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White Paper

Enhancing the Solubility of Active Pharmaceutical Ingredients Using Hot Melt Extrusion and Polyvinyl Alcohol

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Solubility of the active pharmaceutical ingredient (API) in an oral formulation is critical for absorption from the gastrointestinal (GI) tract and the intended therapeutic effect. Ensuring that an API has the necessary solubility can be challenging for drug developers and formulators. If limitations in solubility cannot be successfully addressed, a new chemical entity (NCE) is unlikely to advance in the development pipeline. Addressing this potential roadblock to clinical success is becoming increasingly important as NCEs continue to become larger and more lipophilic and, as a result, less soluble.[1]

The importance of solubility is reflected in the biopharmaceutics classification system (BCS).[1] The BCS correlates *in vitro* solubility and permeability with the potential *in vivo* performance of drug molecules and categorizes them in four classes. BCS Class I, for example, includes molecules that have both high solubility and permeability and are expected to have good absorption in the GI tract. BCS Class II compounds 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 which have both low solubility and permeability. The BCS was originally used by the US Food and Drug Administration (FDA) as a regulatory tool for the basis for biowaiver applications for immediate release formulations to reduce the need for additional *in vivo* studies for bioavailability and bioequivalence.[2]

As shown in Figure 1, approximately 70–90% of pipeline candidates/NCEs and about 40% of marketed APIs have solubility issues.[3]

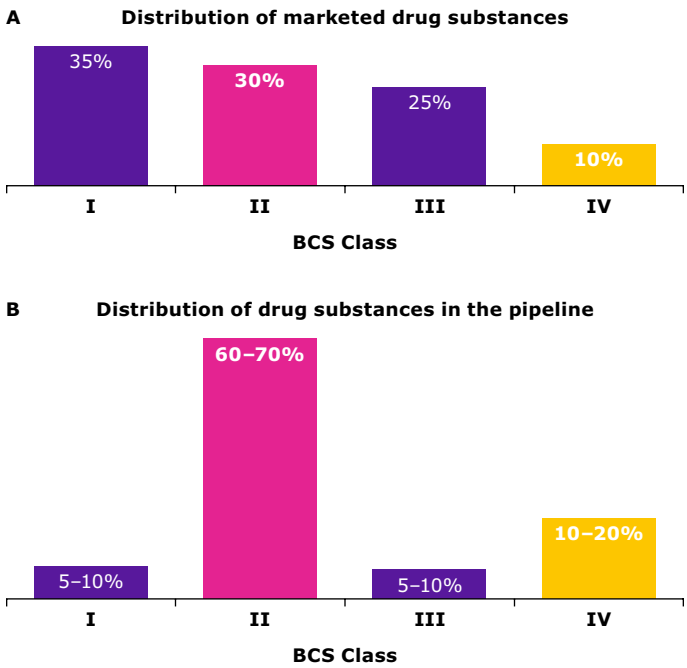

Figure 1.

Current distribution of marketed drug substances (**A**) and drug substances in the pipeline (**B**) classified in the different BCS classes.

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Expanding upon the BCS, the developability classification system (DCS) introduced key modifications to improve applicability to formulation development.[4] The system helps formulators address poorly soluble APIs by identifying root causes and providing guidance on solubility enhancing techniques such as the use of excipients. Dissolution rate can be enhanced by the use of an excipient, while solubility can be enhanced via solid-state modification.

As part of the DCS, BCS Class II molecules were divided into two sub-categories: DCS Class IIa and DCS Class IIb. DCS Class IIa molecules are dissolution-limited while DCS Class IIb molecules have such low solubility that no matter how quickly the drug gets into solution, there will not be a measurable impact on absorption.

For a detailed exploration of the DCS and recommendations for addressing dissolution limited DCS IIa molecules, please refer to our white papers entitled *The Developability Classification System (DCS): Enabling an Optimized Approach for Formulation of Poorly Soluble Molecules*[5] and *Poloxamer: A Simple and Powerful Solution for Accelerating Dissolution.*[6]

This white paper describes how hot melt extrusion (HME) and a specially-engineered grade of polyvinyl alcohol (Parteck® MXP polyvinyl alcohol 3-82 Emprove® Essential Ph Eur; referred to in this publication as Parteck® MXP 3-82 PVA) can be used to increase the solubility of DCS IIb molecules.

Use of Polyvinyl Alcohol in HME for Stability and to Inhibit Precipitation

HME has a broad set of applications, including modification of the physical state of APIs with the aim of enhancing solubility. In HME processes, the API is mixed with a matrix polymer, converting the poorly soluble crystalline form of the drug into a more soluble amorphous solid dispersion (ASD; Figure 2). During this process, it is essential that the components are mixed under elevated temperature which induces melting and mixing at a molecular level. HME stabilizes the API in the amorphous form and allows a supersaturated state of the API in solution by inhibiting precipitation which could otherwise interfere with dissolution and efficacy of the drug.

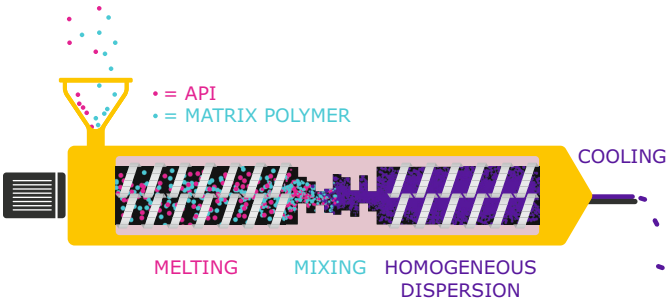


Figure 2.

Simplified schematic of the HME process, visualizing the transition of API and matrix polymer from feeder to extruder die.

Selection of the matrix polymer for use in HME is driven by the intended release profile, thermal characteristics of the API and polymer (e.g., melting point/glass transition temperature), and whether it is suitable to stabilize the API in the ASD and in solution.

In addition to increasing the solubility of APIs, HME offers a number of other benefits. HME is suitable for continuous manufacturing and is solvent-free, which contributes to sustainability goals of the manufacturer and is safer for employees to handle.

When using HME, the suitability of the API and the specific type of matrix polymer must be determined. Key considerations regarding the polymer include degradation temperature, thermoplasticity, and solubilization capacity of the polymer with respect to the API to ensure high drug loadings. Various polymers can be used in HME processes, including polyvinyl alcohol (PVA), cellulose derivatives, polyacrylates and polymethacrylates, polyethylene glycols, and polyvinyl pyrrolidone.[7]

PVA is ideal for use as the polymer in HME due to its ability to enhance solubility, stabilize amorphous APIs, and inhibit precipitation (Figure 3). PVA is well-known and frequently used in oral solid dosage forms in the pharmaceutical industry and categorized as Generally Recognized as Safe (GRAS) by the FDA. Read more about PVA in our white paper entitled *Polyvinyl Alcohol: Revival of a Long-Lost Polymer.*[8]

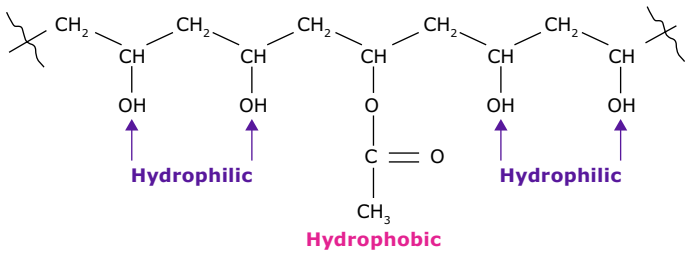


Figure 3.

Structure of a partially hydrolyzed polyvinyl alcohol.

PVA is a thermostable polymer available in different grades, suitable for a variety of applications and follows a common naming convention. Parteck® MXP 3-82 PVA was developed specifically to address challenges in HME with its properties tailored to yield the desired performance and the name reflecting its viscosity and degree of hydrolysis:

- The first number (in this case, 3) specifies the apparent viscosity in mPa·s of a 4% aqueous solution at 20 °C which is also linked to the relative molecular weight of the polymer chain. PVA with a relatively low molecular weight is essential for HME as it will also provide a low melt viscosity during processing.
- The second number (in this case, 82) is the hydrolysis grade which refers to the percentage of acetate groups on the PVA backbone that are hydrolyzed (i.e., have a hydroxyl group) rather than hydrophobic regions (i.e., having an acetate group). This number reflects the ability of the polymer to interact with and stabilize the API and inhibits precipitation.

Parteck® MXP 3-82 PVA has a relatively low viscosity and low molecular weight and its PVA backbone contains 82% hydroxyl groups and 18% acetate groups. This amphiphilic molecular design allows it to form strong interactions with hydrophobic drug molecules, both in solid state and in solution. **These interactions improve stabilization and precipitation inhibition of ASDs, and maintain supersaturation throughout physiologically relevant timescales, even for the most challenging DCS Class IIb APIs.**

Parteck® MXP 4-88 PVA contains 88% hydroxyl groups and 12% acetate groups. This higher hydrolysis grade makes it more hydrophilic and highly suitable for amorphous stabilization of certain challenging molecules. Due to its uniquely high thermal application range, Parteck® MXP 4-88 excipient can be used for solubility enhancement across a very broad melting temperature range, including APIs with very high melting points that are typically considered as unsuitable for HME.[9]

Additional Benefits of Parteck® MXP 3-82 PVA in HME

With an optimized chemical structure, Parteck® MXP 3-82 PVA has an advanced **broad processing window** supporting HME from 130 °C to 210 °C without chemical degradation of the polymer (Figure 4). Even when heated to the temperatures in this range, the polymer retains good viscosity and performance. The purple line in Figure 4 represents the melt viscosity of the polymer as it goes through the extrusion process while the dotted pink line is the threshold at which the process is able to proceed; a viscosity above the pink line will prove difficult for the HME process. Only when temperatures go above 210 °C does the desirable elastic behavior of the polymer change and become more viscous.

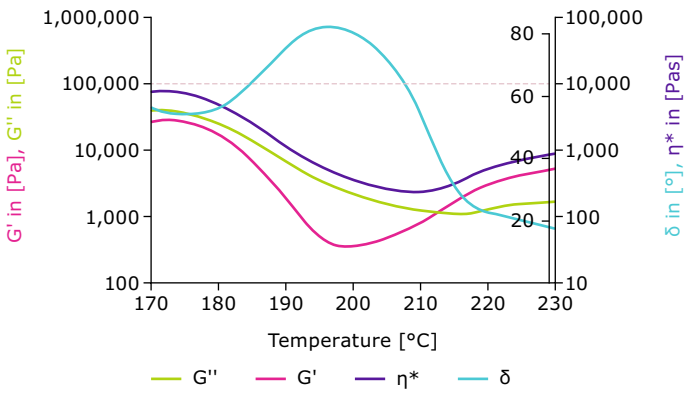


Figure 4.

The thermal behavior of Parteck® MXP 3-82 PVA ensures a broad processing range during the HME process.

ThermoFisher Scientific Haake Mars Rheo60; temperature ramp from 170 °C to 230 °C ΔT/t = 2°/min, oscillating shear stress, CD, γ_0 = 0.1%, f = 1.0 Hz, gap = 1.00 mm, Measuring geometry = D P25/Al + adapter Px.

The elasticity of the polymer is represented by the storage modulus G' and the plastic behavior is represented by the loss module G''. Both parameters are related by tan delta. Overall, a viscoelastic melt behavior was observed for the polymer in the molten state with G'' slightly above G'. A crossover point is observed at about 215 °C indicating changes in the melt. The pseudoplastic melt behavior of the melt provides a shear thinning effect allowing an effective down-streaming also in tiny nozzle geometries therefore expanding the downstream flexibility for creation of final dosage forms.

Figure 5 shows the melt behavior of Parteck® MXP 3-82 PVA and its effect on processability. Data confirm that **process relevant parameters remain steady** and within desirable ranges with use of Parteck® MXP 3-82 PVA. Consistency across these parameters provides a broad application range and ensures an efficient process and final product uniformity. There are relatively few variations in melt temperature which is indicative of a consistent and stable melting process, and torque remains relatively low indicating the equipment is not straining. Feeder and extruder speed are constant throughout the duration of the HME process, as well as the pressure at which the material comes out of the extruder. If the pressure is too high, material must be forced through the die; if the pressure is too low, material is leaking out like a liquid.

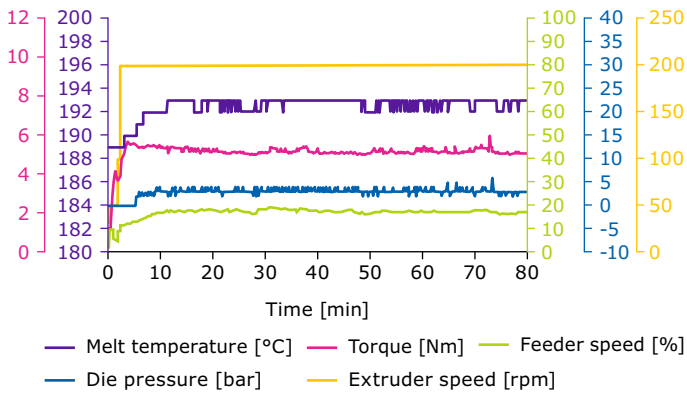


Figure 5.

Process conditions of Parteck® MXP 3-82 PVA throughout an exemplary HME process.

Screw speed 200 rpm, barrel temperature 200 °C, nozzle: 150 °C, feeding rate: 0.2 kg/h.

Most polymers, including PVA, are hygroscopic, changing mass upon exposure to water vapor. Because Parteck® MXP 3-82 PVA shows a low hysteresis between absorption and desorption, **concerns related to hygroscopicity are reduced.** The dynamic vapor absorption results (Figure 6) show that the absorption and desorption curves practically overlap. This indicates that the uptake of water, due to increasing humidity, is reversible and does not affect the internal structure of the substance which would have a significant and unforeseeable impact on the performance in process and final formulation.

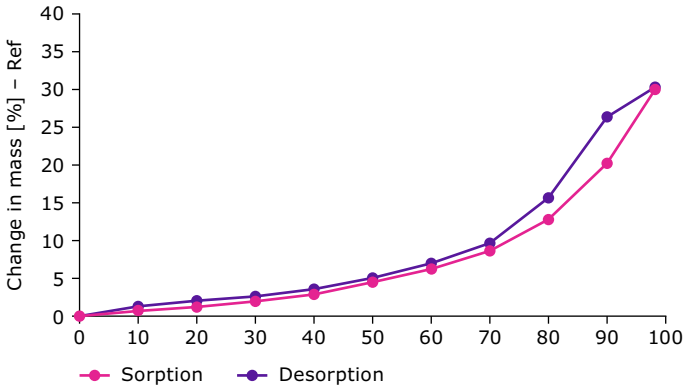


Figure 6.

Dynamic vapor water absorption analysis of Parteck® MXP 3-82 PVA.

HME is an attractive solution for the pharmaceutical industry as it offers a high degree of **flexibility and variability in downstream processing** options. This provides the formulator and manufacturer with a variety of options on how to apply HME and to optimize the process.

As shown in Figure 7, several different final dosage forms are possible with HME, manufactured either by direct shaping or by other downstream processing of the extrudate such as pelletizing, milling or direct tablet compression.[10, 11] Pelletizing and filling capsules are ideal for preclinical or early phase clinical trials where simple composition formulations are suitable. For a commercial formulation, the extrusion strands can be milled into a powder and combined with other excipients via direct compression to form tablets. Other applications include film extrusion where thin films, oral dispersible films and patches are produced. Another important aspect includes the application in advanced manufacturing technologies like and 3D printing, continuous manufacturing and direct compression.

Screening Confirms API Suitability

To rapidly determine if HME for an API and polymer combination is feasible, screening with vacuum compression molding (VCM) can be used (Figure 8). In this technique, the API and polymer are mixed in the VCM and compressed to the smallest possible volume. A vacuum is then applied to compress the mixture further and heat is applied to melt the mixture. The resulting disk was found to very well reflect the extrudate appearance and performance and can be used for subsequent studies as described in the following paragraphs.

Step 1

Insert physical mixture (polymer & API)

Step 2

Apply vacuum to compress the material and to remove remaining air

Step 3

Initiate the heating process

Step 4

Defined cooling step

Figure 8.

Schematic of the vacuum compression molding process.

Figure 7.

A wide range of polymer extrudates can be processed into various dosage forms.

Demonstration of Parteck® MXP 3-82 PVA Benefits in HME

VCM was used to prepare ketoconazole dispersions with a variety of commercially available polymers including Parteck® MXP 3-82 PVA. Dissolution time in fasted state simulated intestinal fluid (FaSSiF) was then evaluated for all formulations. As shown in Figure 9, Parteck® MXP 3-82 PVA had the most prominent supersaturation of all the polymers and this supersaturation was maintained for a longer period of time.

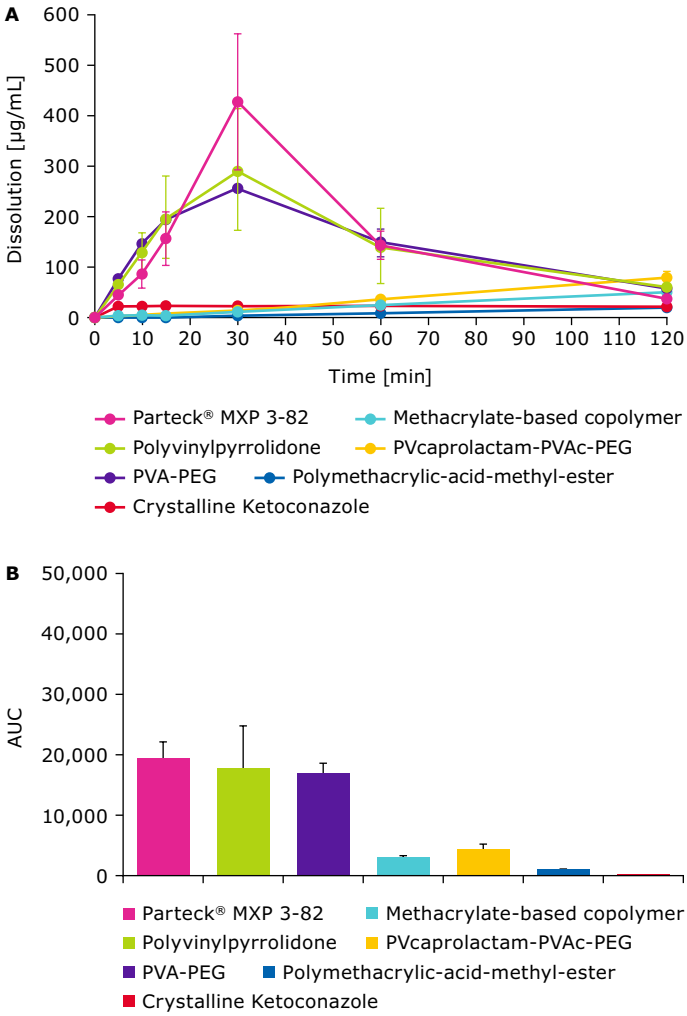


Figure 9.

Dissolution profiles (A) and AUC (B) of solid dispersions with ketoconazole and various commercially available polymers manufactured using VCM screening in comparison to the pure crystalline API.

15 mg disc with 6 mg ketoconazole (drug load 40%) in 8 mL FaSSIF; agitation at 450 rpm, 37 °C, n=3.

To test for stability of the amorphous form under accelerated conditions, thermoplastic dosage forms of 30% ketoconazole, itraconazole, and indomethacin with Parteck® MXP 3-82 PVA were produced using VCM, a simple and easy process for screening. Results confirm that **good amorphous stability** was achieved for all three APIs using Parteck® MXP 3-82 PVA (Figure 10). While there was crystallinity in some samples, these and further optimization to ensure a fully amorphous API in the final formulation is possible.

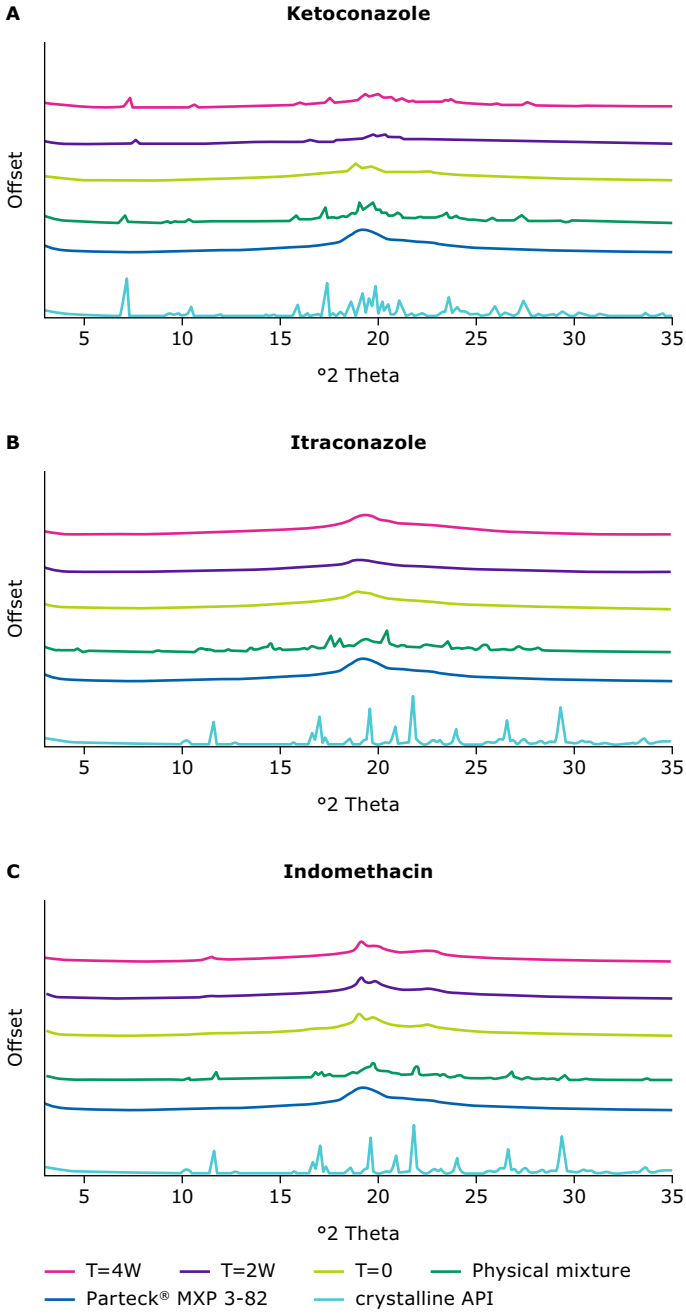


Figure 10.

XRD analysis of ketoconazole-, itraconazole-, and indomethacin-Parteck® MXP 3-82 PVA extrudates directly after manufacture using VCM and after storage (2, 4 weeks at 40 °C/75% rH) in comparison to the physical mixture of both and pure crystalline API.

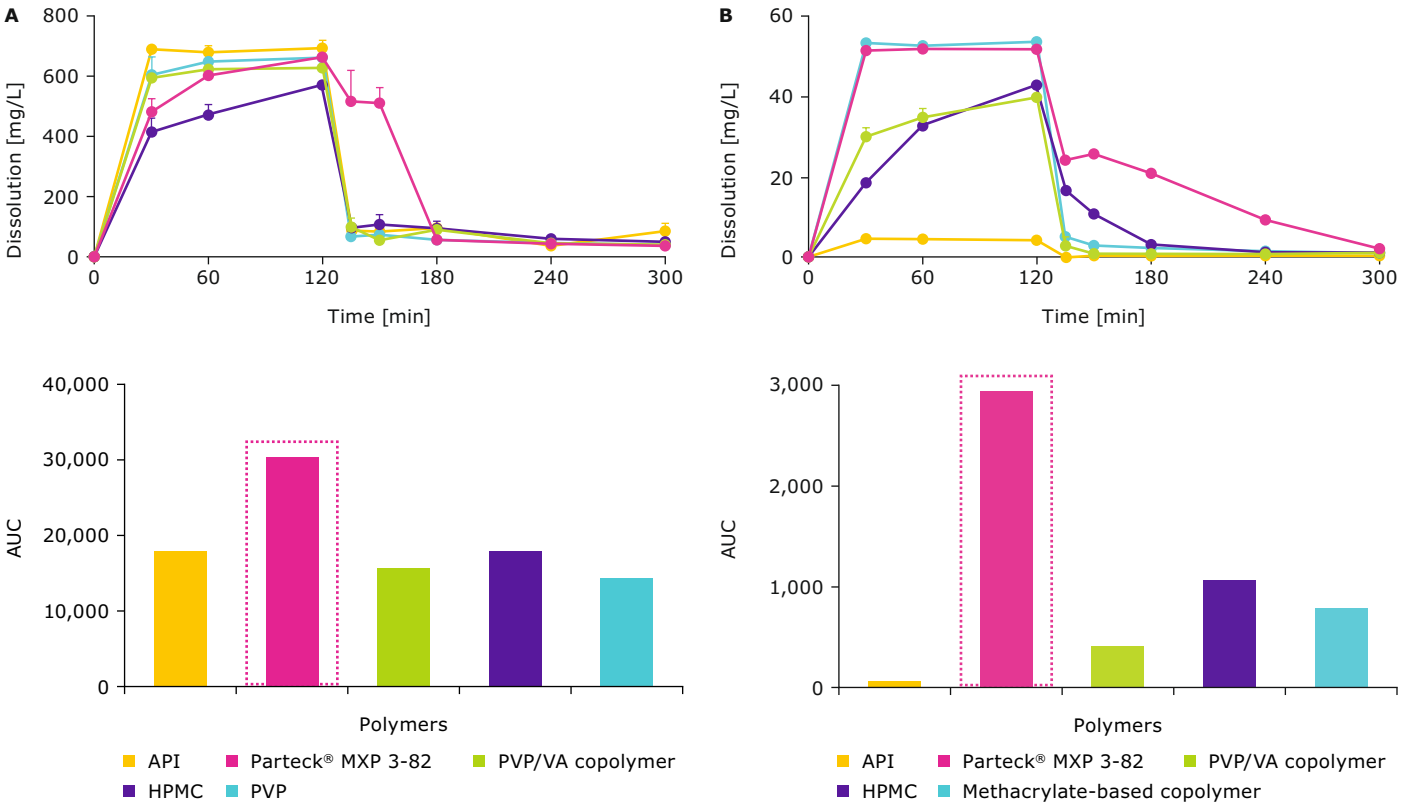


Figure 11.

pH shift dissolution of hot-melt extruded ketoconazole (**A**) and itraconazole (**B**) formulations using various polymers in comparison to crystalline API.

HME formulation 20% drug load (500 mg ketoconazole/37.5 mg itraconazole); 750 mL 0.1 M HCl for 120 minutes, add 250 mL phosphate buffer pH 6.8; paddle speed 50 rpm, total run time 300 minutes, n = 3.

Two-phase dissolution experiments in which the pH was shifted from acidic (pH 1) to basic (pH 6.8) were performed to test the ability of polymers to **inhibit precipitation.** If the drug and the polymer interact well in solution, the polymer will prevent the drug from precipitating. Ketoconazole, a weak base, is ionized in stomach acid and good solubility at pH 1 was observed for all polymers tested. When the ketoconazole formulations were transferred from the acidic to a neutral or even basic environment in which the drug is no longer ionized, only Parteck® MXP 3-82 PVA inhibited until 180 min precipitation (Figure 11A).

The amphiphilic polymer structure of Parteck® MXP 3-82 PVA interacts with the hydrophobic ketoconazole in solution and prevents immediate precipitation to a substantial level as shown by the area under the curve (AUC) of the dissolution. An approximately two-fold increase in the amount of drug available for absorption was enabled by inhibiting precipitation and extending supersaturation by about 40 minutes.

This effect was even more pronounced for itraconazole, a notoriously challenging molecule to formulate because it is relatively large, relatively hydrophobic, and has a high propensity to precipitate from solution (Figure 11B). Parteck® MXP 3-82 PVA matched the highest dissolution performance in the acidic condition for this basic compound and was the only polymer capable of inhibiting precipitation. As with ketoconazole, the impact on the AUC of the dissolution is quite substantial.

In another study, the ability of different polymers to inhibit precipitation of indomethacin, an acidic API was compared. While the methacrylate-based copolymer had the highest concentration at the beginning of the experiment, it did not inhibit precipitation. **With Parteck® MXP 3-82 PVA, supersaturated conditions were maintained, prolonging the period of time during which the drug was in solution.**

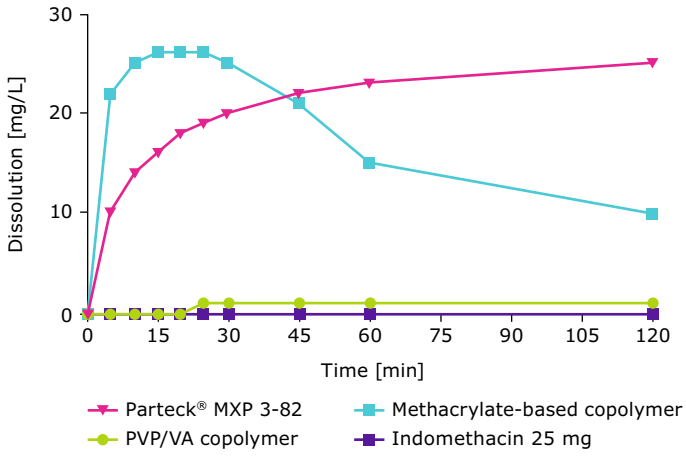


Figure 12.

Comparison of dissolution profiles of hot-melt extruded indomethacin formulations using different polymers. Parteck® MXP 3-82 PVA generated stable release profiles with enhanced supersaturation.

Indomethacin HME formulation 30% drug load in 900 mL SGFsp; paddle speed at 75 rpm, total runtime 120 minutes; n = 3.

30% drug loaded ASDs			
Time points month	Storage condition 25 °C/60% rH	Storage condition 40 °C/75% rH	Storage condition 2–4 °C
T=0	stable	stable	stable
T=6	stable	stable	stable
T=12	stable	stable	stable

DSC PXRD Amorphous stability Dissolution

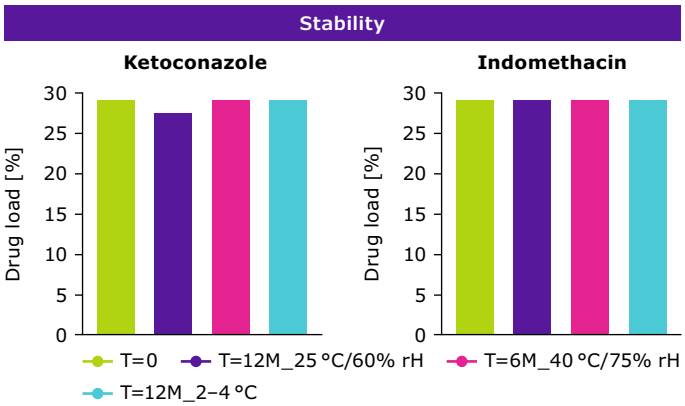


Figure 13.

Storage stability of Parteck® MXP 3-82 PVA formulations with a high drug load (30%) of ketoconazole and indomethacin, confirming using various analytical methods that the formulations were stable for 12 months in all applied storage conditions.

All of the APIs formulated with Parteck® MXP 3-82 PVA at 30% loads, including ketoconazole and indomethacin, were **stable and remained amorphous** for up to 12 months across both normal and accelerated storage conditions as shown in Figure 13. Stability was confirmed based on x-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). There was no appreciable reduction in dissolution of indomethacin over time following storage, even in stress conditions, which indicated these formulations were stable (Figure 14).

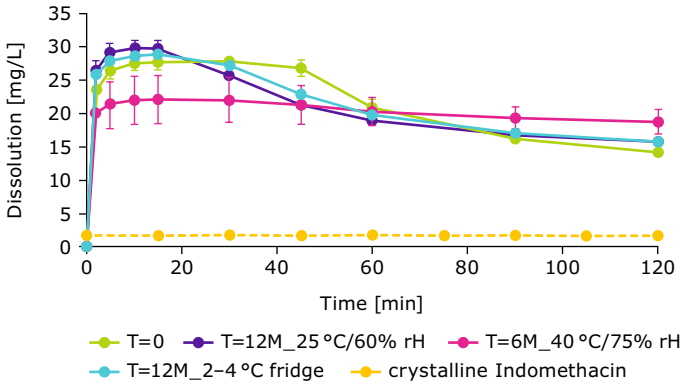


Figure 14.

Dissolution profile of Parteck® MXP 3-82 PVA with 30% indomethacin directly after manufacture and after storage for 6 months at accelerated conditions (40 °C/75% rH) and 12 months at ambient and cold conditions (25 °C/60% rH; 2–4 °C).

HME formulation 30% drug load; 900 mL SGFsp, paddle speed 75 rpm, total run time 120 minutes, n = 3.

1 Flexible, synthetic polymer

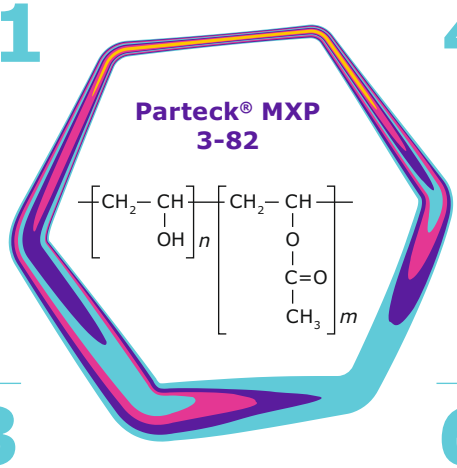
GRAS polymer manufactured to high quality standards and supported by Emprove® documentation

2 Broad processing window

Optimized polymer properties to allow broad processing range

3 Optimized hydrolysis grade

Improve hydrophobic interactions & improved precipitation inhibition



4 Excellent Processability

High drug loads, easy handling & downstream process

5 Formulation Performance

Improved release and prolongation performance of the supersaturated state

6 Stable under various conditions

Long term stability of ASD

Figure 15.

Summary of benefits provided by Parteck® MXP 3-82 PVA for hot melt extrusion.

Conclusion

The choice of matrix polymer is critical to ensure a successful HME process and performance of the final formulation. For early polymer screening only the extent of initial supersaturation is typically used as a critical factor; this is not always sufficient, however. Extended polymer functionalities provide increased flexibility in an already complex ASD formulation development.

The right polymer ensures stability of the ASD formulation and inhibits precipitation which prolongs the amount of time the drug is in solution and available for absorption into the systemic circulation.

Parteck® MXP 3-82 PVA is a synthetically derived PVA engineered to deliver important benefits for HME and opens new possibilities to formulate challenging APIs (Figure 15). The hydrolysis grade has been optimized to offer advanced amphiphilicity which improves hydrophobic interactions between the polymer and the drug, delivering improved formulation performance. Study results presented in this white paper demonstrate that high drug loads can be achieved with Parteck® MXP 3-82 PVA, formulations are stable under various conditions in the amorphous form and have prolonged supersaturation. The excipient can be used to inhibit precipitation and is compatible with advanced manufacturing processes such as direct compression, continuous manufacturing, thin film extrusion, and 3D printing. With a broad processing window, this PVA can be applied to a broad range of APIs with different properties.

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