PharmTech.com
ADVANCING DEVELOPMENT AND MANUFACTURING

Improving the Dissolution of Poorly Soluble APIs with Inorganic Solid Dispersions

Solid dispersions based on organic polymers can have stability issues. Inorganic solids, especially those based on silica chemistry, may be suitable alternatives to organic polymers due to their pre-formed pore system, high absorptivity, and commercial availability in pharmaceutical quality. Mesoporous granulated colloidal silicon dioxide has been studied with class II and IV actives of the Biopharmaceutics Classification System for its ability to improve dissolution. Using suitable formulation strategies, the dissolution of these APIs could be significantly increased. The absorption of poorly soluble APIs onto silicon dioxide can, therefore, be considered a viable formulation path to overcome solubility challenges.

Apr 01, 2017
By Jörg Münzenberg [1], Stephen Moller [2]
Pharmaceutical Technology
Volume 2017 Supplement, Issue 2, pg s12–s15

Mikae l Dam kier /shutterstock.com

Changes in the way new chemical entities are developed and identified have led to a situation where many active pharmaceutical ingredient (API) innovations exhibit poor aqueous solubility. Although numbers deviate (1, 2), there is general agreement that many new drug candidates, especially those coming from synthesis (3), face aqueous solubility challenges. Insufficient solubility may even lead to the abandonment of an otherwise promising new chemical entity.

Although no single formulation approach can solve the issue of poor solubility, a recent survey lists solid dispersion as one of the most promising techniques to overcome this challenge (4). In solid dispersions, the poorly soluble API is finely dispersed in a matrix of another solid (5-7). Traditionally, these formulations use organic polymers (e.g., polyacrylates, polyethylene glycols, polyvinyl pyrrolidones, polyvinyl alcohols) or cellulose derivatives as the matrix (8). Solid dispersions are produced either by the co-spray drying of the API and the matrix polymer or through hot-melt extrusion, where the API is incorporated into the polymer matrix at high shear and elevated temperatures. Solid dispersions aim to transform the API into an amorphous, more soluble form. Using this approach makes the stabilization and long-term stability of the amorphous API crucial to prevent recrystallization.

Researchers have also looked into inorganic carriers for solid dispersions. Among these materials, mesoporous silica (9) and magnesium aluminosilicate (10) but also activated carbon (11) and calcium carbonate (12) have been suggested as matrices for such formulations. Recently, a granulated form of colloidal silicon dioxide (*United States Pharmacopeia-National Formulary* [*USP/NF*]) has gained attention as a matrix for inorganic solid dispersions (13, 14).

Colloidal silicon dioxide is well known in the industry as a glidant that helps to regulate the flow of powders and to increase the mechanical stability of tablets in direct compression processes (15). The material is produced by gas phase hydrolysis of silicon tetrachloride by water produced in a hydrogen flame. The special particle morphology of colloidal silicon dioxide results in a low powder density and a more branched, open structure compared to mesoporous silicon dioxide.

Through spray granulation, this material is densified and made to flow exceptionally well (16). The granules have a much higher powder density than typical colloidal silicon dioxide. Whereas the aggregates of colloidal silicon dioxide are essentially non-porous, the granulate is a mesoporous material with a maximum pore size distribution of approximately 35 nm and a mesopore volume of 1.5 to 1.9 mL/g. This porosity coupled with a high specific surface area and exceptionally high purity qualifies the material as a carrier candidate for pharmaceutical formulations.

Materials and methods

All chemicals including the APIs artemether, itraconazole, and celecoxib, as well as D-α-tocopheryl polyethylenglycol 1000 succinate (TPGS) and hydroxypropyl methylcellulose (HPMC), were obtained from different sources in pharmaceutical quality. Granulated colloidal silicon dioxide (Aeroperl 300 Pharma, Evonik) was used as received from the producer Evonik Resource Efficiency GmbH. To absorb the APIs onto granulated colloidal silicon dioxide (Aeroperl 300 Pharma), the carrier was added to concentrated solutions of the respective API in the given ratios. The solvent was evaporated overnight and the resulting free flowing powder was used as such.

Results

The ability of granulated colloidal silicon dioxide to improve the dissolution of poorly soluble API was tested in experiments done with APIs featuring different dissolution characteristics. Anti-malarial artemether is a Biopharmaceutics Classification System (BCS) class II drug typically used in combination with lumefantrine to treat malaria caused by plasmodium falciparum. **Figure 1** shows dissolution experiments that were carried out using equivalent quantities (20 mg) of the pure drug, as well as preparations of artemether absorbed onto granulated colloidal silicon dioxide (Aeroperl

300 Pharma) using two different active-to-carrier ratios. The dissolution rate of the pure drug was approximately 10% after 20 min, and only about 20% after 180 min. Absorbing the active onto granulated colloidal silicon dioxide tripled and almost even quadrupled the dissolution rate of the artemether. The highest dissolution rates occurred with formulations with lower active loading. The drug release was also more rapid, with more than 50% dissolving in the first 20 minutes for the formulation with 25% API loading. After only 20 min, the absorbed artemether was already dissolved by 40% or more than 50% for the compound with the higher carrier-to-drug ratio compared to approximately 10% for the pure drug. This observation illustrates the ability of colloidal silicon dioxide to strongly accelerate the dissolution of poorly soluble drugs.

Control:	pure artemether (20 mg)
Formulation 1:	artemether (20 mg) absorbed on an equal quantity of a granulated colloidal silicon dioxide (20 mg)
Formulation 2:	artemether (20 mg) absorbed on the threefold quantity of a granulated colloidal silicon dioxide (60 mg)
Dissolution testing:	Powder samples equivalent to 20 mg active were tested in a USP I dissolution apparatus with phosphate buffer solution containing 1 weight % sodium lauryl sulfate at 37±0.5 °C.

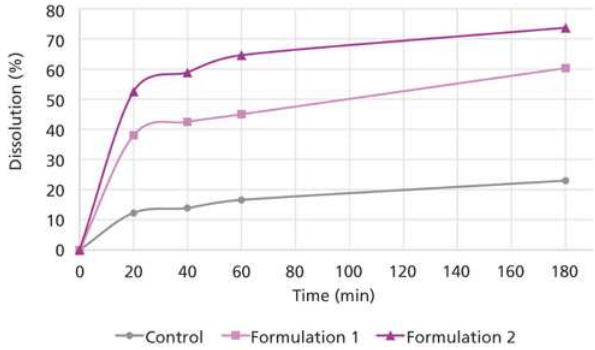

Figure 1: Dissolution of antimalarial drug artemether pure and after absorption on granulated colloidal silicon dioxide (Aeroperl 300 Pharma, Evonik).

However, although granulated colloidal silicon dioxide may accelerate the dissolution of poorly soluble APIs, taking advantage of this effect requires proper wetting of the active by the dissolution medium. Itraconazole, an antifungal agent of the commercial formulation Sporanox, is a hydrophobic powder that is difficult to wet. For itraconazole, the addition of a surfactant is necessary to take full advantage of the dissolution enhancing properties of granulated colloidal silicon dioxide. **Figure 2** provides evidence of the very poor dissolution of itraconazole in the aqueous test media (control). Even after 2 h of contact, less than 5 % of the active was dissolved. Formulating itraconazole with a surfactant (TPGS) (formulation 1) increases the dissolution rate approximately three-fold. When both the API and the surfactant were absorbed onto Aeroperl 300 Pharma, a significant and instantaneous increase of the dissolution rate was observed. The results demonstrate that the absorption of the API onto the silica is the major driver for the improvement in dissolution, and the TPGS is simply aiding in the wettability of the itraconazole.

Control:	pure itraconazole (100 mg)
Formulation 1:	itraconazole (100 mg) dispersed in molten D-α-tocopheryl polyethylenglycol 1000 succinate (TPGS, 100 mg)
Formulation 2:	itraconazole (100 mg) co-absorbed with TPGS (100 mg) on granulated colloidal silicon dioxide (2000 mg)
Dissolution testing:	Powder samples equivalent to 100 mg active were tested in a USP II dissolution tester using 0.1 N HCl as a dissolution medium at a temperature of 37±1°C.

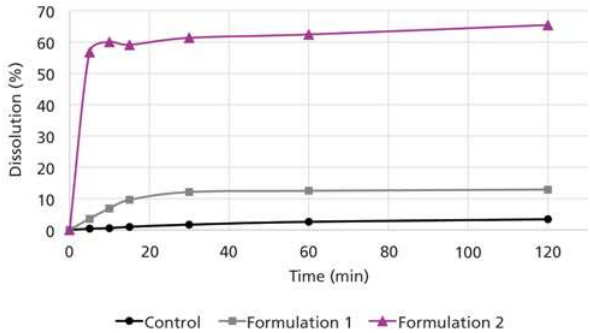

Figure 2: Dissolution of antifungal active itraconazole pure and formulated with granulated colloidal silicon dioxide (Aeroperl 300 Pharma, Evonik).

Although granulated colloidal silicon dioxide can strongly improve the dissolution of APIs, the achieved supersaturation concentration in the medium may not be stable, and recrystallization of the active may occur. This situation was observed for the anti-inflammatory active celecoxib, listed as a BCS class II drug. **Figure 3** shows the poor dissolution of the API in the dissolution medium (control). In formulation 1, the silica provides a large initial boost in dissolution, but recrystallization of the celecoxib causes the concentration to drop rapidly. However, in formulation 2, with the addition of a nucleation inhibitor, HPMC, the dissolution was stabilized and had a larger final amount dissolved at the end of the experiment.

Control:	pure celecoxib (50 mg)
Formulation 1:	celecoxib (50 mg) absorbed on granulated colloidal silicon dioxide (500 mg)
Formulation 2:	formulation 1 mixed with hydroxypropyl methylcellulose (HPMC, 250 mg)
Dissolution testing:	Powder samples equivalent to 50 mg active were tested in a USP II apparatus using FaSSIF v 2 solution (pH 6.5) at a temperature of 37±1 °C.

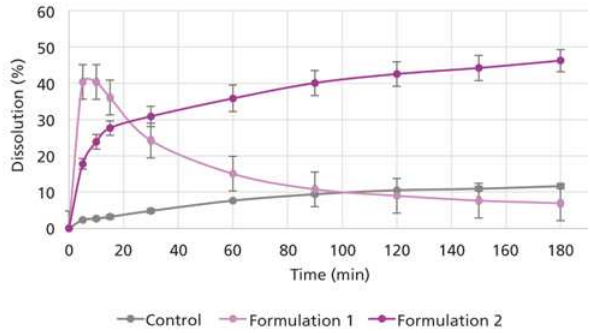

Figure 3: Dissolution of anti-inflammatory active celecoxib pure and formulated with granulated colloidal silicon dioxide (Aeroperl 300 Pharma, Evonik).

Discussion and conclusion

The results show that absorption of APIs on granulated colloidal silicon dioxide has a strong influence on the dissolution behavior. The strong effect inorganic solid dispersions can have on the dissolution of poorly soluble APIs is based on the same mechanisms as their traditional organic counterparts. The actives, through the absorption into the pore system of the inorganic carriers, may be stabilized in the amorphous form, which has a lower energy barrier to dissolution than the crystalline state. Inorganic carriers such as granulated colloidal silicon dioxide have a predefined pore system that takes up the active. The size of the pores in the mesopore range limits the mobility of the absorbed active, and the surface of the granulated colloidal silicon dioxide is covered with hydrophilic silanol groups that can effectively interact with polar groups of the active. Both of these mechanisms stabilize the active on the carrier and, therefore, prevent crystallization.

In addition to stabilization of the amorphous form, the absorption of APIs on inorganic carriers also effectively reduces the particle size of the API. Although the absorbed active may still be in the crystalline form, the reduction in particle can also lead to higher dissolution rates. One example is actives that fall in class IIa of the Developability Classification System defined by Butler and Dressman (17) that are characterized by very slow dissolution rates. Through strong interactions with the granulated, colloidal silicon dioxide matrix, the agglomeration of the crystallites can be

prevented. Absorption of actives on inorganic carriers may, therefore, be an alternative to other methods for particle size reduction (e.g., milling), that effectively reduce the particle size but due to agglomeration, fail to give sufficient dissolution.

Most technologies that improve dissolution rates require additional excipients to be used in the formulations. Using inorganic solids as a carrier for the active is no exception from this rule. However, granulated colloidal silicon offers a high absorption capacity so that high loadings on the carrier can be achieved. The technique, therefore, is a viable technique to overcome solubility challenges for drugs with doses up to 150 to 300 mg depending on the type of solid dosage form.

References

1. M. Lindenberg, S. Kopp, J.B. Dressman, *Eur. J. Pharm. Biopharm.* 58, 265-278 (2004).
2. A.K. Nair et al., *The AAPS Journal* 14 (4) 664-666 (2012).
3. C.H. Dubin, *Drug Delivery Technology* 6 (6) 34 (2006).
4. A. Siew, P. van Arnum, *Pharm. Techn. Europe* 25 (6) 54-57 (2013).
5. A. Siew, *Pharm. Tech. Europe* 26 (10) 14-19 (2014).
6. C. L.-N. Vo, C. Park, B.-J. Lee, *Eur. J. Pharm. Biopharm.* 85, 799-813 (2013).
7. S. Janssens, G. van den Mooter, *J. Pharm. Pharmacology* 61, 1571-1586 (2009).
8. A. Siew, Pharm. Tech. Europe 28 (7) 16-20 (2016).
9. S.P. Rigby, M. Fairhead, C.F. van der Walle, *Curr. Pharm. Design*. 14 1821-1831 (2008).
10. M. Maniruzzaman et al., *Int. J. Pharm.* 496, 42-51 (2015).
11. P. Zhao et al., *Eur. J. Pharm. Biopharm.* 80, 535-543 (2012).
12. D. Preisig et al., *Eur. J. Pharm. Biopharm.* 87, 548-558 (2014).
13. Q. Wei, C.M. Keck, R.H. Müller, *Int. J. Pharm.* 482, 11-20 (2015).
14. T. Meer et al., *J. Pharm. Investigation* 43 (4) 279-285 (2013).
15. R. Tawashi, *Pharmazeutische Industrie* 26, 682 - 685 (1964).
16. K. Deller, H. Krause, J. Meyer, D. Kerner, W. Hartmann, H. Lansink-Rotgerink/Evonik Degussa GmbH, Granulate auf Basis von pyrogen hergestelltem Siliciumdioxid, Verfahren zu ihrer Herstellung und ihre Verwendung," European Patent 725037, January 1996.
17. J.M. Butler, J.B. Dressman, *J. Pharm. Sci.* 99 (12) 4940-4954 (2010).

About the Authors

Jörg Münzenberg, PhD*, is senior manager, Applied Technology, Evonik Resource Efficiency GmbH, Rodenbacher Chaussee 4, 634567 Hanau, Germany, Tel.: +49 6181 59 2217, joerg.muenzenberg@evonik.com [3]; and Stephen Moller is application scientist, Evonik Corporation, 2 Turner Place, Piscataway, NJ 08855, US, Tel.: +1 732 981 5110, stephen.moller@evonik.com [4].

*To whom all correspondence should be addressed.

Article Details

"Solid Dosage Drug Development/Manufacturing 2017," supplement to *Pharmaceutical Technology* Vol. 41, No. 4
Pages: s12–s15

Citation

When referring to this article, please cite it as J. Münzenberg and S. Moller, "Improving the Dissolution of Poorly Soluble APIs with Inorganic Solid Dispersions," in "Solid Dosage Drug Development/Manufacturing 2017," supplement to *Pharmaceutical Technology* 41 (4) 2017.

Source URL: http://www.pharmtech.com/improving-dissolution-poorly-soluble-apis-inorganic-solid-dispersions

Links:
[1] http://www.pharmtech.com/j-rg-m-nzenberg
[2] http://www.pharmtech.com/stephen-moller
[3] mailto:joerg.muenzenberg@evonik.com
[4] mailto:stephen.moller@evonik.com