

Improving solubility – a close look at available approaches

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Introduction

The need to improve the solubility of active pharmaceutical ingredients (APIs) has been rising for decades. Today, this need is increasingly pressing, as the number of APIs that are poorly water-soluble (based on their BCS classification) is growing: while around 40% of APIs on the market show poor solubility, approximately 60% of new molecular entities (NMEs) have been reported to have solubility challenges, which represents a significant increase.[1] As a result, solubility-enhancing techniques have become an area of focus for pharmaceutical formulators. But why is the solubility of an API deemed so important in the pharmaceutical world? For an oral formulation, API solubility and permeability are critical factors for the absorption of the API in the gastrointestinal tract and its bioavailability at the site of action. However, the need for APIs with a good solubility or, where this is not the case, the need for ways to enhance solubility is not limited to oral formulations but is also a prerequisite for parenteral administration forms, as injectables or subcutaneous injection typically require the API to be present in a solubilized form.

Different approaches to solubility enhancement are available (see Figure 1). Chemical approaches such as salt and prodrug formation are typically more feasible in early development stages, as they fundamentally alter the API's chemical nature.

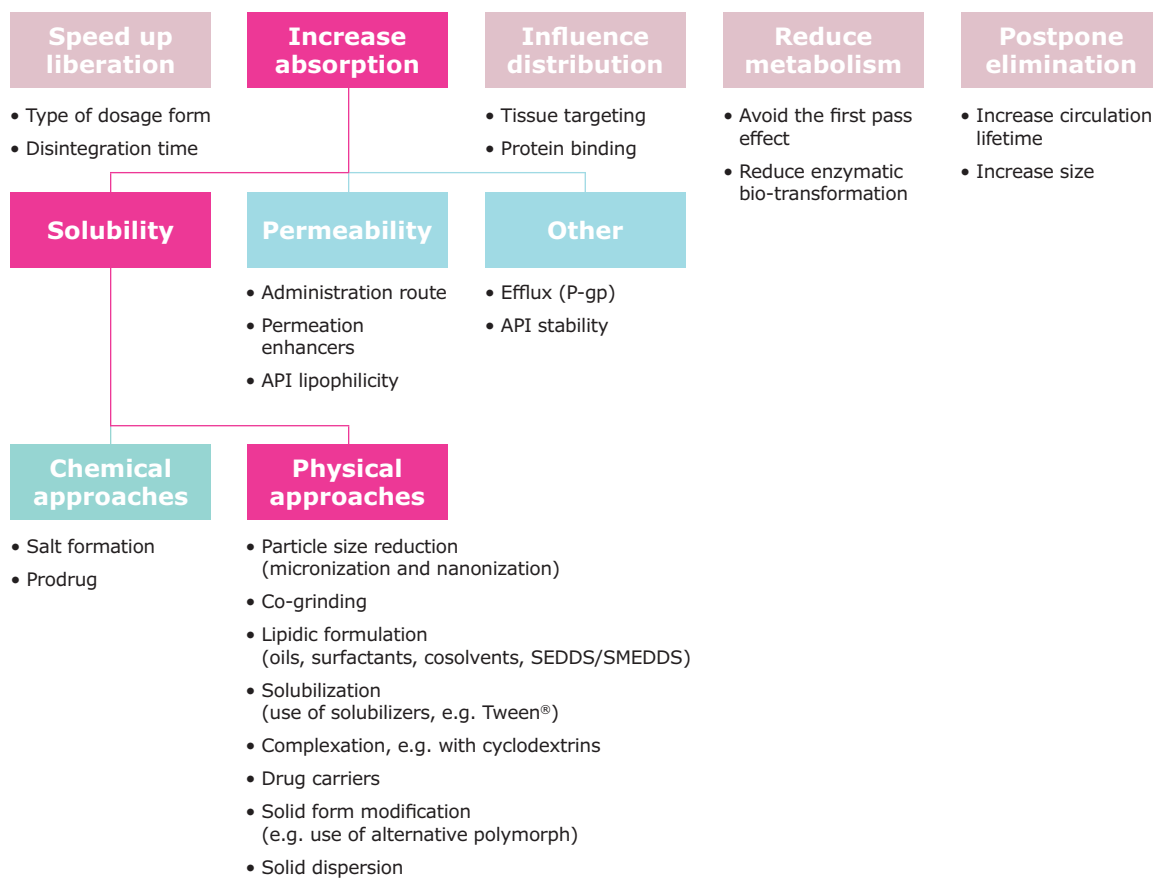
Physical approaches include:

- particle size reduction
- use of solubilizers
- complexation of the API
- loading of the API onto drug carriers
- using a more soluble polymorph
- formulating solid dispersions and solutions

These physical approaches in particular are highly relevant during formulation development. To find the right approach for the respective API and to achieve the desired performance of the final drug product *in vivo*, multiple technologies are typically considered and evaluated.

Figure 1:

Overview of different approaches used to improve API bioavailability, highlighting techniques commonly applied for solubility enhancement.



In this paper, we will focus on three techniques for modifying the physical state of APIs with the aim of enhancing solubility by converting the poorly soluble drug from its crystalline form into a stabilized amorphous structure. These three techniques are the use of drug carriers, spray-drying, and hot-melt extrusion. The latter two are often applied in the manufacture of solid dispersions and solid solutions. This approach dates back to Sekiguchi and Obi, who first introduced eutectic mixtures as a means for solubility enhancement.[1] Goldberg et al. further investigated this topic, coming to the conclusion that solid solutions – homogeneous, single-phase mixtures of the components – showed enhanced dissolution rates compared to eutectic mixtures.[2-5] In their 1971 publication, Chiou and Riegelman defined the term ‘solid dispersion’ – a definition that remains commonly accepted today – and gave an overview of different types of solid dispersion and their properties and methods of manufacture. In a solid dispersion, the API is generally dispersed or dissolved within a polymeric matrix, either in its crystalline or amorphous state or, in the case of solid and glassy solutions, at a molecular level.[6] Figure 2 gives an overview of the different types of solid dispersions, showing also that most are multi-phasic systems. The choice of

matrix polymer influences the dissolution rate of the dispersed or dissolved drug. For example, in solid solutions where the API is molecularly dispersed within the matrix, the dissolution rate is determined by the polymer properties. This makes the solid dispersion/solid solution approach applicable to both immediate-release and sustained-release formulations, depending on the matrix polymer applied. In the present article, the focus is on immediate-release systems, as these are one possible option for solubility enhancement of poorly water-soluble APIs. Solid dispersions and solid solutions can be manufactured in a variety of ways. In the literature, formulation techniques are typically classified into two types of approach: melting techniques and solvent techniques.[7] In his 1999 review, Serajuddin discussed the breakthroughs and challenges that came with the increased interest in solid dispersions. As explanations for the then very limited number of marketed solid dispersion-based products, he proposed difficulties with formulating the solid dispersion itself as well as formulation of the final dosage form including scale-up, reproducibility, the stability of the formulation’s components and the availability of suitable polymeric carriers.[8] Today, several of these difficulties seem to have been reduced – for instance, scale-up, due to

extensive investigation of possible approaches as well as established manufacturing methods like hot-melt extrusion, plus the increased availability of both small- and large-scale equipment for solid dispersion manufacture, which allows for an easier transition from lab

to production scale.[9] However, some hurdles remain: in particular, the relatively limited number of polymeric excipients suitable for pharmaceutical use is still perceived as a severe limitation of this approach.

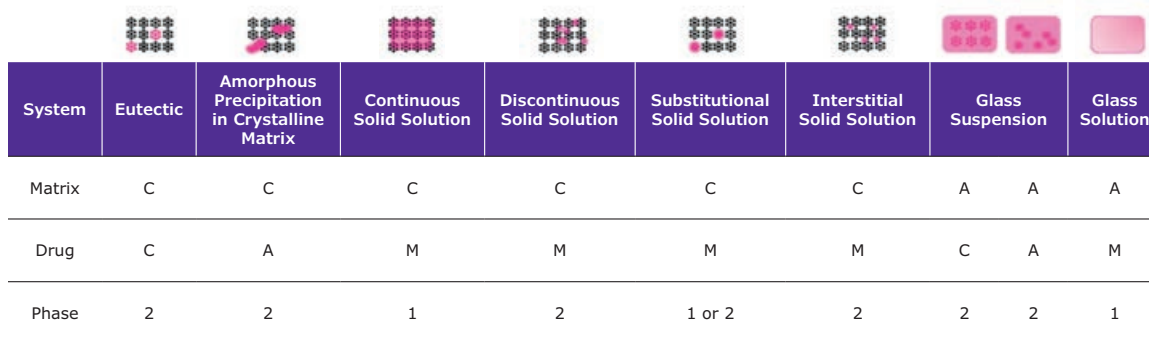


Figure 2: Visualization of possible types of solid dispersion, based on the information presented by Dhirendra et al.[6]

A Amorphous, **C** Crystalline, **M** Molecularly dispersed

This publication will compare hot-melt extrusion as one possible melting technique approach and spray-drying as one possible solvent technique approach for creating solid dispersion formulations.

Loading the API onto a silica-based drug carrier is an approach that has attracted considerable interest in the past decade. The API is adsorbed in its amorphous form onto the surface of the drug carrier and within its (meso-)porous particle structure. This makes this method a viable option for solubility enhancement, which is why it will be explored as an alternative to the solid dispersion approaches in this publication.

In general, with all solubility-enhancing technologies where supersaturated systems are achieved, there is also a potential for spontaneous recrystallization of the API, hindering its performance. Luckily, there are several ways to address this challenge, such as by adding recrystallization-inhibiting excipients; however, these will not be covered in-depth within this paper. A recent review by Price et al. gives a thorough summary of the background and the approaches for stabilization of the supersaturated state, focusing especially on precipitation inhibition, and highlighting available excipients that can be used and tools for selecting them.[10]

Hot-melt extrusion

Hot-melt extrusion (HME) is a technology that has long been used in the plastics and food industry and that was first applied for pharmaceutical formulation in 1971 by

El-Egakey et al.[11] Various research groups studied and refined this approach further, specifically focusing on pharmaceutical applications.[12, 13] HME is not only suitable for solid dispersion but also for the manufacture of formulations with different release kinetics, such as sustained-release dosage forms.[14-16] The benefits of this technology include its suitability for continuous manufacturing processes and its flexibility in relation to the variability of instrument set-up, process settings, the polymeric matrix used and the various types of downstream equipment available. As such, the equipment set-up, process settings and excipients used may be tailored as needed for the respective API(s) and final drug performance.[17, 18]

Due to the excellent formulation possibilities that HME technology offers, interest in it has grown within the pharmaceutical sector. The number of scientific publications on, and patents for, HME technology has continued to rise since the 1980s, ultimately resulting in a number of HME-based formulations on the market. An overview of marketed products based on amorphous solid dispersions by Wyttenbach et al. shows the relevance of HME technology for this segment, as 42% are manufactured via HME, 32% via spray-drying and 26% via other available technologies.[19] There are challenges with this technology that need to be overcome, however. Temperature is a very critical factor. In order to formulate an amorphous solid dispersion, the API needs to be dissolved at the molecular level within the polymer matrix. HME achieves this by

utilizing elevated temperature and shear forces throughout the extrusion process. When defining the process and choosing a polymeric matrix, the glass transition temperature (T_g), melting temperature (T_m) and degradation temperature (T_{deg}) of all components including the API have to be taken into careful consideration. One has to be aware that local temperature rises may occur, depending on the process set-up, e.g. due to friction, and that processing via HME imposes temperature stress upon both the API and excipient(s). Also, a carrier polymer with a high T_g may not be a suitable choice for a temperature-sensitive API. Difficulties have been experienced particularly when the T_g is relatively close to the T_{deg} . In these cases, the use of a plasticizer may prove helpful, as this lowers the T_g of the polymeric carrier and improves its processability.[20] The choice of polymer is also the key determinant of the release performance of the final formulations – depending on the polymer, immediate- or sustained-release profiles are possible. One main drawback of this technology is the relatively limited number of polymers, especially for heat sensitive APIs and APIs with high $T_m > 200$ °C. Available polymers include polyvinylpyrrolidone-co-vinyl acetate, polyvinyl caprolactam-polyvinyl acetate-PEG graft copolymer, and cellulose derivatives such as hydroxypropyl methylcellulose and hydroxypropyl methylcellulose acetate succinate. One might think that the development of novel polymers should be pursued more intensively to overcome this limitation. However, in the pharmaceutical world, there are significant hurdles to the use of novel excipients that have to be considered. Besides elaborate safety assessments and regulatory requirements, there is a general reluctance to utilize novel excipients, as this may result in unplanned costs and delays during the (already quite challenging) process of bringing a drug formulation to market.

Fortunately, there are polymers available that have been used in other pharmaceutical applications for decades and that have a well-described safety profile; such a polymer that has been explored for use in HME applications very recently is polyvinyl alcohol (PVA).[21-23]

PVA is a synthetic polymer produced by the polymerization of vinyl acetate and partial hydrolysis of the resulting esterified polymer. First discovered in 1924 by Herrmann and Haehnel [24, 25], PVA has been used in approved drug products for decades. As early as 1951, PVA was listed as a suitable polymer for coatings of pharmaceutical drug products in a pharmaceutical reference handbook.[26] PVA also has a long history of use in other applications such as the food and cosmetic industries. It is generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA) – a GRAS notice has been filed on the application of PVA in the solid oral coatings sector – and evaluations of PVA toxicity and safety by different authorities are available, as well as scientific publications on this topic. The acceptable daily intake (ADI) for humans is 50 mg/kg body weight as identified by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2003. To summarize, there is well-founded scientific evidence for the safety of PVA.[27-33]

Moreover, PVAs are very stable under thermal stress. The T_{deg} of PVAs is up to 250°C. The first PVA-based polymeric carrier specifically developed for use in HME is Pardeck® MXP. Critical factors for hot-melt extruded solid dispersions, such as flowability, melt viscosity, thermostability, API compatibility and extrudate stability, were considered and investigated during the development of this new pharmaceutical excipient. Its good compatibility with a wide range of APIs of different physicochemical properties is shown in Table 1.

Table 1:

Solubility enhancement and drug loadings of selected APIs after extrusion with Pardeck® MXP

*Maximum API load is defined as the maximum amount of API present in an amorphous state in the extrudate observed for experimental data.

**Plasticizer is required to make the extrusion feasible or easier.

API	T_m of API [°C]	API Load Achieved* [%]	Solubility Enhancement [max.]
Ibuprofen**	78	30	2 x
Cinnarizine	118 – 122	< 20	10 x
Indomethacin	151	50	3 x
Ketoconazole	146	35	17 x
Naproxen	152	30	4 x
Atorvastatin	159 – 160	55	154 x
Itraconazole	166.5	30	80 x
Carbamazepine	204	30	2 x
Telmisartan**	260	15	35 x

One of the APIs used in hot-melt extruded formulations with the PVA-based Parateck® MXP excipient was itraconazole. As well as exploring the effect on solubility and dissolution characteristics, special emphasis was placed on the miscibility of the API and polymer – including an analysis of the API distribution within the polymeric carrier at different drug loadings – and the level of drug loading that can be achieved while still ensuring an amorphous system and a stable extrudate.

The X-ray diffraction (XRD) results in Figure 3 show that the API is present in its amorphous state in the extrudate up to drug loadings of 40% (w/w), possibly even higher. This was confirmed by differential scanning calorimetry (DSC) analysis (for sample results, see Figure 4). The distinct melting point of crystalline API at about 166 °C is not observed in the extrudate, indicating the amorphous state of the API. A prominent glass transition can be detected at about 60 °C followed by slight indications of mesophase transitions between 70 °C and 90 °C. As a result, it was concluded that the system present is a two-phase system of amorphous API and amorphous carrier – a glass suspension (see also Figure 2 for different types of solid dispersion systems). To assess the quality of the manufactured extrudate and to allow for a prediction of its storage stability, the distribution of itraconazole within the PVA matrix was investigated using scanning electron microscopy/energy dispersive spectroscopy (SEM-EDS). This analytical technique allows for the chemical characterization of a sample, making it possible to investigate the distribution of the API within the polymeric matrix. In the present case, employing a chlorine marker for itraconazole and an oxygen marker for the PVA matrix, it was observed that while the distribution is very homogeneous within extrudates of drug loadings as high as 30% (w/w), API clusters were present in the extrudate with a drug loading of 40% (w/w; see Figure 5). A homogeneous distribution of the API within the polymeric carrier is not only important for the long-term stability of the extrudate but is also of utmost importance for the content uniformity of the final drug product. For this reason, further assessments of the extrudate performance were limited to the 30% (w/w) extrudate while omitting the 40% (w/w) extrudate.

The *in-vitro* dissolution of the extrudate (30% w/w drug load) showed a significant increase in initial dissolution rate compared to the pure crystalline API (see Figure 6). The amount of dissolved API after 120 min of dissolution was approx. 120 times higher with the extrudate than for the untreated drug substance. The stability of the extrudate was investigated over a period of 12 months under cold, long-term and accelerated conditions. No change in the dissolution profile was observed under any of the conditions (see Figure 6). In addition to dissolution, DSC analysis and high-performance liquid chromatography were employed to assess the effect of storage on the extrudate. No recrystallization or degradation of the API was observed via these methods (data not shown). Therefore, it was confirmed that the formulated amorphous solid dispersion system of itraconazole as the model API and the PVA-based matrix Parateck® MXP shows good stability over time with regard to the physical state of the API, degradation stability and dissolution performance. The suitability of Parateck® MXP as a polymeric matrix for use in HME was also confirmed for other APIs including indomethacin, atorvastatin and telmisartan (see Table 1).

Compared to marketed formulations of the same API, Parateck® MXP formulations are remarkably simple with regard to processing and formulation composition (see Figure 7). A comparable dissolution profile to a marketed tablet that was also manufactured using solubility enhancement techniques was achieved, with the Parateck® MXP extrudate formulation showing an increased initial dissolution rate. In addition to filling of the milled or pelletized extrudate into capsules, direct compression of the milled extrudate into tablets and direct shaping of tablets were also successfully employed as alternative downstream processing methods.[34] Overall, it was demonstrated that Parateck® MXP has a wide application range: it is suitable for a variety of APIs, multiple types of final dosage form, and drug formulations with diverse release profiles, including immediate and sustained release.[35] Its additional applications for solubility enhancement extend beyond conventional hot-melt extrusion for solid oral dosage forms as described above, and include the manufacture of films as well as additive manufacturing techniques such as 3D-printing. [36-39]

When working on formulations with enhanced API solubility, it is critical to not only achieve a supersaturated state but also to maintain this thermodynamically unstable state. Often, precipitation inhibitors need to be added to prevent recrystallization of the API in solution. It has been successfully shown in the literature that PVA inhibits the precipitation of poorly water-soluble itraconazole as a model API and is superior to HPMC and other commonly used precipitation inhibitors. An extrudate using a mixture of PVA and

copovidone as the carrier showed the best supersaturation, benefiting from the added value of each one of the individual polymers. [40]

These findings confirm the excellent suitability of the PVA-based excipient Parteck® MXP for solubility enhancement using HME processes, and show that its amphiphilic nature allows it to also act as a precipitation inhibitor after dissolution.

Figure 3:

XRD graph of itraconazole-Parteck® MXP extrudate with different drug loadings (5 – 30% w/w) compared to the pure crystalline API and PVA placebo extrudate.

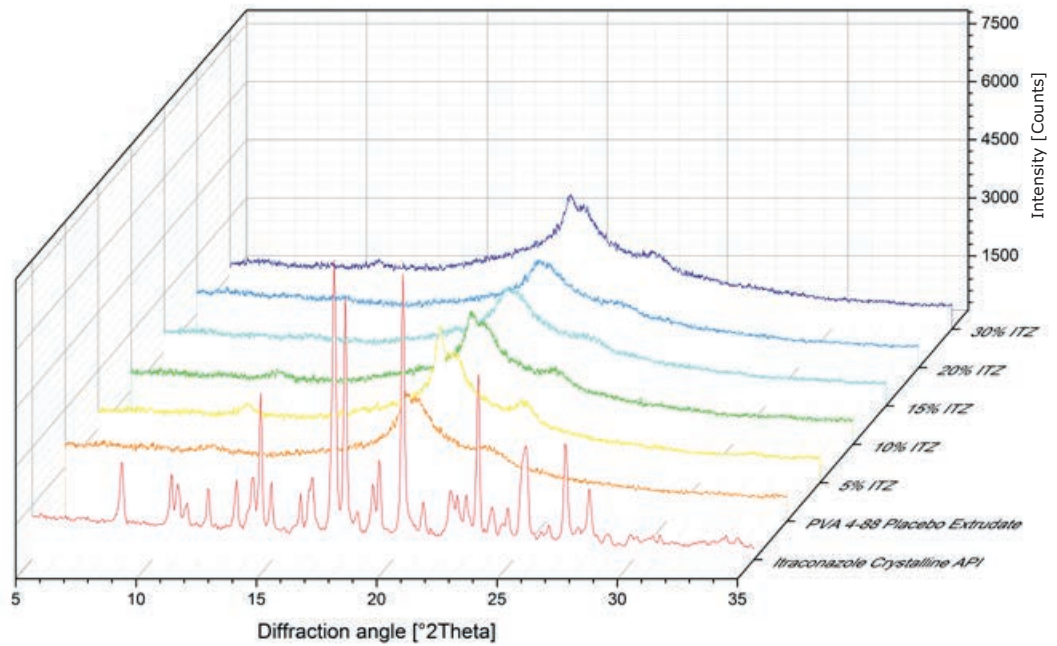
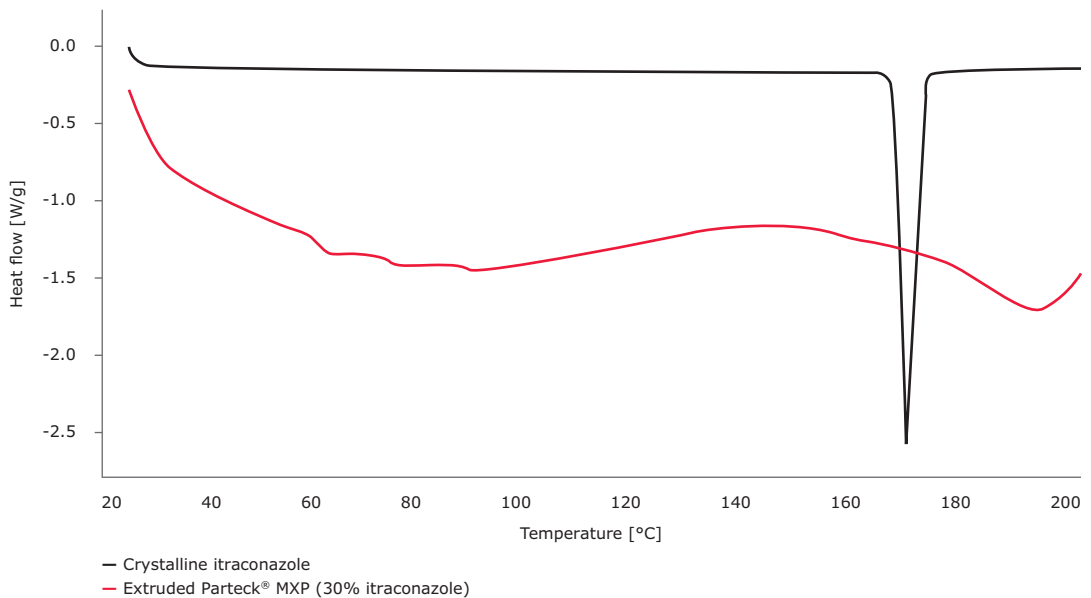


Figure 4:

DSC thermogram of itraconazole-Parteck® MXP extrudate (drug loading 30% w/w) in comparison to the pure crystalline API



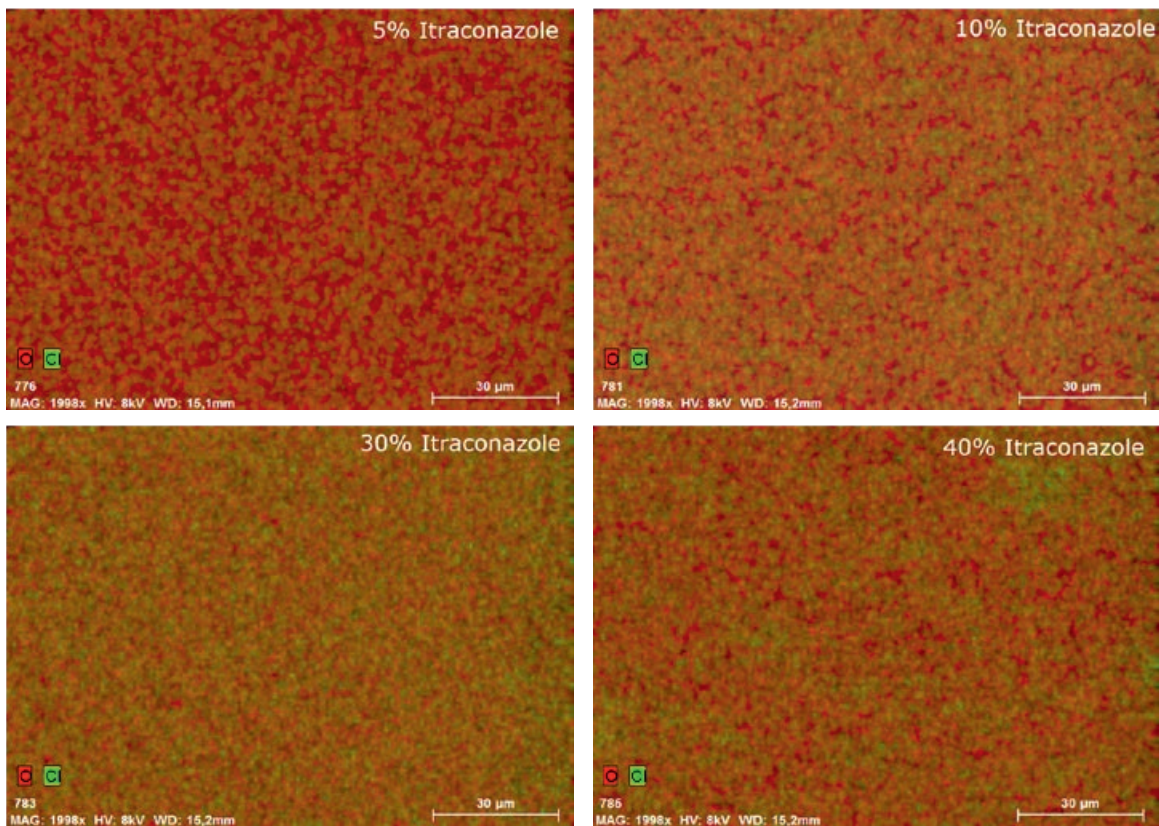


Figure 5: SEM-EDS measurements of hot-melt extruded itraconazole-Parteck® MXP formulations with different drug loadings (5 - 40% w/w). Green indicates itraconazole (chlorine marker), red indicates PVA (oxygen marker).

(Analysis conditions: Samples were sputtered with 2 nm platinum to avoid charging effects, and a cooling stage at 5 °C was used to minimize beam damage. Parameters: 8 keV/Working distance: 15mm/beam intensity 10/measurements performed under high vacuum.)

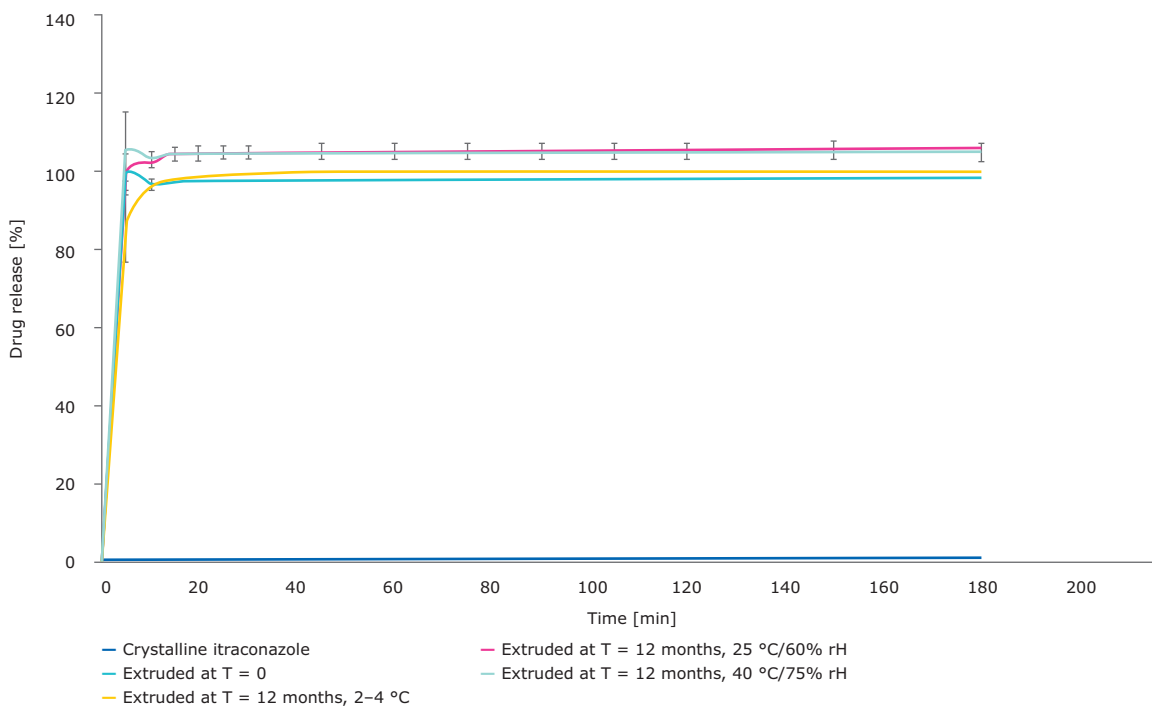
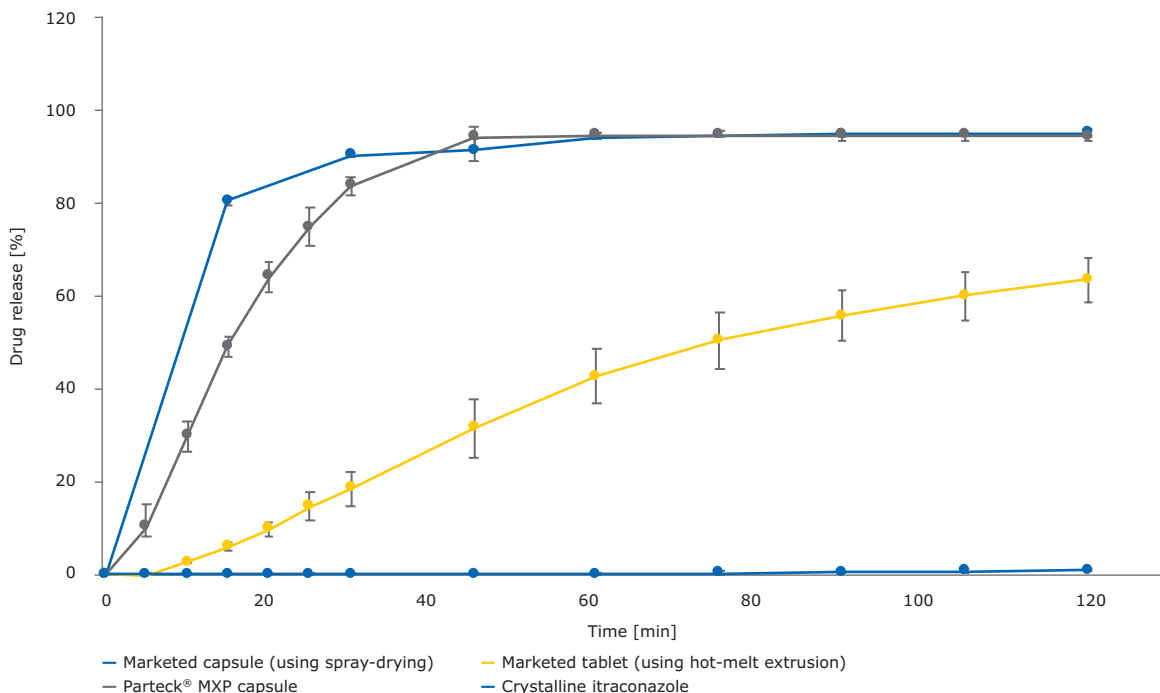


Figure 6: Dissolution profile of hot-melt extruded itraconazole-Parteck® MXP formulation (drug loading 30% w/w) after 0 and 12 months at low temperature, room temperature and at accelerated conditions compared to the pure crystalline API.

(Dissolution conditions: FDA-recommended method for itraconazole, 900 mL SGF, 37 °C, 100 rpm, 100 mg itraconazole, drug loading 30% w/w, n=3)

Figure 7:

Capsule formulation of itraconazole-Parateck® MXP extrudate compared to two marketed final drug products, both employing solubility enhancement techniques. Dissolution profiles are shown in comparison to the pure crystalline API.



(Dissolution conditions: FDA-recommended method for itraconazole, 900 mL SGF, 37 °C, 100 rpm, milled extrudate with a drug loading of 30% w/w corresponding to an amount of 100 mg itraconazole in the final formulation filled into a capsule, n=3)

Parateck® MXP capsule

Parateck® MXP (PVA)

Marketed capsule (using spray-drying)

Parateck® MXP (PVA), Lactose, NaCl

Marketed tablet (using hot-melt extrusion)

Colloidal SiO₂, Crospovidone, Hydrogenated vegetable oil, HPMC, MCC, Lactose, Mg Stearate, PEG, Talc, TiO₂

Drug carriers

Mesoporous silica materials have been used in the pharmaceutical sector since the early 1970s; the first publication on silica's suitability for drug adsorption and dissolution enhancement was by Monkhouse and Lach in 1972.[41] The suitability of silica-based drug carriers for controlled release formulations was first described by Vallet-Regi et al. in 2001.[42] Loading the API onto mesoporous silica drug carriers was found to be another viable approach for enhancing the solubility of poorly water-soluble APIs.[43-45] In a similar way to the other approaches described above, the API is typically transformed into the amorphous form during the process, exhibiting an improved apparent solubility. It is essential that the silica particles have a large surface area as well as mesopores so that the API can embed itself in the porous surface structure of the carrier particles, which may then be formulated into solid oral dosage forms (see Figure 8 for schematic overview). While the loading process involves the use of organic solvents, it has been

shown that these are completely removed during the process. One benefit of this technology compared to spray-drying – another technique requiring the use of organic solvents – is that no common solvent for the API and carrier (in the case of spray-drying, the API and polymer) needs to be identified, merely a suitable solvent for the API. In spray-dried and hot-melt extruded solid dispersions, the amorphous API is distributed within the typically glassy polymer, which offers the opportunity for molecular movement and may result in a recrystallization of the API. By contrast, loading the amorphous API onto the silica drug carrier surface stabilizes it via adsorption. The drug molecule is then sterically hindered and molecular movement is very unlikely. This is a major advantage, as it overcomes instability effects during storage that result from the conversion of the amorphous form of the API into a more thermodynamically stable but less soluble form – which is one of the key challenges with solid dispersion formulations.

The silica-based carrier Parateck® SLC exhibits a highly functional surface structure with disordered mesopores and a large and easily accessible surface area of approximately 500 m²/g. This allows for the deposition of high API loads. In the present study, the physical state of the API and the effect of the loading process on dissolution performance were investigated with various model APIs in order to assess the suitability of the excipient and technology for solubility enhancement. Additional investigations included an analysis of API distribution on the carrier surface as well as *in-vivo* studies to confirm the bioavailability-enhancing performance that was seen *in vitro*.

Prior to loading the API onto Parateck® SLC, a suitable organic solvent from which the API will be loaded has to be determined. It is important to choose a solvent with an appropriate boiling point, as this is critical for easy removal of the solvent after the loading process. Using the solvent impregnation method, the API solution is added drop-wise to the silica powder via a cannula. The loading process itself needs to be performed in a well-ventilated environment suitable for handling organic solvents, using nitrogen and gas removal to prevent solvent condensation. Continuous stirring ensures a homogeneous distribution of the API and, following the complete addition of the API solution, a drying step is required to remove the solvent used. This loading technique requires no specialized equipment, merely commonly available laboratory equipment. At production scale, it requires the additional use of established manufacturing equipment for solid dose formulations, such as a high shear mixer. However, special requirements – e.g. relating to the use of organic solvents – need to be taken into consideration.

Using carvedilol as the model API, API amounts corresponding to a drug loading of 25% (w/w) were loaded onto Parateck® SLC. DSC analysis confirmed the absence of crystalline API after the loading process (see Figure 9). Dissolution tests showed that the dissolution performance of the API was successfully enhanced by the method used: compared to the pure crystalline API, both the initial dissolution rate and the maximum dissolved concentration of the API were increased, reaching a supersaturation level of 2.34 times above saturation solubility after 120 minutes of dissolution (see Figure 10A).

Compared to a marketed product of the same API, the silica-based formulation also showed an increased initial dissolution rate and reached supersaturation levels with the dissolved amount of API 1.8 times higher than for the marketed product (see Figure 10B).

Using fenofibrate as the model API, drug loadings of 30% (w/w) were successfully loaded onto Parateck® SLC. XRD and DSC analysis results confirmed the amorphous state of the API after loading (see Figure 11). To better understand the distribution of the API on the carrier surface, SEM-EDS measurements were conducted with markers for the respective components. It was confirmed that the API is distributed homogeneously on the entire carrier particle surface including the inner porous structure, an important aspect for achieving high drug loadings (see Figure 12).

Several publications have reported that mesoporous silica-based dosage forms offer the potential to improve the absorption of poorly soluble drugs after oral administration. Dressman et al. used fenofibrate as a model drug to study the ability of mesoporous silica to improve release by means of a ‘spring’ effect in *in vitro* biorelevant dissolution tests. The addition of various polymers to provide a ‘parachute’ effect – that is, to keep the drug in solution after its release – was investigated. The properties of fenofibrate-loaded porous silica substantially improved the dissolution profile of fenofibrate under fasted state conditions compared with both the pure drug and the marketed product. Adding a polymer such as hydroxypropyl methylcellulose acetate succinate (HPMCAS) or others sustains the higher release of fenofibrate from the silica carrier, resulting in a combined ‘spring and parachute’ effect – loading the drug onto the silica causes a ‘spring’ effect, while the polymer enhances this and adds a sustaining ‘parachute’. For fenofibrate, a silica-to-polymer ratio of 4:1 w/w appears to have an optimal effect (for HPMCAS). Dissolution results under conditions simulating the fasted state in the small intestine for fenofibrate-loaded silica with HPMCAS added in a 4:1 w/w ratio show very substantial improvement over the marketed, nanosized product.[43]

Dissolution testing confirmed the suitability of the silica-based drug carrier Parateck® SLC for enhancing the solubility of the model API fenofibrate *in vitro*, showing an increase of the initial dissolution rate compared to the pure API. To verify the relevance of these results, *in-vivo* bioavailability studies were performed by O’Shea et al., who demonstrated that the ability of mesoporous silica Parateck® SLC to enhance the solubility and dissolution behavior of poorly water-soluble fenofibrate as a model API indeed has a positive effect on its bioavailability in pigs (see Figure 13). [46] The positive *in-vivo* effect of API loading onto a silica-based drug carrier was also confirmed by Puchert et al. in a rat study.[47]

To summarize the results, it was demonstrated that loading onto Parateck® SLC not only improves API solubility and dissolution performance *in vitro*, but also increases *in-vivo* bioavailability, thus making it a suitable approach for the formulation of poorly water-soluble APIs. While HME and

spray-drying methods typically require additional processing steps such as milling of the extrudate in the case of HME and pre-compaction in the case of spray-dried powders prior to further processing, API-loaded Parateck® SLC can be used directly in the tableting process.

Figure 8:

Schematic overview of the functionality of inorganic (meso-) porous drug carriers

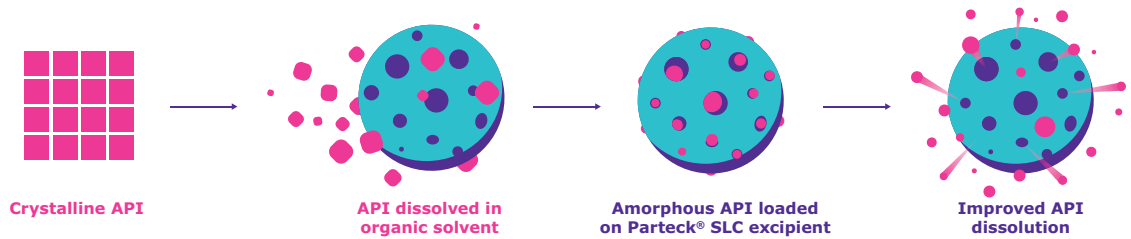
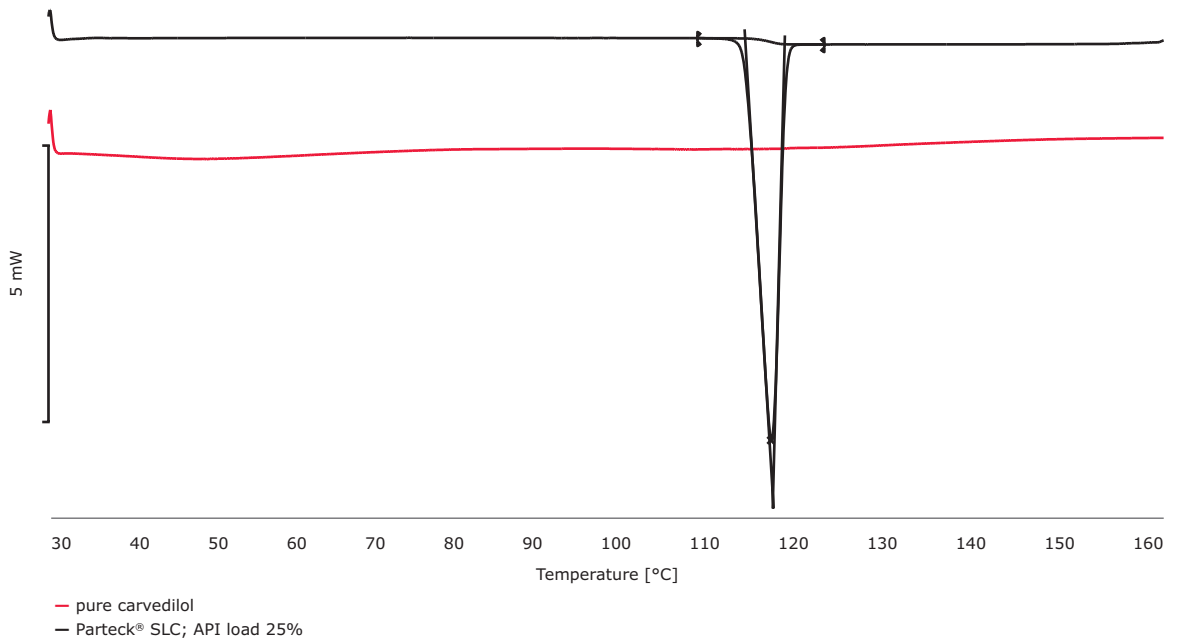


Figure 9:

DSC thermogram of pure model API carvedilol and API loaded onto Parateck® SLC (drug loading 25% w/w)



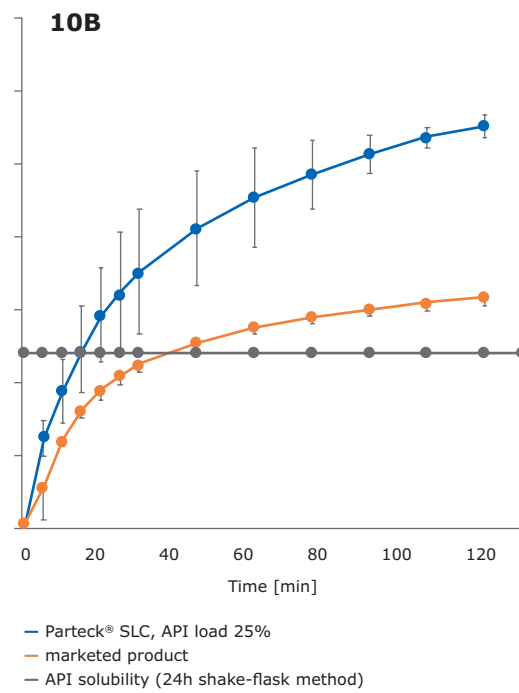
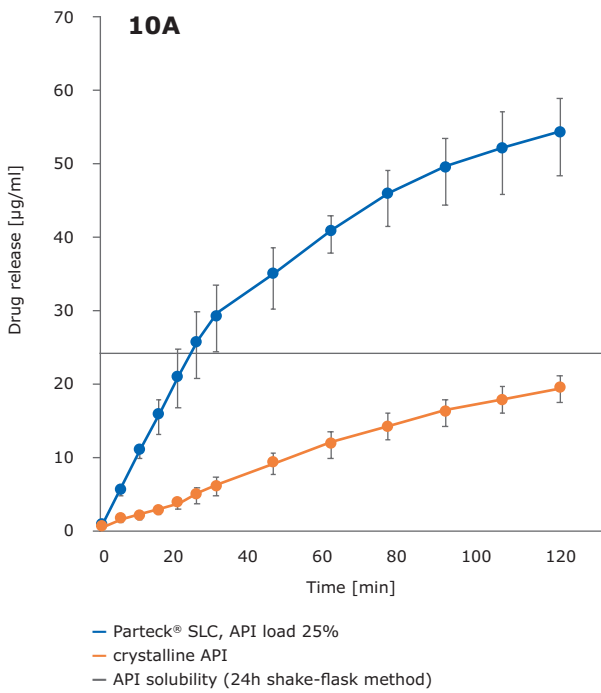


Figure 10:
Dissolution profile of model API carvedilol loaded on Parateck® SLC (drug loading 25% w/w) compared to A) pure crystalline API and B) a marketed product of the same API.

(Dissolution conditions 10A: USP apparatus 2, 1000 mL phosphate buffer at pH 6.8, 37 °C, 75 rpm, weighted samples corresponding to an amount of 50 mg API, n=3;

Dissolution conditions 10B: USP apparatus 2, 500 mL phosphate buffer at pH 6.8, 37 °C, 75 rpm, marketed product and API-loaded Parateck® SLC corresponding to an amount of 25 mg API, n=3)

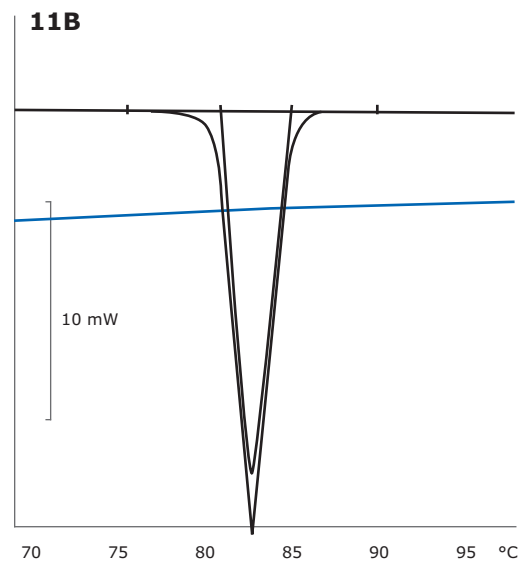
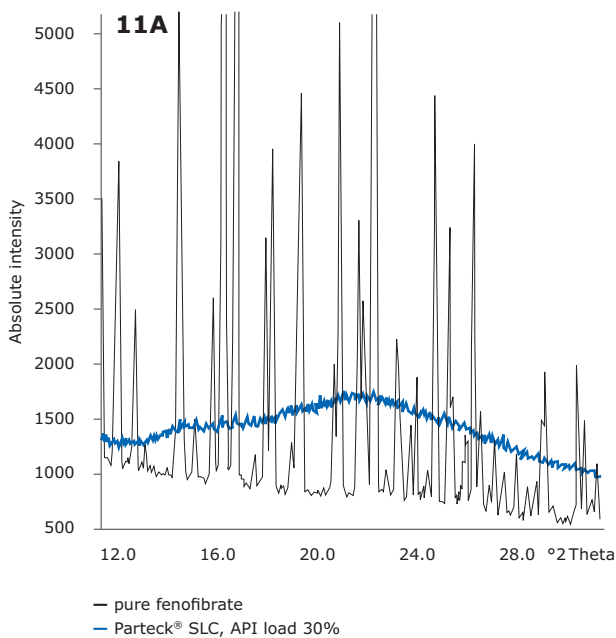


Figure 11:
Solid state analysis of fenofibrate-Parateck® SLC formulation in comparison to pure crystalline API: A) XRD graph and B) DSC thermogram.

Figure 12:

SEM-EDS measurements after microtome sectioning to highlight the distribution of the respective components: A) SEM-EDS measurement showing the pure silica carrier without the use of markers, and SEM-EDS measurement with markers for B) the silica carrier (blue), C) the resin required by this analytical technique (red) and D) the API (yellow).

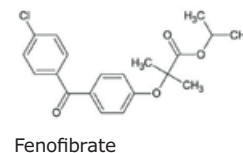
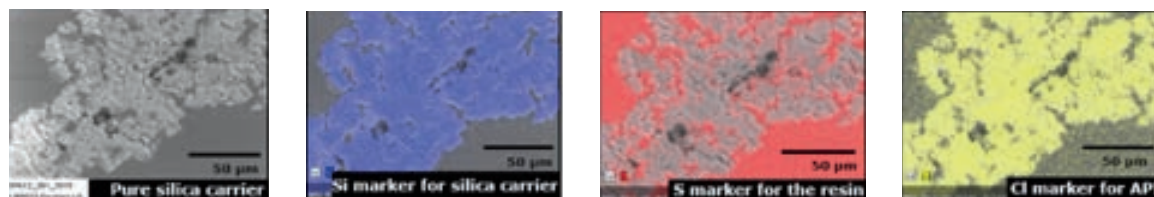
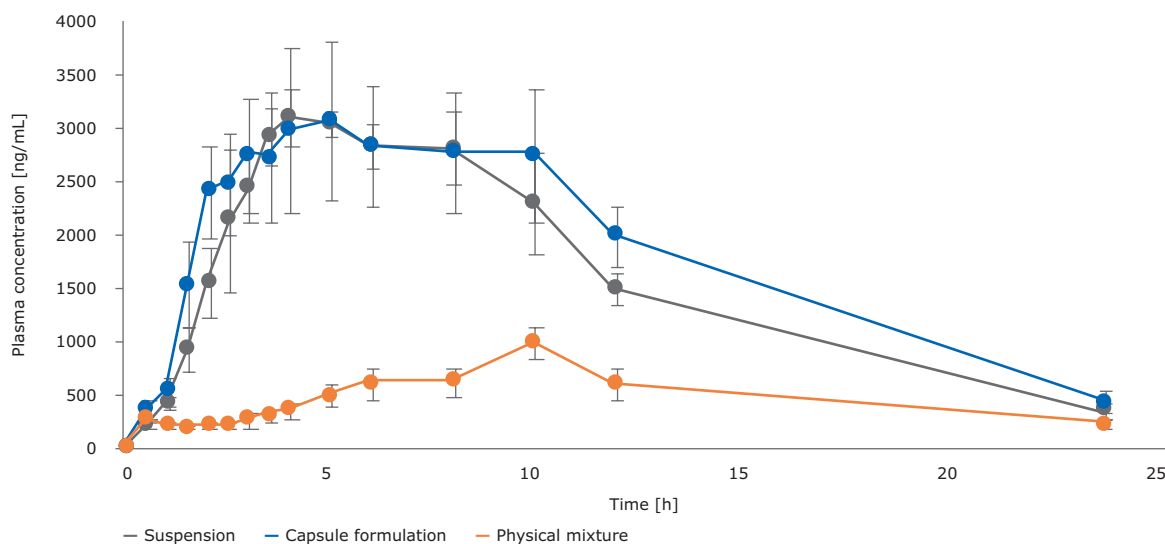


Figure 13:

In-vivo bioavailability in fasted pigs for a loaded fenofibrate-Parateck® SLC formulation with added HPMC-AS, both as a suspension in 25 mL of water and filled into a capsule with the addition of mannitol and NaHCO₃, compared to a physical mixture of all components (n=6).[46]



Spray-drying

Spray-drying of liquids via atomization was first described in the late 19th century by Percy.[48] This process transforms a liquid solution or suspension into a powdered solid. Typically, the liquid is atomized via a nozzle, transforming it into fine droplets. The droplets then encounter the drying gas in the drying chamber, and dry to form solid particles. These are then separated from the gas, typically in a cyclone or bag filter, and collected. A prerequisite for spray-drying, regardless of whether the purpose is mere particle size reduction or the preparation of a solid dispersion, is the solubility of all components in one common solvent – aqueous or organic. The process as a whole, as well as additional information on the solvent choice and process parameter settings, has been described in detail elsewhere.[49, 50] Benefits of this technique include short process times and its suitability for continuous manufacturing processes. The drawbacks are

mostly related to the use of high amounts of organic solvents, which are typically required to allow for processing of poorly water-soluble drugs via spray-drying. In particular, the fact that a common solvent is needed for the API and polymer, in amounts that reduce the viscosity to a level that also allows for atomization of the solution, may present a challenge in formulation. Spray-dried powders also typically exhibit a fairly low bulk density that can make them difficult to handle, especially at larger scales, not to mention dusting issues. The physicochemical properties of the spray-dried powders may not only cause handling difficulties but also introduce challenges in later formulation or manufacturing steps. As well as low bulk density, these potentially problematic properties include poor flowability, inherent compressibility and suboptimal wetting characteristics.

The spray-drying process to enhance solubility via the manufacture of solid dispersions has been extensively studied by various research

groups, and a number of review papers on it have been published, giving a good overview of aspects of the technology, the available data, and recent and potential developments. [49, 51, 52] In direct comparisons, the spray-drying method was able to achieve better results than HME in some cases, depending on the API.[53-57] Since the temperature impact is lower than with HME, the spray-drying process is generally more suitable for heat-sensitive APIs. However, one has to be aware that reducing the process temperature might result in an increased amount of residual solvent and thus possible toxicity issues. In addition, higher amounts of residual solvent might also affect the physicochemical characteristics of the spray-dried product, potentially leading to reduced storage stability because of a lowered T_g due to the plasticizing effect of the solvent, for instance.[49] Depending on the residual solvent content, a secondary drying step may be necessary. A lesser stabilizing effect on amorphous APIs in dissolution was reported for spray-drying compared to HME.[58] The particle size and morphology were shown to strongly affect the dissolution profile. Both of these parameters may be influenced by a variety of process parameters such as nozzle type, spray rate, solution viscosity and drying rate.[9, 51] This is why it is critical to understand the effects of process parameters on final product performance, not only for successful formulation development but also to ensure consistency after scale-up to production scale. Yield is one parameter reported to be strongly dependent on the process scale. While typical values for laboratory scale may only be in the range of up to 70%, process yield at production scale is reported to be up to 90% or higher. [59]

Several more recent publications address some of these challenges, suggesting possible solutions such as a 3-fluid nozzle that allows for the dissolution of the API and excipient in different solvents.[60] As with hot-melt extruded formulations and formulations using silica-based drug carriers to enhance solubility,

spray-dried formulations may also require the addition of precipitation inhibitors to maintain the achieved supersaturated state and thus support improved bioavailability.[9]

Spray drying is currently the best-established and most widely-used solubility enhancement technique apart from micronization of the API (which is not covered in this paper). It is also used for other applications such as the preparation of powders intended for inhalation. However, there are publications which point out the drawbacks of this technology, which is why the choice of solubility enhancement technique must be considered case-by-case and with particular focus on the API and final formulation requirements.

Conclusion

There is no "one size fits all" approach available for enhancing the solubility of APIs. A formulation approach that works for one API might not be suitable for another. As such, it is increasingly important for formulators to be able to choose from a number of available solutions at hand. Spray-drying, hot-melt extrusion and silica-based drug carriers are all viable options for solubility enhancement, each exhibiting unique benefits. Generally speaking, thermostable APIs with a low melting point are potentially suited to HME, while for APIs that have a high melting point and are thermosensitive and highly soluble in organic volatile solvents, spray-drying and the use of a silica-based drug carrier present viable approaches. Of course, there are many additional aspects that should also be taken into consideration. Table 2 summarizes the technologies discussed and their benefits and drawbacks. Which method is the most appropriate to achieve the formulation target depends on the API, its physicochemical properties and the intended final formulation.

Table 2:

Summary of benefits and drawbacks of the technologies discussed

	Benefits	Drawbacks
Hot-melt extrusion	<ul style="list-style-type: none"> • Solvent-free technology • Suitable for continuous processes • Technology often already used in pharmaceutical industry (at lab scale, but not yet to the same extent at production scale) • Variability of release profile and final dosage type (depending on polymer and down-processing technique used) • Typical drug loading of 30-40%; however, even higher amounts reported in literature • Process yield: >90% 	<ul style="list-style-type: none"> • Not suitable for temperature-sensitive APIs • Limited availability of polymeric carriers • Storage stability (e.g. due to recrystallization of amorphous API) • Additional milling step typically required (prior to tableting/capsule filling) • API-polymer interactions, depending on material choice
Drug carriers	<ul style="list-style-type: none"> • Low temperature impact • Solvent only has to be suitable for API • Easy solvent removal • Limited interactions with API due to high inertness of silica material • Simple and cost-effective set-up • Low investment for lab tests • Loaded material suitable for direct tableting or capsule filling • Typical drug loading of 30-40% • Process yield: >90% 	<ul style="list-style-type: none"> • Organic solvent needed, though in lower amounts than for spray-drying • Technology not widely used in pharmaceutical industry
Spray-drying	<ul style="list-style-type: none"> • Suitable for continuous processes • Technology often available at CDMO/CMOs 	<ul style="list-style-type: none"> • Organic solvent needed in high amounts • Common solvent required for API and polymer • API-polymer interactions, depending on material choice • Typical drug loading of 20-30% • Process yield: typically 80-90%, e.g. due to losses during the post-drying step required to reach the ICH limit for residual solvents • Risk of in-process API recrystallization due to rapid drying of the droplets • Physicochemical properties of the spray-dried solid dispersion (e.g. low bulk density) may make formulation and/or production more difficult. • Additional compaction step often needed to improve powder characteristics and allow for automated tableting processes

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