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White Paper

The Developability Classification System (DCS): Enabling an Optimized Approach for Formulation of Poorly Soluble Molecules

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Ensuring sufficient solubility for orally delivered solid dosage forms is a critical step in their development. Most, if not all, of the absorption of these dosage forms takes place in the small intestine, where the drug must be sufficiently dissolved in the gastrointestinal fluids to pass through the membrane and into the systemic circulation. If the drug is not soluble in gastrointestinal fluids, this process cannot occur and the intended physiological effect will not be realized.

The importance of solubility is highlighted in the biopharmaceutics classification system (BCS).[1] The BCS framework originated in the 1990s and sought to correlate *in-vitro* solubility and permeability with the potential *in-vivo* performance of drug molecules. In the system, molecules are categorized based on the combination of solubility and permeability. BCS Class I, for example, includes molecules that have both high solubility and permeability, and as such are expected to have good absorption in the gastrointestinal tract. BCS Class II compounds, on the other hand, have low solubility and high permeability, while BCS Class III molecules have high solubility and low permeability. The most challenging class of molecules are those categorized as BCS Class IV; these molecules have both low solubility and permeability. The BCS was originally used by the US Food and Drug Administration (FDA) as the basis for biowaiver applications for immediate release formulations in order to reduce the need for additional *in-vivo* studies for bioavailability and bioequivalence.[2] Still today, this framework is important for regulatory considerations, as referenced by the recent publication from the FDA regarding BCS-based biowavers.[3]

Since the introduction of the BCS, the solubility landscape of marketed drugs continues to evolve.[4] It is conservatively estimated that approximately 40 to 60% of approved drugs suffer with poor solubility (BCS Class II or BCS Class IV). The same assessment applied to drug candidates in development reveals that 60 to 90% of drugs are classified as poorly soluble and risk failure due to poor performance and poor absorption in the gastrointestinal tract.[5]

This white paper explores the developability classification system (DCS), a recent advancement based on the BCS system but, instead of focusing on regulatory aspects, this framework assists formulators in the development of poorly soluble drug formulations.[6] This is achieved by identifying the root cause for low solubility and providing strategies for molecules that are either dissolution limited or solubility limited.

The Developability Classification System

Expanding upon the BCS, the DCS introduced key modifications to improve applicability to formulation development. For example, biorelevant media was introduced to provide a more reliable assessment of *in-vivo* solubility, and the BCS Class II was further divided into two sub-categories: DCS Class IIa and DCS Class IIb. Another modification was the shift in dose solubility ratio, resulting in a lower threshold for a molecule to be considered “soluble”.

As a result, the appearance of the DCS is different than the BCS, with the cut-off between DCS I and III and DCS IIa/b and IV appearing at a dose-solubility ratio of 500, as opposed to 250 in the BCS. Furthermore, the BCS II portion of the graph is split into two sections in the DCS to represent DCS IIa and IIb.

This line, which separates the two sub-categories, is the solubility-limited absorbable dose (SLAD) line. The line uses a ratio of solubility and permeability to determine if an increase in dissolution rate will have a measurable impact on overall absorption. Based on this ratio, a drug molecule is placed either above or below the SLAD line. Molecules above the line are

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dissolution rate-limited (DCS Class IIa). Theoretically, if the maximum solubility is reached faster, absorption of the molecule can be enhanced; development should therefore focus on the dissolution rate. Molecules below the SLAD line (DCS Class IIb) have such a low solubility that no matter how quickly the drug gets into solution, there will not be a measurable impact on absorption. The fundamental challenge with DCS IIb molecules is therefore solubility.

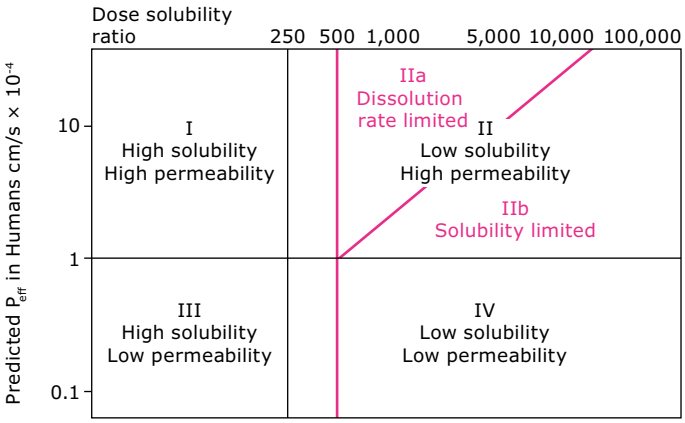


Figure 1.

The DCS is a modified version of the BCS, modifications in the DCS are shown in pink.

The value of having two new classifications to guide development of solubility enhanced formulations is clear. A more granular understanding of the root causes of solubility limitations – whether driven by dissolution rate or intrinsic solubility – can be used to guide design of optimized formulations rather than relying on trial and error. Figure 2 provides a workflow for selecting the best formulation strategy based the DCS class of a molecule.

For dissolution rate-limited compounds, DCS IIa, if the dissolution rate can be enhanced, a very simple and effective formulation can be developed. This could be accomplished either with reducing the particle size, accelerating disintegration, incorporating wetting agents or surfactants, or replacing hydrophobic excipients with hydrophilic excipients to reduce the retardation effect of excipients on the formulation. In contrast, for molecules below the SLAD line – DCS IIb, solubility limited compounds - the formulation must address the intrinsic solubility. This could require modification of the chemical structure of the molecule or of the solid state of the molecule using solid dispersion technologies such as hot melt extrusion (HME), spray-dried dispersion (SDD), or use of carriers such as mesoporous silica.

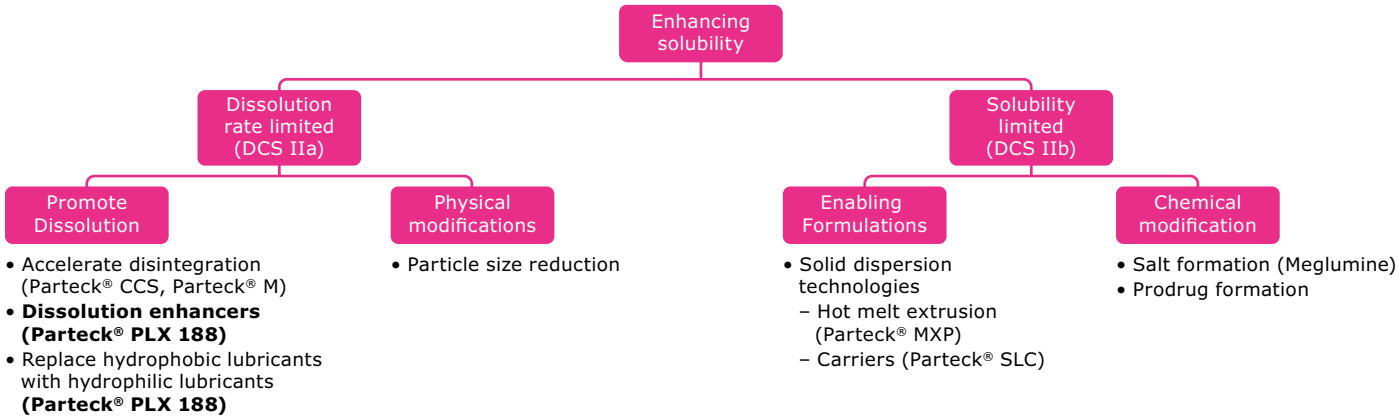


Figure 2.

Selection of the formulation strategy for poorly soluble molecules can be guided by the DCS class of the molecule.

Formulation Strategies for DCS IIa Molecules

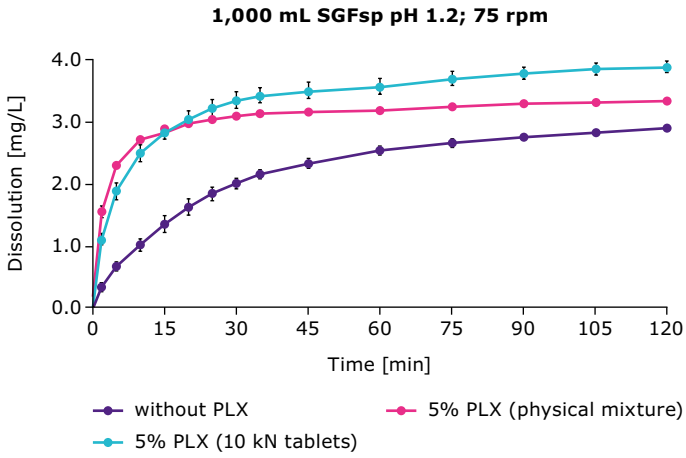
As described above, the main techniques for enhancing dissolution rates are particle size reduction or creating a more favorable dissolution environment by altering the formulation components. The effect of both formulation strategies is related to the impact on dissolution as described in the Noyes Whitney Equation. Specifically, this equation describes how dissolution rate is related to particle surface area, wetting and immersion.[7]

For particle size reduction, an increase in surface area results in an increased dissolution rate. For incorporation of surfactants or removal of hydrophobic excipients, the wetting and immersion of molecules in the dissolution media is improved, which is related to the chemical structure of the excipients. Surfactants, for example, such as poloxamer, consist of hydrophilic and hydrophobic components. The hydrophobic component can bind to the drug molecule while the hydrophilic component binds with the aqueous phase and effectively pulls the molecule into solution by accelerating the contact point between the molecule and the media.

Poloxamers are frequently used in pharmaceutical dosage forms and are especially useful when working with DCS Class IIa molecules. Parteck® PLX 188 is a multifunctional high-quality excipient that is specifically designed for dissolution enhancement of DCS Class IIa molecules. A block copolymer of polyethylene oxide and polypropylene oxide, it provides the dual hydrophobic and hydrophilic effect needed to enhance dissolution rate. Parteck® PLX 188 excipient can also be used as a hydrophilic lubricant, thus allowing the removal of hydrophobic lubricants such as stearates. Figure 3 shows how Parteck® PLX 188 excipient can be used to enhance dissolution rate of itraconazole.

Parteck® PLX 188 excipient is also compatible with direct compression and has an optimized particle size distribution making it well-suited for continuous manufacturing processes. Figure 4 shows that direct compression yields hard and consistent tablets in terms of size, shape, and weight even when the excipient is at a high percentage (30%) in the tablet blend.

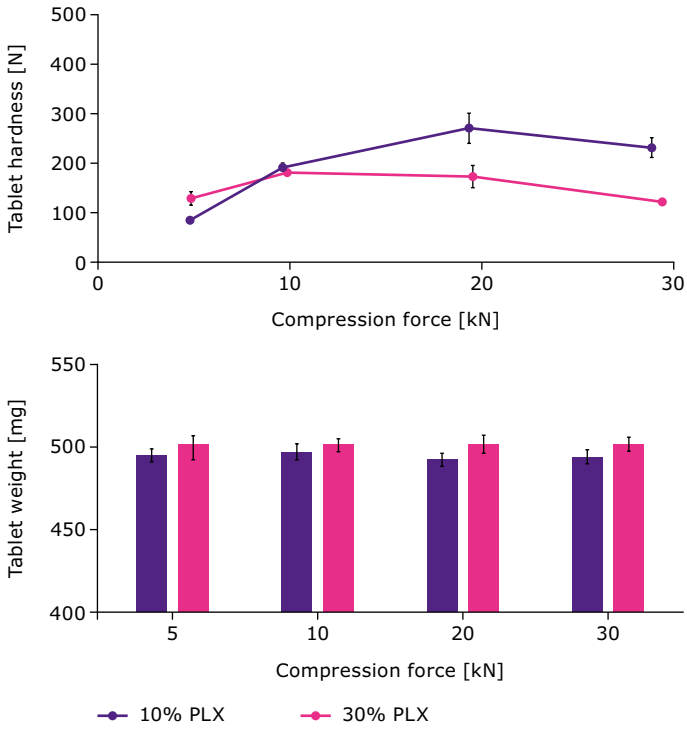
From a regulatory perspective Parteck® PLX 188 excipient is multi-compendial and exceeds the regulatory requirements for specified formaldehyde content. As an Emprove® Essential qualified product, Parteck® PLX 188 excipient also comes with an extensive array of quality and regulatory documentation that can assist in the filing of applications to regulatory authorities and for internal risk assessments and Quality by Design (QBD) approaches.



Component	Content [%]
Parteck® PLX 188	5
Itraconazole	20
Parteck® M 200 DC mannitol	69
Crosscarmellose sodium (CCS)	5
Magnesium stearate	1

Figure 3.

Dissolution of itraconazole formulated with Parteck® PLX 188 excipient.



Component	%
Parteck® PLX 188	10/30
Parteck® M 200 DC mannitol	84/64
Crosscarmellose sodium (CCS)	5
Magnesium stearate	1

Figure 4.

Tablet hardness and weight following direct compression of dosage forms containing Parteck® PLX 188 excipient.

Formulation Strategies for DCS IIb Molecules

Compared with DCS Class IIa, DCS Class IIb molecules present a greater challenge to formulators due to their truly low solubility. In this case, the formulation must be fundamentally altered to ensure enhanced solubility and generation of supersaturation, or solubility above thermodynamic concentrations. One way to accomplish this is with solid-state modification of the crystalline form, which is the most common solid-state in pharmaceutical pipelines.

The crystalline solid-state, while good for stability, can be an issue for DCS IIb molecules, as the strong crystal bonds that hold the crystal lattice together must be broken for solubilization to occur. The amorphous solid state, on the other hand, while chemically identical to the crystal, does not contain a crystal lattice and the energy required to solubilize this state is substantially lower. Therefore, the amorphous solid state is substantially more soluble than its crystalline counterpart (Figure 5).

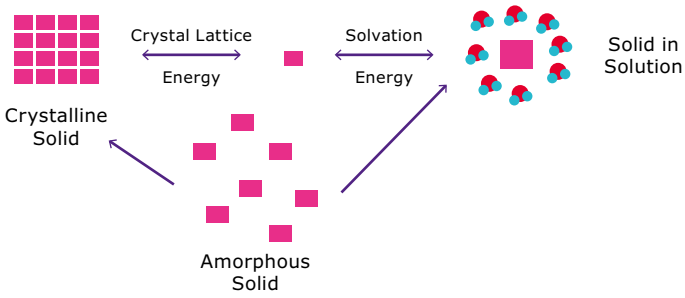


Figure 5.

Solubility of DCS IIb molecules can be enhanced with the amorphous form.

However, the amorphous solid state is not usually an energetically stable solid state, and is prone to re-crystallize back to the thermodynamically stable crystalline form. Therefore, to take advantage of the enhanced solubility that this solid state can provide, formulation technologies must be used to prevent recrystallization and stabilize the amorphous form.

The most common amorphous formulations are polymeric amorphous solid dispersions which contain a combination of drug and polymer, where the polymer is used as a matrix to stabilize the amorphous form of the molecule. The two main strategies for achieving this are spray-drying or melting of the mixture of drug and polymer. In spray-drying, the mixture of drug and polymer are dissolved in a favorable co-solvent; the solution is then spray dried into an SDD. In the melt-approach – HME – the drug and polymer are mixed, melted and extruded. In both approaches, the active pharmaceutical ingredient (API) is immobilized and stabilized in the amorphous solid state. The polymer essentially restricts the mobility of the drug, prevents recrystallization, and stabilizes the amorphous form.

Parteck® MXP excipient is a synthetic 4-88* polyvinyl alcohol that has been specifically engineered for the HME process and is compatible with stable and high drug loads. Parteck® MXP excipient also has high thermal stability, offers flexibility in downstream processing, and has optimized physical properties for HME processes. From a regulatory perspective, Parteck® MXP excipient is multi-compendial, conforming to the United States, European, Japanese and Chinese Pharmacopoeias.

Thermal stability of the polymer is a crucial consideration in HME, especially when formulating drugs with very high melting points. Parteck® MXP excipient offers increased solubility across a full range of APIs with no indication of chemical or physical instability (Table 1), also for challenging molecules such as telmisartan, which has a melting point of 260 °C.

API BCS II&IV	T_m of API	Loading Capacity	Solubility Enhancement (max.)
Ibuprofen**	78 °C	> 30%	2 ×
Cinnarizine	118–122 °C	< 20%	10 ×
Indomethacin	151 °C	> 50%	3 ×
Ketoconazole	146 °C	> 35%	17 ×
Naproxen	152 °C	> 30%	4 ×
Atorvastatin	159–160 °C	> 55%	154 ×
Itraconazole	167 °C	> 30%	80 ×
Carbamazepine	204 °C	> 30%	2 ×
Telmisartan**	260 °C	> 15%	35 ×

Table 1.

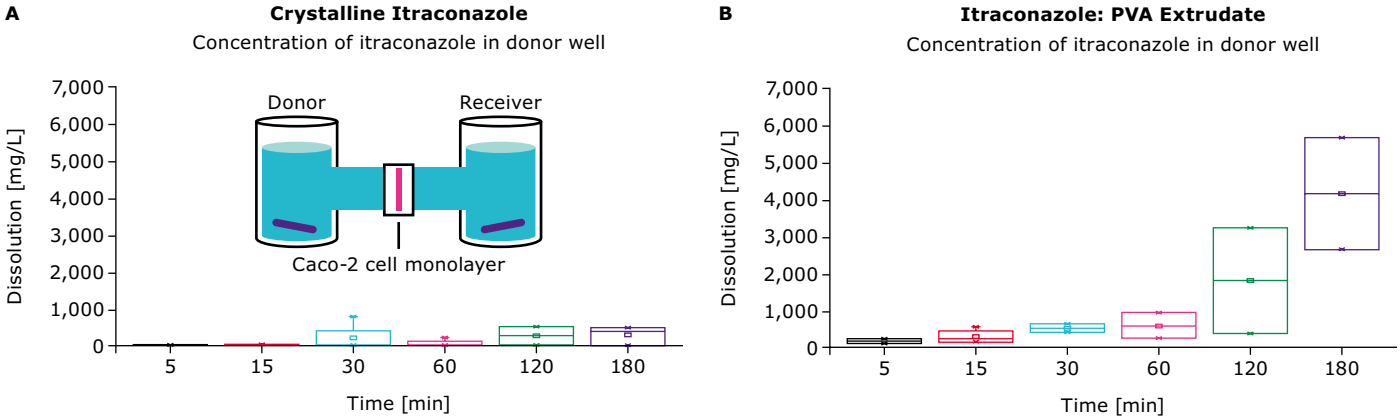
Parteck® MXP enhances solubility for a diverse set of APIs with different melting points.

* The PVA grade naming convention (e.g. 4-88) specifies the apparent viscosity in mPas of a 4% aqueous solution at 20 °C (first number) and the hydrolysis grade (second number).

** Plasticizer required.

Figure 5 demonstrates how Parteck® MXP excipient, when extruded with itraconazole, increases dissolution in a biphasic dissolution apparatus. The apparatus consists of a donor phase and a receiver phase separated by a monolayer of CaCo-2 cells and can be used to differentiate between dissolution and absorption. With crystalline itraconazole, the solubility in the donor well is low (Figure 6A) while the itraconazole extruded with Parteck® MXP excipient demonstrates a roughly tenfold enhancement in solubility (Figure 6B).

Figure 7 shows the amount of itraconazole absorbed through that CaCo-2 cell monolayer into the receiver phase. A very low concentration of the crystalline itraconazole is absorbed (A) compared to an approximately 20 to 50 fold enhancement for the itraconazole extruded with Parteck® MXP excipient.



Conditions: Milled extrudates itraconazole: PVA, 30% drug load. Measurement made using iDAS permeability system, Donor buffer: HBSSg, pH 6.5, Receiver buffer: HBSSg, pH 7.4, containing 4.5% BSA modified SGF, 37 °C, stirring

Figure 6.

Comparison of dissolution of crystalline itraconazole (A) and itraconazole extruded with Parteck® MXP excipient (B).

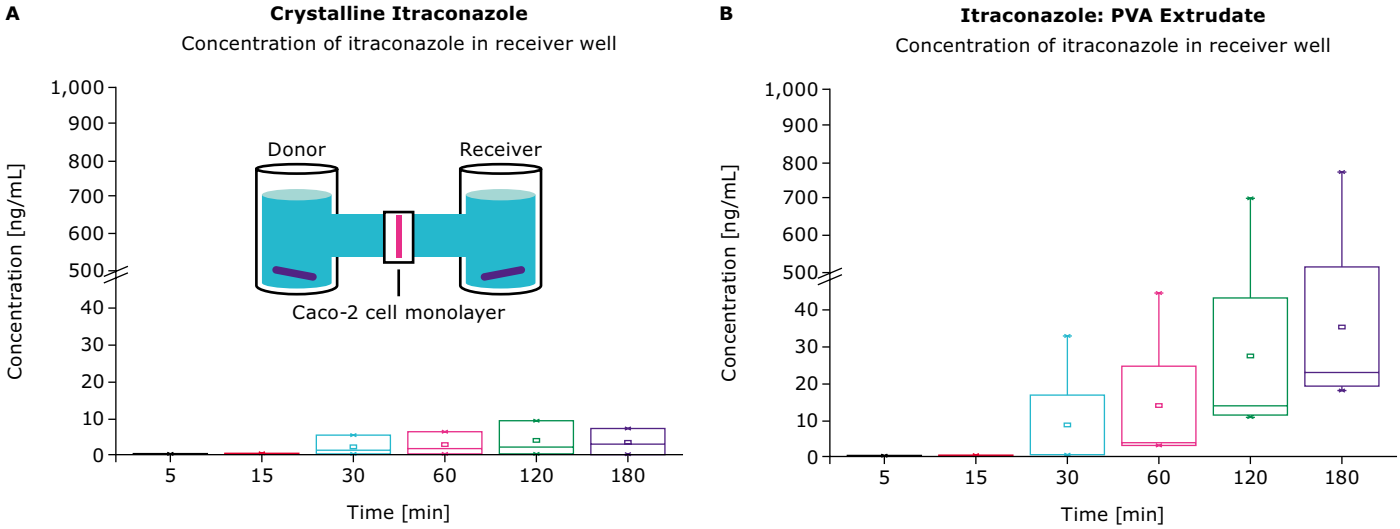


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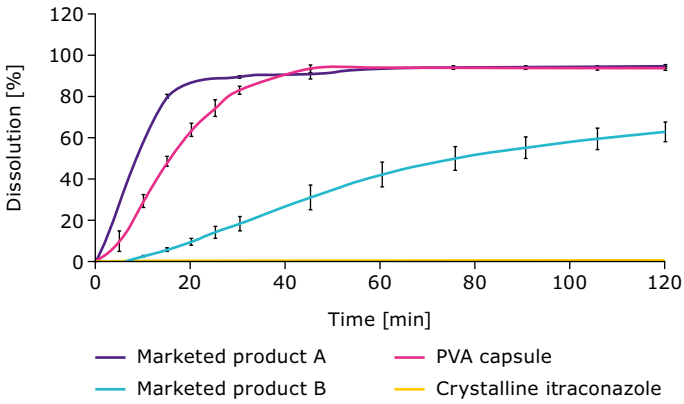
Figure 7.

Comparison of absorption of crystalline itraconzole (A) and itraconazole extruded with Parteck® MXP excipient (B).

Dissolution of itraconazole formulations with Parteck® MXP excipient were also compared to commercially available HME and SDD formulations of the drug (Figure 8). Parteck® MXP excipient formulations show a very strong dissolution performance compared to the commercially available HME formulation and outperforms the commercially available SDD formulation. Furthermore, the formulation with Parteck® MXP excipient was much simpler that the others, requiring fewer additional excipients.

In summary, solid-state modification using Parteck® MXP excipient in HME can be used to create a fundamental shift in the magnitude of the solubility of the molecules and is thus well-suited for DCS Class IIb molecules.



Dissolution method: FDA recommended conditions for itraconazole capsules, 900 mL SGF, 37 °C, 100 rpm, 100 mg itraconazole, 30% drug load.

Parteck® MXP capsule:
PVA
HPMC (Capsule)

Marketed product B using spray drying:
Glucose syrup
Hypromellose
Indigo carmin
Macrogol 20,000
Starch
Sacrose
Titanium dioxide

Marketed product A using hot melt extrusion:
Colloidal SiO_2
Crospovidone
Hydrogenated vegetable oil
HPMC
MCC
Lactose
Mg stearate
PEG
Talc
Titanium dioxide

Figure 8.

Comparison of Parteck® MXP excipient formulations with commercially available products.

While polymers are the gold standard for solid dispersion technologies, alternative approaches have been used to great success, such as mesoporous silica. Silicon dioxide has been used for decades in pharmaceutical applications primarily as a glidant. In addition, mesoporous silica is generally recognized as safe (GRAS) by the FDA. Parteck® SLC excipient is a mesoporous silica carrier and, from a regulatory perspective, conforms to the United States Pharmacopoeia and European Pharmacopoeia.

Parteck® SLC excipient is a mesoporous silica carrier with 6 nm pores, which are critical for stabilization of the amorphous form. It stabilizes the amorphous form of a poorly soluble molecule by steric confinement in its nanosized pores. In short, molecules are first dissolved in an organic solvent, which breaks down the crystal lattice. This concentrated solution of the drug is then combined with Parteck® SLC excipient which, like a molecular sponge, is able to adsorb the solution within its porous structure. The solvent is then removed, and the molecule is left confined within the 6 nm pore and therefore stabilized in its amorphous form (Figure 9).

At a very basic level, this can be achieved using simple laboratory equipment such as rotary evaporators, or syringe pumps, but this process has also been validated at commercial scale.

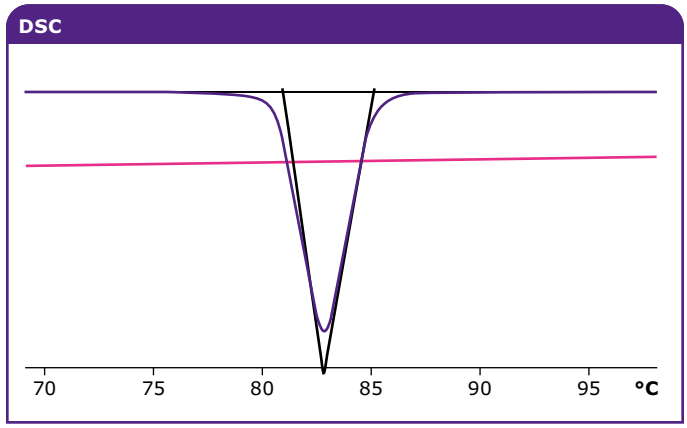


Figure 9.

DSC thermogram of fenofibrate in its crystalline state and after loading on Parteck® SLC excipient.

The suitability of this approach was investigated for a variety of APIs, including fenofibrate, a poorly soluble molecule typically categorized as DCS Class IIb. DSC results presented in Figure 9 confirm the amorphous state of fenofibrate after loading on Parteck® SLC excipient. Dissolution of a fenofibrate loaded silica is shown in Figure 10. Enhancement of the inherent solubility of fenofibrate requires use of a precipitation inhibitor to stop the inevitable precipitation out of the super saturated state.

The biorelevant dissolution of fenofibrate loaded silica in a suspension and a capsule were compared to a reference capsule containing the crystalline fenofibrate (Figure 10A). There was substantial improvement in dissolution of the mesoporous silica formulations and the inherent solubility when loaded onto Parteck® SLC excipient. The data correlates with *in-vivo* bioavailability in pigs (Figure 10B). Both the silica suspension and the silica capsules substantially outperform the crystalline fenofibrate and enhanced the oral bioavailability of this molecule.

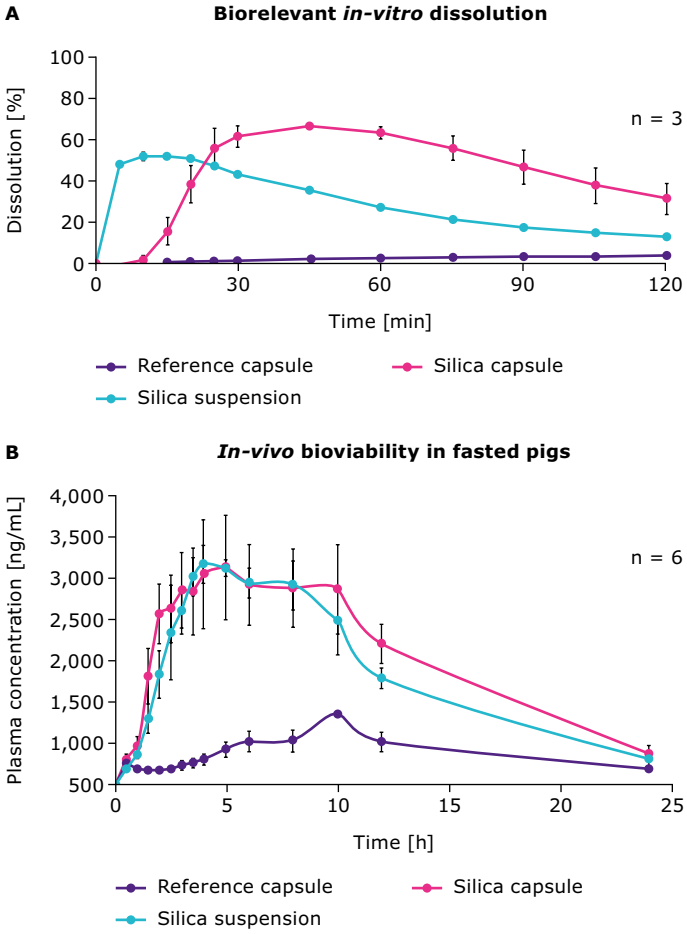


Figure 10.

In-vitro dissolution (A) and *in-vivo* bioavailability (B) of fenofibrate loaded onto Parteck® SLC excipient.

Conclusion

The DCS is an extremely useful tool for decision making during development of poorly soluble drug formulations. By enhancing understanding of the root causes of solubility issues, the number of resources needed to develop formulations can be significantly reduced and applied in a more directed and strategic manner.

The DCS is designed to allow differentiation of Class IIa and Class IIb molecules. Class IIa molecules have a slow dissolution rate and therefore simple strategies such as particle size reduction or incorporation of wetting agents or surfactants such as Parteck® PLX excipient can be used. Parteck® PLX 188 is a single excipient that provides multiple functionalities, improves process efficiency via an enhancement of dissolution, and is also compatible with future manufacturing capabilities. In contrast, DCS Class IIb molecules have low solubility and require more complex formulation to enhance their inherent solubility. One example is stabilization of the amorphous solid state using amorphous solid dispersions, such as with Parteck® MXP excipient and HME or via loading onto a porous carrier such as Parteck® SLC excipient.

With solubility remaining a critical part of formulation development, access to a diverse set of excipients is essential. Once the underlying cause of low solubility is defined with the DCS, a variety of solutions can be explored and applied to help ensure the success of a new therapeutic.

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