Technical Information

Soluplus®

Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer for pharmaceutical use

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1. Introduction

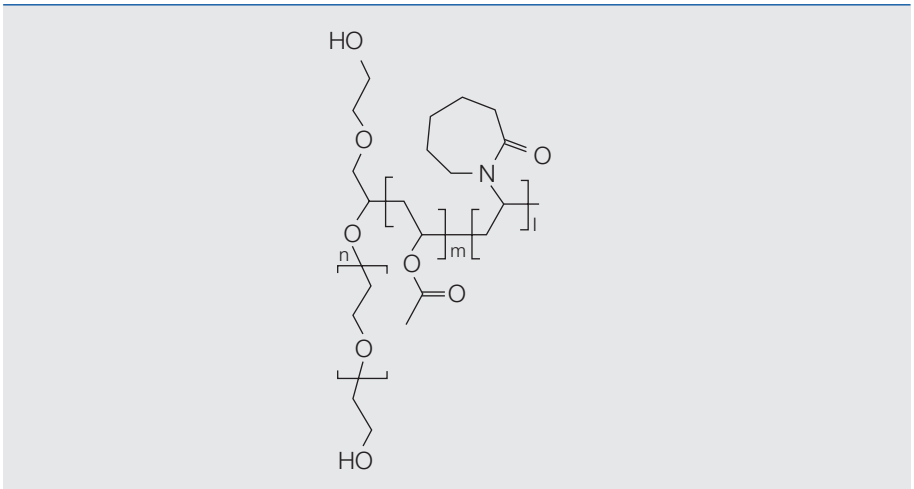
Soluplus® is a polymeric solubilizer with an amphiphilic chemical structure.

It can act as a matrix polymer for amorphous solid dispersions (ASDs), is capable of solubilizing poorly soluble drugs in aqueous media and can increase the bioavailability of poorly soluble drugs. Soluplus® is particularly suitable for the application in hot melt extrusion but can also be applied in e.g., spray drying, drug-polymer layering or twin-screw granulation.

Soluplus® is a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer which means that side chains of polyvinyl caprolactam-polyvinyl acetate are attached to a polyethylene glycol backbone. Soluplus® is available as free-flowing white to slightly yellowish granules with a faint characteristic odor.

2. Chemical & Physical Properties

Structural formula



Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer
PEG 6000 / vinylcaprolactam / vinyl acetate
13 / 57 / 30 (w/w/w)

CAS number

936030-92-1

Molecular weight

The average molecular weight determined by gel permeation chromatography is approximately 118,000 g/mol (nominally in the range of 90 000 – 140 000 g/mol). A representative molecular weight distribution is shown in Figure 1.

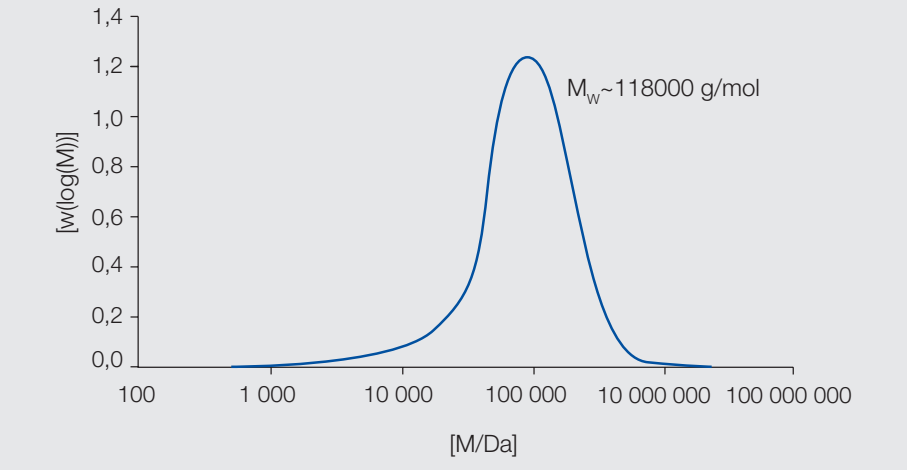


Figure 1: Gel Permeation Chromatography; Reference: PMMA

Critical Micelle Concentration

The critical micelle concentration (CMC) of Soluplus® in water at 7.6 mg/L is derived from the concentration dependent surface pressure curve (Figure 2). The diameter of micelles ranges typically from 70 to 100 nm (pH 7 phosphate buffer).

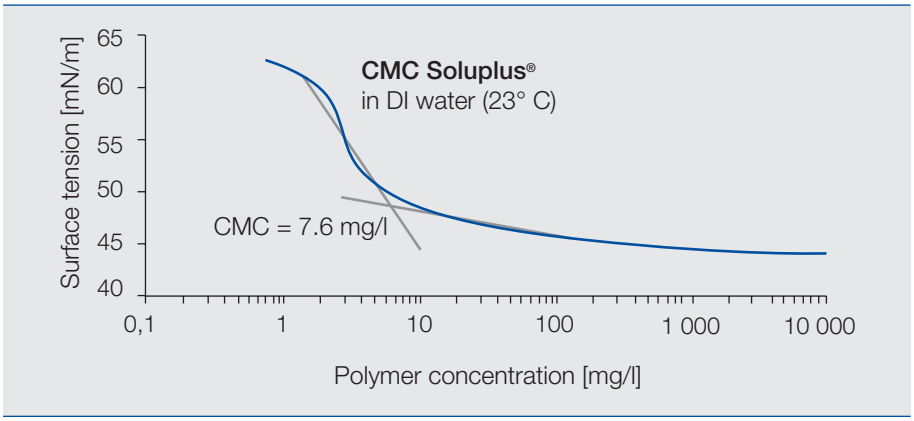


Figure 2: Determination of critical micelle concentration of Soluplus® based on surface tension dependent on polymer concentration

HLB

Approximately ~14

Glass Transition Temperature

~70 °C

K-value

31-41 (1% in ethanol)

Solubility and Solution Viscosity

Soluplus® is soluble in water. Furthermore, it is soluble in acetone (up to 50%), methanol (up to 45%), ethanol (up to 25%), dimethylformamide (up to 50%) and in mixtures of (1:1 m/m) methanol/ acetone (up to 50%) and (1:1 m/m) ethanol/acetone (up to 45%). Solubility of Soluplus® in common solvents is shown in Figure 3. Higher polymer concentrations may result in a cloudy or turbid solutions. This is due to formation of colloidal Soluplus® micelles.

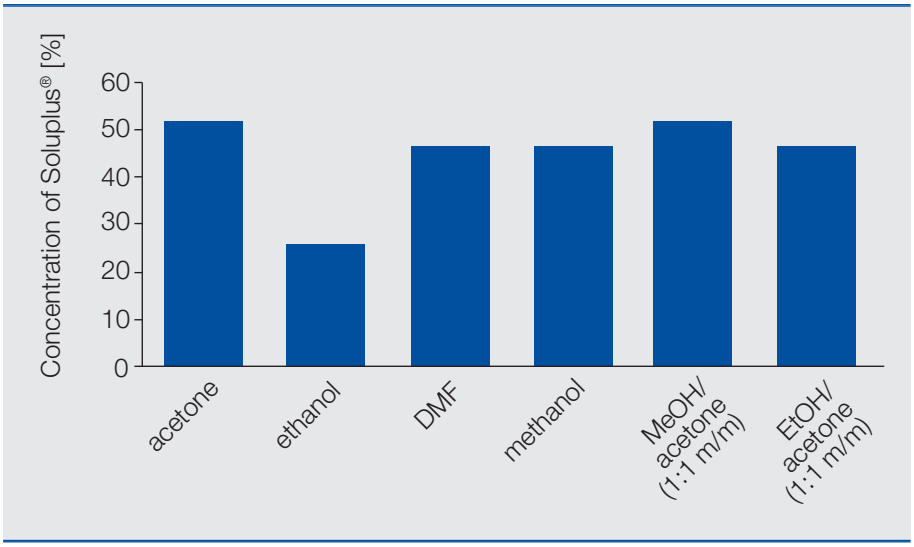


Figure 3: Solubility of Soluplus® in various solvents

The phenomenon of turbidity/ cloudiness is more pronounced at elevated temperature (~40 °C), which is the lower critical solution temperature (LCST). Thus, when the polymer solution is heated at or above its LCST, a clear polymer solution turns cloudy or turbid due to formation of larger micelles. The phenomenon is reversible upon cooling the polymer solution.

Soluplus® is not soluble in medium-chain triglyceride Kollisolv® MCT and poloxamer 124 (Kollisolv® P124).

Soluplus® is soluble in Kollisolv® PEG 400 up to 25% (w/w). The data in Figure 4 shows the viscosity of a Soluplus® in PEG 400 solution. Data was acquired at 60 °C on a HAAKE Rotovisco with coaxial cylinder DG 43 and a plate-plate PP 60 geometry at a shear rate of 100 s^{-1}.

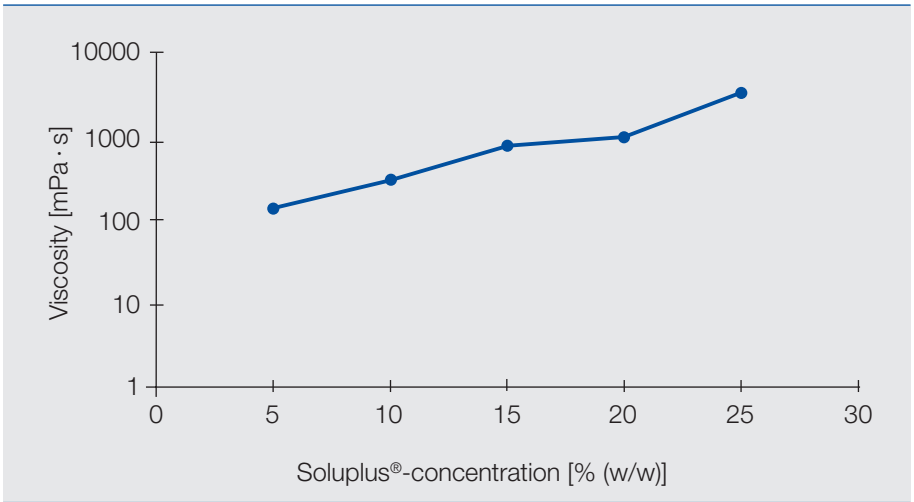


Figure 4: Viscosity of Soluplus®-in-Kollisolv® PEG 400 solution

Soluplus® is soluble in Kollisolv® PG (propylene glycol) up to 2.5% (w/w). The data shown in Figure 5 shows the viscosity of a Soluplus® in PG solution and was obtained at 60 °C on a HAAKE Rotovisco with coaxial cylinder DG 43 and a plate-plate PP 60 geometry at a shear rate of 100 s^{-1}.

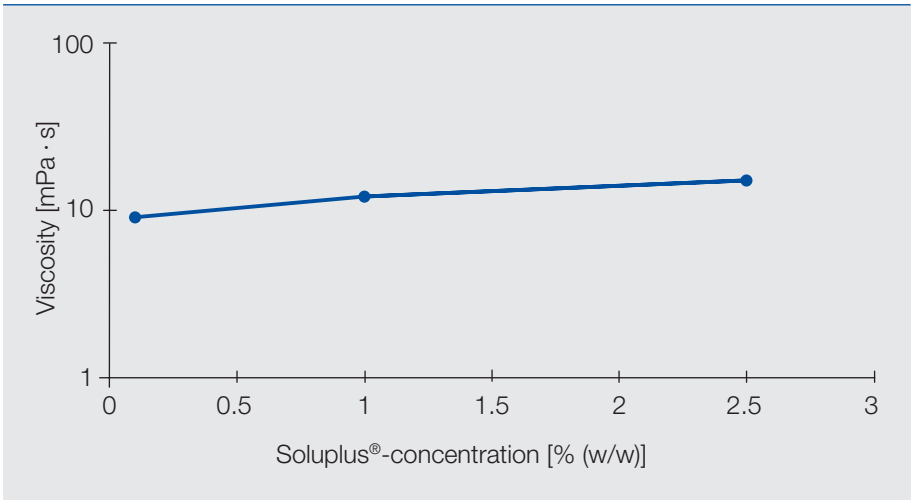


Figure 5: Viscosity of Soluplus® in propylene glycol solution

Figure 6 shows the solution viscosity of Soluplus® for different solid contents in water and at distinct temperatures. Data was acquired with a cone-plate geometry at 100 s^{-1}.

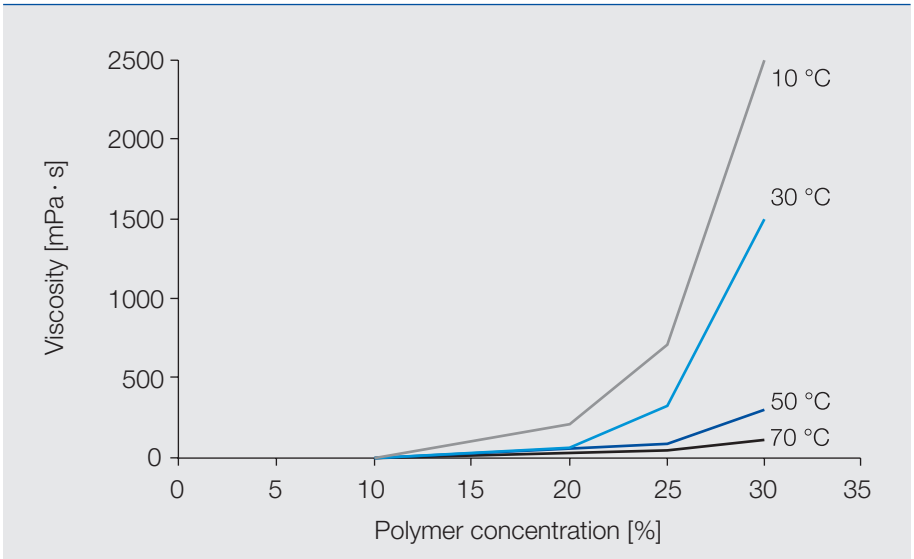


Figure 6: Solution viscosity of Soluplus® at different solid contents at distinct temperatures.

Melt Viscosity

For the application in hot melt extrusion, melt viscosity behaviour is important. The values shown in Figure 7 were obtained on a capillary rheometer.

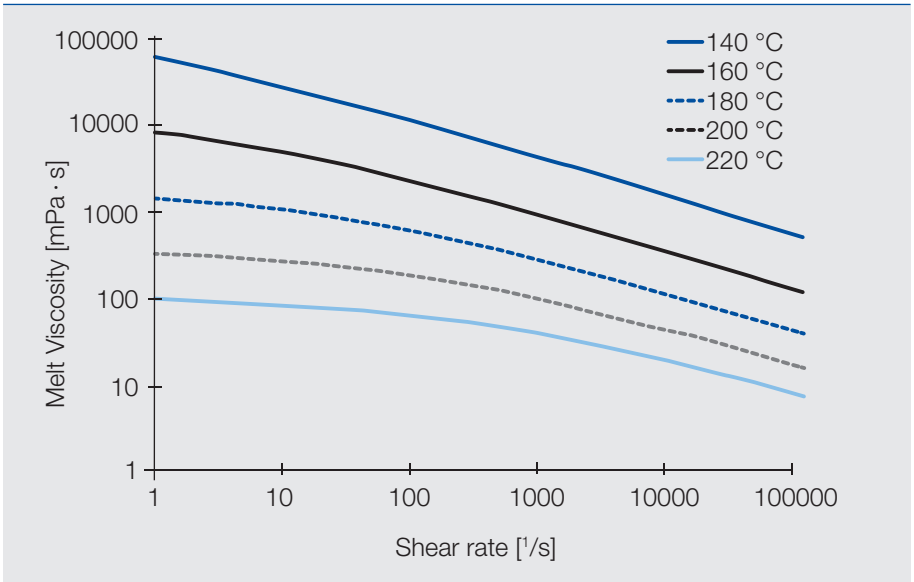


Figure 7: Temperature dependent melt viscosity of Soluplus® at different shear rates

Specific Heat Capacity

The following graph shows the specific heat capacity c_p and the heat enthalpy for Soluplus® dependent on temperature.

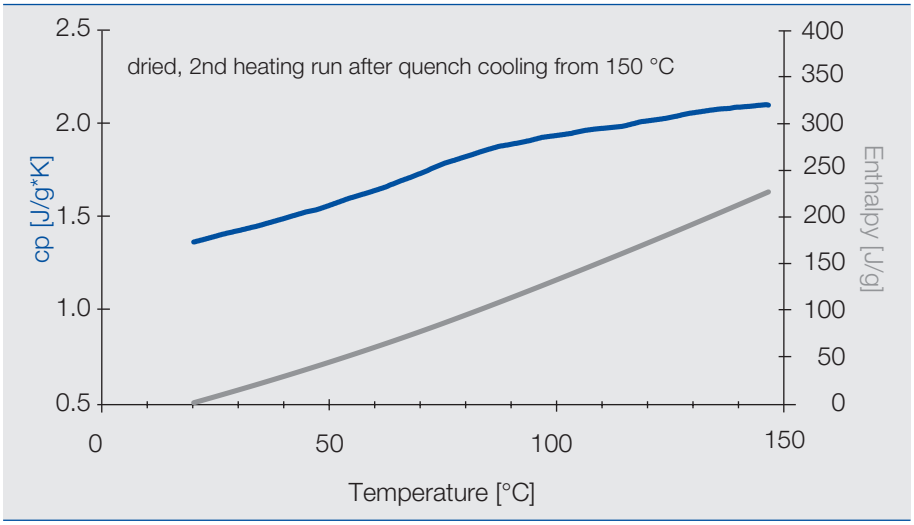


Figure 8: Heat capacity and enthalpy of Soluplus® dependent on temperature

Density

The density of Soluplus® granules was determined at room temperature using a helium pycno-meter and found to be 1.082 g/cm³.

Angle of Repose

The typical angle of repose for Soluplus® granules determined according to the method by Dr. Pfrengle is 27.5°.

Particle Size and Shape

Soluplus® is provided as large granulates with a mean diameter in the range of 350 microns (determined by laser diffraction); Scanning electron microscopy images of Soluplus® granules are shown in Figure 9. The particles show the structure of a spray granulated material.

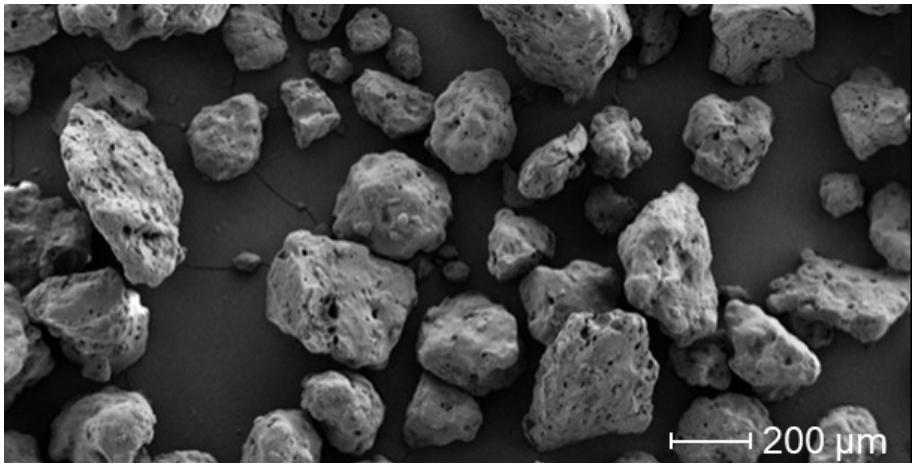


Figure 9: Scanning electron microscope image of Soluplus® granulates

3. Example application(s)

Solubilization

The solubilization capacity of the amphiphilic Soluplus® polymer can be tested by determination of the saturation solubility of a poorly soluble API in a polymer solution. Phosphate buffer as solvent (e. g. pH 7.0) assures comparable conditions and solubility effects due to pH shifts can be avoided.

Procedure:

A 10% Soluplus® solution in phosphate buffer is oversaturated with a discrete API and stirred for 72 h at room temperature. The resulting suspension is filtered through 0.45 µm filter and the content of solubilized drug in the filtrate is determined by UV spectroscopy.

Figure 10 shows the results of the solubility enhancement of Soluplus® for various drugs in comparison to the pure API solubilities in phosphate buffer pH 7.0:

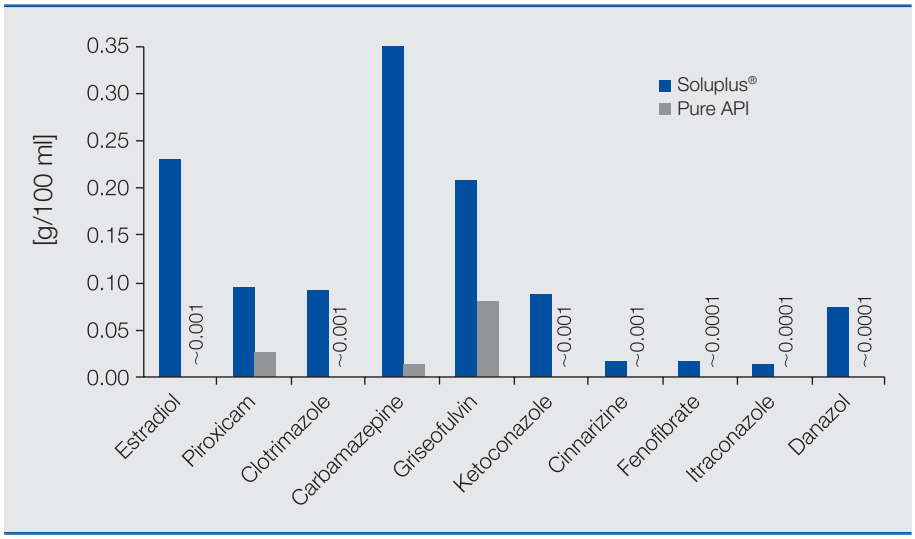


Figure 10: Saturation solubility of pure APIs or in presence of 10% Soluplus® after 72 h in phosphate buffer pH 7.0

Capacity for Amorphous Solid Solutions

Soluplus® is designed for solubilizing high concentrations of poorly water-soluble APIs in amorphous solid dispersions (ASDs). ASDs can be produced using a multitude of technologies including, but not limited to: Hot melt extrusion, spray drying, and drug-polymer layering.

In order to screen for solid dispersion effectiveness, the following procedure is recommended:

Choose an appropriate solvent that dissolves the API as well as Soluplus® (e. g. ethanol, methanol, acetone, dimethylformamide). Dissolve both substances with gentle stirring, then cast the solution on a glass plate as a thin film. It is recommended to utilize a scraper that leads to a film of approximately 120 µm. The < 120 µm dry film enables fast drying and avoids recrystallization of the poorly soluble drug. Subsequent drying should be performed in a vacuum drying cabinet (50 °C, 10 mbar, 30 min) to ensure a fast and complete drying of the film. Test several concentration ratios of drug to polymer in incremental steps (e. g. 20, 30, 40 and 50%). Samples should be examined using polarized light (recommended) or optical microscopy; crystalline API should be visible in ranges beyond the solubility limit. This can serve as starting point for formulation development. Additional solubilizers (e.g. Kolliphor® RH 40) or plasticizers (e.g. Kollisolv® PEG 1450) can also be incorporated into the solution for formulation optimization.

Hot Melt Extrusion

Soluplus® exhibits a low glass transition temperature (T_g) of approximately 70 °C and is therefore perfectly suitable for hot melt extrusion which is typically carried out at temperatures minimum 20 °C above the glass transition temperature.

The relatively low glass transition temperature of Soluplus® allows extrusion at lower temperatures compared to other known polymers, resulting in less thermal stress for APIs. A comparison of the Tg of various extrudable polymers is shown in Figure 11.

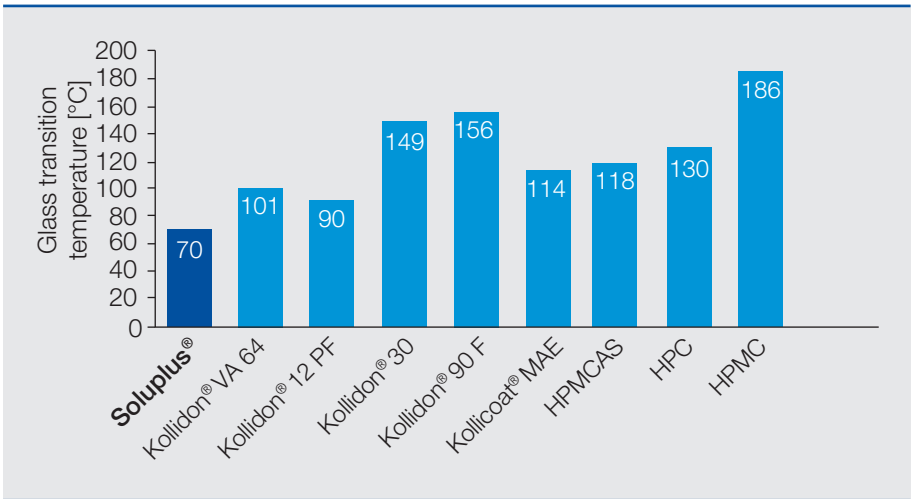


Figure 11: Glass transition temperature of Soluplus® in comparison with standard polymers used in extrusion

The melt viscosity of Soluplus® is rather low compared to well-known extrudable polymers such as Kollidon® VA 64 (Figure 12).

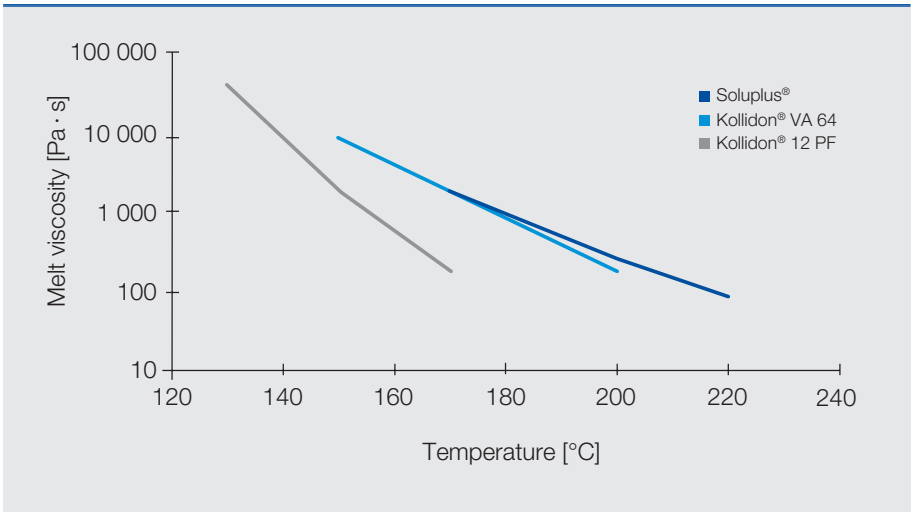


Figure 12: Determination of melt viscosity of polymers using a rotary viscosimeter equipped with a plate-plate setup at angular frequency of 1.6 rad/s

Exemplary, in a standard 16 mm twin-screw extruder, temperatures from 120 °C to 220 °C can be applied when working with Soluplus®. The polymer shows no chemical degradation even after extrusion at 220 °C. Incorporation of an API may enable even lower temperatures than 120 °C.

A solid solution of fenofibrate (melting point ~77 °C) at 20% drug load was prepared at 100 °C using a twin screw co-rotating extruder with a 16 mm diameter at 200 rpm and 1 kg/h. In vitro release profile based on USP II apparatus (50 rpm, 700 mL 0.8 M HCl) is shown in Figure 13.

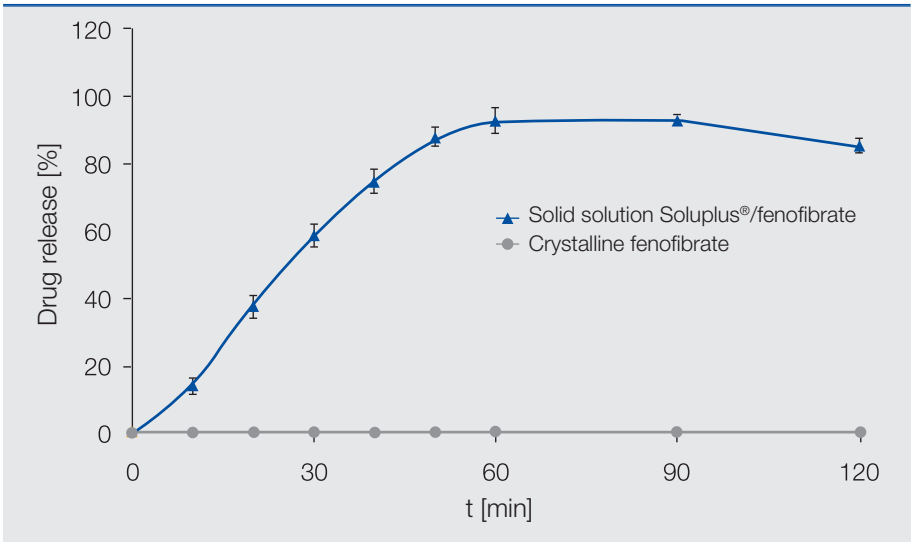


Figure 13: Drug release profile of crystalline fenofibrate compared to a solid solution based on Soluplus®

Importantly, APIs do not need to be melted during extrusion to produce an ASD. For example, itraconazole (melting point ~166 °C) was extruded at 150 °C which is notably lower than the melting point of the API. In vitro drug release profiles are shown in Figure 14.

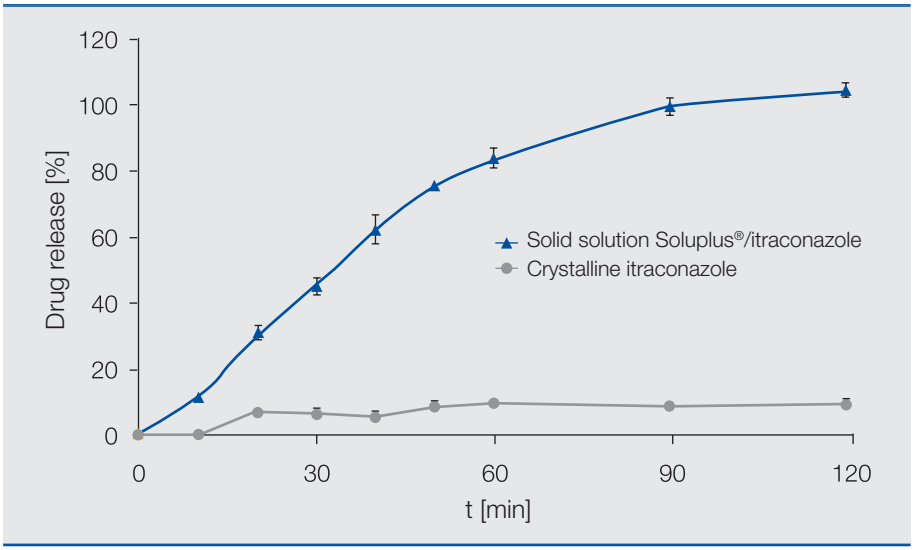


Figure 14: Drug release profile of crystalline itraconazole compared to a solid solution based on Soluplus®

Spray Drying

Soluplus® provides excellent solubility in common organic solvents and it´s low solution viscosity (see section 2) is favorable for spray draying. Recommended solvents for spray drying include methanol, ethanol and acetone. Optimum concentrations for spraying range from 5 to 30% w/w depending on solvent, viscosity, API load and other spray dryer conditions. An formulation of 20% poorly water-soluble API ritonavir at 20% w/w in Soluplus® is shown in Figure 15.

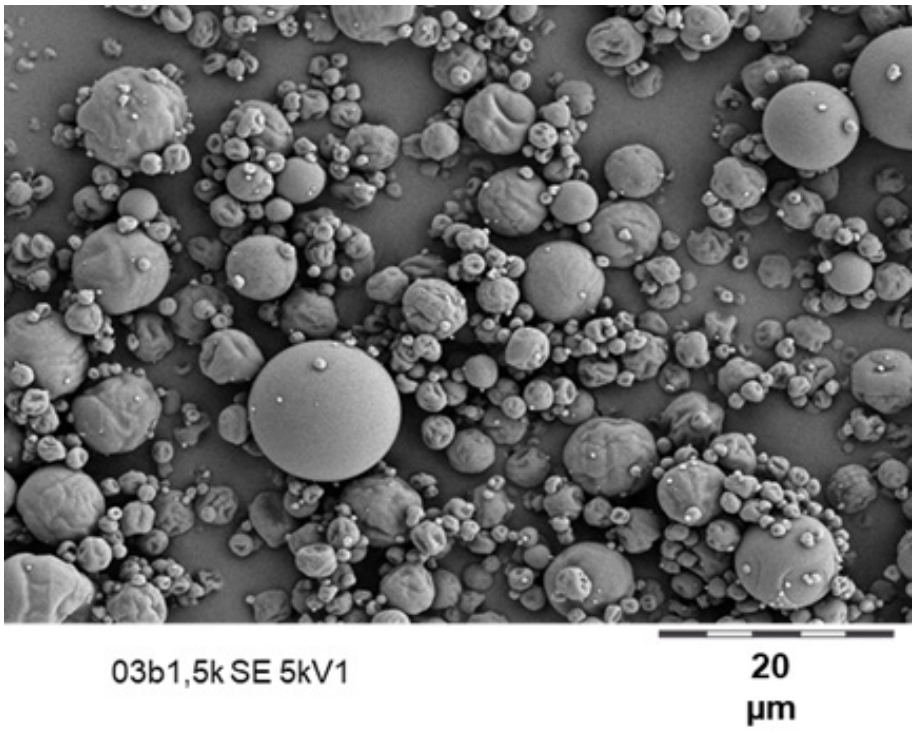


Figure 15: Scanning electron microscope image of a spray dried Soluplus® ASD containing ritonavir

Drug Polymer Layering

Soluplus® can effectively be layered on beads, spheres, mini-tablets or other fluidized granules using a conventional fluid bed coater. Similar to spray drying, Soluplus® should first be dissolved together with the poorly water-soluble API in a mutually effective solvent (e.g. ethanol, methanol, acetone). For the spray layering process it is important to take care for proper coating of the substrate and the avoidance of spray drying of the solution. This is typically controlled with solvent type, solids concentration and temperature profile in the bed. In the following example, the poorly water-soluble API carbamazepine was spray coated using Soluplus® dissolved in ethanol (ratio 1:2:37 carbamazepine:Soluplus®:ethanol). The mass gain was approximately 10%.

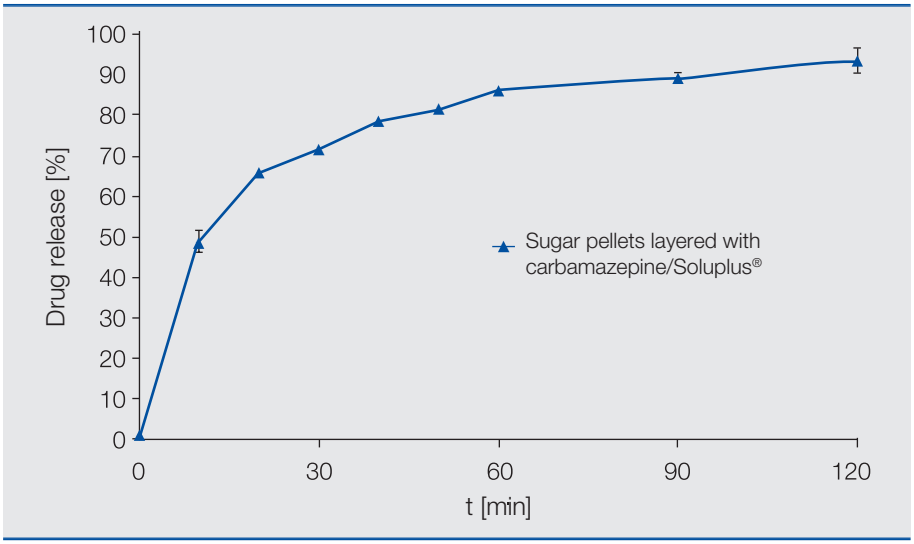


Figure 16: Dissolution rate of sugar pellets layered with carbamazepine/Soluplus®

Capsule formulation

Once an amorphous solid dispersion is formed, it can be loaded into a hard gelatin capsule. It is recommended to mill the ASDs down to an appropriate and desired size and to add a disintegrant (e.g. Kollidon® CL) at a concentration of 10-15% w/w and optionally, a non-soluble filler (e.g. microcrystalline cellulose). The use of a disintegrant in capsules with Soluplus based ASDs has shown to improve the dissolution process by preventing agglomeration of ASD particles. An example formulation is shown below:

Capsule formulation:	
Solid solution	70%
Kollidon® CL	15%
Microcrystalline cellulose	15%

Tablet formulation

ASDs from hot melt extrusion or spray drying also be compressed into tablets. It is recommended to include 5-10% disintegrant (e.g. Kollidon® CL) to such tablets containing Soluplus® ASDs. An example formulation is shown below:

Tablet formulation:	
Solid solution	60%
Microcrystalline cellulose (Avicel PH 102)	29%
Kollidon® CL	10%
Magnesium stearate	0.5%
Aerosil 200	0.5%

Bioavailability

The bioavailability enhancement potential of Soluplus® was demonstrated in a case study with three poorly water-soluble APIs in three formulation configurations:

- Crystalline API: 95% API + 5% disintegrant
- Physical Mixture: 15% API + 80% Soluplus® + 5% disintegrant
- Amorphous Solid Dispersion: 95% ASD + 5% disintegrant

The APIs and dose were as follows: Itraconazole (10 mg/kg bw), danazol (30 mg/kg bw), and fenofibrate (10 mg/kg bw). ASDs were produced using a 16 mm twin screw co-rotating extruder. All formulations were administered to Beagle dogs in a fasted state (n=5).

Itraconazole ASDs were produced at 1kg/hr, 200 rpm and 150 °C. The results shown in Figure 17 highlight a clear increase in bioavailability in the ASD formulation.

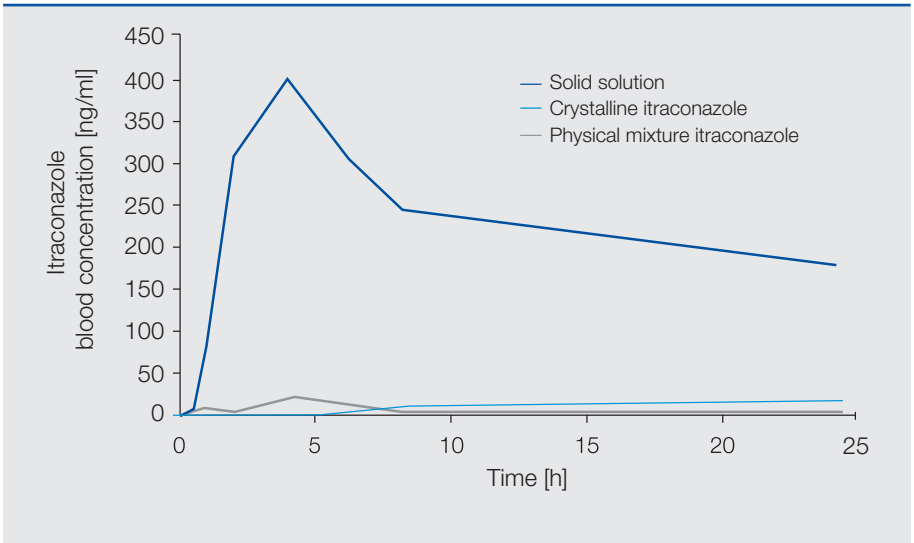


Figure 17: Blood concentration of itraconazole formulated as solid solution or physical mixture with Soluplus® compared to its crystalline form

Danazol formulations were extruded at 0.9 kg/h, 200 rpm, and 140 °C. The results also show a significant increase in bioavailability vs. the crystalline API or the physical mixture (Figure 18):

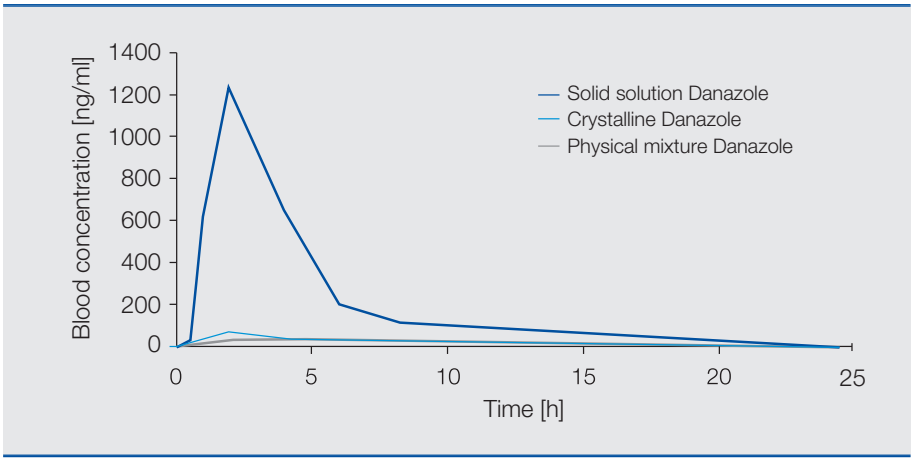


Figure 18: Blood concentration of danazole formulated as solid solution or physical mixture with Soluplus® compared to its crystalline form

Fenofibrate ASDs were extruded at 0.7 kg/h, 200 rpm and 95 °C; in this case both the ASD formulation as well as the physical mixture exhibited large increases in bioavailability – this is due to the ability of Soluplus® to increase drug solubility in aqueous environments. This effect is known for some APIs and may be tested using similar means.

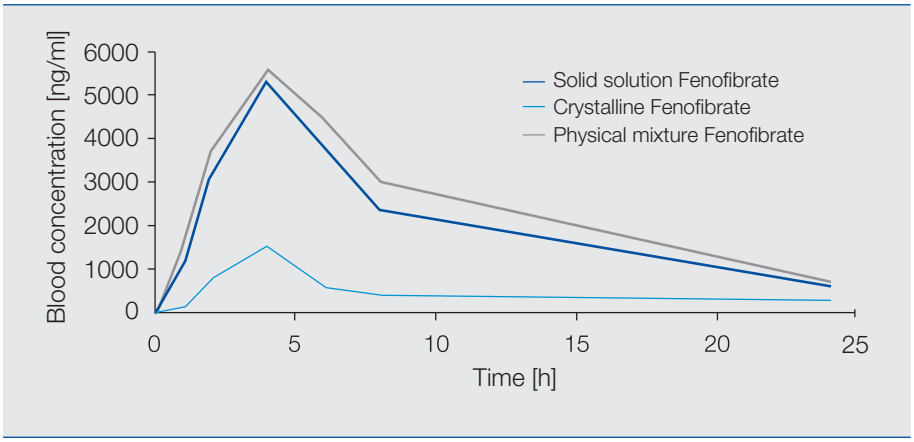


Figure 19: Blood concentration of fenofibrate formulated as solid solution or physical mixture with Soluplus® compared to its crystalline form

4. Stability & Safety

The product is typically stable for 36 months after date of production provided storage under recommended conditions. The actual retest period and storage conditions can be found in the document “Quality & Regulatory Product Summary” in RegXcellence.
The actual version of the safety data sheet is accessible via MyProductWorld and send with every consignment.

5. Available Articles and Packaging

List PRD number(s) and article numbers of commercial articles and sample articles

PRD-No.*	Product name	Article numbers	Packaging	
30446233	Soluplus®	50539897	0.5 kg	PE bottle
		50477909	12.5 kg	PE drum

* BASF’s commercial product number.

6. Documents, Quality & Regulatory Information

Virtual Pharma Assistants

Meet your Virtual Pharma Assistants! MyProductWorld, RegXcellence® and ZoomLab™

www.virtualpharmaassistants.com

MyProductWorld: article numbers, sample order, safety data sheet, sustainability information

RegXcellence: specification, compliance documents, regulatory product summary

ZoomLab: formulation assistance to predict starting formulations and expedite drug development

September 2024