SAFC®
Pharma/Biopharma Raw Materials

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Parteck® MXP

Technical Information

Content

Introduction to hot melt extrusion

It is estimated that around 70 % of drugs in the pharmaceutical pipeline are poorly soluble but highly permeable. For these new chemical entities (NCEs), a formulation solution that increases solubility can be the key factor in whether a drug candidate advances to market. Solid dispersion technologies, in particular hot melt extrusion (HME), offer such solutions to this formulation challenge.

HME is a solvent-free process which, through heating and mixing, creates a solid amorphous solution of the active pharmaceutical ingredient (API) and a matrix polymer. The process breaks down the crystalline structure of the API, leading to increased solubility and rate of dissolution into solution. This relatively uncomplicated method results in an extrudate intermediate (API:polymer solid solution) which can then be further processed for final drug formulation.

Currently, there are few polymers on the market that are designed for the conditions of HME. Available polymers should be characterized not only for their solubility-enhancing ability but also for their stability (degradation temperature, T_{deg}), API solubilization capacity (key parameter for high API load), the stability of the API (little to no reactivity or API degradation), and the stability of the extrudate (in particular for high API loads). While these features can be API-specific, an improved understanding of them aids in establishing the design space and application range of a polymer in an HME application.

Introduction to Parteck® MXP and main benefits

Our new excipient, Parteck® MXP, is specifically designed and characterized for HME applications.

Main benefits of Parteck® MXP at a glance

Simple

- **Simple, synthetic polymer**
  GRAS polymer, compliant with USP, Ph Eur, and JPE; little to no variability from batch to batch
- **Easy to use**
  Optimized for flowability and miscibility with APIs, low melt viscosity, good batch homogeneity
- **Flexible release kinetics**
  One polymer, one extrudate, many formulation options

Soluble

- **Water-soluble polymer**
  Better dissolution performance than water-insoluble polymers
- **High solubilization capacity**
  The minimum API load achieved with the majority of model APIs assessed was 30 % (10 – 15 % is market standard)
- **Increases solubility over a broad range of APIs**
  Nine of nine BCS Class II APIs assessed demonstrated increased solubility

Stable

- **High degradation temperature (T_{deg})**
  No degradation up to and above 250 °C, broadening the HME API application range
- **Stable extrudates under various conditions**
  No recrystallization or degradation was observed under cold, room-temperature and accelerated conditions
- **Inert excipient for hot melt extrusion**
  Little to no chemical instability was found across APIs assessed

Emprove® Program

We market Parteck® MXP as part of our Emprove® Program, which combines outstanding quality with comprehensive documentation and excellent service.

Each product in the portfolio is complemented with three types of dossiers to help facilitate your qualification, risk assessment and process optimization efforts: Material Qualification Dossier, Quality Management Dossier and Operational Excellence Dossier. They provide information on the manufacturing process, stability data, elemental impurity information, product quality reports, analytical procedures, and much more. The Emprove® Program includes 400 pharma raw and starting materials and a selection of filtration and single-use products.

The dossiers can be accessed online in our new Emprove® Suite. All our subscribers to the Emprove® Suite get 24/7 access to all dossiers of the entire Emprove® portfolio for two years, with up to five accounts per company. The Material Qualification Dossier continues to be available free of charge at www.merckmillipore.com

For more information about the Emprove® Program, visit www.merckmillipore.com/emprove or ask your local sales representative.

Performance

Range of APIs

Hot melt extrusion is a solvent-free process and, as a formulation technology, has a large potential pool of insoluble (BCS II and IV) APIs to which it can be applied. However, this API range can be limited due to factors such as the thermostability of the API and/or polymer, the compatibility of the API and polymer (and plasticizer, where necessary), and undesired chemical interactions with the polymer which can lead to degradation of the API. For this reason, APIs from different chemical families and with varying physicochemical properties were selected (Table 1) for evaluation with Parteck® MXP. As Parteck® MXP has a high degradation temperature (≥ 250 °C), an API with a high melting temperature was included as a model high-temperature/poorly soluble API.

API (BCS II)	MW (g/mol)	pK_a	T_m (°C)	LogP	Charge	Aqueous solubility (mg/mL, 25 °C)
Ibuprofen	206.28	4.91	78	3.97	-1	0.021
Cinnarizine	368.51	8.4	118 – 122	5.19	1	0.00172
Ketoconazole	531.43	6.75	146	4.3	0	0.00931
Indomethacin	357.79	4.5	151	4.27	-1	0.000937
Naproxen	230.26	4.19	152	3.29	-1	0.0511
Atorvastatin	558.64	4.33	159 – 160	4.41	-1	0.000495
Itraconazole	705.63	3.70	166.5	5.90	0	0.00964
Carbamazepine	236.27	15.96 (SA) -3.8 (SB)	204 – 206	2.1	0	0.152
Telmisartan	514.62	3.65 (SA) 6.13 (SB)	260	7.7	-1	0.0035

Table 1: Physicochemical properties of selected APIs

Homogeneity of API in physical blend and extrudate

For all APIs, the API and Parteck® MXP were directly physically blended, then loaded into the feeder for extrusion. The miscibility and homogeneity of the physical blend and the extrudate were assessed, since the homogeneity of the starting physical blend can impact the homogeneity of the resulting extrudate.

	Indomethacin concentration	Average	SD
Sample 1	30.9%	30.8%	0.006
Sample 2	31.0%		
Sample 3	30.7%		
Sample 4	31.8%		
Sample 5	30.6%		
Sample 6	30.0%		

Table 2: Homogeneity assessment of indomethacin: Parteck® MXP physical blend (Pre-extrusion)

Method:
NMR analysis of the indomethacin content (target drug percentage: 30 %) within physical blend of indomethacin and Parteck® MXP

Solubility enhancement of APIs

For the APIs assessed, solubility was enhanced in all cases with no detectable degradation of the API. Dissolution studies were performed using FDA-recommended conditions.

API (BCS II)	Drug load	Solubility enhancement (max.)	Dissolution medium
Ibuprofen	30 %	2-fold	SGF
Cinnarizine	20 %	10-fold	Acetate buffer pH 4.5
Ketoconazole	30 %	17-fold	SGF
Indomethacin	30 %	3-fold	FeSSIF
Naproxen	30 %	4-fold	Phosphate buffer pH 7.4
Atorvastatin	30 %	154-fold	Phosphate buffer pH 6.8
Itraconazole	30 %	80-fold	SGF
Carbamazepine	30 %	2-fold	Water
Telmisartan	15 %	35-fold	Phosphate buffer pH 7.5

Table 3: Solubility enhancement of selected APIs after extrusion with Parteck® MXP

Further examination of the API dissolution curves showed that dissolution was rapid, and in many cases, maximum solubility was reached in under 15 minutes. This rapid dissolution can likely be attributed to the fact that Parteck® MXP is a water-soluble polymer and thus does not limit the dissolution rate, an issue which often happens when a poorly water-soluble polymer is used in HME.

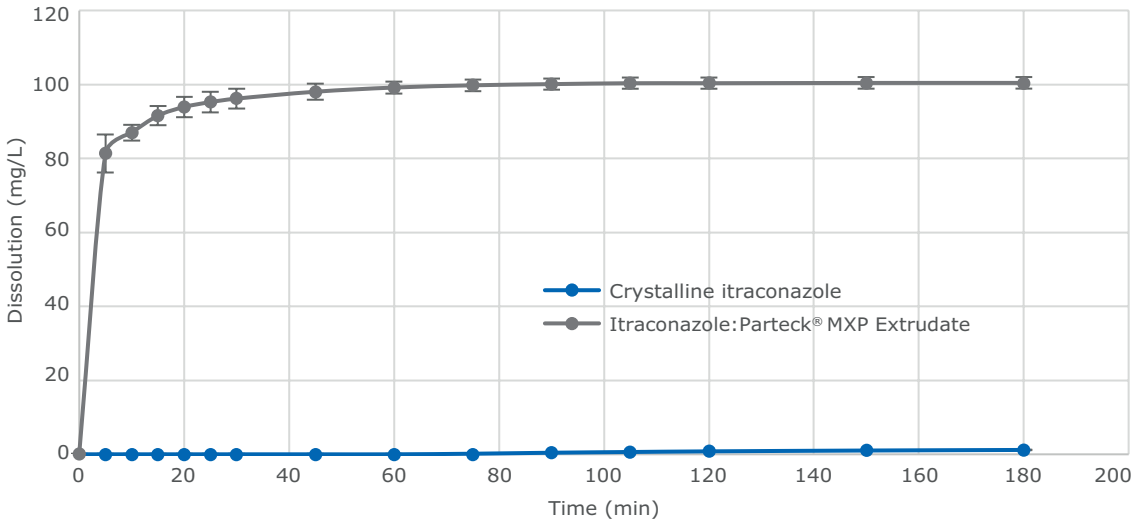


Figure 1: Dissolution of itraconazole: Parteck® MXP extrudate (milled)

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

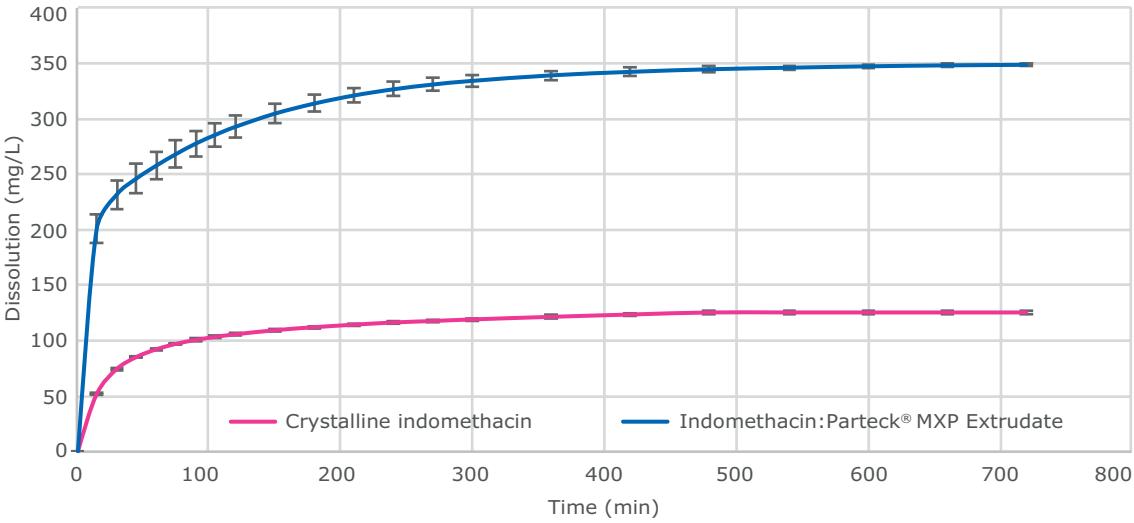


Figure 2:
Dissolution of indomethacin: Parteck® MXP extrudate (milled)

Dissolution method: FDA-recommended conditions for indomethacin 500 mL, FeSSIF, 37 °C, 75 rpm, 150 mg indomethacin, 30 % drug load; N=3

Drug load

The achievable drug load or amount of drug in the API:polymer extrudate can affect downstream formulation development for oral solids. If the drug load is too low, this may be insufficient to achieve the target efficacious dose strength while remaining within the boundaries of patient-friendly dosages (sizes and frequency).

In previous studies, the solubilization capacity for HME has been attributed to the hydrogen bonding potential of the polymer; higher H-bonding potential typically leads to better miscibility and blending of the API and polymer, resulting in higher achievable drug loads and potentially less risk of recrystallization. Parteck® MXP has a high potential to form hydrogen bonds due to its numerous –OH groups, giving it a high potential to mix with APIs at the molecular level and better solubilize and stabilize the API into the polymer matrix.

Stability of the extrudate

The stability of the API:polymer extrudate (and the resulting final formulation) is a critical factor when determining which polymer to use. The amorphous solid dispersion may be instable, in particular when a high API load is targeted, increasing the likelihood of recrystallization.

After extrusion and milling, the stability of three different API:Parteck® MXP extrudates was assessed under three different conditions: cold (2 – 4 °C), room temperature (25 °C, 60 % relative humidity (rH)), and accelerated (40 °C, 75 % rH). At each time point, the extrudates were measured using DSC (to assess the amorphous state), HPLC (to assess API degradation), and repeat dissolution. For all three examples, no instability was found throughout the testing period (see results in Table 4 and Figure 3).

API	Storage conditions	Time	Results*
Itraconazole	Low: 2 – 4 °C	6 M	Stable under all conditions
Ibuprofen	Room: 25 °C, 60 % humidity	6 M	Stable under all conditions
Indomethacin	Accelerated: 40 °C, 75 % humidity	6 M	Stable under all conditions

Table 4: Summary of stability results

* DSC (to assess the amorphous state), HPLC (to assess API degradation), and repeat dissolution; Drug load: 30 % in all extrudates.

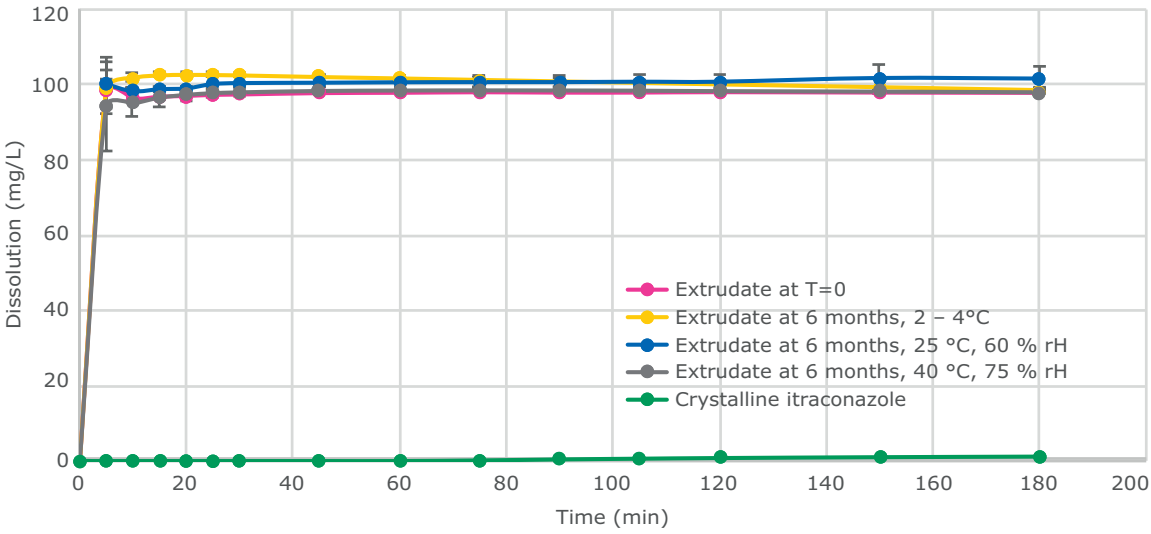


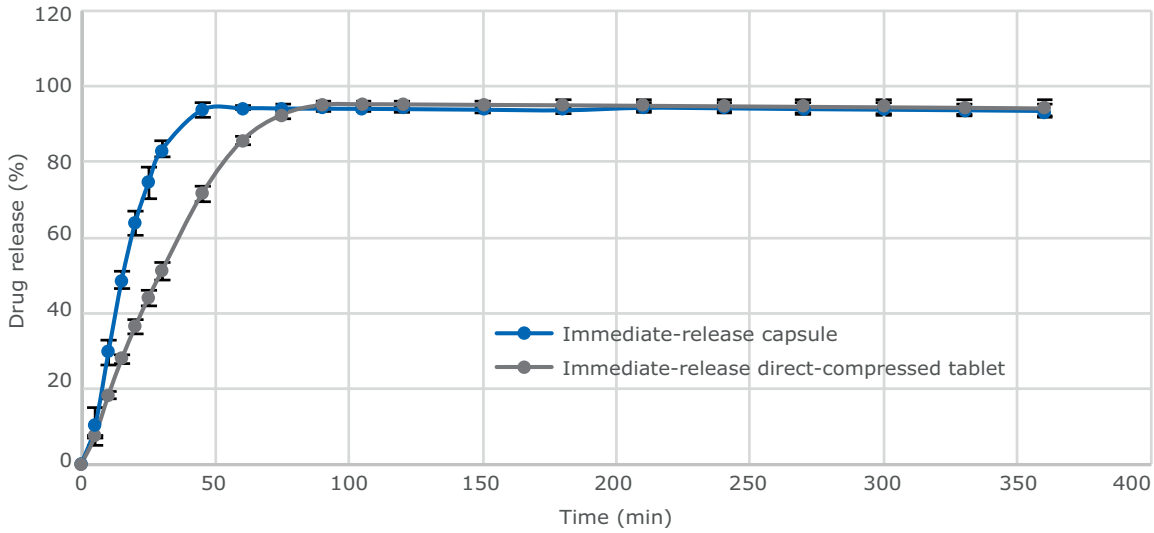
Figure 3: Example of repeat dissolution of itraconazole: Parteck® MXP extrudates (milled) at 6 months

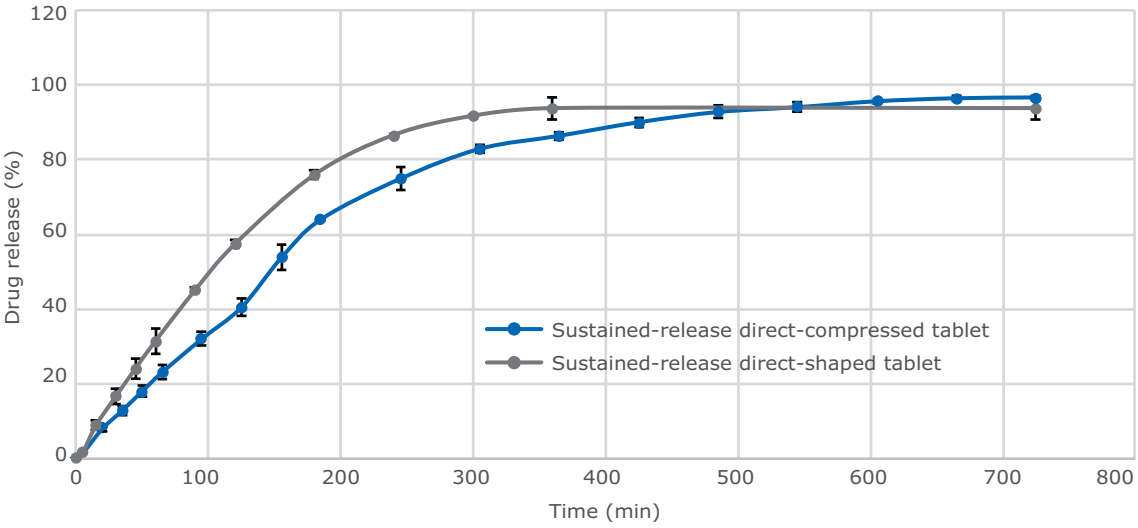
Dissolution method: FDA-recommended conditions for itraconazole, 900 mL SGF, 37 °C, 100 rpm, 100 mg itraconazole, 30 % drug load; N=3

Final formulation

Once the challenges of solubility enhancement have been overcome, difficulties in the final oral formulation can arise. These can vary based on the intended final release kinetics (immediate release vs. sustained release), final dosage form (capsules vs. tablets), and the inherent properties of the API and/or polymer themselves (e. g., poor aqueous solubility).

Parteck® MXP can ease the effort in final formulation. Using the same API:Parteck® MXP extrudate, four different final formulations have been evaluated, to date: immediate-release capsules, immediate-release compressed tablets, sustained-release compressed tablets, and sustained-release direct-shaped tablets.





Figures 4A and 4B: Sample formulations using itraconazole: Parteck® MXP extrudates

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

For capsule formulation, immediate-release (IR) capsules can be formulated easily and directly using pelletized extrudate. Here, varying pellet sizes from 0.5 mm to 3.0 mm were created directly after extrusion, then filled into capsules. In all cases, the resulting dissolution curves demonstrated immediate release kinetics. This ability to simply formulate the pelletized extrudate with a resulting IR dosage can significantly decrease the time to pre-clinical *in vivo* testing and even to first-in-human clinical trials.

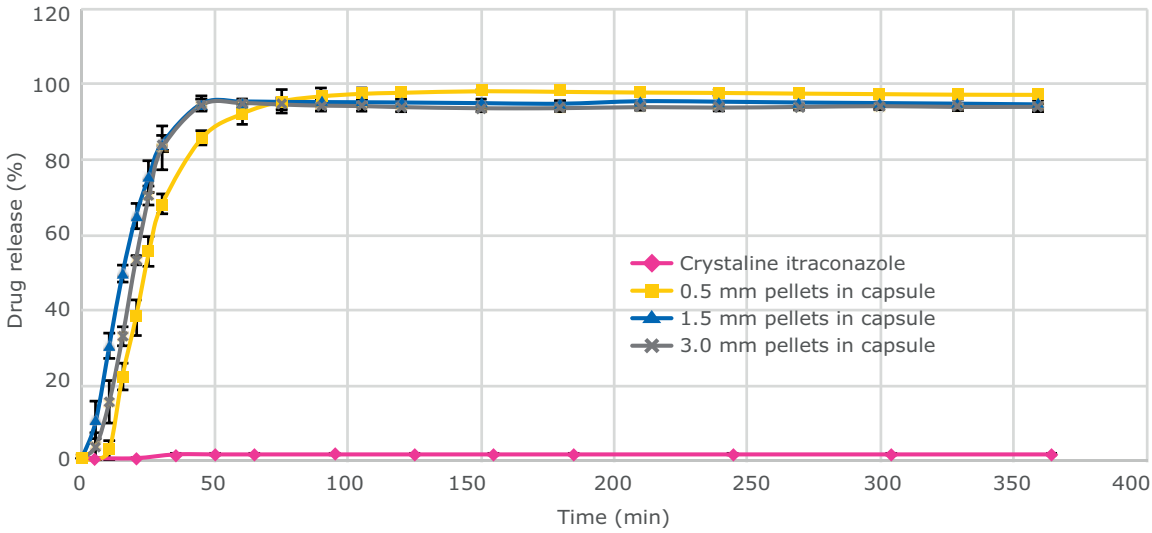


Figure 5: Immediate release of itraconazole: Parteck® MXP capsule formulations

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

For tablet formulation, extrusions of a drug with Parteck® MXP can be formulated into either immediate-release or sustained-release tablets. While tablet composition may vary based on the API, final release kinetics, and desired physical characteristics of the tablet, the sample formulations developed with itraconazole:Parteck® MXP were easy to formulate, show little to no dilution of the drug:polymer extrudate (0 – 15 % of the sustained-release tablet compositions is comprised of other excipients), and possess a number of desired characteristics such as hardness and resistance to dose dumping.

Appearance and properties

Composition and CAS registry number

Parteck® MXP is milled polyvinyl alcohol (PVA 4-88) with a special particle size. It contains no additives, and conforms to all relevant regulations and major pharmacopoeias in the ICH region.

- Polyvinyl alcohol (Ph Eur, USP, JPE)
- CAS registry number 9002-89-5

Appearance and properties

Parteck® MXP is a near-white pulverized powder, the properties of which can be found in Tables 9 and 10. While these do not affect the manufacture of the final drug product after extrusion, they can influence the feeding and extrusion process.

The full product specification can be found at www.merckmillipore.com

Bulk density (g/mL)	0.53 ± 0.02
Tapped density (g/mL)	0.74 ± 0.02
PSD (0.5) (µm)	60 – 80
Loss on drying (%)	1 – 3
Angle of repose (°)	35

Table 9: General properties of Parteck® MXP

Particle size distribution

Batch	Dv10 (µm)	Dv25 (µm)	Dv50 (µm)	Dv75 (µm)	Dv90 (µm)
1	20	39	65	102	150
2	15	31	57	93	141
3	17	35	61	97	145

Table 10: Particle size distribution of three Parteck® MXP production batches (measured via laser light scattering with dry dispersion).

Hygroscopicity (Dynamic vapor sorption, DVS)

Parteck® MXP is slightly hygroscopic. It is recommended to dry the material before extrusion (see technical recommendations section). Store in tightly sealed packaging under dry conditions.

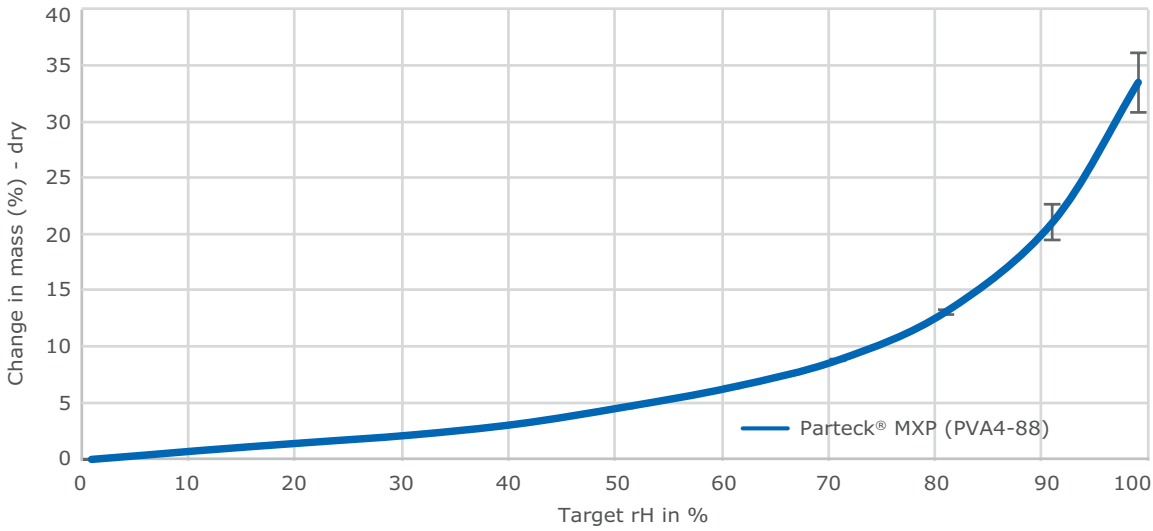


Figure 6: Dynamic vapor sorption isotherm for Parteck® MXP at 25 °C

Thermal properties of Parteck® MXP

Parteck® MXP is a semi-crystalline polymer and thus possesses both a glass transition (T_g) temperature and a melting temperature (T_m). The semi-crystalline nature of Parteck® MXP has not proven to be a limiting factor in this application. For 75 % of the model APIs assessed, no plasticizer was necessary to achieve an amorphous solid dispersion (see technical recommendations for advice on plasticizers). Once extruded, the API and polymer form an amorphous extrudate which has been demonstrated to be remarkably stable, even under accelerated conditions (see Table 4, Figure 3)

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

Table 11: Key temperature characteristics of Parteck® MXP

Most notably, Parteck® MXP has a very high degradation temperature. This can allow for extrusion at temperatures above 200 °C without degradation of the polymer, broadening the application range of HME to include more thermostable compounds.

180 °C **210 °C** **230 °C** **250 °C**

Figure 7: Visual comparison of Parteck® MXP extrudate at various temperatures

Finally, the melt viscosity of the polymer can impact melting and mixing in the extruder. If the melt viscosity is too high, the required mechanical energy may also be too high, resulting in equipment breakage and/or breakdown. If the melt viscosity is too low, the mixing process may be less effective in creating an amorphous solid dispersion.

Parteck® MXP has been found to have an appropriate melt viscosity for HME applications.

Melt viscosity at $D = 200s^{-1}$	Melt viscosity at $D = 1200s^{-1}$
345.3 ± 7.8	174.0 ± 1.7

Table 12: Melt viscosity of Parteck® MXP

Solubility

Parteck® MXP is a water-soluble polymer. For solvent screening (film casting) guidance, refer to the technical recommendations section.

Solvent	Boiling point	Solubility at room temperature 25 °C	Solubility when organic solvent heated
MeOH	65 °C	0.07 mg/mL	1.07 mg/mL at 50 °C
EtOH	78 °C	0.04 mg/mL	1.17 mg/mL at 50 °C
Acetone	56 °C	0.03 mg/mL	No data available
Acetonitrile	82 °C	0.06 mg/mL	0.87 mg/mL at 50 °C
MTBE	55 °C	0.05 mg/mL	No data available
DMF	153 °C	0.06 mg/mL	15.9 mg/mL at 90 °C
DMSO	189 °C	17.1 mg/mL	20.2 mg/mL at 50 °C
DCM	40 °C	0.06 mg/mL	No data available
NMF	203 °C	0.06 mg/mL	19.2 mg/mL at 90 °C
THF	66 °C	0.09 mg/mL	0.98 mg/mL at 50 °C

Table 13: Solubility of Parteck® MXP in various solvents

Methods and Recommendations

Extrusion

- Drying: Before the hot melt extrusion process, Parteck® MXP can be dried at 105 °C for 3 hours. After this, losses during drying will be less than 0.1 %.
- Extrusion temperature: Parteck® MXP can be used on standard extruders with 3 – 5 heat zones for thermoplastic processing. Sample extrusion parameters without drugs for a 5-heat-zone extruder (Mini Compounder KETSE 12/36 von Brabender® GmbH & Co. KG, Duisburg, Germany):

Recommended extrusion temperature (°C)	Through-put (g/h)	Screw speed (rpm)	SMEC (KJ/kg)
*190/190/190/190/190	170	170	8

(*the extrusion temperature can be reduced to 140 °C if plasticizer is added, please see recommendation of plasticizer, Table 15)

The above conditions are for PVA alone. Temperatures are subject to change based on formulation (plasticizer, API characteristics, etc). For plasticizer recommendations, please contact us. The extrusion temperature should not be above 250 °C, as higher temperatures may cause the material to degrade. Residence time should not exceed 10 minutes. If the flowability of the drug:excipient mixture is not ideal for feeding the extruder, add 1-2 % Aerosil® (Evonik Degussa GmbH, Essen, Germany) to improve it.

Parteck® SI is a sorbitol which is manufactured through spray-drying. It was found that Parteck® SI had better plasticizing properties and performance in HME over crystalline sorbitol.

Composition	HME processing temperature (°C)	Extrudate
Parteck® MXP without sorbitol	190	Transparent
Parteck® MXP / Parteck® SI (5:1)	160	Transparent
Parteck® MXP / Parteck® SI (4:1)	150 – 160	Transparent
Parteck® MXP / Parteck® SI (3:1)	150	Transparent
Parteck® MXP / Parteck® SI (2:1)	140 – 150	Transparent
Parteck® MXP / Parteck® SI (1:1)	140	Transparent

Table 15: Recommended plasticizer (if necessary) and effect on extrusion conditions

Solvent solubility and film casting

Recommendation to film casting method:

As many times there is a limitation on the amount of API available for initial solid dispersion testing, a film casting assessment may be performed to quickly assess the potential API:polymer compatability (polymer screening), API load, and stability. There are a number of suitable solvents and/or solvent mixtures that enable the pre-experiment film casting for insoluble drugs prior to extrusion. The solubility of Parteck® MXP was evaluated in different organic solvents at 25 °C, as well as with initial heating of the polymer in the solvent, which was then cooled to room temperature before measurement of the solubility. We recommend DMSO (min. 17 mg/mL at 25 °C) and DMF (0.06 mg/mL) as the solvents which achieve the highest solubility of the polymer at 25 °C. If the solubility at 25 °C is insufficient to achieve the concentration required for pre-extrusion polymer screening assessment, we recommend the heating and cooling process to increase the kinetic solubility of Parteck® MXP in the organic solvent.

For additional recommendations on film casting and polymer screening conditions, please contact us.

The typical technical data above serve to generally characterize the excipient. These values are not meant as specifications and they do not have binding character. The product specification is available separately at: www.merckmillipore.com

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