gastrointestinal fluids but often lack sufficient bio-availability. Recent studies have shown that AEROPERL® 300 Pharma, a granulated type of colloidal silicon dioxide can help overcome the insufficient dissolution of such APIs.



**Figure 1**  
Simplified classification of API behavior according to the Biopharmaceutics Classification System (BCS)

### Topic

**AEROPERL® 300 Pharma:**  
an inert carrier to improve the dissolution of APIs

**AEROPERL® 300 Pharma:**  
a carrier for "liquisolid" formulations and "self-emulsifying drug delivery systems"

**AEROPERL® 300 Pharma:**  
product introduction

### Exhibitions 2012:

**CPhI in Madrid**  
on October 9 – 11,  
hall 4 booth A32

**Lecture on:**  
AEROPERL® 300 Pharma:  
a new excipient featuring  
versatile advantages for an  
efficient pharmaceutical  
production,  
October 10, 1 – 1 : 25 p.m.  
at Speakers' Corner

**AAPS in Chicago,**  
October 15 – 18

**CPhI in Mumbai,**  
November 21 – 23

**PharmTech in Moscow,**  
November 26 – 29

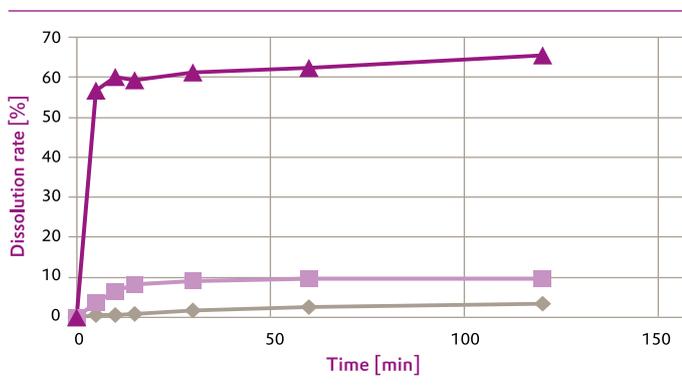
## AEROPERL® 300 Pharma an inert carrier to improve the dissolution of APIs

The absorption of APIs of low solubility on inert carriers has become an important strategy to increase the bioavailability of BCS Class II APIs. By absorbing the API on the carrier the available surface for dissolution can be increased. The API can be stabilized in a form with superior solubility, e.g. in an amorphous state. The strategy has been discussed for quite a while in the scientific literature as the “solid dispersion” technique. There is abundant literature available utilizing specifically tailored ordered mesoporous silica carriers. Unfortunately, most of these silica materials are not available on a commercial scale or at reasonable costs. AEROPERL® 300 Pharma is an inert and highly absorptive carrier available in commercial quantities at reasonable prices enabling formulators to use this formulation strategy.

In order to absorb the API on the carrier different methods have been proposed in the literature. In most of these methods the API needs to be dissolved in a suitable solvent. The solution can then be completely absorbed in the pores of the silica (e.g. by spraying the solution on the silica) or silica is dispersed into the solution. In both methods, the solvent is then removed by evaporation. Often temperatures above the crystallization temperature of the API are applied to prevent crystallization of the API in the pores of the carrier. Other solubility enhancers as surfactants can be added to the solution for an even bigger effect on the solubility.

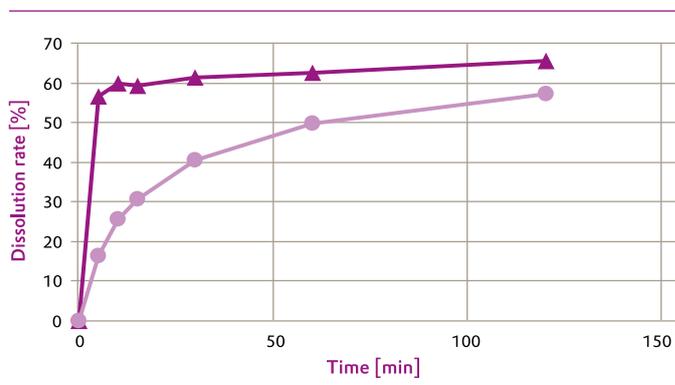
Another method to produce API silica solid dispersions uses a hot melt mixing process in which a physical mixture of the API with silica is prepared and this mixture then heated to temperatures above the melting point of the API, and then cooled to obtain a solid dispersion. In Figure 2 it is demonstrated how AEROPERL® 300 Pharma can be used to increase the solubility of the poorly soluble API itraconazole<sup>1</sup>.

For this study the dissolution behavior of pure itraconazole (formulation 1) was compared to a formulation containing itraconazole in d- $\alpha$ -tocopheryl polyethylene glycol 1000 succinate (TPGS) as an excipient surfactant (formulation 2)<sup>2</sup> and a formulation in which the drug and TPGS were adsorbed on AEROPERL® 300 Pharma (formulation 3)<sup>3</sup>. 0.1N HCl was used as the dissolution medium, mimicking stomach conditions<sup>4</sup>. For comparison purposes a mixture of itraconazole and TPGS was also loaded on AEROSIL® 200 Pharma (formulation 4)<sup>5</sup> and this formulation also subjected to the same dissolution test (see Figure 3). At certain intervals samples were taken from the dissolution medium and analyzed for their itraconazole concentration by HPLC<sup>6</sup>.



**Figure 2**

Dissolution behavior for itraconazole in pure form (formulation 1, ♦), formulated with TPGS (formulation 2, ■) and formulated with TPGS and AEROPERL® 300 Pharma (formulation 3, ▲)



**Figure 3**

Dissolution behavior of itraconazole formulated with TPGS and adsorbed on AEROSIL® 200 Pharma (formulation 4, ●) and AEROPERL® 300 Pharma (formulation 3, ▲)

<sup>1</sup> Study conducted by Prof. J. Dressman, A. Fuchs. Itraconazole is a slightly alkaline antifungal drug. Complete results of this study to be published in the poster session at the AAPS Annual Meeting in Chicago in October 2012.

<sup>2</sup> Formulation 2: 100 mg itraconazole was dispersed in 100 mg molten TPGS. The dispersion was solidified by cooling and ground by mortar and pestle.

<sup>3</sup> Formulation 3: 100 mg itraconazole and 100 mg TPGS were dissolved in a mixture of 9 parts of ethanol and 1 part of concentrated HCl. The solution was given to 2000 mg of AEROPERL® 300 Pharma and homogenized until the complete solution was absorbed by the carrier. The solvent was then removed in an oven at 50 °C overnight.

<sup>4</sup> For the dissolution experiment an Erweka DT 6 dissolution tester with paddles was used. The dissolution medium (500 ml) was held at a temperature of 37 ± 1 °C with a stirring rate of 75 rpm. Experiments were run for 2 h with sample points at 5 min, 10 min, 15 min, 30 min, 60 min and 120. Each sample (2 ml) was filtered through CHROMAFIL PET-20/15 MS disposable filters with a pore size of 0.2 µm before analysis.

<sup>5</sup> Formulation 4: 100 mg itraconazole and 100 mg TPGS were dissolved in a mixture of 9 parts of ethanol and 1 part of concentrated HCl. The solution was given to 1000 mg of AEROSIL® 200 Pharma and homogenized until the complete solution has been absorbed by the carrier. The solvent was then removed in an oven at 50 °C overnight.

<sup>6</sup> A VWR Hitachi Organizer Elite LaChrome HPLC instrument was used for analyses. A LiChroCart 150-4.6 Rp-18e (5 µm) column was used as the stationary phase. The mobile phase consisted of acetonitrile (1300 ml), Milli-Q-Water (699 ml) and triethylamine (1.06 g) which was adjusted to pH 3.0 with H<sub>3</sub>PO<sub>4</sub> (85 %).

As clearly evident from Figure 2 itraconazole has only very limited solubility in the dissolution medium (formulation 1). Dissolution can be increased by a factor of 2 by formulating the API with TPGS as a surfactant (formulation 2). But still only about 10% of the itraconazole is dissolved within 2 h. Only formulation 3 in which itraconazole together with TPGS is absorbed on AEROPERL® 300 Pharma gives a dissolution pattern that can be used to formulate the drug into a tablet, leading to 10 fold dissolution increase of the API compared to its pure form. Figure 3 compares the dissolution behavior of itraconazole dissolved

in HCl acidified ethanol and absorbed on either AEROSIL® 200 Pharma (formulation 4) or AEROPERL® 300 Pharma (formulation 3). Although both carriers lead to similar dissolution rates after 2 h AEROPERL® 300 Pharma is clearly superior as the drug is dissolved much faster. After only 5 min the AEROPERL® 300 Pharma formulation (formulation 3) released 50% of the itraconazole while the dissolution of formulation 4 is less than 20%.

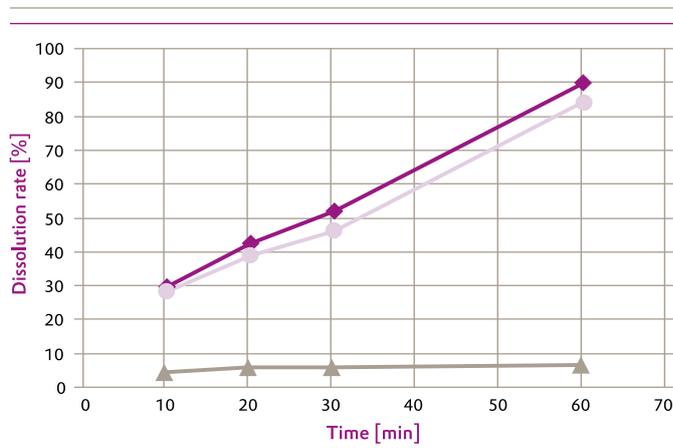
In another example, figures 4 shows how AEROPERL® 300 Pharma can be used in a capsule formulation to improve the dissolution behavior of bicaluta-

mide<sup>7</sup>. Details of the formulations are shown in table 1. The dissolution behavior of amorphous bicalutamide (formulation 5)<sup>8</sup> was compared to formulations in which bicalutamide together with a wetting agent was absorbed on AEROPERL® 300 Pharma (formulation 6 and 7)<sup>9</sup>. A sodium lauryl sulfate solution (1%) was used as the dissolution medium<sup>10</sup>.

Figure 4 clearly demonstrates the positive effect of AEROPERL® 300 Pharma on the dissolution behavior of bicalutamide.

Ingredients	Formulation 5	Formulation 6	Formulation 7
Bicalutamide	50	50	50
AEROPERL® 300 Pharma		284	284
Wetting agent: Polyethylene-glycol 400 Propylenglycol		50	50
<b>Total</b>	<b>50</b>	<b>384</b>	<b>384</b>

**Table 1**  
Formulations of bicalutamide capsules (all values in mg)



**Figure 4**  
Dissolution behavior of hard gelatin capsule formulations of amorphous bicalutamide (▲ formulation 5), bicalutamide and polyethylene glycol 400 loaded on AEROPERL® 300 Pharma (◆ formulation 6) and bicalutamide and propylenglycol loaded on AEROPERL® 300 Pharma (● formulation 7)

<sup>7</sup> Study conducted with Prof. P.D. Amin, Institute of Chemical Technology, Mumbai, India. Bicalutamide is an anti-androgen used in the treatment of prostate cancer.

<sup>8</sup> Bicalutamide was melted at 200 °C, solidified by cooling and ground by mortar and pestle before employing filling the material in hard gelatine capsules.

<sup>9</sup> Polyethylene glycol 400 or propylenglykol was loaded on AEROPERL® 300 Pharma. The pretreated carrier was then immersed in a solution of bicalutamide (500 mg) in acetone (20 ml) under stirring. Stirring was continued till the evaporation of acetone left a freely flowing powder behind. The absorbate was used in the capsule formulations 6 and 7. Hard gelatine capsules were used for the capsule formulations.

<sup>10</sup> The dissolution behaviour was studied in 1000 ml sodium lauryl sulfate solution (1%) at 37 °C in a USP type II apparatus with a paddle speed of 50 rpm. Capsules were put in capsule sinkers to prevent them from floating. At periodic intervals samples were taken from the dissolution medium and analyzed for their bicalutamide concentration by UV spectrophotometric method at 273 nm (U.S. Food and Drug Administration, Dissolution Methods, Bicalutamide).

## AEROPERL® 300 Pharma: a carrier for “liquisolid” formulations and “self-emulsifying drug delivery systems”

In the “liquisolid” approach APIs of poor water solubility are dissolved or dispersed in a water miscible, non-volatile solvent and that solution is absorbed on an inert carrier. Dissolving the drug in a solvent reduces barriers to dissolution such as a crystal lattice or wetting the API surface, saving time.

In “self-microemulsifying drug delivery systems” (SMEDDS) or “self-nano-emulsifying drug delivery systems”

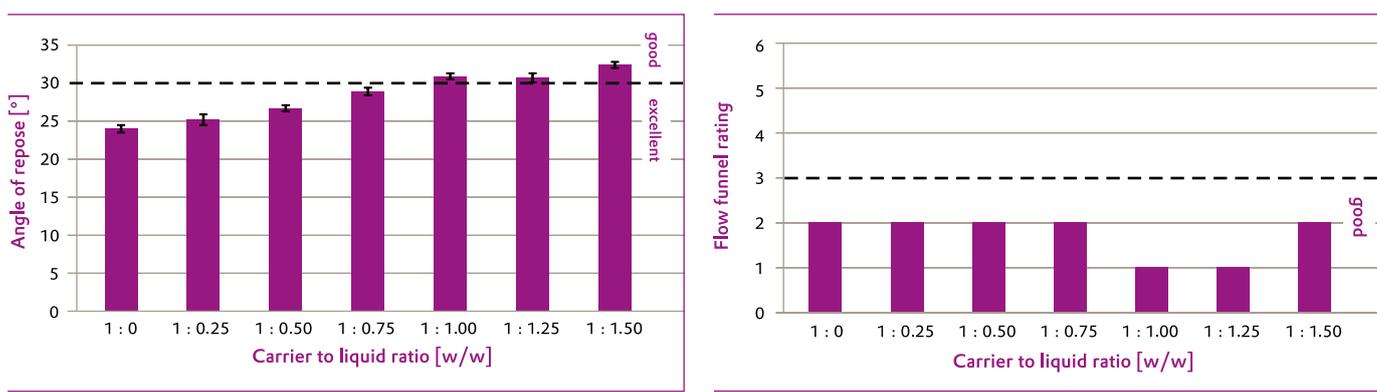
(SNEDDS) the API is present in form of a liquid formulation. Such a formulation spontaneously forms an emulsion in the micro- or nano-scale range if exposed to an aqueous environment (e.g. digestive juices). The liquid formulations consist of oil, surfactant, drug and co-emulsifier or solubilizer and have been reported to be able to improve the bioavailability of APIs with low solubility.

In both the “liquisolid” as well as the SMEDDS/SNEDDS concepts the API is present in a liquid form which makes it difficult to use these concepts to produce tablets.

AEROPERL® 300 Pharma can be used to absorb such formulations and turn them into free flowing powders that can easily be used for direct tableting processes. In figure 5 an example how

AEROPERL® 300 Pharma can be used as a carrier for a pharmaceutical dimethicone is shown<sup>11</sup>. The carrier to liquid ratio was altered from 1:0.25 to 1:1.5. All absorbates exhibit excellent to good flowabilities.

AEROPERL® 300 Pharma loaded with an equivalent mass of dimeticone was used for tableting<sup>12</sup>. Tablets of 12 mm with a dimeticone loading of 162 mg were obtained exhibiting a tablet mass variation of 0.5%, a crushing strength of 123 N, a radial tensile strength of 1.45 MPa and a friability of 0.1%.



**Figure 5** Flowability of dimethicone absorbates on AEROPERL® 300 Pharma, measured as the angle of repose and the flow through an orifice

<sup>11</sup> To prepare the dimethicone absorbates 40 g of AEROPERL® 300 Pharma were filled in the mixing chamber of a Somakon MPL-1 mixer (Somakon Verfahrenstechnik, Selm, Germany). An amount of Dimeticone 100 Ph. Eur. (Caesar & Lorenz GmbH, Hilden, Germany) necessary for the individual preparation was added to the carrier within 30 s while mixing at 2000 rpm. Several batches were combined and homogenized in a Turbula T2F mixer (Willy A. Bachofen GmbH, Nidderau, Germany). Flowability of the powders was tested

using methods of angle of repose and flow through an orifice as exemplified in USP 1174. For the flow of an orifice glass flow funnels with orifices between 2.5 mm (funnel 1, indicating very good flow) up to 24 mm (funnel 6, indicating poor flow) were used.

<sup>12</sup> AEROPERL® 300 Pharma was loaded with the same mass of Silbione DM 1000 (Bluestar Silicones, Lyon, France) using the same technique as already described. The resultant powdery absorbate was used to produce a tableting

powder composition (50 w.-% AEROPERL® 300 Pharma/ dimeticone absorbate, 50 w.-% Avicel PH 101, FMC Biopolymer, Brussels, Belgium). All components were passed through a 710 µm sieve before mixing in a tumbling mixer (Turbula T2F, Willy Bachofen GmbH, Nidderau, Germany) for 10 min at 67 rpm. The powder mixture was turned into 650 mg tablets with a diameter of 12 mm by a Korsch EK O single punch press (Korsch AG, Berlin, Germany).

## AEROPERL® 300 Pharma: product introduction

AEROPERL® 300 Pharma is a granulated form of a colloidal silicon dioxide consisting of spherical particles with a mean diameter of approximately 30 µm. The absorption capacity is approximately 150 g liquids on 100 g of the carrier. Traditional colloidal silicon dioxide products such as AEROSIL® 200 Pharma and AEROSIL® 300 Pharma are chemically very pure forms of silicon dioxide with a rather low tamped density of approximately 50 g/l. AEROPERL® 300 Pharma features the same chemical purity exemplified by an extraordinarily low heavy metal content as well as the absence of any organic impurities but has a much higher tamped density of approximately 280 g/l. Due to the high tamped density and the spherical particle shape dust formation is reduced and powder flowability improved, making handling and storage of the product much easier.

AEROPERL® 300 Pharma is produced according to the GMP guidelines of the International Pharmaceutical Excipients Council (IPEC) and tested against the monographs for “Colloidal Silicon Dioxide” (USP/NF) and “Silica Colloidal Anhydrous” (Ph. Eur.).

For more information please visit our webpage [www.aerosil.com](http://www.aerosil.com) that allows to download of more information after a simple registration process.



**Figure 6**  
Scanning electron microscopy (SEM) image of AEROPERL® 300 Pharma.



**Figure 7**  
Comparison of the volumes of 6 g each of AEROSIL® 200 Pharma (left), AEROPERL® 300 Pharma (middle) and Syloid® 244 FP (right, commercial silicon dioxide by Grace Davison GmbH)

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**EVONIK**  
INDUSTRIES

**Evonik Resource Efficiency GmbH**

Business Line Silica  
Rodenbacher Chaussee 4  
63457 Hanau  
Germany

PHONE +49 6181 59-12532

FAX +49 6181 59-712532

[ask-si@evonik.com](mailto:ask-si@evonik.com)

[www.evonik.com](http://www.evonik.com)

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