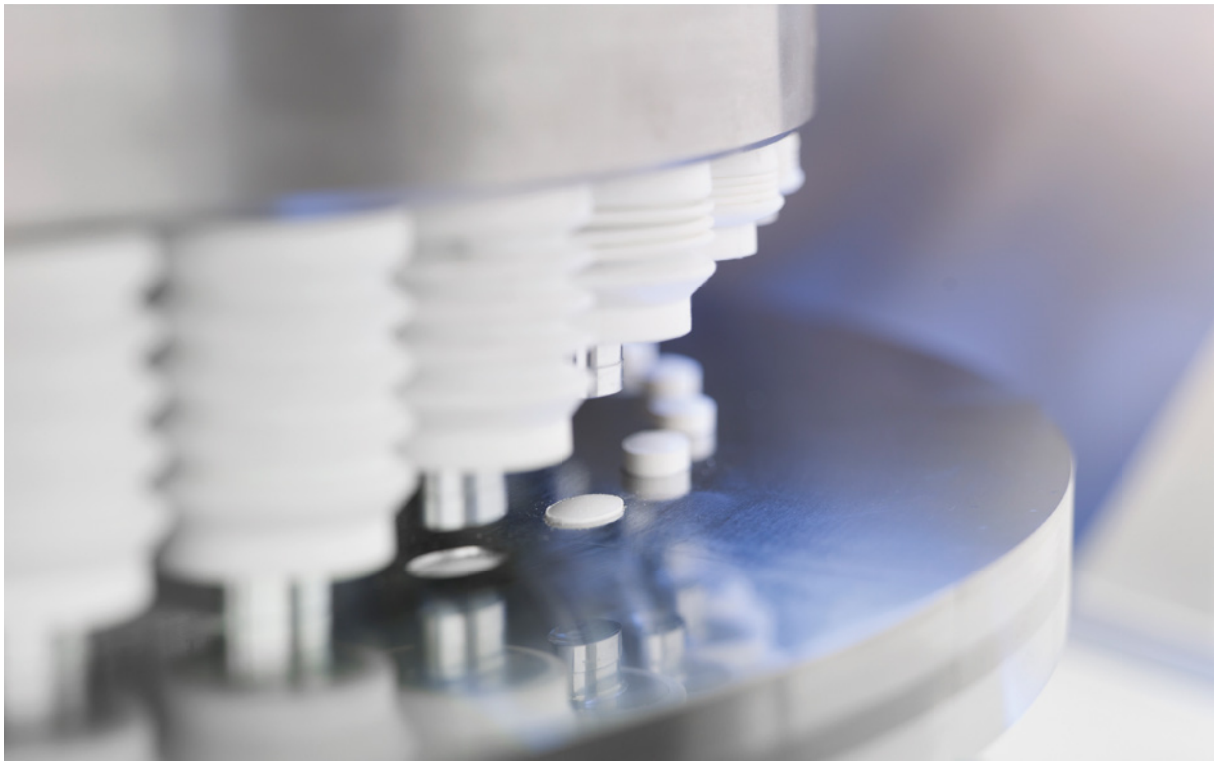
TECHNICAL INFORMATION 1424

# AEROSIL® Pharma colloidal silicon dioxide

## Designed for improved powder flow and cost efficient solid dosage form production



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# 1. Glidants: the fundament of cost efficient tablet production

Higher health care expenses due to the aging population constantly increase the cost pressure on pharmaceutical producers. The economy of production receives a stronger focus over the last few years, especially in generics manufacturing. Because of this, efficient processes like direct compression have seen a boost, since they require less processing steps and excipients in the formulation.

Successful implementation of direct compression tableting relies heavily on favorable flow conditions of the employed powder mixture[1]. Optimal powder flow is a prerequisite for highly productive tableting operations. On top of the economic factors, inadequate powder flow can lead to tablet weight variability issues and out of specification batches. AEROSIL® Pharma glidants[2] help to optimize the flow of powder, which is vital for cost efficient production of high quality tablets.

Favorable powder flow is not only a prerequisite for direct compression but also relates to other processes in the health care industry, such as:

- **Filling of capsules and sachets with pharmaceutical powders**
  Filling capsules and powder sachets requires optimal powder flow to achieve high productivity and content uniformity.

- **Automatic dosage of ingredients**
  With the rise of continuous pharmaceutical production, good powder flow is key to have favorable productivity and consistency in production.

- **Handling of APIs with small crystal size**
  Crystal micronization can be an effective way to improve the dissolution of some APIs, as well as safeguarding the dosage uniformity of formulations containing highly potent actives. However, the smaller the API crystals get, flow becomes worse and the agglomeration tendency increases. Blending AEROSIL® Pharma colloidal silicon dioxide[3] with these micronized APIs can inhibit the agglomeration, preserving the desired effect.

[1] D. McCormick, Evolutions in direct compression, Pharmaceutical Technology 29 (4) (2005) 52 – 62.
[2] The term “glidant” is often used to describe different functions in the tableting processes. Materials such as talc and stearates are described as a glidant, although their main function is lubrication to reduce friction between the tablet and the die walls in the ejection step. In this brochure, glidant is solely meant to describe the function of a flow aid in a compression mixture or other powder.
[3] This brochure uses the term "colloidal silicon dioxide" in the sense of the USP/NF monograph for silica products produced by flame hydrolysis. Products of this kind are also known as fumed silica in other industries. The products are not to be mistaken as “colloidal silica” or “silica sol”, which represents dispersions of spherical silica particles in a fluid (typically water). For an overview of the different forms of silica please refer to the chapter "Silica" in Ullmann's Encyclopaedia of Industrial Chemistry, Wiley and Sons."

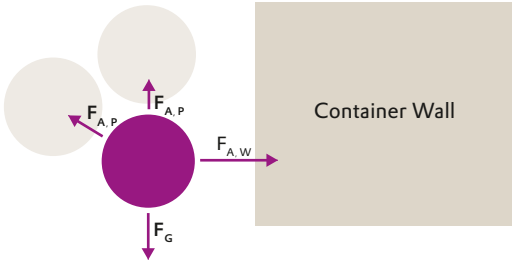
## 1.1. THEORETICAL MODELS FOR POWDER FLOW

As favorable powder flow is a prerequisite for the production of solid dosage forms, it is important to understand the reasons why the flow of powders can be impeded. Typical models for the flow properties of powders look at the balance of forces that a particle experiences in a defined situation. Most models use the gravitational forces acting on the particle as the driver for powder flow. Attractive forces between the particles in the powder and between the particle and the container wall oppose the gravitational forces (see Figure 1).

Powders flow well if the gravitational forces are higher than the sum of the counteracting attractive forces. Typically, this is the case for powders with large particles and high particle density. For smaller and less dense particles, powder flowability deteriorates if the particle size falls below a critical value[4].

The attractive forces can be due to van der Waals interactions, electrostatic (Coulomb) forces in dry powders, or liquid bridges between the particles if the powder is moist or hygroscopic. For dry powders at rest, with short inter-particle distances, van der Waals forces are the dominating attractions. Hamaker described these attractive forces for ideally spherical particles with the well-known equation given in Figure 2.

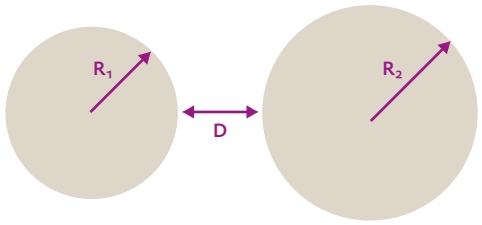
**FIGURE 1:** Forces acting on a particle




$F_G$: Gravitational force
$F_{A,P}$: Attractive particle/particle interations
$F_{A,W}$: Attractive interation between particle and container wall

In moist or hygroscopic powders, liquids can gather in the dimples or pores of particles, and thereby result in the formation of inter-particle bridges. These bridges exert especially high attractive forces between the particles (figure 3).

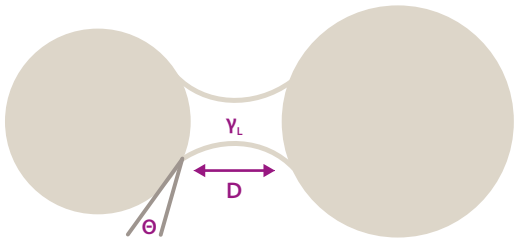
**FIGURE 2:** Hamaker equations for van der Waals forces between spherical dry powder particles.




$$F_{vdW} = \frac{A}{6D^2} \times \frac{R_1 R_2}{R_1 + R_2}$$

A is the material specific Hamaker constant[5], which typically lies in a range between $10^{-18}$ and $10^{-20}$ J.

**FIGURE 3:** Attractive forces in moist or hygroscopic materials if liquid bridges are formed $\gamma_L$ represents the surface tension of the liquid.




$F = f(\Theta, \gamma_L, \text{particle geometry}, D)$
$\gamma_L$: Interfacial tension of Liquid

[4] I. Zimmermann, M. Eber, K. Meyer; Nanomaterials as flow regulators in dry powders, Z. Physik 218 (2004) 51 – 102.
[5] H.C. Hamaker, The London van der Waals attraction between spherical particles, Physica 4 (10) (1937) 1058 –1072.

Different approaches to calculate these forces have been discussed in the literature, both for the adhesion between two spheres[6] as well as those between a sphere and a plate[7,8]. Whatever the models are, there is agreement that the forces are dependent on the particle distance, the particle surface and properties of the liquids (surface tension, viscosity).

AEROSIL® Pharma glidants can decrease the van der Waals forces, as well as, eliminate liquid bridges between host powder particles. When it is mixed with the host powder, AEROSIL® Pharma particles adsorb on the surface of the host particles. As shown in figure 4, the distance between the host powder particles increases which leads to a decrease of the inter-particle van der Waals forces and an improved flow of the host powder. In moist or hygroscopic powders AEROSIL® Pharma colloidal silicon dioxide absorbs the liquid acting as a glue between the host powder particles, thereby improving powder flow. Such a situation is shown in figure 5.

**FIGURE 4:** Powder flow enhancing mechanism of AEROSIL® Pharma glidants in dry powders

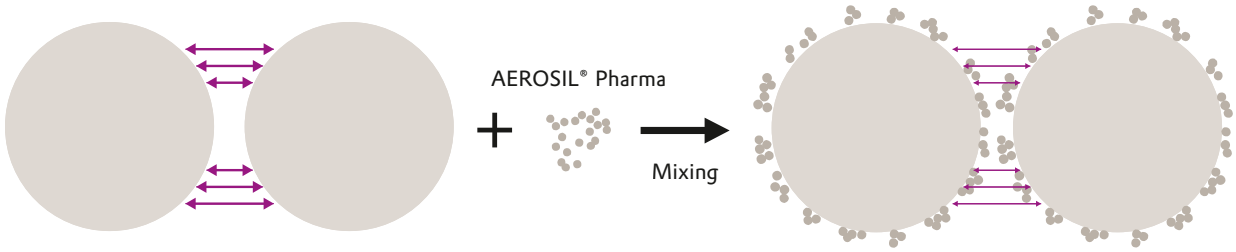
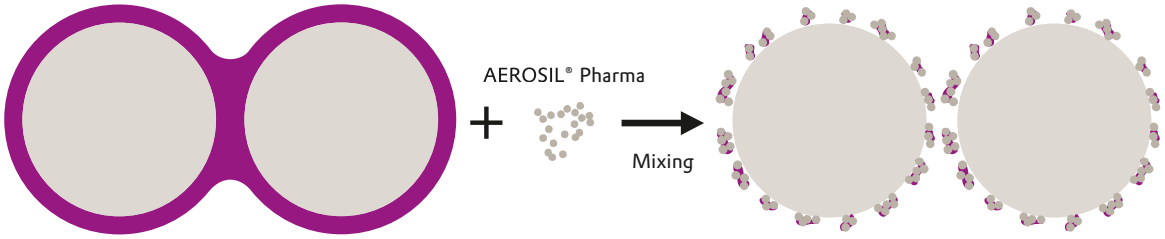



**FIGURE 5:** Powder flow enhancing mechanism of AEROSIL® Pharma glidants in moist or hygroscopic powders




[6] T Gillespie, W.J Settineri, The effect of capillary liquid on the force of adhesion between spherical solid particles, J. Colloid and Interface Science 24 (1967) 199 – 202. See also the comments on this paper by N.L. Cross, R. G. Picknet (J. Colloid and Interface Science 26 (1968) 247 – 249) and H.M. Princen (J. Colloid and Interface Science 26 (1968) 249 – 253).
[7] K. Hotta, K. Takeda, K. Iinoya, The capillary binding force of a liquid bridge, Powder Technology 10 (1974) 231 – 242.
[8] A. Marmur, Tip-surface capillary interactions, Langmuir 9 (7) (1993) 1922–1926.

# 2. Spotlight on AEROSIL® colloidal silicon dioxide glidants

AEROSIL® Pharma colloidal silicon dioxide is a preferred choice in pharmaceutical manufacturing due to its high purity, consistent quality and efficiency. Table 1 gives an overview of all AEROSIL® and AEROPERL® Pharma products with their characteristic physico-chemical properties and their compliance to the different pharmacopeia monographs.

**TABLE 1:** Physico-chemical properties of AEROSIL® and AEROPERL® Pharma colloidal silicon dioxide

| | AEROSIL® 200 Pharma | AEROSIL® 200 VV Pharma | AEROSIL® 300 Pharma | AEROSIL® R 972 Pharma | AEROPERL® 300 Pharma |
|---|---|---|---|---|---|
| **CHARACTER** | | | | | |
| Type | Powder | Densified powder | Powder | Powder | Granulate |
| Behavior in water | Hydrophilic | Hydrophilic | Hydrophilic | Hydrophobic | Hydrophilic |
| **TYPICAL PHYSICO-CHEMICAL PROPERTIES*** | | | | | |
| Specific surface area (BET, $m^2/g$) | 175–225 | 175–225 | 270–330 | 90–130 | 260–320 |
| Tamped density (g/l) | Appr. 50 | Appr. 120 | Appr. 50 | Appr. 50 | Appr. 280 |
| pH | 3.5–5.5 | 3.5–5.5 | 3.5–5.5 | – | 3.5–5.5 |
| **PHARMACOPEIA COMPLIANCE** | | | | | |
| Europe (Ph. Eur.) | Silica, colloidal anhydrous | Silica, colloidal anhydrous | Silica, colloidal anhydrous | Silica, hydrophobic colloidal | Silica, colloidal anhydrous |
| USP/NF | Colloidal Silicon Dioxide | Colloidal Silicon Dioxide | Colloidal Silicon Dioxide | Hydrophobic Colloidal Silica | Colloidal Silicon Dioxide |
| JP | Light anhydrous silicic acid | – | Light anhydrous silicic acid | – | – |
| India (IP) | Colloidal Silicon Dioxide | – | – | – | – |

* Typical values for informational purposes only.

**AEROSIL® 200 Pharma** is the traditional glidant, helping to obtain the optimal powder flow required by today's high-speed tablet presses. Since the first time AEROSIL® 200 Pharma was used as a glidant[9], challenges in formulating solid dosage forms have become more complex. Tablet powders of different average particle size, composition and moisture sensitivity are common in the industry, requiring specialized products to be able to compete in the increasingly cost sensitive health care environment. To support the industry to cope with these challenges, Evonik has broadened its AEROSIL® Pharma portfolio to provide optimal glidants for any tableting process.

**AEROSIL® 200 VV Pharma** is the glidant solution for customers facing limitations in their storage facility. This product is a densified version of AEROSIL® 200 Pharma that, on top of requiring less than half of the storage space, also creates less than half of the packing waste. The densification also leads to a less dusty product with stronger agglomerates, which makes it a preferred free flow additive for host powders with a higher particle size.

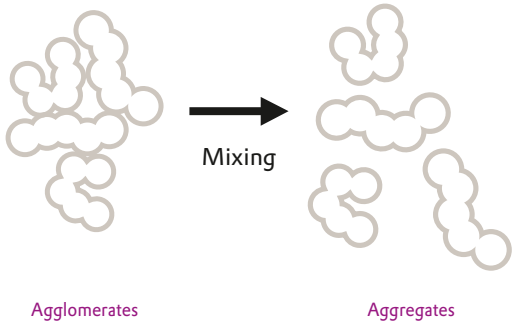
**AEROSIL® 300 Pharma** features an exceptionally high specific surface area. The material therefore has particularly favorable anti-caking performance. The addition of AEROSIL® 300 Pharma has a strong influence on tablet stabilities.

**AEROSIL® R 972 Pharma** is a surface modified fumed silica that, different from the other AEROSIL® Pharma colloidal silicon dioxides, is water repellent. The hydrophobic nature of the material helps when working with water sensitive APIs[10], improving the storage stability[11] or influencing the disintegration time of oral dosage forms. This product is also exceptionally good at keeping API particles from agglomerating.

**AEROPERL® 300 Pharma** is not a typical glidant but due to its porosity can be used as a carrier, e. g. to assist with poorly soluble active pharmaceutical ingredients.

All AEROSIL® Pharma products feature an agglomerated aggregate structure. The agglomerates found in the original bags are broken up during mixing with the other components of the formulation. The higher the applied shear forces are during the mixing and the longer the mixing time is, the further the agglomerates are broken up to the final aggregate stage.

**FIGURE 6:** Agglomerate structure of AEROSIL® Pharma products




[9] R. Tawashi, On direct compression of tablets, Pharmazeutische Industrie 26 (1964) 682–685 [in German].
[10] Moisture-activated granulation process, Krka Tovarna Zdravil DD, WO 2010089105.
[11] T.A. Ahmed, K.M. El-Say, M.F. Mahmoud, A.M. Samy, A.A. Badawi, Miconazole nitrate oral disintegrating tablets: in vivo performance and stability study, AAPS Pharm. Sci. Tech. 13 (3) (2012) 760 – 771.

# 3. Powder flow enhancement with AEROSIL® Pharma colloidal silicon dioxide

**For taking full advantage of the powder flow enhancing effect of AEROSIL® colloidal silicon dioxide some factors need to be taken into account:**

- Composition of the host powder
- Particle size, shape and structure of the host powder
- Mixing process to be employed
- AEROSIL® Pharma colloidal silicon dioxide type and concentration

In order to illustrate these points, pharmaceutical lactose[12] (Granulac®, Meggle Group, Germany) and microcrystalline cellulose (Vivapur®, JRS Pharma GmbH, & Co. KG, Germany) were analyzed as models for host powders mixed with AEROSIL® Pharma glidants. The lactose is composed of edged, non-porous particles that cause the material to have a comparatively high bulk density (see figure 7). The microcrystalline cellulose, in contrast, features round-shaped particles of agglomerated fibers. Due to the porosity, the material has a comparatively low bulk density.

The results presented in figure 8 of case study 1 indicate that host powders of different compositions, particle size and shape may require a customized flow additive. Overall, the most effective flow additive in the study is AEROSIL® R 972 Pharma. For crystalline non-porous materials such as lactose with particle sizes below 100 µm also AEROSIL® 300 Pharma proved to be highly effective. In situations where other factors than van der Waals forces are responsible for poor powder flow (such as the fiber-shaped Vivapur® 105) it is advised to eliminate these factors first by processing before AEROSIL® Pharma glidants are added for flowability enhancement.

The necessary free flow additive concentration is dependent on the individual host powder and the processing equipment. For efficient powder flow improvement, a situation as shown in figure 4 needs to occur. Rather than covering the host powder surface with a complete layer of AEROSIL® Pharma particles, there needs to be a situation in which there are just enough of the silica particles present to prevent direct contact of the host powder particles.

As the agglomerated structure of AEROSIL® Pharma products is broken down in the mixing process, long mixing times and high shear forces decrease the size of the silica particles. This leads to the following considerations:

- The finer the host powder is the more host powder surface needs to be covered with AEROSIL® Pharma particles. For fine powders therefore higher AEROSIL® Pharma dosage is advisable.
- Host powders with bigger particles require bigger AEROSIL® Pharma particles on their surface. Long mixing times may break down the AEROSIL® Pharma aggregates too far for efficient powder flow improvement.

Figure 8 shows the relation of the powder flow properties of lactose with changing AEROSIL® Pharma colloidal silicon dioxide concentration.

[12] The outstanding performance of colloidal silicon dioxide for flow enhancement of lactose was also proven in an external study by P. York, The use of glidants to improve the flowability of fine lactose powder, Powder Technology 11 (1975) 197 – 198.

**CASE STUDY 1**

# Powder flow of microcrystalline cellulose and lactose of different particle size and their mixtures with AEROSIL® Pharma colloidal silicon dioxide products

## FORMULATIONS, PROCESSING AND POWDER FLOW ASSESSMENT

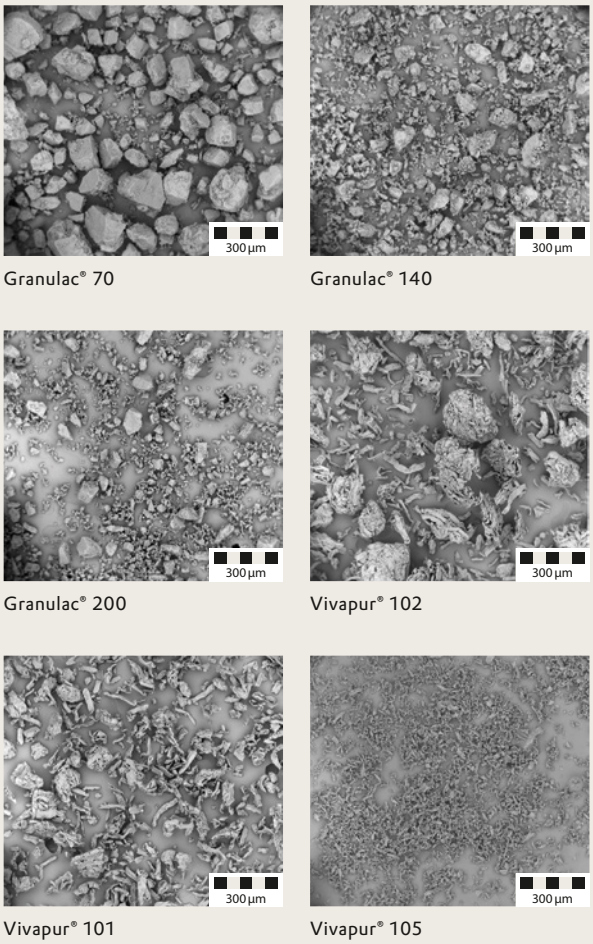
Simple binary powder mixtures of non-compression lactose and microcrystalline cellulose products with 0.5 w.-% AEROSIL® Pharma products were prepared. The host powders were selected to reflect different particle size ranges.

| d50 particle size | Lactose[13] | Microcrystalline Cellulose[14] |
|---|---|---|
| ~ 100 µm | Granulac® 70 | Vivapur® 102 |
| ~ 50 µm | Granulac® 140 | Vivapur® 101 |
| ~ 25 µm | Granulac® 200 | Vivapur® 105 |

Equivalent volumes of the excipients were mixed with 0.5 w.-% of the different AEROSIL® Pharma products in a tumbling mixer (Turbula T2F, Willy Bachofen AG, Switzerland) for 10 min at a revolution of 67 rpm using equivalent fall heights of the powder in the mixing bottle.

The powder flow was assessed by the angle of repose method.

**FIGURE 7:** Scanning electron microscopy images of the host powders




Granulac® 70 | Granulac® 140

Granulac® 200 | Vivapur® 102

Vivapur® 101 | Vivapur® 105

[13] Granulac® products are manufactured by Meggle Group Wasserburg, Gemany. The producer gives the following d50 particle size for the products: Granulac® 70: 107 µm, Granulac® 140: 46 µm, Granulac® 200: 27 µm.

[14] Vivapur® products are manufactured by JRS PHARMA GmbH & Co. KG, Germany. The particle sizes (d50) for the selected materials is given by the producer for Vivapur® 102: 100 µm, Vivapur® 101: 65 µm, Vivapur® 105: 25 µm.

**FIGURE 8:** Powder flow results (angle of repose)

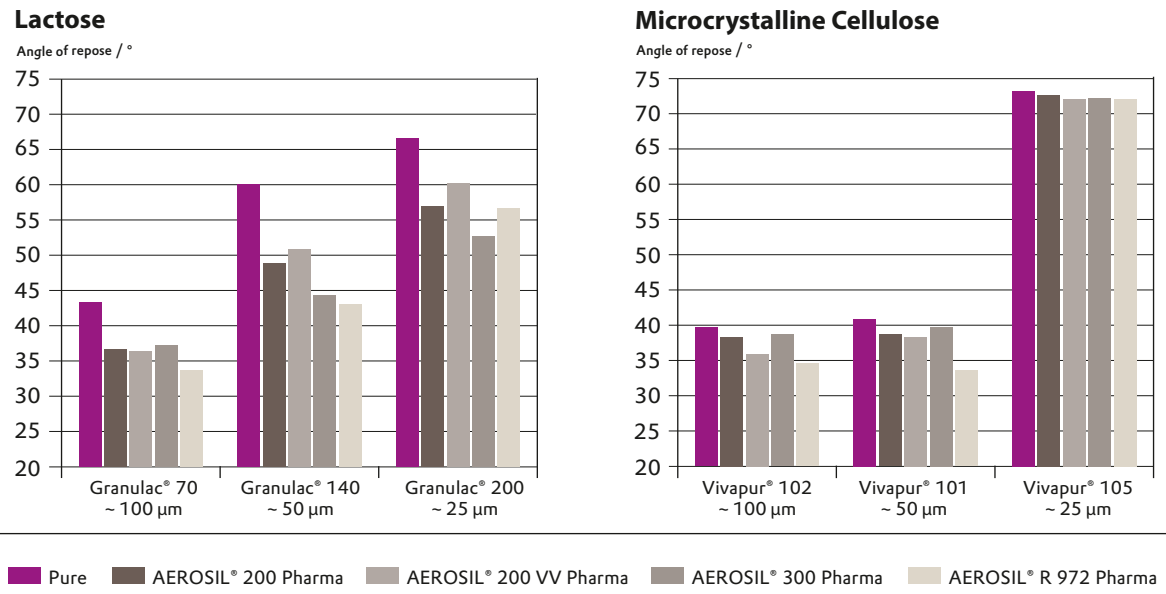
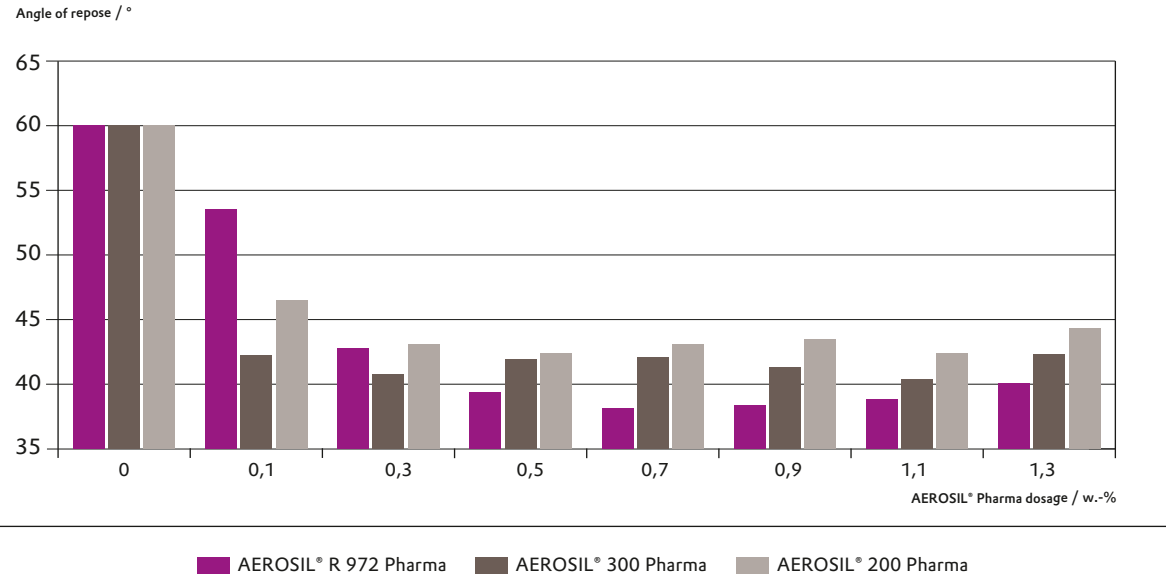



**FIGURE 9:** Powder flow of Granulac® 140 (d50 particle size: 46 µm) in dependence of AEROSIL® Pharma dosage



**RECOMMENDATIONS**

- AEROSIL® R 972 Pharma in many situations has the best powder flow enhancing performance. As the material is water repellent, it can also provide moisture protection for the host particles.
- For powders with coarse or porous particles AEROSIL® 200 VV Pharma may provide better powder flow. Due to the compaction step during its production the material has bigger and more rigid agglomerates that are not milled down as easily during mixing.
- As a starting point an AEROSIL® Pharma concentrations of 0.5 w.-% is recommended. By using higher or lower concentrations and varying the mixing conditions the perfect concentration and processing can easily be evaluated experimentally.

# 4. Optimizing tablet properties by the addition of AEROSIL® Pharma colloidal silicon dioxide

The efficiency of colloidal silicon dioxide glidants to influence tablet weight and tablet weight variation is a well-established fact[15]. Insufficient powder flow can lead to erratic filling of the die with the powder mixture, which ultimately leads to deviating tablet mass. Since this also influences the active pharmaceutical ingredient (API) dosage, this is a serious condition that needs to be avoided. A practical example of this is shown in Case Study 2 that relates powder flowability, determined by different methods (figure 11), with tablet weight and tablet weight variation (figure 10). Powder flow results determined by the angle of repose and shear cell methods correlate well with the differences in tablet weight and the tablet weight variation in the batch. As a contrast, the assessment of powder flow by the compressibility index does not correlate well with the tablet results. Pure lactose (with added lubricant) has the worst flow behavior of all mixtures, which was identified by the angle of repose and the shear cell results. The poor flow leads to an incomplete and variable filling of the die of the tablet press, reflected by the low tablet weight and a strong weight variation between individual tablets of the same compression batch. The strong improvement of the flow properties achieved with AEROSIL® 200 Pharma and AEROSIL® R 972 Pharma translate into higher tablet weights and strongly reduced tablet weight variation.

[15] LL. Augsburger, R.F. Shangraw, Effect of glidants in tabletting, J. Pharmaceut. Sci. 55 (4), 1966, 418 – 423.

CASE STUDY 2

# Powder flow versus tablet mass and tablet mass variation for directly compressed pharmaceutical lactose

## FORMULATION

| INGREDIENT | CONTROL | AEROSIL® PHARMA CONTAINING FORMULATION |
|---|---|---|
| Lactose[1] (Granulac® 140) | 99.0 w.-% | 98.5 w.-% |
| **AEROSIL® Pharma glidant** | **–** | **0.5 w.-%** |
| Magnesium stearate[2] | 1.0 w.-% | 1.0 w.-% |

[1] Granulac® 140, Meggle Wasserburg GmbH, Germany
[2] Magnesium Stearat, Caesar & Loretz GmbH, Germany

## PROCESSING

Lactose was mixed by hand with the respective AEROSIL® Pharma glidant and the mixture was passed through a 710 µm mesh. The powder was then mixed in a tumbling mixer (Turbula T2F, Willy Bachofen AG, Switzerland) for 10 min at 67 rpm. Magnesium stearate sifted through the same sieve was added and the final powder mixture was subjected to another 5 min of mixing under the same conditions. The powder mix was divided to perform powder flow tests or tableting experiments. Part of the powder was then turned into tablets with a diameter of 12 mm using a single punch press (EK-0, Korsch AG, Germany) with the die height kept constant for all mixtures. A selection of 20 tablets were characterized for their tablet weight and tablet weight variation using standard pharmacopeia methods and an Erweka TBH 30 MD analyzer (Erweka GmbH, Germany).

**FIGURE 10:** Tablet mass and tablet mass variation

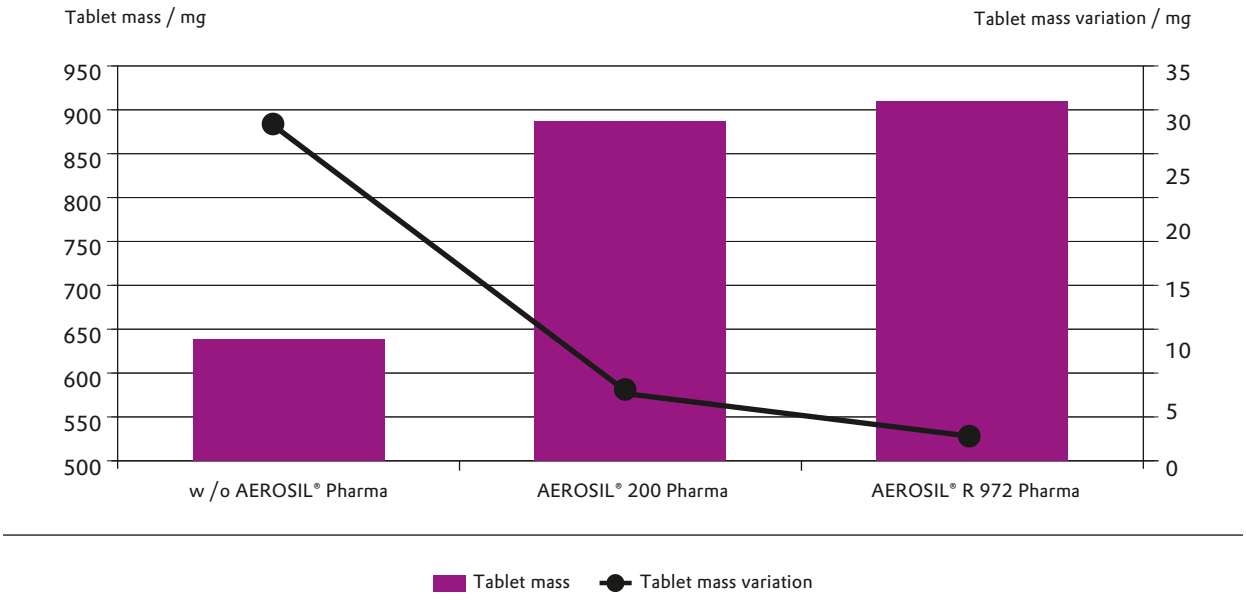
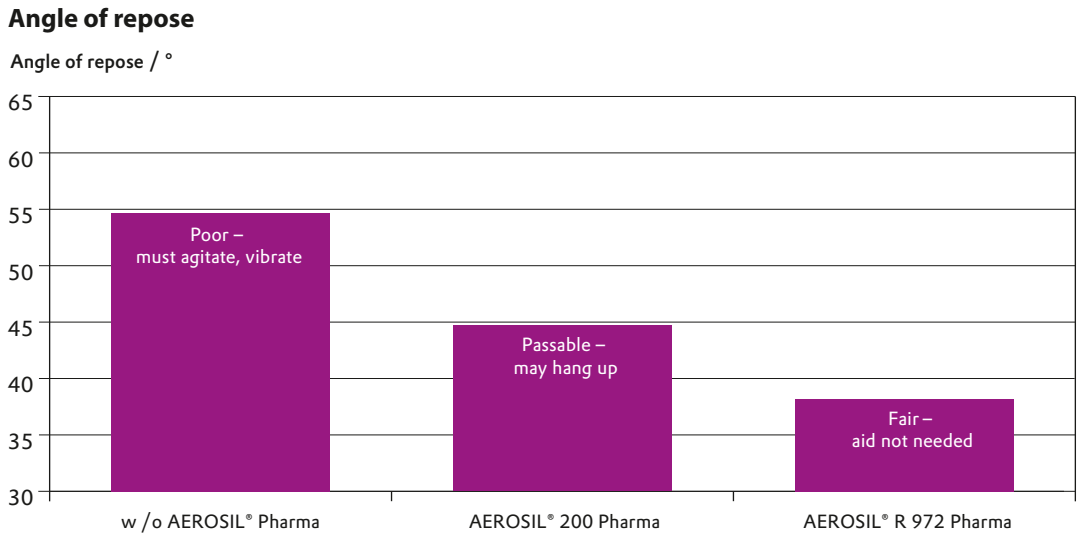
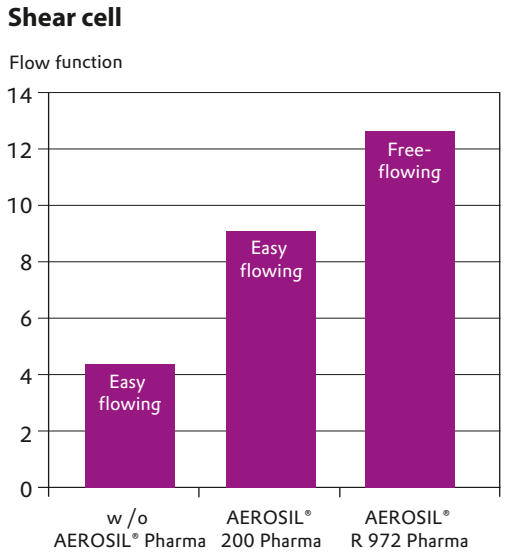
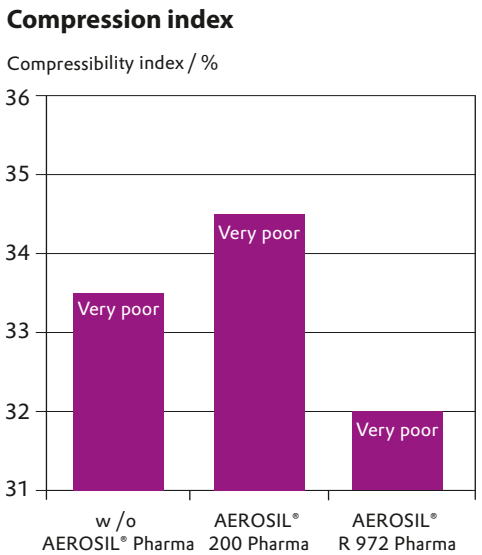


**FIGURE 11:** Assessment of powder flowability by different methods

Rating of the flow properties according to USP/NF monograph "Powder Flow" (1174) for angle of repose and compressibility index.
For flow function results of shear cell measurements the rating was done according to literature[16].




[16] D. Schulze, Vergleich des Fließverhaltens leicht fließender Schüttgüter, Schüttgut 2 (3) (1996) 347 – 356 [in German]. Similar content in English can be downloaded from http://www.dietmar-schulze.com/grdle1.pdf

Although optimized powder flow, optimized tablet weights and API dosage consistency are highly important, they are not the only benefits of AEROSIL® Pharma colloidal silicon dioxide. Case study 3 exemplifies how the mechanical tablet properties and tablet disintegration time can be improved by addition of AEROSIL® Pharma products.

Adding hydrophilic AEROSIL® Pharma products to the formulation helps formulators to achieve more stable tablets with a strongly reduced friability already at a very low dosage. While AEROSIL® 200 Pharma and AEROSIL® 300 Pharma significantly improve the crushing strength and friability at a dosage of only 0.2 w.-%, the compacted AEROSIL® 200 VV Pharma needs a little higher concentration to achieve the same effect (see figures 12 and 13). However, the biggest improvement of the mechanical tablet properties are achieved with AEROSIL® Pharma concentrations above 0.5 w.-% in the compression mix. AEROSIL® 300 Pharma has the biggest effect on the mechanical stability. Adding AEROSIL® Pharma products offers an alternative and cost effective approach to improve tablet stability than by other possible measures such as increasing the binder content.

Using the hydrophobic AEROSIL® R 972 Pharma enables formulators to influence the hydrophobicity of the formulation. AEROSIL® R 972 Pharma added at concentrations above 0.5 w.-% prolongs the disintegration time that can help with overly hydrophilic formulations (see figure 13)[17]. The water resistance of the tablets can also help to work with formulating water sensitive APIs into the tablets[18,19].

[17] Reducing the water absorption has already been described for zinc oxide, titanium dioxide, magnesium oxide, magnesium carbonate, talc, corn starch, silica gel and lactose by Gstirner and Pick, Influence of AEROSIL® and AEROSIL® R 972 on the water absorption capacity of powders, Archiv der Pharmazie, 302 (8) (1969) 590 – 604 [in German].
[18] Betahistine composition, Disphar International B.V., WO 2015053620.
[19] Oral dissolvable pharmaceutical dosage form for the treatment of oral diseases, Lacer S.A., WO 2016102502.

CASE STUDY 3

# Influence of AEROSIL® Pharma products on tablet properties

## FORMULATION

| INGREDIENT | CONTROL | AEROSIL® PHARMA CONTAINING FORMULATION |
|---|---|---|
| Paracetamol/Acetaminophen[1] | 70.0 w.-% | 70.0 w.-% |
| Microcrystalline cellulose[2] | 26.5 w.-% | ad 100[3] |
| Corn starch[4] | 3.0 w.-% | 3.0 w.-% |
| AEROSIL® Pharma glidant | – | 0.2–1.1 w.-% |
| Magnesium stearate[5] | 0.5 w.-% | 0.5 w.-% |

[1] Acetaminophen USP/Paracetamol Ph Eur Dense Powder, Type 5541, Mallinckrodt Pharmaceuticals, United Kingdom
[2] Avicel® PH 101, FMC Biopolymer Europe NV, Belgium
[3] Dependent on AEROSIL® Pharma dosage different amounts of the MCC binder have been used. The dosage ranges from 25.4 w.-% (AEROSIL® Pharma colloidal silicon dioxide concentration 1.1. w.-%) to 26.3 w.-% (AEROSIL® Pharma concentration 0.2 w.-%).
[4] Maisstärke, Caesar & Loretz GmbH, Germany
[5] Magnesium Stearate, Caesar & Loretz GmbH, Germany

## PROCESSING

All components except the magnesium stearate were hand-blended and passed through a 710 µm sieve. The combined powders were then mixed in tumbling mixer (Turbula T2F, Willy A. Bachofen AG, Switzerland) for 10 minutes at 67 rpm. Magnesium stearate was passed through a 710 µm sieve, added to the mixture and the complete mixture then mixed under above mentioned conditions for another 5 min. The powder was then turned into tablets with a diameter of 12 mm and a tablet weight of approximately 800–850 mg using a single punch press (EK-0, Korsch AG, Germany) with compression forces of 15 and 25 kN. Of the tablet batch 20 arbitrarily selected tablets were characterized for their mechanical stability (crushing strength, friability) and disintegration time[20].

[20] Tablets were characterized using standard equipment and methods according to the pharmacopeia: mechanical tablet parameters Erweka TBH 30 MD, tablet disintegration: Erweka ZT131 (all of Erweka GmbH, Germany).

**FIGURE 12:** Tablet crushing strength

**Compression force 25 kN**

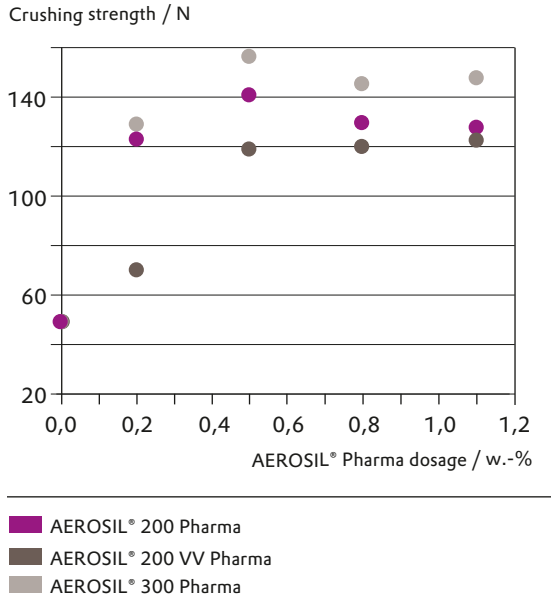



**FIGURE 13:** Tablet friability

**Compression force 25 kN**

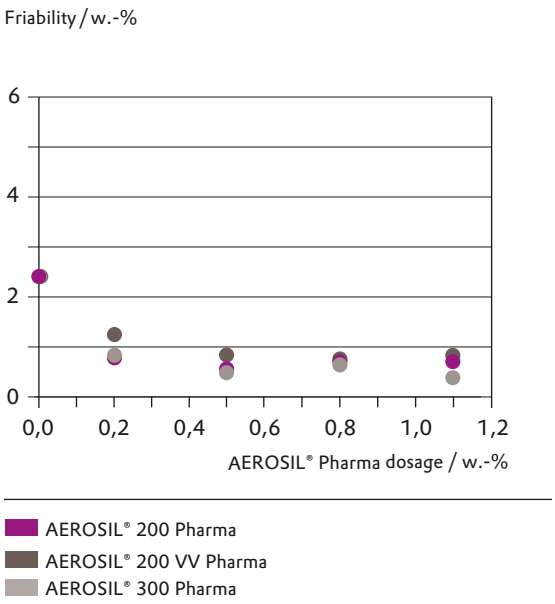
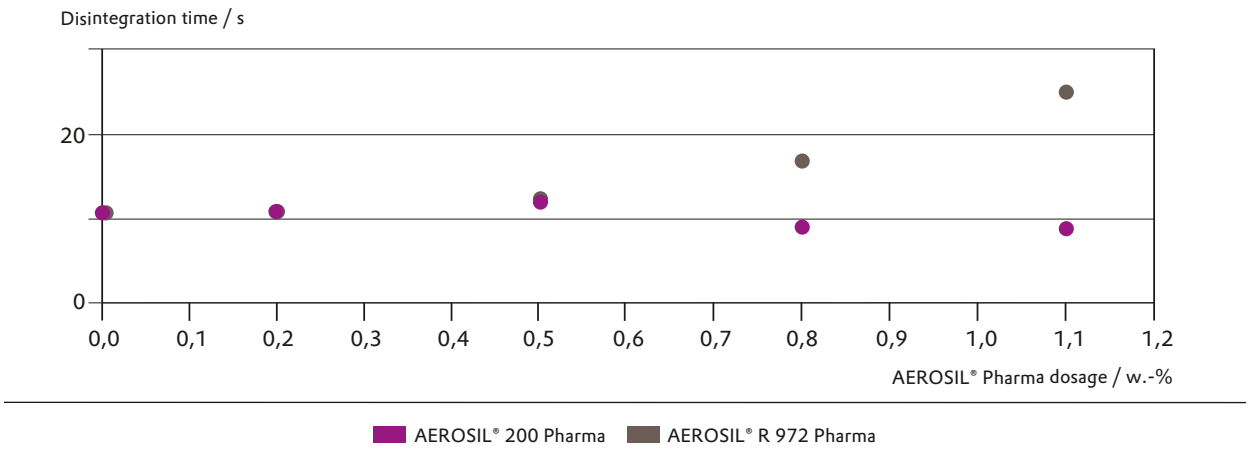



**FIGURE 14:** Tablet disintegration time

**Compression force 25 kN**



## PROCESSING RECOMMENDATIONS:

- The concentration recommendations given in Case Study 3 may not be representative for all possible direct compression formulations. Formulators need to optimize the required AEROSIL® Pharma colloidal silicon dioxide dosage based on experimental findings for their individual formulation.

- The choice of the AEROSIL® Pharma colloidal silicon dioxide product is dependent on the individual formulation. Hydrophilic AEROSIL® Pharma products have a higher efficiency on the mechanical tablet properties. As a recommendation, 0.5 w.-% can be used as the starting concentration; and this can be optimized by increasing or decreasing the dosage and checking the formulation properties.

- To take full advantage of the AEROSIL® Pharma colloidal silicon dioxide it is recommended to add the glidant at an early stage to the compression mix. To prevent inactivation of the silica through agglomeration it is advised to premix the colloidal silicon dioxide with part of the other powder components and sift this mixture before addition to the complete compression mix. This process safeguards the break-up of the AEROSIL® agglomerates and maximizes its efficiency.

- For powder mixing, traditional equipment used in the industry such as free fall mixers (e. g. v-shaped mixers, double cone mixers) or mechanical mixers (e. g. plowshare mixers) that apply only low shear forces can be used. Adding the premix that contains the AEROSIL® Pharma colloidal silicon dioxide as the first component to the mixer often gives better mixing results.

- Due to its high specific surface area, colloidal silicon dioxide can absorb other components of the compression mix. This is also true for stearates or stearic acid often used as lubricants in tableting processes which gives rise to the often cited "incompatibility" of these products with the glidants[21]. To prevent the inactivation of the lubricant we recommend to add the lubricant later in the mixing process than the AEROSIL® Pharma colloidal silicon dioxide.

[21] C.F. Lerk, G.K. Bolhuis, SS. Smedama, Interaction of lubricants and colloidal silica during mixing with excipients (I and II), Pharmaceutica Acta Helvetica 52 (3) (1977) 33–44.

# 5. Supplementary information

Besides their role as glidants, AEROSIL® Pharma colloidal silicon dioxide also supports the pharmaceutical industry with other formulation challenges such as:

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

Evonik provides an extensive set of technical information in other brochures that can be downloaded from the **www.aerosil.com** webpage. The set of brochures is constantly updated and extended to cover more applications of AEROSIL® and AEROPERL® Pharma colloidal silicon dioxide in pharmaceutical manufacturing. Please select "Pharmaceuticals" under "Industries" to access this literature.

A complete overview of the products, their way of production and regulatory background is included in Technical Information TI 1415 (AEROSIL® and AEROPERL® Pharma Colloidal Silicon Dioxide Products).

The use of AEROPERL® 300 Pharma as a carrier to improve the dissolution of poorly soluble active pharmaceutical ingredients is the topic of Technical Information TI 1414 (AEROPERL® 300 Pharma: Improving the dissolution of poorly soluble APIs).

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