SAFC®
Pharma & Biopharma Raw Material Solutions

White Paper

Improving the Bioavailability of Challenging APIs using Hot Melt Extrusion with Polyvinyl Alcohol

Authors: Daniel Joseph Price and Thomas Kipping

New molecular entities (NMEs) are becoming larger and more lipophilic and, as a result, less soluble. While approximately 40% of active pharmaceutical ingredients (APIs) currently on the market show poor solubility, it is estimated that between 60 and 90% of compounds in development have solubility challenges.[1,2] For an oral formulation, API solubility and permeability are critical factors for absorption in the gastrointestinal tract. As a result of this, solubility-enhancing techniques have become an area of focus for pharmaceutical formulators. If limitations in solubility cannot be successfully addressed, an NME is unlikely to advance in the development pipeline, as absorption from the GI tract will be limited. This in turn reduces the overall effect of the molecule, as absorption is a critical component of the LADME (liberation, absorption, distribution, metabolism, elimination; Figure 1) model of drug pharmacokinetics.

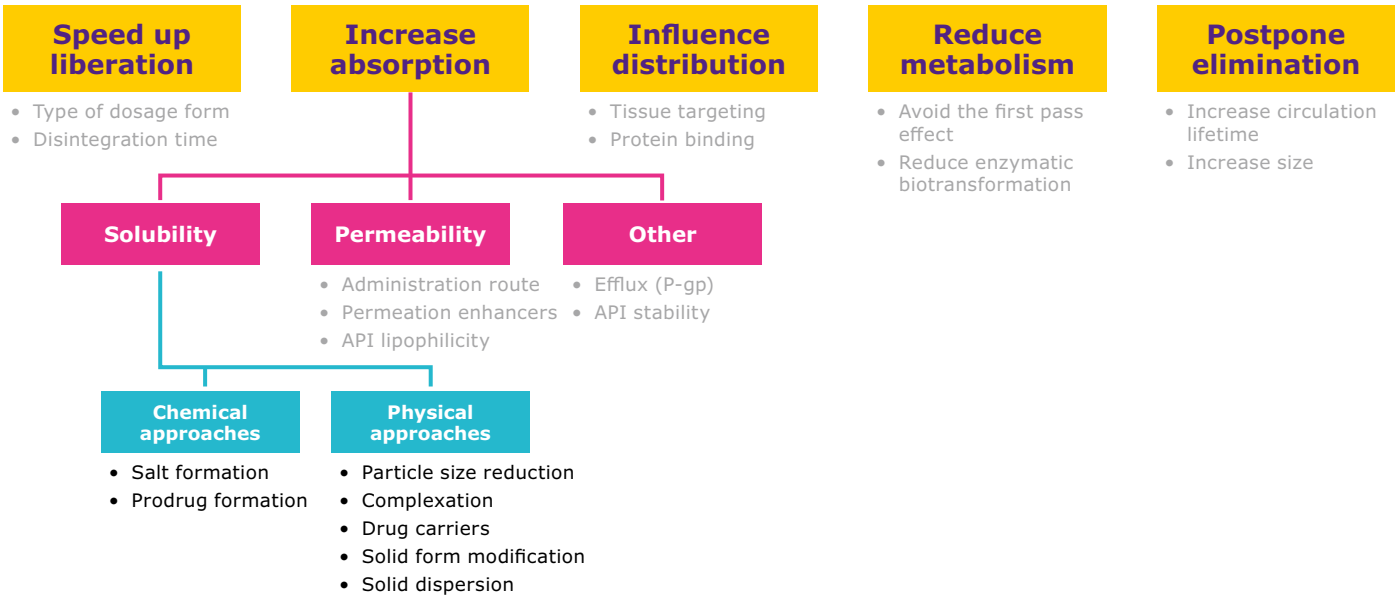


Figure 1.

A wide range of strategies can be used to enhance bioavailability by influencing LADME.

The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

Expanding upon the LADME model, one can identify strategies to improve the oral absorption of a poorly soluble molecule. Specifically, absorption can be increased through improvements in solubility and/or permeability, as well as other means including reducing elimination via P-gp transporters. To improve solubility, chemical approaches such as salt and prodrug formation are typically only feasible very early in development, as they fundamentally alter the chemical nature of the API. However, there is a fine balance between achieving potent activity in the chemical substrate and good physicochemical properties, with the latter often taking priority. Therefore, physical (or post-synthetic) approaches are highly relevant during formulation development and include:

- Particle size reduction
- Use of surfactants in co-solvent systems
- Complexation of the API, for example to cyclodextrins
- Use of alternative polymorphs
- Stabilization of amorphous form *via:*
  - Loading onto carrier systems
  - Immobilization in polymeric solid dispersions

Multiple technologies are typically considered and evaluated to find the right approach for the respective API and to achieve the desired performance of the final drug product *in vivo*.

This white paper will focus on solid dispersion – specifically, the use of hot melt extrusion (HME) to modify 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 form.

Hot Melt Extrusion using Polyvinyl Alcohol

To form a solid dispersion using HME, the API is molecularly dispersed in a polymer matrix[3] using elevated temperature and the mechanical force provided by extruder screws (Figure 2). Advantages of HME include enhanced solubility and bioavailability of the API; flexibility in drug release properties; suitability for both immediate and sustained release; and compatibility with continuous and solvent-free manufacturing. HME also provides great versatility; potential downstream options include direct shaping of the extrudate into tablets or other downstream processing of the extrudate such as pelletizing, milling and direct tablet compression.

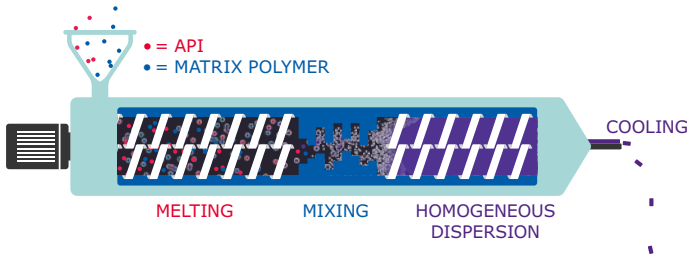


Figure 2.

The API is mixed with a matrix polymer in the extruder to enable homogeneous dispersion of the API within the polymer.

When developing an HME formulation, the suitability of the API and polymer for the process must be considered, especially their degradation temperatures, which often is a limiting factor. Good thermoplasticity of the polymer is also a prerequisite for HME. A high solubilization capacity of the polymer with respect to the API is also desirable, as this allows for high drug loadings. Recent work has expanded upon analytical and *in silico* tools to assess compatibility of drugs with polymers which can also be applied to the HME formulation.[4,5]

Various polymers can be used in HME processes including cellulose derivatives, polyacrylates and polymethacrylates, polyethylene glycols, and polyvinyl pyrrolidone (PVP). Recently, polyvinyl alcohol (PVA) has been highlighted as a polymer particularly well-suited for HME.[6,7,8] PVA is a synthetic polymer produced by polymerization of vinyl acetate and partial hydrolysis of the resulting ester-based polymer. First discovered in 1924,[9,10] PVA has been used in approved drug products for decades[11] and is generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA).[12] Furthermore, there is a body of scientific literature on the suitability of PVA for oral ingestion. The acceptable daily intake (ADI) for humans is 50 mg/kg of body weight as identified by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

in 2003. PVA with a hydrolysis grade between 85 and 89 percent fulfills the requirement of all three major pharmacopoeias, USP, Pharm. Eur., and the JPE. To summarize, there is well-founded scientific evidence for the safety of PVA.[13,14,15,16,17,18]

PVA is a thermoplastic polymer, which shows a pseudo-plastic viscosity behavior; with an increased shear rate, the viscosity drops slightly which benefits the HME process. The higher the shear forces, the easier the extrusion – including high throughput rates, improved downstream processing, optimized melt flow through the channels and extended process ranges.

The PVA-based Parteck® MXP excipient is specifically developed for use in HME; with excipient particle properties resulting in a constant process and flow through the extruder, leading to high reproducibility. Table 1 summarizes the key properties of Parteck® MXP.

Product Properties	
Bulk density [g/mL]	0.53 ± 0.02
Tapped density [g/mL]	0.74 ± 0.02
Particle size (D50) [µm]	60 – 80
Loss on drying [%]	< 3.0
Angle of repose [°]	35
Hydrolysis grade [%]	85 – 89
Solubility [%] (max. in water)	33
Mass average molar mass	approx. 32,000
pH-value (4%/water)	5.0 – 6.5

T_g (by DSC)	T_m (by DSC)	T_d (by TGA)
40 – 45 °C	170 °C	> 250 °C

Temperature	Melt Viscosity D=200 (s^{-1})	Melt Viscosity D=1,200 (s^{-1})
210 °C	702 Pa·s	283 Pa·s
230 °C	345 Pa·s	174 Pa·s

Table 1.

Physicochemical and powder properties of Parteck® MXP excipient make it well-suited for use in HME.

Screening Tools

To ensure successful formulation development, suitable polymers for use with HME must be identified at an early stage. One of the most common screening methods is solvent film casting, in which polymers and the API are dissolved in a suitable solvent which is then rapidly removed. One shortcoming of this approach, however, is that the process differs significantly from the HME process itself and, as such, its predictability is rather limited: no heat is involved and, in most cases, the method is not applicable for water-soluble polymers. Given the limitation of solvent film casting, two alternative screening methods: differential scanning calorimetry (DSC; Figure 3) and vacuum compression molding (VCM; Figure 4) were evaluated for preparing amorphous solid dispersions using HME. Several commercially available polymers, including Parteck® MXP, were assessed in combination with a poorly soluble model compound (ketoconazole) for HME processing. Drug load was kept constant at 20%. All samples were analyzed with respect to their solid state and dissolution behavior. A dedicated dissolution method was used to enable the screening of small sample amounts.

Step 1 Mixture of API and Polymer in DSC pan

Step 2 Close the DSC pan

Step 3 Initiate dedicated heating program

Step 4 Remove cover of DSC pan, perform further analysis

Figure 3.

Schematic view of DSC screening method.

Step 1 Insert physical mixture (polymer & API)

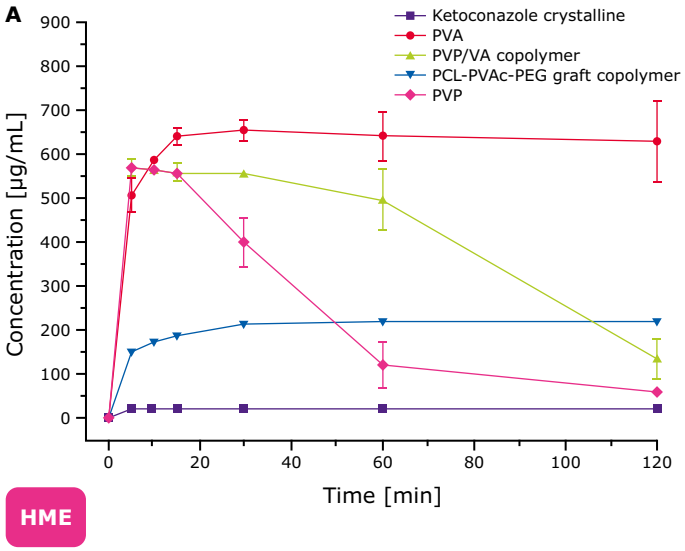
Step 2 Apply vacuum to compress the material and to remove remaining air

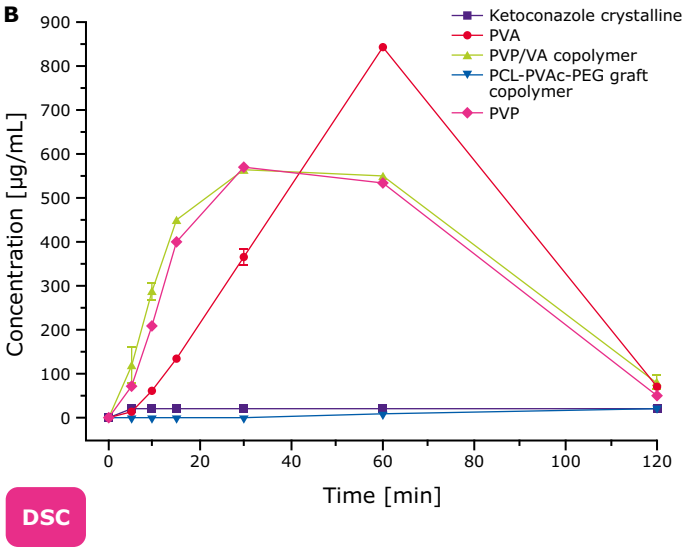
Step 3 Initiate the heating process

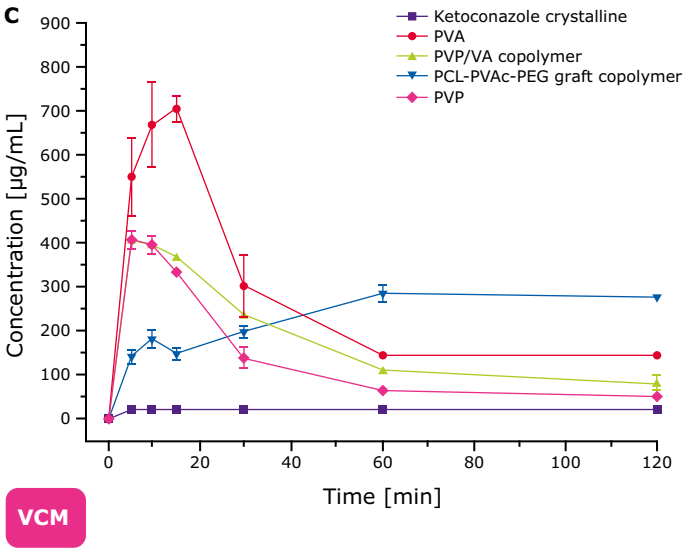
Step 4 Defined cooling step

Figure 4.

Schematic view of the VCM screening method.







A comparison of the results for the hot melt extruded formulations and the DSC screening methods showed difference in release characteristics (Figure 5). In the study, PVA extrudates generated high supersaturation both in the screening method and the HME; the PVP and polyvinylpyrrolidone-vinyl acetate copolymer (PVP/VA) behaved in a similar manner in both methods, whereas the graft copolymer showed a low performance in both.

A direct comparison of hot melt extruded formulations and the VCM screening showed similar rankings with a very good prediction of how the formulation will perform in the HME process.

Both DSC and VCM show high potential for estimating the performance of final HME formulations. The results can be used to identify high-potential candidates for further development. The DSC method can be easily carried out using existing devices and is of great interest for preliminary testing. The limitations of the DSC approach are the restricted sample amounts and the direct relation of release characteristics to the performance of HME formulations.

VCM technology, however, provides the advantage of more versatile and homogenous sample generation, enabling highly reliable sample preparation. The increased sample amount allows for further processing steps, resulting in a realistic estimation of formulation performance.

Implementing these technologies in early formulation screening can provide a clear advantage over traditional systems, as they allow a fast assessment of formulation performance and thus facilitate accelerated development.

Figure 5.

Direct comparison hot melt extruded formulation of ketoconazole (A) vs. DSC screening (B) and VCM screening (C).

Solubility Enhancement

To assess successful amorphous drug loads and subsequent solubility enhancement, nine different model APIs with low solubility according to the Biopharmaceutics Classification System (BCS) were extruded with Parteck® MXP excipient (Table 2). The BCS categorizes molecules according to their solubility and permeability[19]:

- I: high solubility, high permeability
- II: low solubility, high permeability
- III: high solubility, low permeability
- IV: low solubility, low permeability

Figure 6 summarizes the T_m distribution of 67 BCS II and IV compounds. A selection of APIs with a wide range of melting temperatures were chosen to reflect the normal distribution of melting points in poorly soluble compounds.

In all cases, a significant increase in API solubility was observed – ranging from 2- to 150-fold enhancement in apparent solubility compared to the unmodified crystalline drug. A drug load of 30% (w/w) was successful for seven of the nine extrudates, with some as high as 55% (w/w).

These results confirm that Parteck® MXP excipient can be used to produce hot melt extrudates with high drug-loads and substantial improvements in apparent solubility, even for high melting point APIs typically discounted for HME formulation.

API BCS II&IV	T_m of API	Loading Capacity	Solubility Enhancement (max.)
Ibuprofen*	78 °C	> 30%	2 x
Cinnarizine	118–122 °C	< 20%	10 x
Indomethacin	151 °C	> 50%	3 x
Ketoconazole	146 °C	> 35%	17 x
Naproxen	152 °C	> 30%	4 x
Atorvastatin	150 – 160 °C	> 55%	154 x
Itraconazole	167 °C	> 30%	80 x
Carbamazepine	204 °C	> 30%	2 x
Telmisartan*	260 °C	> 15%	35 x

*Plasticizer required

Table 2.

Parteck® MXP excipient loading capacity and solubility enhancement using 9 different model APIs.

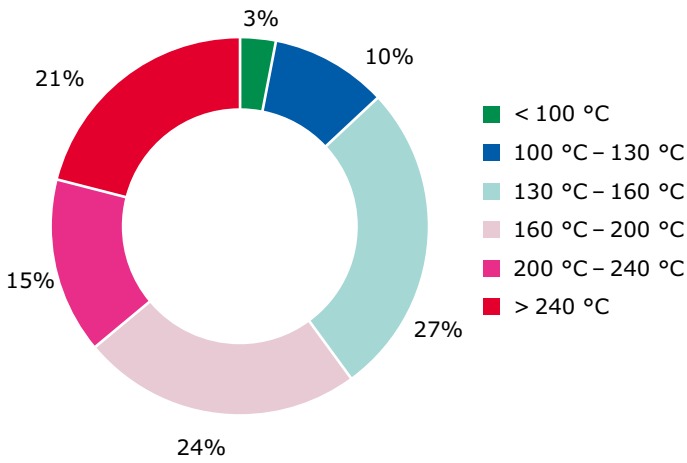


Figure 6.

T_m distribution of 67 BCS II and IV compounds.

Molecular Interactions

Consideration of drug-polymer interactions on the molecular level can improve the likelihood of successful HME formulation development. This is especially true when considering the impact of the polymer on maintaining drug concentrations in solution, which was recently described in a critical review article by Price and co-workers.[4]

In the following study, solid-state characterization of an extruded formulation was performed using indomethacin as a model compound to identify possible interactions. Mixtures of the API and Parteck® MXP excipient were pre-blended and processed via HME. The same extrudates were used for the studies and drug loading (30% indomethacin). Fourier-transform infrared spectroscopy (FTIR) was utilized to gain detailed insight into the solid state of the matrix. Solid-state NMR measurements were performed using heteronuclear correlation spectroscopy (HETCOR) to evaluate 1H – 13C interactions in the solid state. 1H-NMR and 2D 1H/1H nuclear Overhauser effect spectroscopy (NOESY) was conducted to gain insight into the prolongation of the supersaturated state of the formulation upon dissolution. Finally, a molecular dynamics (MD) simulation was performed to visualize interactions between the API and polymer.

FTIR analysis showed that at 30% drug loading, vibrational shifts in benzoyl regions indicate the formation of hydrogen bonds between the PVA and indomethacin (Figure 7). At higher drug loadings, the predominant interactions were between API molecules.

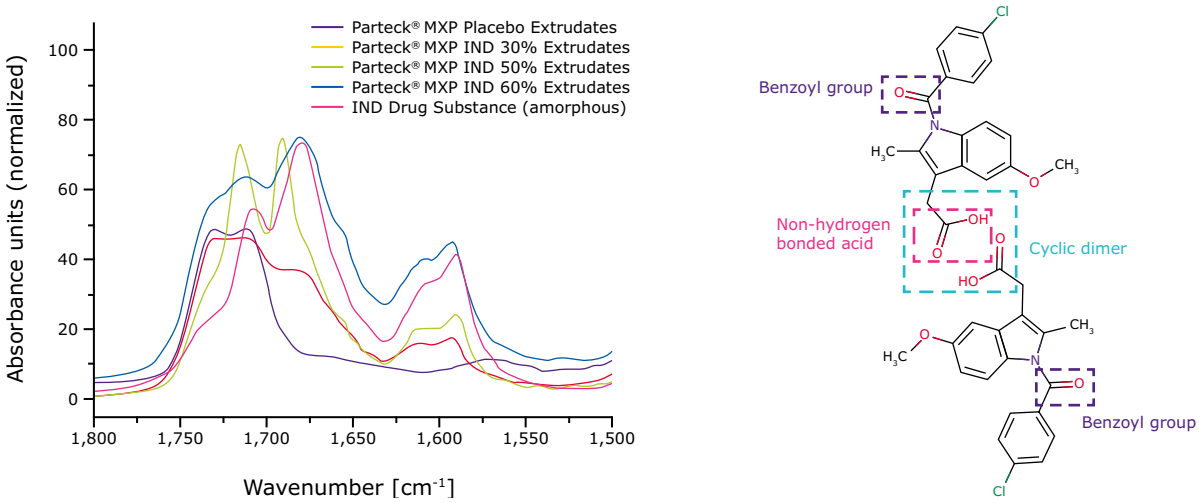


Figure 7.

FTIR measurements of indomethacin (IND)-loaded PVA matrices and corresponding structural relations.

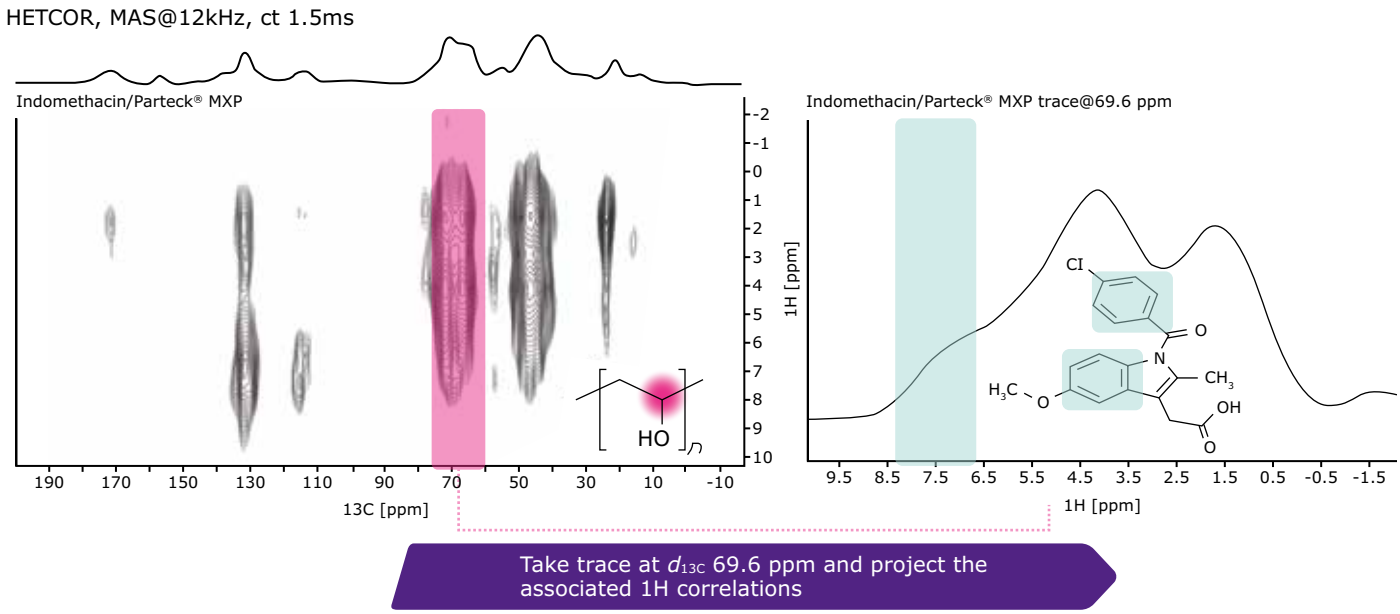


Figure 8.

Homogenous distribution was confirmed by uniform 1H T1 relaxations and a correlation of PVA backbone to aromatic parts of API was observed.

Uniform T1 relaxational vibration in the HETCOR analysis confirmed indomethacin was distributed homogenously throughout the polymer matrix (Figure 8). This is an important observation, as homogeneity is a critical attribute for the long-term stability of a polymeric amorphous solid dispersion (ASD).[3] Furthermore, in agreement with the FTIR data, solid-state interactions between the API and PVA were observed.

Further evidence of this prominent interaction between indomethacin and PVA was found in the 2D NOESY spectrum, specifically between the hydrophobic PVA backbone and the lipophilic functionalities within indomethacin (Figure 9).

Figure 10 shows the output of the MD simulation, in which an indomethacin molecule is inserted into a simplified PVA bulk. In the simulation, the hydrophilic hydroxyl groups in PVA rotate away from the hydrophobic API molecule, leaving the hydrophobic PVA backbone accessible to interact with the aromatic moieties of the API. Indeed, this is in line with recent work in the literature describing the importance of interactions between hydrophobic polymeric backbones and increasingly hydrophobic API moieties for effective formulation performance.[4]

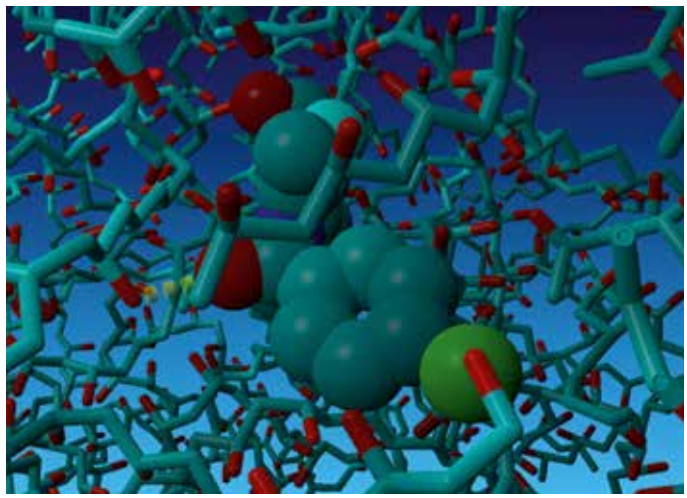


Figure 10.

Molecular interactions between indomethacin (ball-model) and a simplified PVA matrix (stick-model). PVA takes a dedicated conformation enabling an interaction between PVA backbone and aromatic structures of the API.

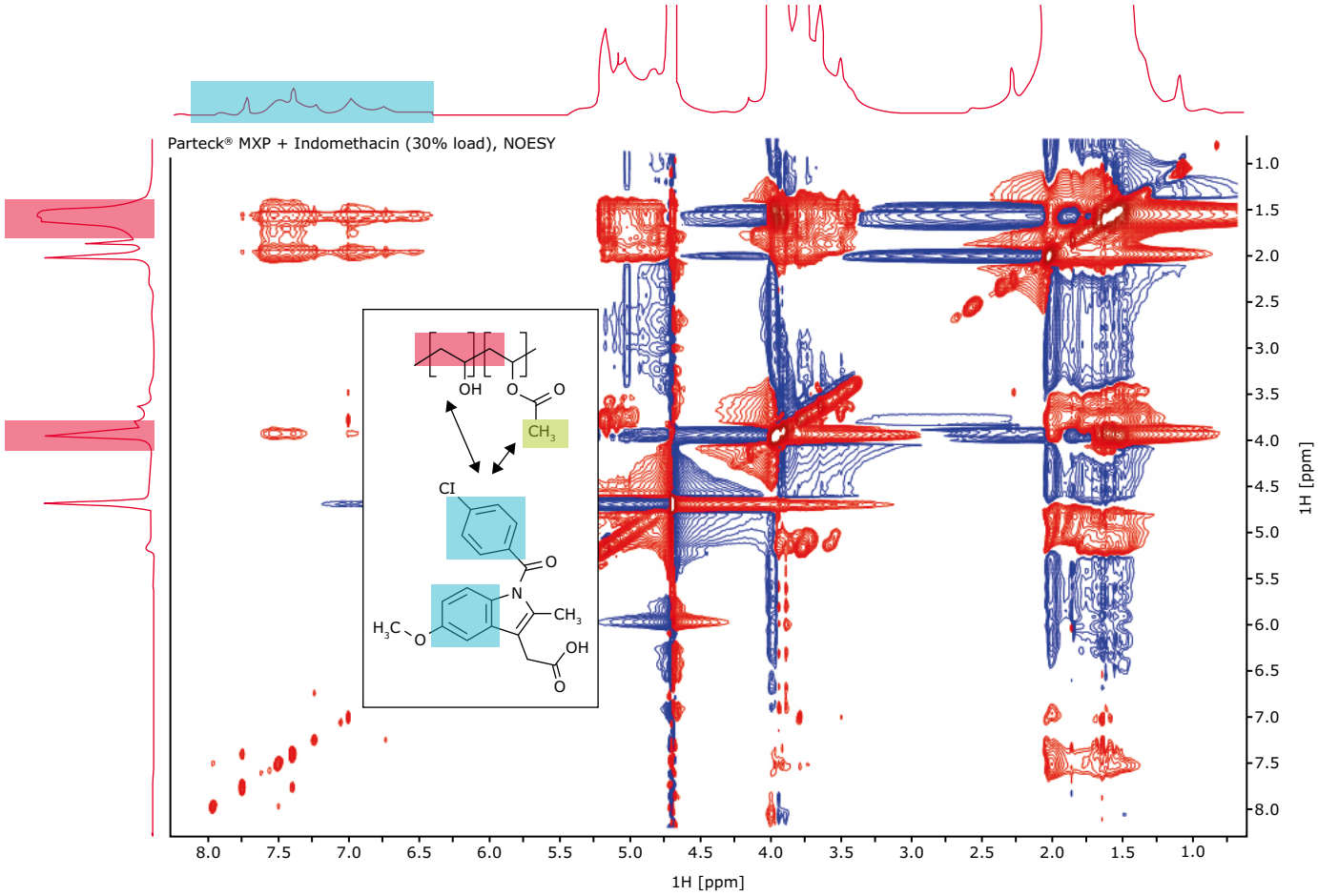


Figure 9.

Two-dimensional 1H/1H NOESY of extruded matrices in D_2O.

Impact of PVA on Supersaturation Stability and Absorption

The combination of complimentary API interactions with surface-activity makes PVA an optimal inhibitor to prevent the precipitation of supersaturated API upon dissolution. As shown in Figure 11, PVA prolonged the supersaturated state of the poorly soluble weak base itraconazole after a pH-shift from a gastric to intestinal environments. Supersaturation upon transfer from the acidic stomach to the more neutral intestines is an important problem to overcome in the development of poorly soluble weak bases.

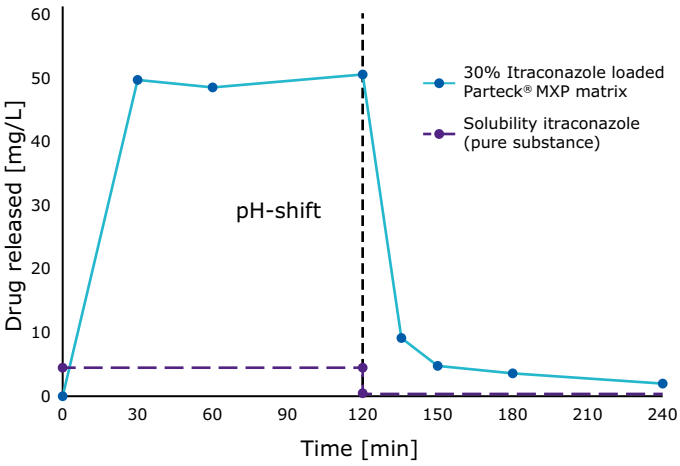


Figure 11.

Dissolution behavior of 30% itraconazole-loaded Parteck® MXP matrices during pH-shift.

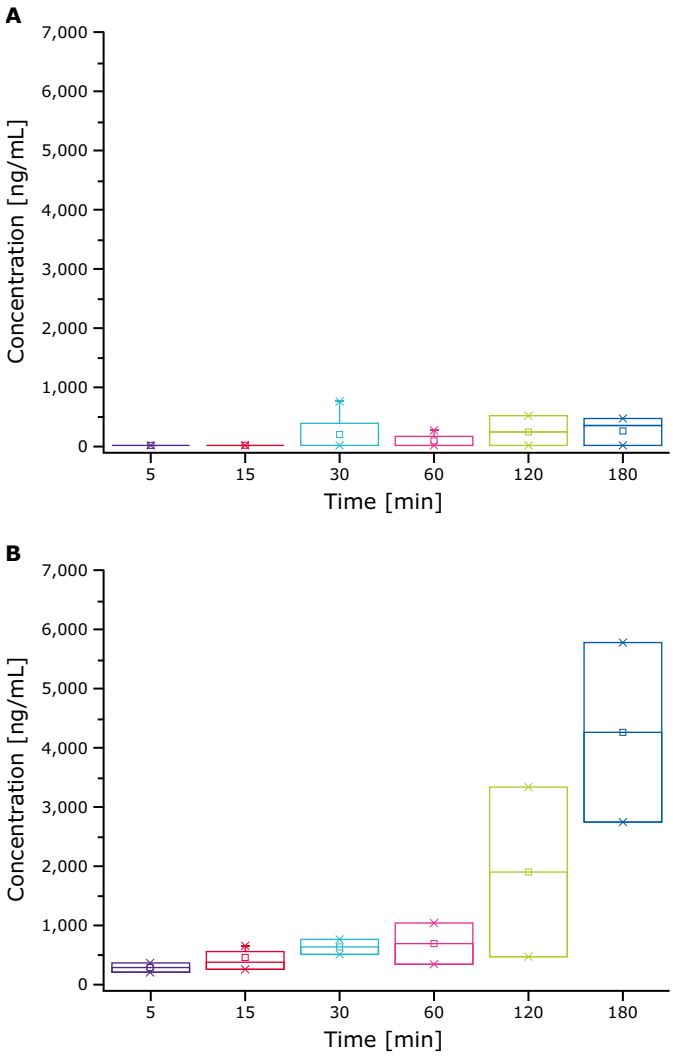


Figure 12.

Direct comparison of itraconazole concentrations in the donor well. Crystalline itraconazole (A) versus HME formulation with 30% itraconazole and Parteck® MXP excipient (B).

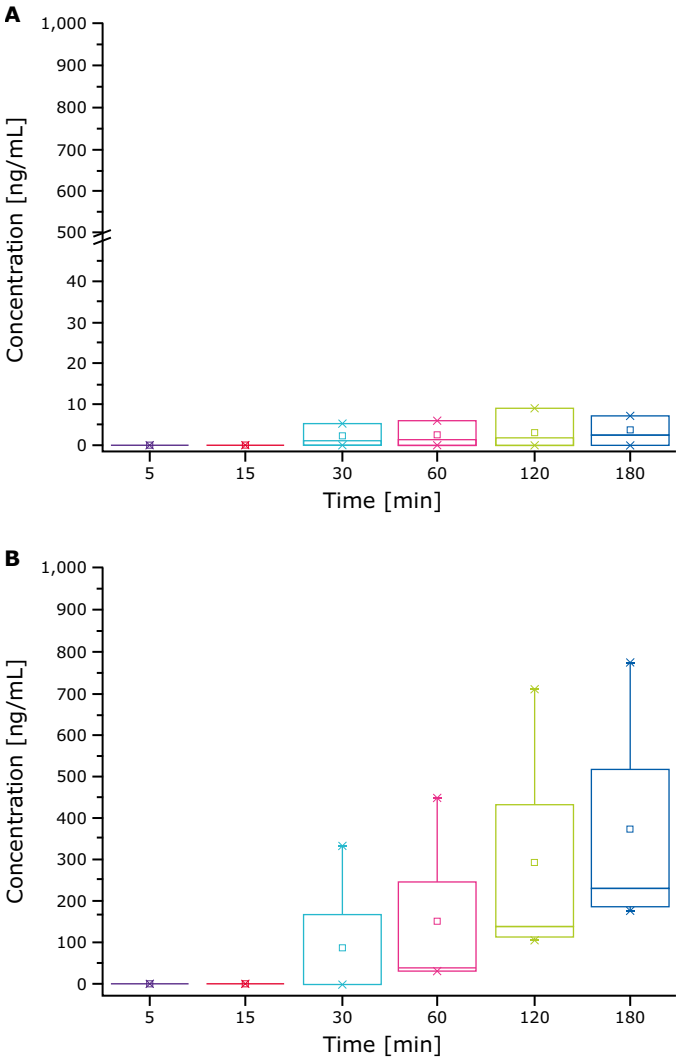


Figure 13.

Concentration of itraconazole in the receiver well after permeation. Crystalline itraconazole (A) versus HME formulation with 30% itraconazole and Parteck® MXP excipient (B).

However, the importance of precipitation inhibition extends beyond weak bases, and is an essential consideration when developing solubility enhancing formulations of BCS class II compounds. Without effective precipitation inhibition after dissolution, the concentrations of API in solution will significantly decrease, resulting in a lower than expected bioavailability. To demonstrate the importance of supersaturation and precipitation inhibition on absorption, *in vitro* biphasic dissolution studies were performed in an IDAS™ 1 system, in which 3 mg of API were dosed (max conc. 0.375 mg/mL).

Figure 12 shows crystalline itraconazole (A) versus the HME formulation with 30% drug load and Parteck® MXP excipient (B) in the donor well. The concentration of the crystalline itraconazole slightly increased over time but remained low. The HME formulation showed a much greater 10-fold increase in concentrations in the donor well.

With these high concentrations in the donor well, supersaturation is generated. Without effective precipitation inhibition, concentrations would rapidly decrease and reduce absorption. However, as shown in Figure 13, itraconazole HME formulations with Parteck® MXP excipient are rapidly and substantially absorbed through the cell membrane and into the donor well, at concentrations 50-fold higher than the crystalline API.

This study demonstrates the advantages of PVA as a solid dispersion excipient to enhance dissolution and absorption of poorly soluble compounds, contributing to enhanced solubility, sustained supersaturation, and subsequently increased absorption. The advantage of PVA can also be leveraged in ternary systems. A study from Wlodarski et al. demonstrated the superior dissolution behavior of ternary systems comprising a mixture of polyvinyl alcohol and copovidone due to enhanced supersaturation.[20]

Formulation Flexibility

Parteck® MXP excipient can be used in a range of downstream processes to formulate a variety of final dosage forms. PVA extrudates can be milled and compressed into tablets, milled or pelletized and filled into capsules, or processed into direct-shaped tablets using injection molding. Film extrusion and filament production to enable 3D printing is also possible.

A recent study performed by Palekar et al. utilized the modular adaptation of filament properties by combining PVA and polyols.[21] In this way the mechanical strength of the filaments can be individually adjusted to the required target.

Parteck® MXP excipient can be used in both sustained and immediate release formulations, which makes it very versatile for use in HME. For example, an itraconazole-PVA (30%/70%) extrudate was further processed to yield several different oral formulations: capsules (extrudate was pelletized prior to filling), directly compressed tablets (extrudate was milled prior to blending with further excipients and compressed) and direct-shaped tablets.

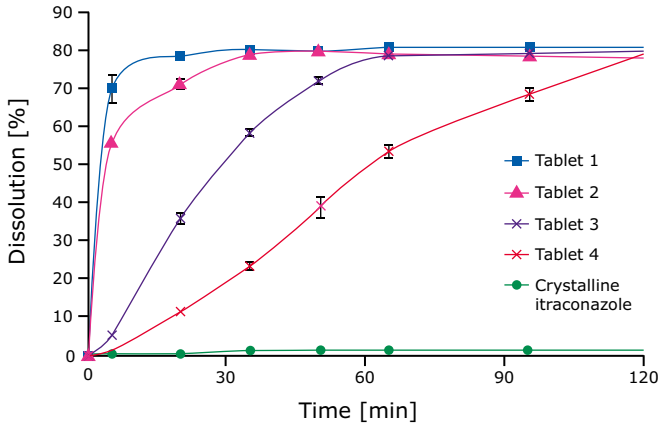
Pelletized extrudate simply filled into capsules, helps to accelerate progress from preclinical to clinical testing for immediate release formulations (Figure 14A). In addition, the ability to use different size pellets creates greater flexibility when fine-tuning release kinetics based on the surface area of the pellet.

In the case of directly compressed tablets formulated using milled extrudate, both immediate and sustained release profiles were achievable depending on the overall formulation (Figure 14B).

B

Directly compressed tablets: Immediate and sustained release

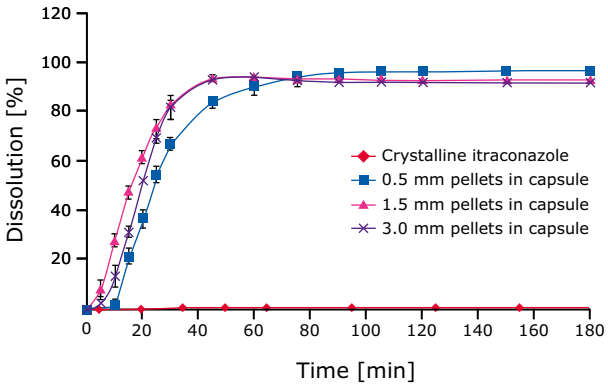
	Tablet 1	Tablet 2	Tablet 3	Tablet 4
Extrudate [%]	50	50	50	60
Microcrystalline cellulose [%]	10	10	10	10
K_2CO_3 [%]	–	–	14.75	10
NaCl [%]	14.75	14.75	–	–
Magnesium stearate [%]	0.5	0.5	0.5	0.5
Lactose [%]	16.25	16.25	16.25	11
Silica [%]	1	1	1	1
Crospovidone [%]	7.5	7.5	7.5	7.5
Compressed force [kN]	15	10	10	10
T_{max} [min]	15	30	60	120



Dissolution method: FDA-recommended conditions for itraconazole, 900 mL SGF, 37 °C, 100 rpm, formulated extrudate with 30% drug load; n=3

A

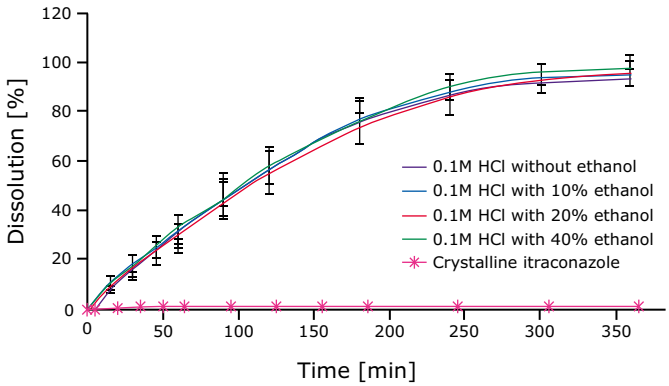
Capsules: Immediate release



Dissolution method: FDA-recommended conditions for itraconazole, 900 mL SGF, 37 °C, 100 rpm, 100 mg itraconazole, n=3

C

Direct-shaped tablets: Sustained release



Dissolution method: 900 mL of medium, 37 °C, 100 rpm, 200 mg itraconazole, n=6

Figure 14.

A range of final dosage forms with different release kinetics can be achieved with Parteck® MXP excipient: Dissolution from itraconazole-Parteck® MXP capsules – immediate release (A). Directly compressed tablets – sustained release and immediate release, depending on the tablet composition (B). Dissolution profile of direct-shaped tablets – sustained release and no dose dumping effect in up to 40% ethanol (C).

Varying the amount of extrudate and adding inorganic salts enables modification of release kinetics, due to the different dissolution kinetics of the PVA polymer in the presence of NaCl vs. K_2CO_3, with the slower dissolution in the latter also resulting in a slower dissolution of the API.

Direct-shaped tablets demonstrated sustained release kinetics, due to the substantially larger surface area of the dosage form, which allows PVA to gel in contact with water[22], slowing the release from the tablet (Figure 14C). In addition, it was shown that no significant changes of the release profile occur upon the addition of 10 – 40% ethanol, an FDA requirement for sustained release formulations.

Conclusion

Pharmaceutical HME, although an established technology, has gained prominence in recent years as one of the amorphous formulation technologies of choice due to benefits associated with high and stable drug loads; dosage form flexibility; solvent-free processing and compatibility with the important area of continuous pharmaceutical manufacturing. The polymer-space for HME is broad and diverse, spanning natural and synthetic chemical space.

Parteck® MXP excipient is a fully synthetic polyvinyl alcohol, that has been specifically engineered with optimal viscosity and particle characteristics for trouble-free extrusion. Particularly advantageous is the unusually high thermal stability that this excipient can offer, expanding the formulation space to high melting point APIs, for which HME is normally discounted early in development. Flexibility also extends to downstream processing, as extrudates produced with Parteck® MXP excipient can be processed in a flexible and bespoke manner, to yield the desired release profile for individual APIs. Upon dissolution, the robust solubility enhancement achieved with Parteck® MXP excipient is observed over a broad range of APIs, independent of melting point.

In addition, Parteck® MXP excipient can sustain high concentrations of API in solution due to effective interaction between the hydrophobic polymer backbone with hydrophobic moieties of the API. This is complimented by the amphiphilic nature of the PVA and its ability to adopt a dedicated conformational structure. The result is an optimal precipitation inhibition effect to sustain drug concentrations for physiological timescales. Due to the combination of these properties, Parteck® MXP excipient can provide a simple and efficient route to bioavailability enhancement for poorly soluble compounds.

References

1 Loftsson T., Brewster ME., Pharmaceutical applications of cyclodextrins: basic science and product development. J Pharm. Pharmacol. 62 (2010) 1607–1621.

2 Thayer, A. M., Finding solutions. Chem. Eng. News 2010. 88, 13–18.

3 Ditzinger F., et al., Lipophilicity and hydrophobicity considerations in bio-enabling oral formulations approaches – a PEARRL review. Journal of Pharmacy and Pharmacology, 2019. 71(4): 464–482.

4 Price DJ., et al., Approaches to increase mechanistic understanding and aid in the selection of precipitation inhibitors for supersaturating formulations – A PEARRL Review. J. Pharm. Pharmacol., 2018 (epub ahead of print). doi: 10.1111/jphp.12927.

5 Price DJ., et al., Calculation of drug-polymer mixing enthalpy as a new screening method of precipitation inhibitors for supersaturating pharmaceutical formulations. Eur. J. Pharm. Sci., 2019. 132, 142–156, doi: t10.1016/j.ejps. 2019.03.006.

6 De Jaeghere W., et al., Hot-melt extrusion of polyvinyl alcohol for oral immediate release applications. International Journal of Pharmaceutics, 2015. 492 (1-2): p. 1–9.

7 Zheng M., et al., Polyvinyl Alcohol in Hot Melt Extrusion to Improve the Solubility of Drugs. European Pharmaceutical Review, 2017(3).

8 Kasselkus A., et al., Polyvinyl alcohol – Revival of a long lost polymer. BioProcess Online. July 23, 2018.

9 Haehnel W. and Herrmann W. O., A process for the preparation of polymeric vinyl alcohol, US1672156 and DE450286, 1927.

10 Herrmann W. O. and Haehnel W., Über den Polyvinylalkohol. Berichte der deutschen chemischen Gesellschaft (A and B Series), 1927. 60(7): p. 1658–1663.

11 Helfand W. H. and Cowen D. L., Evolution of Pharmaceutical Oral Dosage Forms. Pharmacy in History, 1983. 25(1): p. 3–18.

12 FDA, Agency Response Letter GRAS Notice No. GRN 000141 [Polyvinyl Alcohol], U.S. Food and Drug Administration (FDA), Editor. April 28, 2004.

13 Sixty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Polyvinyl alcohol, in Safety evaluation of certain food additives and contaminants, World Health Organization, Editor. 2004: Geneva. p. 137–153.

14 European Food Safety Authority, Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to the use of polyvinyl alcohol as a coating agent for food supplements; Question number EFSA-Q-2005-017. The EFSA Journal, 2005. 294: p. 1–15.

15 DeMerlis C. C. and Schoneker D. R., Review of the oral toxicity of polyvinyl alcohol (PVA). Food and Chemical Toxicology, 2003. 41(3): p. 319–326.

16 Kelly C. M., et al., Subchronic toxicity study in rats and genotoxicity tests with polyvinyl alcohol. Food and Chemical Toxicology, 2003. 41(5): p. 719–727.

17 Rodwell D. E., et al., Effects of polyvinyl alcohol administered in the diet to rats on fertility, early embryonic development, growth and development. Food and Chemical Toxicology, 2003. 41(5): p. 729–737.

18 Nair B., Cosmetic Ingredient Review Expert Panel, Final Report On the Safety Assessment of Polyvinyl Alcohol. International Journal of Toxicology, 1998. 17(5 suppl): p. 67–92.

19 Amidon G. L., et al., A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. Pharmaceutical Research, 1995. 12(3): p. 413–420.

20 Palekar S., Nukala PK., Mishra SM., Kipping T., Patel K., Application of 3D printing technology and quality by design approach for development of age-appropriate pediatric formulation of baclofen. International Journal of Pharmaceutics. 2019. 556: p. 106–16.

21 Wlodarski K., Zhang F., Liu T., Sawicki W., Kipping T., Synergistic Effect of Polyvinyl Alcohol and Copovidone in Itraconazole Amorphous Solid Dispersions. Pharmaceutical Research, 2018. 35(1): p. 16.

22 Kasselkus A. and Weiskircher-Hildebrandt E., et al., What's Old Is New: The Rebirth of Polyvinyl Alcohol for Enhanced Solubility and Sustained Release Formulations. American Pharmaceutical Review, 2018. 21(7).

MilliporeSigma
400 Summit Drive
Burlington, MA 01803

For additional information, please visit **EMDMillipore.com**
To place an order or receive technical assistance, please visit **EMDMillipore.com/contactPS**

We provide information and advice to our customers on application technologies and regulatory matters to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect to any rights of third parties. Our information and advice do not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose.

MilliporeSigma, the Vibrant M, Parteck and SAFC are trademarks of Merck KGaA, Darmstadt, Germany and/or its affiliates. All other trademarks are the property of their respective owners. Detailed information on trademarks is available via publicly accessible resources. © 2020 Merck KGaA, Darmstadt, Germany and/or its affiliates. All Rights Reserved.

Lit. No. MS_WP6723EN
09/2020