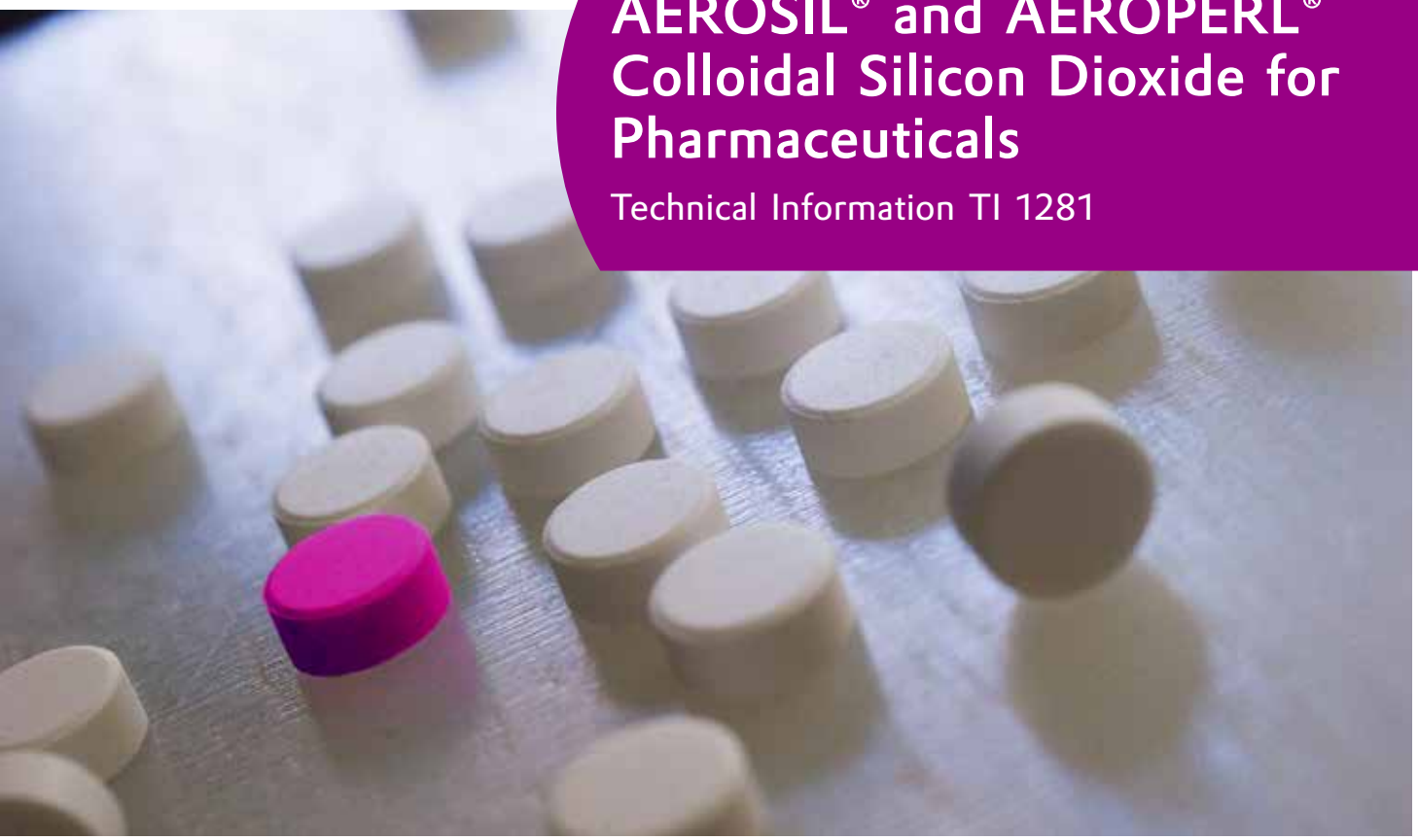
EVONIK INDUSTRIES

AEROSIL® and AEROPERL® Colloidal Silicon Dioxide for Pharmaceuticals

Technical Information TI 1281



AEROSIL® AEROPERL®

Evonik. Power to create.

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1 AEROSIL® and AEROPERL® colloidal silicon dioxide – much more than glidants

AEROSIL® colloidal silicon dioxide[1] has been used as a pharmaceutical excipient since the early days of direct compression tabletting[2,3,4]. In its traditional role as a glidant, AEROSIL® colloidal silicon dioxide helps to obtain the optimal powder flow required by today's high speed tablet presses.

But AEROSIL® and AEROPERL® colloidal silicon dioxide are more than just glidants for direct compression processes. It can help the pharmaceutical industry with today's challenges such as:

- incorporating liquid or hard to crystallize active pharmaceutical ingredients into a solid dosage form (e.g. natural active oils)
- improving the dissolution of low solubility active pharmaceutical ingredients (BCS class II drugs).
- helping to run granulation processes much more efficiently and economically.

In order to assist our customers to face the challenges of a much more cost sensitive health care system, Evonik Industries offers several types of colloidal silicon dioxide to give formulators a wide range of options for improving their products and processes:

- **AEROSIL® 200 Pharma** has been used for over forty years to improve the flow properties of pharmaceutical powders. It is highly dispersed, very dry and pure with a tapped density of approximately 50 g/L.

- **AEROSIL® 200 VV Pharma** is AEROSIL® 200 Pharma that has been densified after manufacture to increase its tapped density from approximately 50 g/L to approximately 120 g/L. This densified product produces considerably less fine dust when used than traditional colloidal silicon dioxide products and requires much less storage space. Therefore, as a rule, the venting of the work area (and hence product loss) can be reduced. Expenses for post-use clean up effort and packaging disposal can be optimized.

- **AEROSIL® 300 Pharma** is a new hydrophilic colloidal silicon dioxide type which has been created for applications requiring a very high specific surface area. The specific surface area is approximately 300 m^2/g (compared to approximately 200 m^2/g for AEROSIL® 200 Pharma).

- **AEROSIL® R 972 Pharma** is colloidal silicon dioxide surface-modified with dimethylsilyl groups. The hydrophobic nature of AEROSIL® R 972 Pharma makes it an excellent glidant that is easily mixed in, making it a preferred choice when gentle mixing conditions are required. It does not absorb moisture which can provide remarkable flow and stability performance.

- **AEROPERL® 300 Pharma** is a granulated form of colloidal silicon dioxide. The spherical granules have a diameter of approximately 30 µm, giving the product a much higher tapped density of about 280 g/L compared to the non-granulated products. AEROPERL® 300 Pharma can be used as an absorbent for liquid active pharmaceutical ingredients and as a moisture scavenger, e.g. in moisture activated dry granulation processes (MADG) as well as a high density and low dust glidant.

All AEROSIL® products are white, fine, light, amorphous solids consisting of highly pure silicon dioxide. The properties and benefits of the various products are summarized in **Table 1** below.

Table 1
Colloidal silicon dioxide products for pharmaceuticals

Product	Properties	Benefits
AEROSIL® 200 Pharma	Hydrophilic	• Traditional glidant for solid dosage forms • Thickener for pharmaceutical oils
AEROSIL® 200 VV Pharma	Hydrophilic (Densified)	• Excellent glidant for most solid dosage forms • Improved handling: less dust, less clean-up • Reduced storage space requirements
AEROSIL® 300 Pharma	Hydrophilic High surface area	• Highly efficient thickener for pharmaceutical oils • Very high specific surface area (BET)
AEROSIL® R 972 Pharma	Hydrophobic	• Optimal glidant performance in many powder mixtures • Easy to mix in, requiring only gentle mixing processes • Stabilization of suspensions
AEROPERL® 300 Pharma	Hydrophilic (Granulate)	• Excellent absorbent for liquid API's • Moisture scavenger for improved storage stability of tablets • Improves the bioavailability of BCS class II drugs • Low dust, high density granulate

[1] 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". 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."
[2] Galenic considerations on AEROSIL® (in German) von Czetsch-Lindenwald, H. Die Pharmazie 12(12) (1957) 589.
[3] Galenic considerations on AEROSIL® II (in German) von Czetsch-Leisenwald, H, Die Pharmazie 12(12) (1957) 810.
[4] On direct compression of tablets (in German) Tawashi, R. Pharmazeutische Industrie 26 (1964) 682.

2 Manufacture and Properties

2.1 AEROSIL® colloidal silicon dioxide production and product characteristics

AEROSIL® colloidal silicon dioxide is manufactured by the hydrolysis of silicon tetrachloride in a hydrogen/oxygen flame according to the following chemical reaction:

$$SiCl_4 + 2\,H_2 + O_2 \rightarrow SiO_2 + 4\,HCl$$

Varying the process conditions results in products with different specific surface areas .The raw materials used are exclusively of inorganic origin and are very pure, resulting in products with exceptionally low heavy metal content that meets major compendial requirements.

The hydrophilic colloidal silicon dioxide products AEROSIL® 200 Pharma, AEROSIL® 200 VV Pharma, AEROSIL® 300 Pharma and AEROPERL® 300 Pharma all have a silicon dioxide content of more than 99.8 % by weight (based on the dried substance) and are thus pure amorphous silica. No animal or vegetable raw materials or solvents are used in the manufacturing processes. Due to the high chemical purity AEROSIL® and AEROPERL® colloidal silicon dioxide feature good compatibility even with the most heavy metal sensitive active pharmaceutical ingredients. Siloxane and silanol groups are present on the surface and the silanol groups are responsible for the high affinity for water and polar compounds. Hydrophilic AEROSIL® colloidal silicon dioxide is able to adsorb considerable quantities of water without any change in its state of aggregation.

During the manufacture of AEROSIL® colloidal silicon dioxide, the vaporized silicon tetrachloride reacts with water (formed by a hydrogen oxygen flame) to form the primary particles of silicon dioxide (**Figure 1a**). The particle size mentioned in the Pharm. Eur. monograph Silica Colloidal Anhydrous refers to the size of these primary particles. However, these particles do not remain isolated, but collide, and sinter together, resulting in branched chain aggregates. (**Figure 1b**).

The aggregates are the smallest actual units of colloidal silicon dioxide. Once the aggregates cool down to below the fusion point, additional collisions result in mechanical entanglement and bonding of the chains, called agglomeration. Because agglomerates (**Figure 1c**) are only bound through weak forces, they can easily be broken down to aggregates during mixing or dispersion.

2.2 Hydrophobic Post-Treatment

To produce hydrophobic AEROSIL® R 972 Pharma, hydrophilic colloidal silicon dioxide is treated with dimethyldichloro silane in a consecutive reaction step that follows immediately after the generation of silica particles as described above (**Figure 2**). This step too, is conducted at high temperature. As a result, dimethylsilyl groups are irreversibly covalently bound to the surface of the colloidal silicon dioxide particles by very stable siloxane bonds (**Table 2**), resulting in a product that does not mix with water.

Table 2
Average bond dissociation energies (at 298 K) of selected chemical bonds.

Bond type	Bond dissoc. energy in kJ/mol	Bond dissoc. energy in kcal/mol
C – C	approx. 345 – 350	approx. 80 – 85
Si – C	approx. 345 – 360	approx. 80 – 85
Si – O	approx. 452 – 460	approx. 105 – 115

2.3 Densification

AEROSIL® agglomerates are irregular in size and shape and do not pack well. The considerable amount of void space between the agglomerates is responsible for the low tapped density of traditional colloidal silicon dioxide and small agglomerates are responsible for the dustiness.

Figure 1
Schematic representation of **A** primary particles (the smallest recognizable individuals), **B** Aggregates (Primary particles connected with each other that cannot be broken apart), and **C** Agglomerates (aggregates that are held together by weak forces).

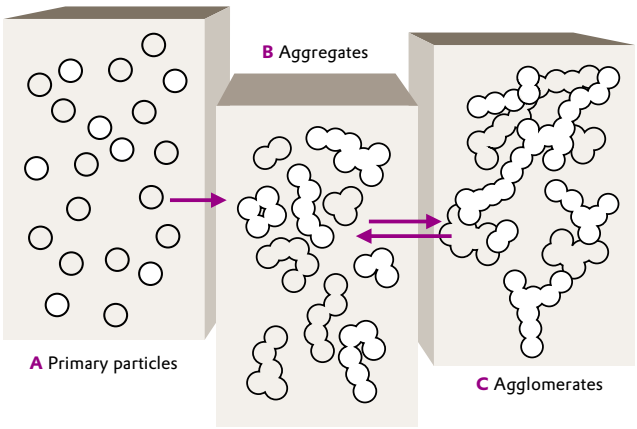
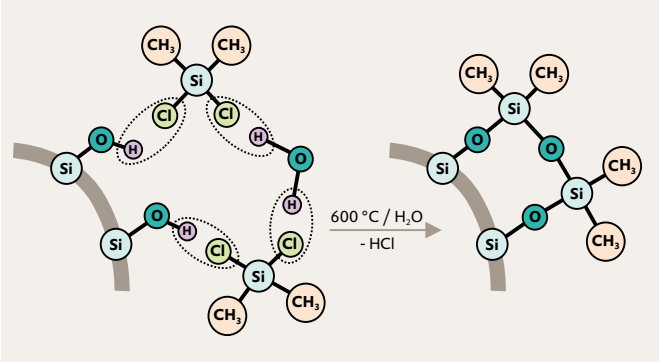


Figure 2
Hydrophobic AEROSIL® R 972 Pharma is produced by treating hydrophilic AEROSIL® colloidal silicon dioxide with dimethyldichloro silane.



AEROSIL® 200 VV Pharma is a densified grade. Using a purely mechanical densification technology, air is removed from between the agglomerates. The result is larger, more-stable secondary agglomerates that produce considerably less fine dust (particles < 10–20 µm in size) than traditional non-densified colloidal silicon dioxide (**Figure 3**). Due to the purely physical nature of the densification process the typical physico-chemical properties as specific surface area are not affected. The only difference of the two products is the tapped density, which for AEROSIL® 200 VV Pharma is about 120 g/L compared to 50 g/L for the non densified AEROSIL® 200 Pharma.

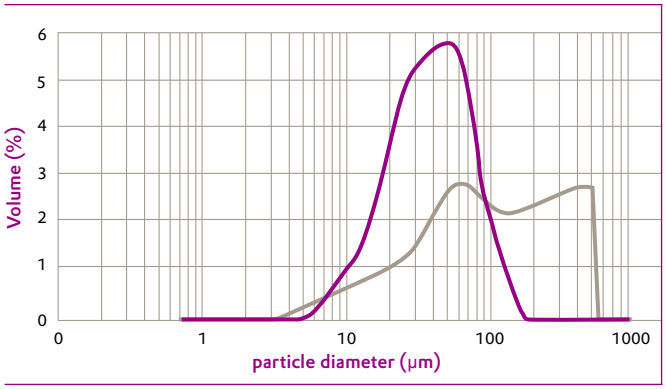
In many solid dosage forms, densified products perform at least as well as, or even better than, their non-densified counterparts.

Literature

Investigation of compacted hydrophilic and hydrophobic colloidal silicon dioxides as glidants for pharmaceutical excipients.
Jonat, S., Hasenzahl, S., Drechsler, M., Albers, P., Wagner, K. W., Schmidt, P. C. Powder Technology, 141 (1-2) (2004) 31-43.

Investigation of the glidant properties of compacted colloidal silicon dioxide by angle of repose and X-ray photoelectron spectroscopy,
Jonat, S., Albers, P., Gray, A., Schmidt, P. C., European Journal of Pharmaceutics and Biopharmaceutics 63 (2006) 356 – 359.

Figure 3
Dry powder particle size distribution of agglomerates of AEROSIL® 200 Pharma (purple line) and AEROSIL® 200 VV Pharma (gray line) directly taken from the bags. Values were measured using a laser diffraction method (Coulter, dry powder module).
AEROSIL® 200 VV Pharma contains proportionally more larger agglomerates (> 100 µm) and significantly fewer smaller agglomerates ("dust" < 20 µm).



AEROSIL® 200 Pharma Diff. Volume %
AEROSIL® 200 VV Pharma Diff. Volume %

2.4 Granulation

AEROSIL® powder and densified grades are irregularly shaped and in spite of their high surface area have only limited absorption capacity. In a specialized production process the AEROSIL® powder can be transformed into spherical granules (**Figure 4**). The granulate AEROPERL® 300 Pharma has an average particle size of 30–40 µm, with only minor portions of the product lying outside that range (**Figure 5**). The material has a very high tapped density of about 280 g/L unmatched by any AEROSIL® product (**Figure 6**). Due to its spherical particle shape AEROPERL® 300 Pharma possesses exceptional flowability. It also imparts enhanced flow properties to powder mixtures in which AEROSIL® 200 Pharma and AEROSIL® R 972 Pharma are hard to mix in homogenously due to differences in density. The granules feature a meso- and macroporous structure which can be used to absorb liquid active pharmaceutical ingredients, transforming them into a free flowing powder that can be used for tabletting. The high absorption capacity of the granulated product enables it to be used as a moisture scavenger in moisture sensitive formulations and in specialized processes such as moisture activated dry granulation (MADG).

Figure 4 Scanning electron microscopy image of AEROPERL® 300 Pharma

Figure 5
Particle size distribution of AEROPERL® 300 Pharma, measured by laser diffraction (Cilas). The D_{50} value of the particles is 33 µm.

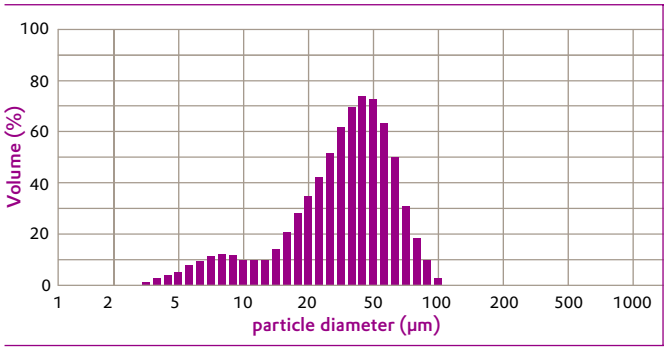


Figure 6
Bulk density of AEROPERL® 300 Pharma Bulk volume of 8.0 g of AEROPERL® 300 Pharma (middle) compared to equivalent mass of AEROSIL® 200 Pharma (left) and a competitor precipitated silica product for pharmaceutical applications (Syloid® 244 FP, Grace Davison Discovery Science, right)

All Pharma grades are tested according to the European and United States Pharmacopoeia methods and have appropriate certificates of analysis. AEROSIL® 200 Pharma and AEROSIL® 300 Pharma are also tested against the compendial specification in the Japanese Pharmacopoeia. All product specifications and certificates of analysis are regularly updated to reflect the relevant changes in the Pharmacopoeia monographs.

Testing the compendial compliance of the pharmaceutical grades of AEROSIL® requires a high analytical effort. For AEROSIL® 200 Pharma 28 different parameters need to be analyzed, compared to only 4 parameters for the standard grade.

2.5 Standard and Pharmaceutical Grades

AEROSIL® and AEROPERL® colloidal silicon dioxide products which are specially produced to fit the standards of the pharmaceutical industry are characterized by the suffix "Pharma" in the product name. Available as pharmaceutical grades are AEROSIL® 200 Pharma, AEROSIL® 200 VV Pharma, AEROSIL® 300 Pharma, AEROSIL® R 972 Pharma and AEROPERL® 300 Pharma. Although the manufacturing processes for the pharmaceutical and the standard grades are basically identical only "Pharma" grades are truly in line with the requirements of pharmaceutical production. AEROSIL® and AEROPERL® Pharma grades are produced according to GMP guidelines of the International Pharmaceutical Excipients Council (IPEC) for pharmaceutical excipients. Full traceability of all raw materials and production conditions and stringent hygiene protocols followed during bag filling are guaranteed.

Table 3
International Pharmacopoeia monographs for AEROSIL® and AEROPERL® Pharma grades

Products	European Pharmacopoeia	US Pharmacopoeia	Japanese Pharmacopoeia
AEROSIL® 200 Pharma	Silica, colloidal anhydrous	Colloidal silicon dioxide	Light anhydrous silicic acid
AEROSIL® 200 VV Pharma	Silica, colloidal anhydrous	Colloidal silicon dioxide	– *
AEROSIL® 300 Pharma	Silica, colloidal anhydrous	Colloidal silicon dioxide	Light anhydrous silicic acid
AEROSIL® R 972 Pharma	Silica, hydrophobic colloidal	Silica, hydrophobic colloidal	– **
AEROPERL® 300 Pharma	Silica, colloidal anhydrous	Colloidal silicon dioxide	– *

* AEROSIL® 200 VV Pharma and AEROPERL® 300 Pharma comply with all specification parameters except the volume test.
** There is no monograph for a hydrophobic silica grade in the Japanese Pharmacopoeia.

3 Mode of action

The high chemical purity and inertness of colloidal silicon dioxide makes it a versatile pharmaceutical excipient. Evonik Industries offers the material in different forms, each product form being specially adapted to a number of modes of actions:

- The adhesion of AEROSIL® colloidal silicon dioxide aggregates to pharmaceutical host powders, enhancing their powder flowability (glidant application)
- The absorption of substances, e. g. liquid active pharmaceutical ingredients or water (carrier application)
- The formation of gels in liquids through formation of a three-dimensional network of AEROSIL® colloidal silicon dioxide aggregates (rheology control)

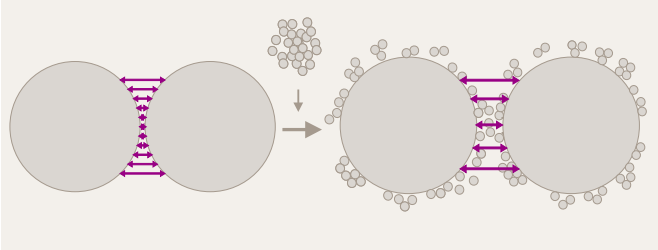
Each of these mechanisms may be used to achieve different effects depending on the dosage form.

3.1 Powder flow regulation with AEROSIL® colloidal silicon dioxide

The flowability of powders is governed by forces between individual powder particles. A number of different forces determine the mechanism of adhesion: van-der-Waals forces, electrostatic forces, liquid bridges and entanglement. Typically the smaller the solid particles are, the more pronounced these effects are, and consequently the more cohesive the powder (i. e. poor powder flow properties). AEROSIL® colloidal silicon dioxide helps to improve the flow of powders by acting to counteract these different mechanisms. Van-der-Waals forces and electrostatic attraction decrease with increasing distance between the particles. Small AEROSIL® aggregates adhere to the surface of the larger powder particles, thereby increasing the distance, and reducing the attractive forces between them (**Figure 7**).

The hydrophilic nature of AEROSIL® colloidal silicon dioxide allows it to attract and preferentially bind moisture, helping to eliminate liquid bridges between solid particles that hinder powder flow. In addition, aggregates of AEROSIL® also fill in voids and irregularities on the particle surface, decreasing entanglement between the larger particles.

Figure 7
Schematic representation of the interparticulate forces that can affect powder flow. **Left:** without glidant.
Right: with AEROSIL® colloidal silicon dioxide as a glidant (represented by the small grey circles).



Literature:

Effect of glidants in binary powder mixtures. *Meyer, K., Zimmermann, I., Powder Technology 139 (2004) 40-54*

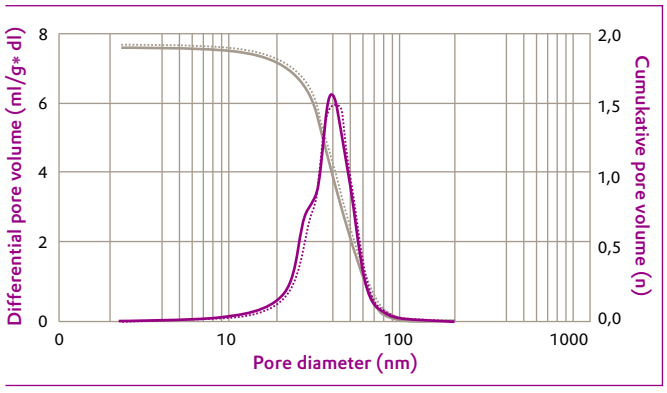
Nanomaterials as flow regulators in dry powders. *Zimmermann, I., Eber, M., Meyer, K., Zeitschrift für Physikalische Chemie 218(1) (2004) 51-102*

Effect of moisture uptake on the particle properties of corn starch (in German). *von Czetsch Lindenwald, H., el Khawas, F., Tawashi, R., J. Soc. Cosmetic Chemists 16 (1965) 251-260*

3.2. Turning liquids into free flowing powders with AEROPERL® 300 Pharma

AEROPERL® 300 Pharma due to its meso- and macroporous particle structure has a high absorption capacity for liquids (**Figure 8**). Because of the small diameter of these pores high capillary forces actually draw the liquid into the voids of the particles. As this is a purely physical absorption mechanism the absorption is independent of the nature of the liquid as long as it has sufficient fluidity and is not too viscous. Both polar as well as non-polar liquids can be absorbed on AEROPERL® 300 Pharma, making AEROPERL® 300 Pharma a favorable choice for all kinds of liquids that need to be transformed into a powder form. Vitamins and active pharmaceutical ingredients can be equally well loaded as fragrances or natural oils and extracts. Because of the high purity and inertness of AEROPERL® 300 Pharma side reactions and decomposition of these compounds catalyzed by heavy metal impurities are minimized. The spherical shape of the absorbates is especially beneficial for their flowability so that the absorbates can easily be used in tabletting and capsule filling processes.

Figure 8
Pore volume distribution of AEROPERL® 300 Pharma
The graph shows the differential (purple) and cumulative (grey) pore volume of AEROPERL® 300 Pharma as measured by N_2 absorption.

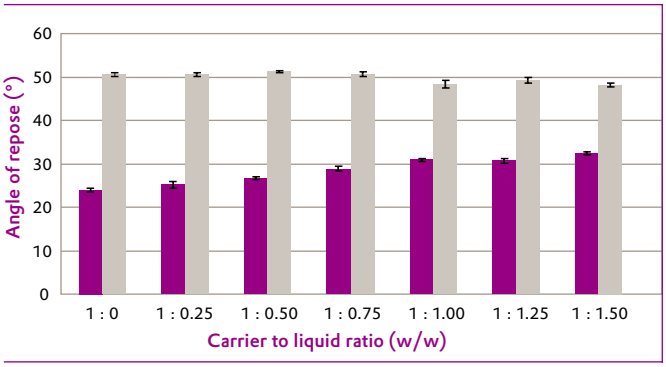


AEROPERL® 300 Pharma can absorb up to 1.5 times of its own weight of liquids. **Figure 9** shows the dependence of the flow properties of the absorbate on the loading with a pharmaceutical dimethicone as a model for a liquid API. An angle of repose of 35 ° indicates good flowability of a powder while values above 46 ° indicate poor flowability. In the flow funnel test a powder flowing through funnels 1, 2 and 3 have very good flowability while powders passing only through funnel 6 have poor flow characteristics.

The absorption properties of AEROPERL® 300 Pharma can also be used to protect a moisture sensitive formulation from absorbing water or to absorb excess moisture in moisture activated dry granulation processes (MADG).

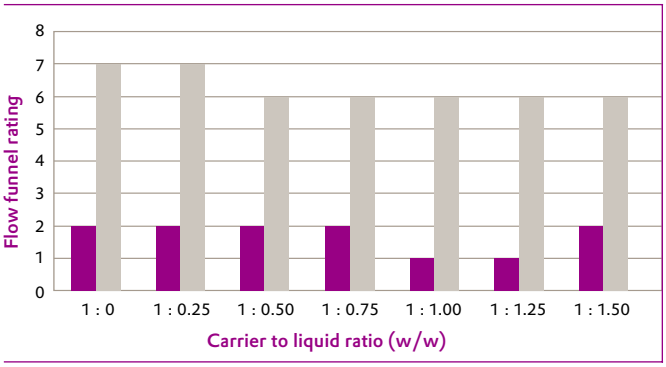
Flowability of AEROPERL® 300 Pharma absorbates depending on their load of pharmaceutical dimethicone oil
Pink columns represent the flowability of absorbates of Dimeticon 100 Ph. Eur. (Caesar & Loretz GmbH, Hilden, Germany) on AEROPERL® 300 Pharma. Grey columns represent the flowability of absorbates with equivalent Dimeticon 100 loading on a competitor precipitated silica excipient (Syolid® 244 FP, Grace Davison Discovery Science). Absorbates were prepared by adding Dimeticon 100 in 30 s to the respective quantity of the carrier while stirring at 2000 rpm in a Somakon MLP-1 mixer (Somakon Verfahrenstechnik UG, Selm, Germany). Several absorbate batches with the same loading were combined and homogenized in a Turbula T2F free fall mixer for 10 min at 72 rpm.

Figure 9 a
shows the angles of repose of the prepared samples as determined according to a USP method (USP 1174).



AEROSIL® 300 Pharma Syloid® 244 FP

Figure 9 b
shows the result of a flow funnel testing of the same absorbates according to a USP method (USP 1174). Glass flow funnels of a diameter of 38 mm with orifices ranging from 2.5 mm (funnel 1) to 25 mm (funnel 6) were used. The smaller the orifice the powder is flowing through (the smaller the funnel number) the better flowing the powder is. Powders passing through funnels up to number 3 are considered to be flowing well. A funnel rating of 7 means the powder did not flow through even the number 6 funnel with the widest orifice.



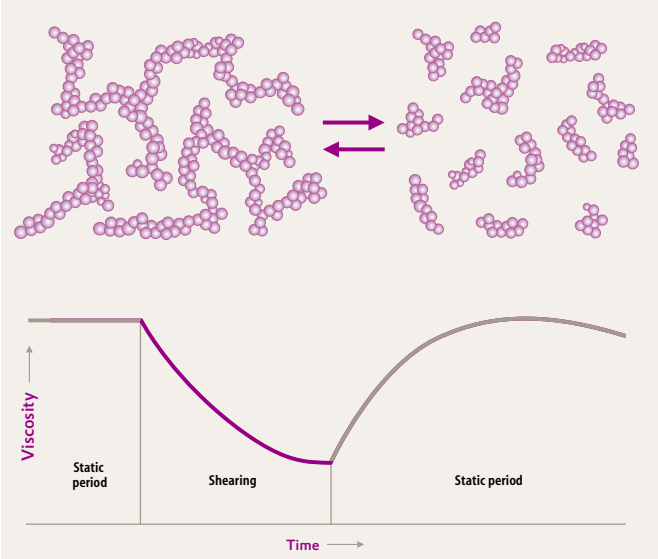
AEROSIL® 300 Pharma Syloid® 244 FP

3.3 Rheology control with AEROSIL® colloidal silicon dioxide

When AEROSIL® colloidal silicon dioxide is dispersed in a non-aqueous liquid gellation can occcur. The colloidal silicon dioxide particles form a three-dimensional inter-particle network in the liquid. This network formation is macroscopically visible as an increase in viscosity of the gel compared to the pure liquid ("thickening").

When shear forces are applied (stirring, shaking) the three-dimensional network is broken down and the viscosity decreases. This is the typical thixotropic/ pseudoplastic flow behavior of gels that contain colloidal silicon dioxide (**Figure 10**).

Figure 10
In liquids, AEROSIL® forms a three-dimensional gel structure between the AEROSIL® particles (left). The gel structure is easily broken down again by shear forces (right). The result is the shear thinning behavior seen in the diagram.



Although the AEROSIL® type used needs to be determined experimentally, as a rule of thumb AEROSIL® 300 Pharma and AEROSIL® 200 Pharma give the highest increase in viscosity in non-polar liquids such as hydrocarbons and dimethicone oils, AEROSIL® 300 Pharma typically being the more effective thickener. The viscosity increase of the hydrophobic AEROSIL® R 972 Pharma generally is often less sensitive to concentration changes and easier to disperse in the oil. For more polar liquids AEROSIL® R 972 Pharma often is the better choice as this product gives higher viscosity than the hydrophilic colloidal silica grades.

Literature

Viscoelastic measurements of silica suspensions in aqueous cellulose derivative solutions.
Ryo, Y., Nakai, Y., Kawaguchi, M., Langmuir 8(10) (1992) 2413-2416

Influence of nonionic surfactants on the viscosity of aqueous silicon dioxide dispersions (in German).
Rupprecht, H., Hofer, J., Pharmazie 38(4) (1983) 236-240

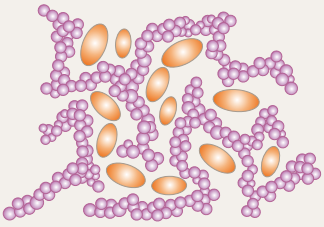
Properties and evaluation of oleogels (in German).
Bombor, R., Horsch, W., Pharmazie 32 (1977) 6

3.4 Stabilization of dispersions with AEROSIL® colloidal silicon dioxide

The three-dimensional network that is formed when AEROSIL® colloidal silica is dispersed in liquids also helps to stabilize dispersions of e. g. insoluble active pharmaceutical ingredients in a formulation. By embedding the dispersed particles in the AEROSIL® colloidal silicon dioxide network their tendency to settle out of the dispersion can be reduced (**Figure 11**). The concentration of the dispersed particles will stay uniform in each compartment of the formulation.

Both the viscosity of the gels as well as the dispersion stabilization performance is dependent on the type of AEROSIL® colloidal silicon dioxide as well as its concentration. For dispersion stabilization high concentrations of AEROSIL® colloidal silicon dioxide are often advantageous but may lead to a too high viscosity. In such cases it is often better to use a product that is a less effective viscosity builder. Because of this, AEROSIL® R 972 Pharma in many formulations is the preferred product for this application.

Figure 11
The formation of a three-dimensional particle network can be used to stabilize dispersions of other particles in liquids.



4 Solid dosage forms

4.1 AEROSIL® colloidal silicon dioxide as a glidant for pharmaceutical powders, tablets and capsules

The most popular pharmaceutical forms are tablets and filled capsules. Both of these solid dosage forms are manufactured from precursor powders that are filled into a fixed volume – either the empty capsule, or the tablet die. In order to maximize output on high speed machinery while fulfilling regulatory requirements for uniformity of unit weight (and therefore of dosage), it is essential that the precursor powder has excellent flow properties.

Just a small amount of AEROSIL® colloidal silicon dioxide can improve the flow and packing characteristics of powders and granules, and thus the accuracy of metering. Hydrophilic AEROSIL® 200 Pharma, AEROSIL® 200 VV Pharma and AEROPERL® 300 Pharma also adsorb moisture readily to help keep powders and granules dry and free-flowing during storage.

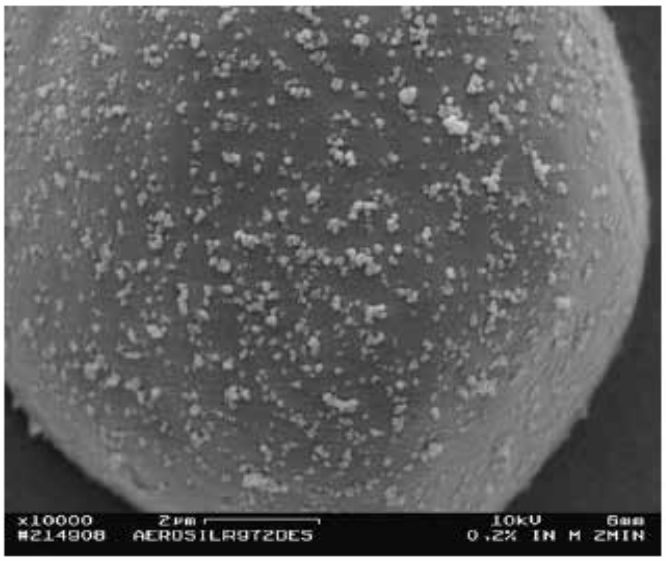


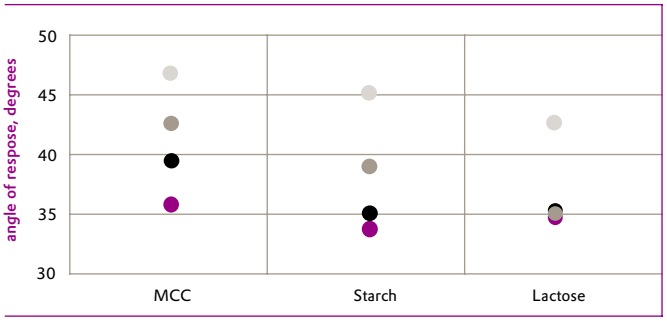
Figure 12
Scanning electron micrograph showing optimal distribution of 0.2 wt.% AEROSIL® R 972 Pharma on the surface of a spherical cornstarch particle.

In general, the more poorly the powder mixture flows, the greater the improvement that can be achieved using AEROSIL® colloidal silicon dioxide as a glidant. To achieve powder flow a situation as in **Figure 12** needs to be achieved. This scanning electron microscopy image shows how AEROSIL® colloidal silicon dioxide agglomerates adhere to the larger host powder particles (represented by corn starch spheres), rendering the surface of the particles uneven and thereby decreasing inter-particle contact. The optimal coverage with AEROSIL® colloidal silicon dioxide needs to be determined experimentally as host powders have different characteristics and morphologies. The most important factors influencing powder flow are the AEROSIL® colloidal dioxide concentration and the mixing conditions.

The necessary AEROSIL® colloidal silicon dioxide concentration usually is between 0.2 and 1.0 wt.% based on the total formulation. It is recommended to start with a concentration of 0.5 wt.% AEROSIL® colloidal silicon dioxide and adjust this amount up or down to find the optimum concentration. Both an incomplete and a more or less complete coverage of the particles need to be avoided as they will negatively influence powder flow. AEROSIL® colloidal silicon dioxide due to its small aggregate size is a highly efficient glidant often requiring concentrations of less than 0.5 wt.% for a strong increase in flowability.

The mixing conditions can have a strong influence on the powder flowability. AEROSIL® colloidal dioxide is delivered in the form of agglomerates which need to be broken down to aggregates to take full advantage of the material. AEROSIL® colloidal silicon dioxide agglomerates are broken into aggregates by the shear forces of the mixing process. The mixing conditions need to be optimized to break up the AEROSIL® colloidal silicon dioxide agglomerates as far as possible without damaging the particles of the host powder. If the particles of the host powder disintegrate during the mixing process, surfaces without proper coverage with AEROSIL® colloidal dioxide aggregates are generated leading to poor powder flow.

Figure 13
Flow of binary mixtures of microcrystalline cellulose (MCC), pre-gelatinized starch, and lactose monohydrate and different AEROSIL® products. In some cases, differences in performance between different AEROSIL® types can be observed, in other cases not.
○ = no AEROSIL® colloidal silicon dioxide
● = with 0.5 wt.% AEROSIL® 200 Pharma
● = with 0.5 wt.% AEROSIL® 200 VV Pharma
● = **with 0.5 wt.% AEROSIL® R 972 Pharma**
(Mixing conditions: 10 minutes in a free-fall mixer at 60 rpm).



AEROSIL® 200 Pharma, AEROSIL® 200 VV Pharma, AEROSIL® R 972 Pharma as well as AEROPERL® 300 Pharma can all be used as glidants for tableting powders. **Figure 13** compares the angle of repose of three common excipients as pure substances and also as binary mixtures with different AEROSIL® colloidal silicon dioxide products. All AEROSIL® types improved the powder flow over the pure excipient. Depending on the excipient, differences in the performance of different AEROSIL® types were also observed.
In general, the energy required to sufficiently break down the agglomerates of different AEROSIL® colloidal silicon dioxide particles is as follows:

AEROSIL® R 972 Pharma < AEROSIL® 200 Pharma < AEROSIL® 200 VV Pharma

Agglomerates of AEROSIL® R 972 Pharma are most easily broken up during mixing. AEROSIL® R 972 Pharma is therefore the product of choice for powder mixtures that require gentle and short mixing.

The densification process used for hydrophilic AEROSIL® 200 VV Pharma results in larger and more stable agglomerates. AEROSIL® 200 VV Pharma is therefore not recommended in the case of soft powders that need gentle mixing. In most other mixtures however, no significant difference between the mixing behavior of AEROSIL® 200 VV Pharma and AEROSIL® 200 Pharma was observed.

AEROPERL® 300 Pharma due to its spherical particle shape and high density is preferentially used in cases when the other glidants cannot be mixed into the tabletting powder due to segregation. It also offers the advantage of a high absorption capacity which can be exploited to keep the tabletting powder free of moisture induced reduction of flow properties.

Processing notes

- Determine the optimum colloidal silicon dioxide concentration (usually between 0.2 and 1.0 % by weight) empirically for each formulation
- To break up larger agglomerates, mix the entire quantity of AEROSIL® colloidal silicon dioxide to be used with a small amount of one of the other excipient powders before screening (sieving). This will prevent re-agglomeration of the AEROSIL®. AEROSIL® should not be pre-mixed with a lubricant such as magnesium stearate.
- Preferred mixers are free-fall (gravity) mixers or mechanical mixers that apply only low shear forces (e. g. plowshare mixers). The premix containing the AEROSIL® colloidal silicon dioxide should be added to the mixer first, followed by the other powdered constituents.
- If one of the constituents is particularly critical – for example it is sticky and/or has poor flowability – it may be helpful to mix it first with the total amount of AEROSIL® colloidal silicon dioxide and then add the other ingredients.
- For granules, AEROSIL® colloidal silicon dioxide can be added to the inner and/or outer phase.

Literature

Mechanism of glidants: Investigation of the effect of different colloidal silicon dioxide types on powder flow by atomic force and scanning electron microscopy.
Jonat, S., Hasenzahl, S., Gray, A., Schmidt, P. C. Journal of Pharmaceutical Sciences, 93(10) (2004) 2365-2644.

Investigation of compacted hydrophilic and hydrophobic colloidal silicon dioxides as glidants for pharmaceutical excipients.
Jonat, S., Hasenzahl, S., Drechsler, M., Albers, P., Wagner, K. W., Schmidt, P. C. Powder Technology, 141 (1-2) (2004) 31-43.

4.1.1 Influence of AEROSIL® glidants on tablet properties

Tablets must meet strict requirements concerning uniformity of weight and active ingredient content. Directly compressible powders often contain AEROSIL® colloidal silicon dioxide as a glidant to obtain the optimal powder flow necessary for high-speed tablet presses, increase throughput and reduce down-time of the press. In addition to its role as glidant, AEROSIL® colloidal silicon dioxide also provides additional benefits in many tablet formulations. Incompatibilities and sintering processes during compression can be avoided. Due to the effect AEROSIL® colloidal silicon dioxide has on the inter-particle forces the efficiency of tablet pressing can be improved, leading to more mechanically stable tablets. In many formulations, hydrophilic AEROSIL® 200 Pharma and AEROSIL® 200 VV Pharma can compensate for the hydrophobic effect of magnesium stearate and improve the dissolution of the tablet.

Figure 14 a
Effect of AEROSIL® 200 Pharma on properties of directly compressed paracetamol tablets formulation.

	Formulation 1	Formulation 2
Paracetamol (Dense Powder 5542, Covidien Mallinckrodt Chemicals Ltd.)	333.3 g	333.3 g
Microcrystalline Cellulose (Avicel PH 101, FMC Biopolymer)	54.3 g	53.1 g
Corn Starch (Caesar & Loretz GmbH)	12.0 g	12.0 g
AEROSIL® 200 Pharma	–	**1.2 g**
Mg stearate (Caesar & Loretz GmbH)	0.4 g	0.4 g
Molding pressure	26.1 kN	25.1 kN

Processing:
1 Preparation of the tablet powder mixture:
  a Pass all components except Mg stearate through a 710 µm sieve.
  b Mix the sieved powders in a tumbling mixer (Turbula T2F, Willy A. Backofen GmbH, Nidderau, Germany) for 10 min. at a speed of 67 rpm.
  c Pass Mg stearate through a 710 µm sieve and add to the powder mixture.
  d Mix the combined powders in a tumbling mixer for 5 min at a speed of 67 rpm.
2 Tablets of 12 mm diameter were pressed using a Korsch PMA single punch press with a pressure of 25–26 kN.
3 Tablets were characterized using standard equipment and methods according to the pharmacopoeia: tablet weight: Erweka TBH30MD, tablet hardness: Erweka TBH30MD, tablet disintegration: Erweka ZT131 (all of Erweka GmbH, Heusenstamm, Germany).

The effect of the addition of AEROSIL® 200 Pharma on a paracetamol formulation is shown in **Figure 14 a+b**. The marked increase in flowability of the tabletting powder not only leads to a reduction of tablet weight variation but also improves the mechanical stability of the tablets.

Processing notes

- Add AEROSIL® colloidal silicon dioxide to the precursor powder mixture to improve its flow (see Section 3.1) and tablet weight uniformity.
- Compared to traditional colloidal silicon dioxide, densified AEROSIL® 200 VV Pharma may increase the bulk and/or tapped density of a powder mixture slightly, which could lead to an increase in tablet weight when the die volume remains constant.
- If magnesium stearate is used, AEROSIL® colloidal silicon dioxide should be mixed with the other ingredients first, before mixing the magnesium stearate in briefly.

Literature

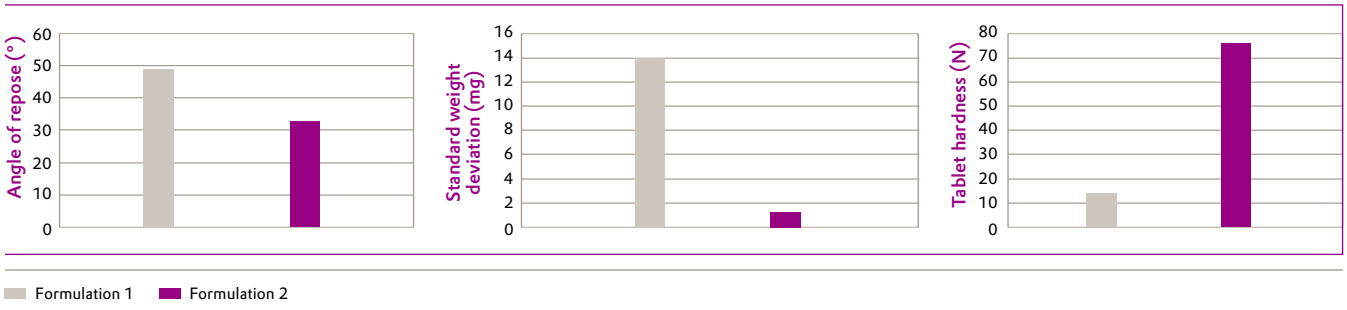
The influence of compression force on the physical characteristics of paracetamol tablets.
Tasic, L., Djuric, Z., Jovanovic, M., Pharmazie 46 (3) (1991) 226-227

Interactions in the ternary powder system microcrystalline cellulose, magnesium stearate and colloidal silica – a solubility parameter approach.
Rowe, R. C. International Journal of Pharmaceutics 45 (3) (1988) 259-261

Film forming properties of tablet lubricants during the mixing process of solids (in German).
Bolhuis, G. K., Lerk, C. F. Acta Pharmaceutica Technologica 23 (1) (1977) 13-20

Interaction of lubricants and colloidal silica during mixing with excipients
Lerk, C. F., Bolhuis, G. K., Smedema, S. S., Pharmceutica Acta Helvetica 52 (3) (1977) 33-44

Figure 14 b



4.1.2 Influence of AEROSIL® glidants on capsule properties

In order to minimize capsule weight variation, the empty capsules must always be filled with the same volume of precursor powder mixture throughout the high-speed process. It is therefore absolutely necessary to avoid non-uniform flow and the formation of powder bridges and cavities on the route between the storage container and the capsule.

For this reason, AEROSIL® colloidal silicon dioxide is used to improve the flow of powders used to fill hard capsules.

Processing notes

- Add AEROSIL® colloidal silicon dioxide to the precursor powder mixture to improve its flow and therefore capsule weight uniformity.
- Compared to traditional colloidal silicon dioxide, densified AEROSIL® 200 VV Pharma may increase the bulk and/or tapped density of a powder mixture slightly, which could lead to an increase in capsule weight when the capsule volume remains constant.

Literature

Hard gelatin capsules II. The capsule filling of powders and effects of glidant by ring filling.
Ito, K., Hitomi, M., Kaga, S., Takeya, Y. Chemical and Pharmaceutical Bulletin 17(6) (1969) 1138-1145.

4.2 Moisture activated dry granulation (MADG)

In cases where direct compression of tabletting powders is not possible, e. g. when the compactability of the powder is insufficient or the necessary uniformity in active ingredient cannot be achieved by this process, granulation processes are often used to condition the powder for the tabletting. Although these processes add to the production costs of the tablet often there is no other technical solution to produce a tablet with the required characteristics. AEROPERL® 300 Pharma can be used to minimize the financial impact of such processes as it helps to minimize the cost of granulation. Moisture activated dry granulation (MADG) – a process developed at Bristol Meyers Squibb in the 1980's – can achieve a drastic reduction of the necessary process steps compared to conventional wet granulation. As MADG uses water for granulation only very sparingly, the process does not involve any drying steps, making it ideal for solvent or heat sensitive active pharmaceutical ingredients. By carefully controlling the process conditions MADG is able to produce the desired particle size distribution of the granules without the additional sizing steps commonly required for wet granulation processes. Batch time can be minimized and the energy cost reduced, for drying the moist granules, giving MADG a clear cost advantage over the traditional processing.

AEROPERL® 300 Pharma is used in MADG to absorb and distribute the small amount of water that is used to make the binder evenly tacky in the mixture. The amount of AEROPERL® 300 Pharma used in the process depends on the necessary binder and therefore water concentration used in the formulation. Usually as little as 1.5 wt.% of AEROPERL® 300 Pharma is sufficient if the water used is 2 wt.% or less.

Processing notes

- Follow the general procedure of I. Ullah as published.
- AEROPERL® 300 Pharma addition should be at the same or slightly lower level than the dosage of the water added to render the binder tacky.
- Add AEROPERL® 300 Pharma before adding the lubricant.

Literature

Moisture-activated dry granulation: a general process.
Ullah, I., Corrao, R.G., Lipper, R.A.. Pharmaceut. Technol. (9) (1987) 48.

Moisture-activated dry granulation, Part 1: a guide to excipient and equipment selection and formulation development. *Ullah, I., Wang, J., Chang, S.-Y., Wiley, G.J., Jain, N.B.,Kiang, S.. Pharmaceut. Technol. (11) (2009) 62.*

Moisture-activated dry granulation, Part 2: the effects of formulation ingredients and manufacturing process variables on granulation quality attributes.
Ullah, I., Wang, J., Chang, S.-Y., Wiley, G.J., Guo, H., Kiang, S., Jain, N.B.,. Pharmaceut. Technol. (12) (2009) 42.

Comparison of moisture-activated dry granulation process with conventional granulation methods for sematilide hydrochloride tablets.
Chen, C.-M., Alli, D., Igga, M.R., Czeisler, J.L.. Drug Develop. Ind. Pharmacy 16(3) (1990) 379.

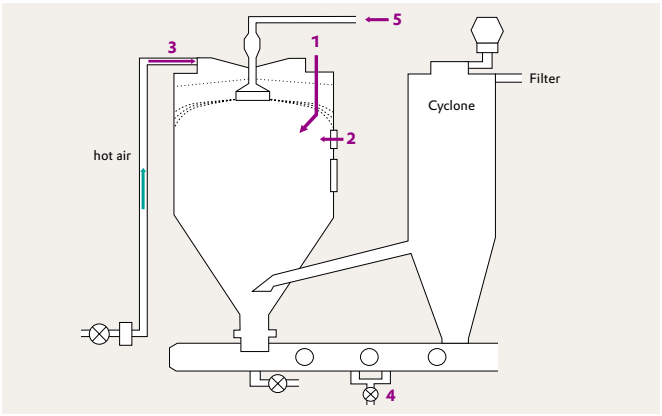
4.3 Spray drying and spray granulation

Spray drying and spray granulation processes are used extensively to produce biopolymers for pharmaceutical use e. g. starch and lactose products but have found only limited use in pharmaceutical production. Spray drying can be used for production of multi vitamin preparations and in the preparation of biological pharmaceuticals. The process can also be used to encapsulate pharmaceutical preparations in a polymer shell, e. g. chitosan. AEROSIL® colloidal silicon dioxide can help to reduce downtime of such processes and lead to a better flowing spray powder. It is recommended to dose AEROSIL® 200 Pharma or AEROSIL® R 972 Pharma independently from the liquid so that the material coats the spray dried powder instead of being incorporated into the spray dried powder particles. For details please see our technical information TI 1365 "AEROSIL® and SIPERNAT® in spray drying applications" which can be downloaded from our website **www.aerosil.com**.

Literature

The adjuvants AEROSIL® 200 and Gelita-Sol-P influence on the technological characteristics of spray-dried powders from Passiflora edulis var. flavicarpa.
De Souza, K. C., Petrovick, P. R., Bassani, V. L., Ortega, G. G., Drug Development and Industrial Pharmacy 26 (3) (2000) 331-336.

Figure 15
Schematic view of a spray dryer indicating the options of AEROSIL® dosing. Preferably AEROSIL® is dosed at positions 1 or 2 separately from the liquid feed. The AEROSIL® particles then coat the spray granules, leading to better granule flow and less caking at the wall of the spray dryer. Other options would be the positions 3 or 4. If AEROSIL® is dosed together with the liquid feed at position 5 it is more likely to be incorporated into the granule than to remain at the outside of the particles.



4.4 Incorporation of liquids into a tablet formulation

For formulating a liquid pharmaceutical ingredient into tablets it is necessary to transform them into a free flowing powder. The exceptional performance of AEROPERL® 300 Pharma in this regard has already been demonstrated in chapter 3.2. Absorbing a liquid on the carrier is only the first step in creating a solid dosage form. In **Figure 16** it is shown how vitamin E acetate absorbed on AEROPERL® 300 Pharma can be included in a tablet. The flowability of the tablet powder mixture is greatly improved with the rising content of the absorbate, leading to lower tablet weight variation. The reduced tablet hardness and increased disintegration times of the tablets with high absorbate content reflect the lower binder concentrations as well as higher hydrophobicity of the tablets.

Dry absorbed emulsion is another concept that uses colloidal silicon dioxide to produce an emulsion in the form of a free flowing powder. Formulations of this kind have shown to have sustained release properties for the formulated drug. AEROPERL® 300 Pharma, AEROSIL® 300 Pharma and AEROSIL® R 972 are excipients which can be especially useful in that concept.

Literature

Granulation by roller compaction and enteric coated tablet formulation of the extract of the seeds of Glinus Lotoides loaded on AEROPERL® 300 Pharma,
Endale, A., T. Gebre-Mariam, T., Schmidt, P.C., AAPS PharmSciTech 9 (1) 2008 31–36.

Dry absorbed emulsion: 2. dissolution behaviour of an intricate formulation,
O, Bellone, C., Berard, V., Rochat-Gonthier, Pourcelot, Y., International Journal of Pharmaceutics 235 (2002) 169–178.

Dry absorbed emulsion: 1. characterization of an intricate physicochemical structure,
Chambin, O, Bellone, C., Champion, D., Rochat-Gonthier, Pourcelot, Y., Journal of Pharmaceutical Sciences 89 (8) 2000 991–999.

Figure 16
Formulation of Vitamin E acetate into a tablet.
Vitamin E acetate (BASF) was loaded on AEROPERL® 300 Pharma in a liquid to carrier ratio of 1 : 1. The absorbate was mixed with Avicel PH 101 (FMC Biopolymer Corp.) in ratios of 10 : 90, 30 : 70, 50 : 50 and 70 : 30 by weight, both components sieved through a 710 µm mesh and mixed in a Turbula T2F free fall mixer for 10 min at 67 rpm. 1 wt.% Mg stearate was added, followed by mixing at 67 rpm for an additional 5 min. Tablets of 12 mm diameter were pressed from the mixture by a Korsch PMA 3 single punch press (Korsch AG, Germany) with a pressure of 9 kN. Tablets were characterized according to pharmacopoeia methods using Erweka TBH30MD and ZT121 (Erweka GmbH, Germany) instruments.

Figure 16 a
Flowability of the tablet powder mixture

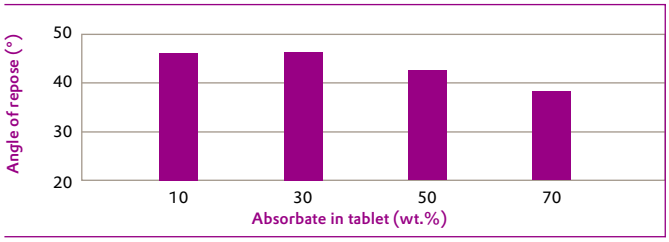


Figure 16 b
Tablet weight variation

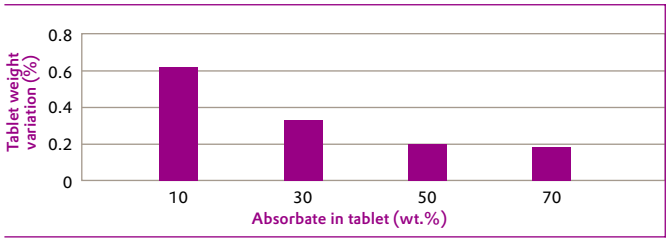


Figure 16 c
Tablet hardness

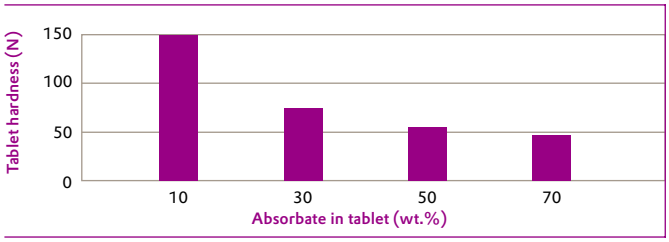
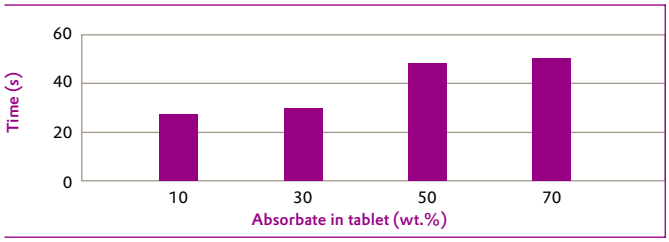


Figure 16 d
Tablet dissolution time



4.5 Improving the dissolution of active ingredients

The majority of newly developed active pharmaceutical ingredients are more hydrophobic than traditional drugs and so formulating them into a therapeutically active dosage form can become challenging. Some API's although being highly potent drugs never make it to the market as it is impossible to formulate them into a drug form with suitable bioavailability. Different strategies have been proposed to increase the solubility of such drugs which according to the biopharmaceutics classification system (BCS) fall into class II (low solubility, high permeability). AEROSIL® and AEROPERL® colloidal silicon dioxide can help with many of the proposed strategies.

API micronisation

Decreasing the particle size will increase the surface area of a given quantity of the crystalline API and may thereby increase the dissolution rate. AEROSIL® 200 Pharma and AEROSIL® R 972 Pharma can be used in the grinding process of API's that cannot be obtained in the right particle size in crystallization to improve the flow properties of the milled API.

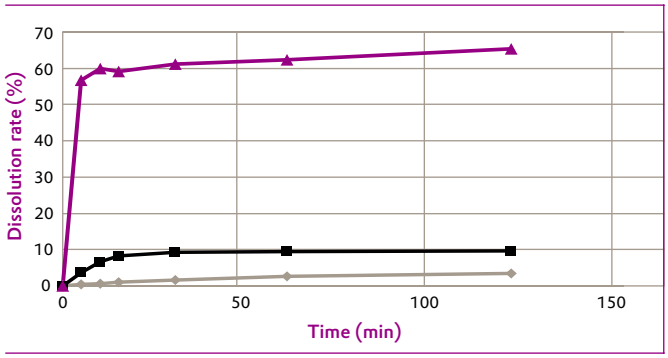
Solid dispersion

The absorption of API's of low solubility on inert carriers has become an important strategy to increase the bioavailability of BCS Class II drugs. 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. Techniques utilizing specifically tailored ordered mesoporous silica carriers can be found in the literature. Unfortunately, most of these silica materials are not available on a commercial scale and at reasonable costs.

AEROPERL® 300 Pharma is an inert and highly absorptive carrier available in commercial quantities and at reasonable prices and therefore is a viable alternative for this formulation strategy.

In **Figure 17** it is demonstrated how AEROPERL® 300 Pharma can be used to increase the solubility of the poorly soluble API itraconazole[5]. In this study itraconazol formulated with d-α-tocopheryl polyethylenglycol 1000 succinate (TPGS) as an excipient surfactant as well as with TPGS and AEROPERL® 300 Pharma were tested for their dissolution behavior in acidic solution mimicking the conditions in the stomach. Dissolution of the AEROPERL® 300 Pharma containing formulation was about 10 times that of the original drug.

Figure 17
Dissolution behavior of itraconazole in aqueous 0.,1 N HCl solution for three different formulations.
Formulation 1 (◆): pure intraconazole (100 mg).
Formulation 2 (■): itraconazol (100 mg) dispersed in molten TPGS (100 mg).
Formulation 3 (▲): itraconazole (100 mg) and TPGS (100 mg) were dissolved in alcoholic HCl, the solution absorbed on AEROPERL® 300 Pharma (2000 mg) and the solvent removed at 50°C.



Liquisolid formulations
In the liquisolid approach API's of poor water solubility are dissolved or dispersed in a water miscible, non-volatile solvent and then that solution is absorbed on an inert carrier. The absorbates need to be coated with AEROSIL® 200 Pharma to absorb any leaching liquid and increase their flowability to be able to process them in direct compression tabletting. By dissolving the drug barriers to dissolution such as the crystal lattice and wetting the API surface, time for solubilization can be dramatically reduced.

Solid self-nanoemulsifying drug delivery systems
Colloidal silicon dioxide such as AEROPERL® 300 Pharma can be used as a carrier for solid self-nanoemulsifying drug delivery systems (S-SNEDDS), enabling the processing of such liquid preparations into solid dosage forms. Self-nano-emulsifying drug delivery systems spontaneously form an emulsion in the nano-scale range if exposed to an aqueous environment. The liquid formulations consist of oil, surfactant, drug and coemulsifier or solubilizer and have been reported to be able to improve the bioavailability of API's with low solubility. Formulating these systems into a solid dosage form requires absorbing them on an inert carrier that does not interfere with the unique features of this formulation approach.

[5] Study conducted by J. Dressman, A . Fuchs, Goethe University Frankfurt. Itraconazol is a slightly alkaline antifungal drug.

Literature

Solid dispersion
Dissolution rate improvement of poorly water-soluble drugs obtained by adsorbing solutions of drugs in hydrophilic solvents onto high surface area carriers,
Friedrich, H., Fussnegger, B., Kolter, K., Bodmeier, R., European Journal of Pharmaceutics and Biopharmaceutics 62 (2006) 171–177.

Liquisolid
Enhanced dissolution rate of glipizide by a liquisolid technique,
Mahajan, H.S., Dhamne, M.R., Gattani, S.G., Rasal, A.D., Shaikh, H.T., International Journal of Pharmaceutical Sciences and Nanotechnology, 3 (4) (2011) 1205–1213.

Liquisolid technique for enhancement of dissolution properties of bromhexidine hydrochloride,
Gubbi, S., Jarag, R, Research Journal of Pharmaceuticals and Technology, 2 (2) (2009) 382–386.
Improvement of dissolution properties of Carbamazepine through application of the liquisolid tablet technique,
Tayel, S.A., Iman, I.S., Louis, D., European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 342–347.

Solid self-nanoemulsifying drug delivery systems (S-SNEDDS)
Solid self-nanoemulsifying drug delivery system (S-SNEDDS) containing phosphatidylchloine for enhanced bioavailability of highly lipophilic bioactive carotenoid lutein,
Shanmugam, S., Baskaran, R. , Balakrishnan, P., Thapa, P., Yong, C.S., Yoo, B.K., European Journal of Pharmaceutics and Biopharmaceutics 79 (2011) 250–257.

Effects of solid carriers on the crystalline properties, dissolution and bioavailability of flurbiprofen in solid self-nanoemulsifying drug delivery systems (solid SNEDDS),
J.H. Kang, D.H. Oh, Y.-K. Yong, H.-G. Choi, European Journal of Pharmaceutics and Biopharmaceutics 80 (2012) 289–297.

4.6 Tablet coating

AEROSIL® colloidal silicon dioxide can make tablet coating processes considerably less time-consuming and more economical. In conventional multilayer processes it is added to the build-up powder and/or to the pigment suspension. The build-up powder thus acquires good flow properties and can be distributed better on the cores. The tablet cores dry faster so that the individual coats can be applied at shorter time intervals. The mechanical strength – especially at the edges – is increased, and twinning is prevented. The adsorption capacity of AEROSIL® colloidal silicon dioxide also ensures that the cores are protected from moisture during coating. AEROSIL® colloidal silicon dioxide also stabilizes pigment suspensions and contributes to the uniform texture of coated tablets.

If – as in most modern coating processes – no build-up powder is employed and only a highly concentrated coating suspension is used, AEROSIL® colloidal silicon dioxide can still be used to stabilize the pigment suspension and improve the texture of the coating. AEROSIL® colloidal silicon dioxide can also be used to fine tune the release properties of tablets coated with EUDRAGIT® polymer.

Processing notes

- Build-up powder: AEROSIL® 200 Pharma, AEROSIL® 200 VV Pharma or AEROSIL® 300 Pharma at levels of 10 to 15 wt.%.
- Pigment suspensions: AEROSIL® 200 Pharma at levels of 0.5 to 2.0 wt.%.
- In all cases: the optimal quantity must be determined separately for each formulation.

Literature

Influence of fumed silicon dioxide on the stabilization of EUDRAGIT® RS/RL 30 D film coated theophylline pellets, *Kucera, S. A., Stimpel, D., Shah, N. H., Malick, W., Infeld, M. H., McGinity, J. W., Pharmaceutical Development and Technology 13 (2008) 245 – 253.*

5 Semisolid dosage forms

5.1 Gels, ointments, and salves

AEROSIL® colloidal silicon dioxide can be used to create gels with a very good spreading behavior if finely dispersed in pharmaceutical oils. These gels are distinguished by a high viscosity that has little dependence on temperature, and by a pronounced thixotropic behavior. Which AEROSIL® colloidal silicon dioxide type to be used and the necessary concentration needs to be determined experimentally. Generally, AEROSIL® 200 Pharma and AEROSIL® 300 Pharma give higher increases in viscosity than the same concentration of AEROSIL® R 972.
AEROSIL® 300 Pharma in the majority of cases is the most effective thickener. But the achievable viscosity increase is also dependent on the oil matrix. Flow diagrams of gels prepared from different oils with 3 wt.% of AEROSIL® 300 Pharma and AEROSIL® R 972 Pharma are shown in **Figure 18**.

AEROSIL® 300 Pharma is clearly the more efficient thickener in dimethicone as well as in paraffin oil. AEROSIL® R 972 Pharma does not form any thixotropic gel with dimethicone but gives at least some thickening effect in paraffin oil. In a polar liquid such as glycerine only AEROSIL® R 972 Pharma results in a thixotropic gel while AEROSIL® 300 Pharma does not lead to gel formation.

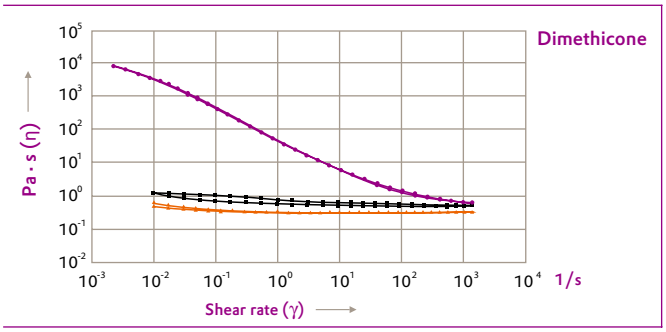
Although the best AEROSIL® colloidal silicon dioxide type needs to be determined for any given formulation, as a rule of thumb, AEROSIL® 300 Pharma mostly works best in non-polar oils while AEROSIL® R 972 Pharma is the most promising candidate for polar liquids. The higher the AEROSIL® colloidal silicon dioxide concentration the more viscous the gel gets.

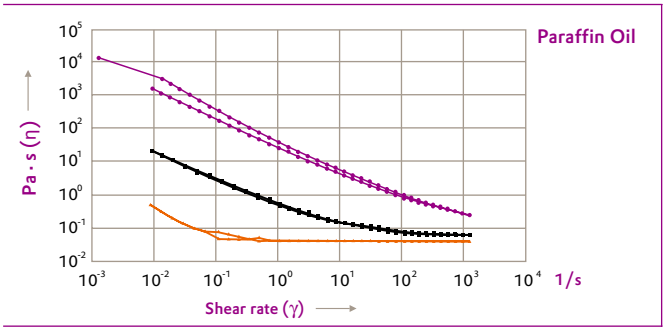
Only AEROSIL® R 972 Pharma is suitable for thickening the oil phase of an emulsion. The hydrophilic grades will migrate into the water phase and won't produce a sustained thickening effect.

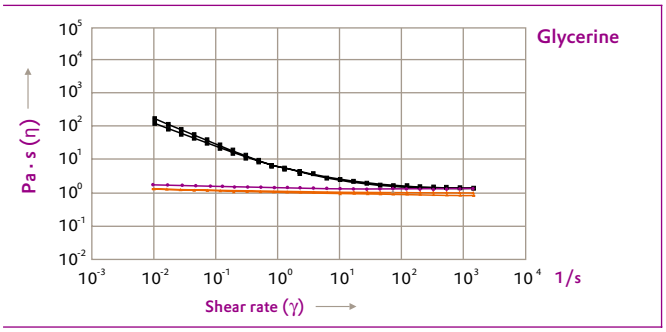
Transparent gels can be produced if the refractive index of the oil is near to that of AEROSIL® colloidal silicon dioxide (1.45).

AEROSIL® colloidal silicon dioxide has also been reported to be a very efficient stabilizer of pharmaceutical emulsions.

Figure 18
Flow diagrams of gels prepared from different oils using AEROSIL® 300 Pharma and AEROSIL® R 972 Pharma ▲ pure oil, ■ oil with 3 wt.% AEROSIL® R 972 Pharma, ● oil with 3 wt.% AEROSIL® 300 Pharma. The AEROSIL® colloidal dioxide was dispersed in the liquid using a dissolver (Dispermat, VWA Getzmann GmbH, Reichshof, Germany) with a speed of 21 m/s for seven minutes. The flow diagrams were measured with a Physica MCR 300 rheometer (Anon Paar GmbH, Graz, Austria) employing a CC27 cylinder measuring system.







Processing notes

- High shear mixers are required to disperse AEROSIL® colloidal silicon dioxide in oils. Rotor-stator or dissolver systems with a tip speed (circumference speed) of 15 m/ sec or more are recommended.
- Always calculate the maximum shear rate that can be achieved on large-scale equipment first and do not exceed this when working with laboratory machines.
- Tip speed is more important than dispersion time.
- Begin with a concentration of 3 wt.% AEROSIL® colloidal silicon dioxide and adjust this up or down, depending on the viscosity desired.

Literature

Investigation of salves containing highly disperse silicon dioxide (in German).
Töricht, E., Erös, I., Pharmazie, 32 (2) (1977) 109–113

5.2 Suppositories

In suppositories AEROSIL® 200 Pharma colloidal silicon dioxide stabilizes the distribution of active ingredients that are either insoluble or poorly-soluble in a suppository base (suspension suppositories). By keeping the API uniformly distributed in the still soft suppository base a homogeneous API concentration in the finished suppository is achieved.

In addition, AEROSIL® colloidal silicon dioxide increases the softening point of the suppository base without changing its melting point, an important property for improving stability in warm climates. The consistency and mechanical stability of the finished suppository are also improved. If active ingredients cause an unwanted reduction in the melting point of the suppository base (especially solution suppositories), this can be prevented by initially "triturating" the substance with AEROSIL® 200 Pharma colloidal silicon dioxide.

AEROSIL® colloidal silicon dioxide may modify the release of active ingredient from suppository formulations.

Processing notes

- Concentrations of 0.5 to 2.0 % by weight are recommended for suppositories.
- Powdered, liquid or pasty active ingredients should be ground or triturated with AEROSIL® 200 Pharma first and, where appropriate, sieved before they are introduced into the molten base.
- Medium shear mixers should be used for semisolid products.
- Add AEROSIL® 200 Pharma first to ensure maximum mixing time.

Literature

Effect of surface reactions between colloidal silicon dioxide and fat-based drug-containing suppositories, I. Influence of colloidal silicon dioxide on rheological behavior (in German).
Haggag, A., Liebl, H., Rupprecht, H., Deutsche Apotheker Zeitung, 118 (11) (1978) 395–398

The influence of additives on a suppository base (in German).
Ritsche, W., Pharmazeutische Industrie 23 (1961) 275–282

5.3 Transdermal therapy systems (TTS)

AEROSIL® 200 Pharma colloidal silicon dioxide can be used both in membrane-controlled and in matrix-controlled transdermal therapy systems as a gel former or to increase the storage and thermal stability. It can also be used as a carrier or absorbent for active ingredients and to improve incorporation or release characteristics.

Processing notes

- AEROSIL® 200 Pharma is recommended at a concentration of between 1 and 5 % by weight.
- Disperse the colloidal silicon dioxide in the medium that contains the active ingredient, polymer (adhesive) and/or other excipients.

Literature

Transdermales therapeutisches System mit hochdispersem Siliziumdioxid.
Klokkers, K., Kramer, K. T., Patent DE 100 33 853 A1, submitted 12 July 2000, pub!ished 31 January 2002; Patent EP 1 301 179 A2, submitted 12 July 2001; Patent WO 02/03969 A2 pubished 17 January 2002

Matrice pour la diffusion continue et progressive d'un principe actif par voie transcutanée.
Florent, P., Patent FR 2 547 502 A1, submitted 15 June 1983

6 Liquid dosage forms

6.1 Suspensions

AEROSIL® 300 Pharma and AEROSIL® R 972 can effectively stabilize dispersions of solids in liquids. AEROSIL® colloidal silicon dioxide by this effect is able to prevent the formation of hard sediments in liquid suspensions. Since each AEROSIL® pharmaceutical grade imparts a unique rheology, it is important to select the most suitable product which provides the desired rheology when mixed into the liquid phase.

The described effect is especially important for pigment suspensions employed for tablet coating.

AEROSIL® 200 Pharma and AEROSIL® 300 Pharma may be used in redispersible powders as a wetting agent.

Processing note

- Use AEROSIL® 200 Pharma or AEROSIL® R 972 Pharma at a concentration of 0.5 to 3 % by weight.

7 Product safety and regulatory information

AEROSIL® colloidal silicon dioxide has been safely used as a pharmaceutical excipient for over 40 years. Current good manufacturing practices as defined for inert pharmaceutical excipients by International Pharmaceutical Excipients Council (IPEC) are followed during the production of AEROSIL® pharmaceutical grades. As for all excipients, however, it is the ultimate responsibility of the pharmaceutical manufacturer to determine the ultimate suitability of AEROSIL® as an excipient in a particular formulation.

7.1 Product safety information

AEROSIL® colloidal silicon dioxide is not harmful when administered orally or topically. It is not irritating to skin and eyes and is unlikely to be absorbed from the gastrointestinal tract in significant amounts. However, it should not be administered parenterally, because untoward tissue reactions or the formation of granulomas could occur.[6] Unlike crystalline silicates, synthetic amorphous AEROSIL® and AEROPERL® colloidal silicon dioxide does not cause silicosis, however it is still not recommended for drug delivery by inhalation. AEROSIL® and AEROPERL® colloidal silicon dioxide is inert toward most active drug ingredients and excipients, incompatibilities are extremely rare. Adsorption of active components is possible, however the amounts are typically low and the process is reversible.[7]

[6] A. Wade, P. J. Weller (Eds.), Handbook of Pharmaceutical Excipients, 2nd Edition, American Pharmaceutical Association, Washington, The Pharmaceutical Press, London, 1994

[7] On the adsorption of drug substances on AEROSIL® in tablets (in German). Gstirner, E., Knipp, J. Pharmazeutische Industrie 24 (1962) 475-48

Table 4
Toxicological data for hydrophilic AEROSIL® 200 Pharma, AEROSIL® 200 VV Pharma, AEROSIL® 300 Pharma and AEROPERL® 300 Pharma

Test	Result
Acute oral toxicity, rat	LD_{50} > 10,000 mg/kg
Acute inhalation toxicity, rat	LC_0: 0.139 mg/l / 4 h (maximum attainable concentration in air. No death occured)
Acute dermal toxicity, rabbit	LD_{50} > 5000 mg/kg bw
Eye irritation, rabbit	not irritating
Skin irritation, rabbit	not irritating
Gentoxicity (in vitro/in vivo)	No evidence of genotoxic potential
Carcinogenicity	No increase in tumor rate
Reproductive toxicity	No findings
Human experience	Silicosis or other substance related illnesses were not observed

Table 5
Toxicological data for hydrophobic AEROSIL® R 972 Pharma

Test	Result
Acute oral toxicity, rat	LD_{50} > 5,000 mg/kg
Acute inhalative toxicity, rat	LC: 0.477 mg/l / 4 h (maximum attainable concentration in air. No death occured)
Eye irritation, rabbit	not irritating
Skin irritation, rabbit	not irritating
Genotoxicity (in vitro)	No evidence of genotoxic potential
Carcinogenicity	No negative effects
Reproductive toxicity	No findings
Human experience	Silicosis or other substance related illnesses were not observed

The surface modification process of the hydrophobic AEROSIL® R 972 Pharma (see section 2.3) does not significantly affect the toxicological properties of the parent silica.

Before working with any product, read its Safety Data Sheet carefully. Safety Data Sheets (also known as MSDS) for AEROSIL® products are available for many countries and in different languages. Safety data sheets may be obtained from your local Evonik Industries sales representative or from our website (www.aerosil.com), after registration.

7.2 Pharmaceutical regulatory status

Table 7 lists the compendial compliance of all AEROSIL® and AEROPERL® pharmaceutical grade products. Colloidal silicon dioxide is included in the FDA Inactive Ingredients Guide. All our pharma products are included in our FDA Drug Master File (DMF) 1115 (Type IV) for inactive ingredients. Drug master files for inactive ingredients (excipients) are completely confidential and do not have an open part. Upon request we can issue a Letter of Authorization to the FDA for consideration of DMF 1115 in a customer's new drug application (NDA or ANDA).

Table 6
Compendial compliance of pharmaceutical grade AEROSIL® and AEROPERL® colloidal silicon dioxide products

Product	Tapped Densitiy (g/l)	DMF (Type IV)	Important Pharmacopoeia Monographs Fulfilled	Comments
AEROSIL® 200 Pharma	approx. 50	1115	• Silica, Colloidal Anhydrous (Ph. Eur.) • Colloidal Silicon Dioxide (USP/NF) • Light Anhydrous Silicic Acid (JP)	
AEROSIL® 200 VV Pharma (densified)	approx. 120	1115	• Silica, Colloidal Anhydrous (Ph. Eur.) • Colloidal Silicon Dioxide (USP/NF)	Generally fulfills JP except for the volume test. No JP or JPE testing is performed
AEROSIL 300 Pharma	approx. 50	1115	• Silica, Colloidal Anhydrous (Ph. Eur.) • Colloidal Silicon Dioxide (USP/NF) • Light Anhydrous Silicic Acid (JP)	
AEROSIL® R 972 Pharma	approx. 50	1115	• Silica, Hydrophobic Colloidal (Ph. Eur.) • Silica, Hydrophobic Colloidal (USP/NF)	No JP monograph for hydrophobic silica exists at this time.
AEROPERL® 300 Pharma	approx. 280	1115	• Silica, Colloidal Anhydrous (Ph. Eur.) • Colloidal Silicon Dioxide (USP/NF)	Generally fulfills JP except for the volume test. No JP or JPE testing is performed

Table 7
Chemical substance inventory status of AEROSIL® products

Product name	CAS-No.	Chemical name	Australia AICS	Canada DSL	China IECSC	Europe EINECS	Europe REACH	Europe C&L Inventory	Japan ENCS	Korea KECI	New Zealand NZIoC	Philippines PICCS	USA TSCA
AEROSIL® 200 Pharma **AEROSIL® 200 VV Pharma** **AEROSIL® 300 Pharma** **AEROPERL® 300 Pharma**	112945-52-5 (ex 7631-86-9)	Silicon dioxide, chemically prepared	regi-stered	regi-stered	regi-stered	231-545-4	regi-stered	notified	1-548	KE-30953 (KE-31-032)	regi-stered	regi-stered	regi-stered
AEROSIL® R 972 Pharma	68611-44-9	Silane, dichlorodi-methyl-, reaction products with silica	regi-stered	regi-stered	regi-stered	271-893-4	exemp-ted	exemp-ted	1-548/ 7-476	KE-10116	regi-stered	regi-stered	regi-stered

7.3 Other regulatory issues

AEROSIL® and AEROPERL® colloidal silicon dioxide is completely inorganic in nature. The production process does not involve plant or animal based raw materials, nor does it involve organic solvents. Standard statements available upon request contain information on BSE/TSE, GMO as well as other criteria. Kosher and Halal Certificates are also available upon request, please contact us.

7.4 Microbial contamination

Because of the high production temperatures, all AEROSIL® products are sterile immediately after manufacture. Packaging and storage of the pharmaceutical grades are performed in accordance with IPEC GMP guidelines for bulk pharmaceutical excipients. Microbiological testing is performed on random samples at regular intervals. Full pallets are shrink-wrapped to prevent contamination. We, and our partners along the logistics chain, do all that we can to ensure that AEROSIL® colloidal silicon dioxide reaches our customers without contamination. However, the unexpected can occur during shipping and storage so we recommend customers perform microbiological checks on the product before using it.

It has been reported in the literature that AEROSIL® colloidal silicon dioxide is not a source of microbial nutrition and that both gram-negative and gram-positive bacteria are unable to survive on dry AEROSIL® colloidal silicon dioxide for more than hours to days, depending on the type of bacteria.[8] The possible survival of some sporogenic microorganisms cannot be completely ruled out even under these conditions.

7.5 Packaging and Storage

AEROSIL® and AEROPERL® colloidal silicon dioxide are packaged and shipped in multi-ply bags, weights vary according to the product and region. Full pallets are shrink-wrapped at the factory.

AEROSIL® and AEROPERL® colloidal silicon dioxide are chemically stable silicon dioxides that could theoretically be stored for many years without any change in its composition. However, because of their large specific surface area they can adsorb volatile substances and moisture from the environment. Proper storage is critical to prevent external contamination of the bags (for example through dust, dirt, or mold). Bags should be inspected thoroughly before opening to prevent contamination of the product.

We recommend that AEROSIL® and AEROPERL® colloidal silicon dioxide be stored in a dry place, in sealed containers protected from volatile substances, and that they be used within two years after its date of manufacture. We also recommend that the shrink wrapping not be completely removed from the pallet, but that an opening be cut to remove only those bags immediately required, and that the opening be resealed.

[8] The behavior of bacteria in highly pure silica acid (in German) Kienholz, M. Pharmazeutische Industrie, 32 (1970) 677-679

7.6 Handling

Evonik Industries has a special team of engineers dedicated to improving the handling of AEROSIL® and AEROPERL® colloidal silicon dioxide in our customers' facilities. With proper equipment AEROSIL® and AEROPERL® products can be handled almost completely dust-free. For more information on these services, please request our Technical Bulletin Fine Particles No. 28, *The Handling of Synthetic Silica and Silicate*.

Even though AEROSIL® and AEROPERL® colloidal silicon dioxide are inert and non-toxic material, there are certain precautions that we recommend because, although not required, they improve the comfort level of persons working with it:

- The work area should be properly ventilated. In the laboratory, work with AEROSIL® and AEROPERL® products in a fume hood. Where ventilation is not available, a dust respirator is recommended at higher concentrations.
- Avoid continued excessive inhalation by using personal protective equipment.
- Wear appropriate eye protection.
- Wash hands after handling AEROSIL® and AEROPERL® products as the product may leave a dry feeling on the skin. Use of protective skin cream and/or gloves is recommended when working with AEROSIL® and AEROPERL® products.
- See the Product Safety Data Sheet for information relevant to maximum work area concentrations and other safety aspects of our products.

In addition, for safety reasons it should be noted that all dry powders such as AEROSIL® and AEROPERL® colloidal silicon dioxide can build up static electrical charges when subjected to friction during conveyance and/or mixing. When handling AEROSIL® colloidal silicon dioxide near flammable or explosive liquids, be sure to take proper safety precautions, such as electrical grounding, inert atmosphere, etc. For further information, please request our Technical Bulletin Fine Particles No. 62, *Synthetic Silica and Electrostatic Charges*.

Besides this Technical Information, other publications on AEROSIL® colloidal silicon dioxide are available upon request through our website **www.aerosil.com**. From the navigation point "Services" you may request or download additional literature. Product Information Sheets for individual products are available through "Products", then "Product Finder" and "Search by industry/effect ".

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