Technical Information

Soluplus®

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1. Introduction

Soluplus® is a polymeric solubilizer with an amphiphilic chemical structure, which was particularly developed for solid solutions.

Due to its bifunctional character, it is able to act as a matrix polymer for solid solutions on the one hand, and, on the other hand, it is capable of solubilizing poorly soluble drugs in aqueous media.

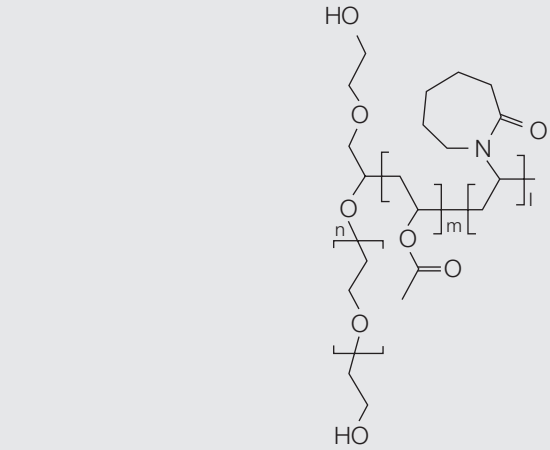
Furthermore, Soluplus® can increase the bioavailability of poorly soluble drugs.

Description

Soluplus® is a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer. It is a free flowing white to slightly yellowish granule with a faint characteristic odor.

2. Technical properties

Structural formula



PEG 6000 / vinylcaprolactam / vinyl acetate
13 / 57 / 30

Appearance

White to yellowish free flowing granules

CAS number

402932-23-4

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.

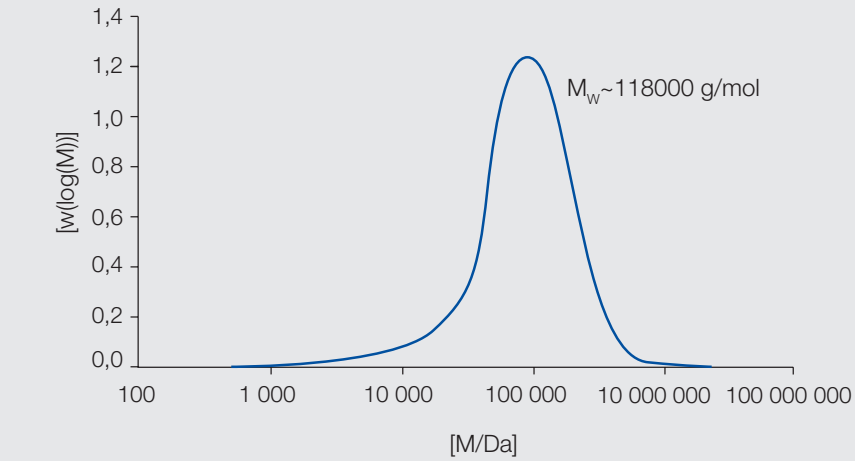


Figure 1: Gel Permeation Chromatography; Reference: PMMA

Critical Micelle Concentration

7.6 mg/L (surface tension curve shown in Figure 2)
Micelles are typically 70 to 100 nm in diameter (pH 7 buffer)

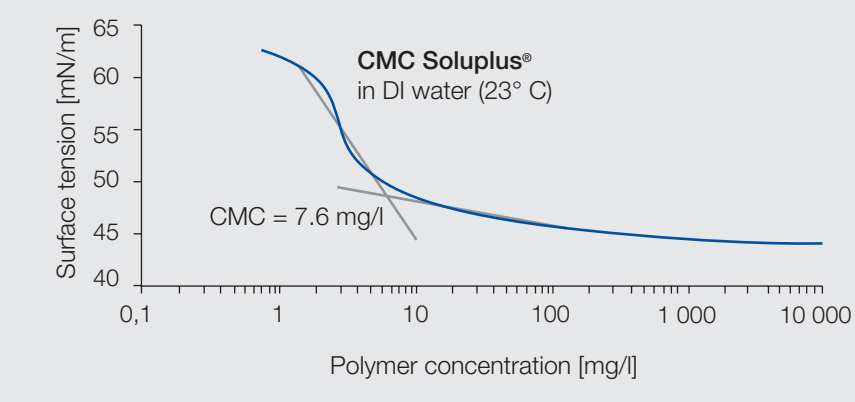


Figure 2

HLB

Approximately ~14

Glass Transition Temperature

~70 °C

K-value

31-41 (1% in ethanol)

Solubility

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%). Higher polymer concentration may result in a cloudy or turbid aqueous solution. This is due to formation of colloidal Soluplus® micelles.

Solubility of Soluplus® in common solvents shown in Figure 3.

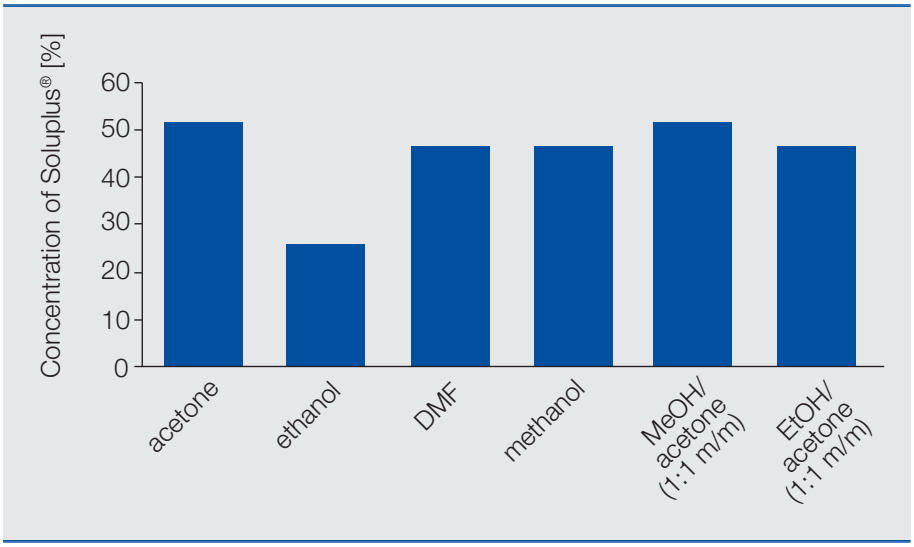


Figure 3

This phenomenon is more pronounced at elevated temperature (~40 °C), which is a 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. This process is reversible upon cooling the polymer solution.

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

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

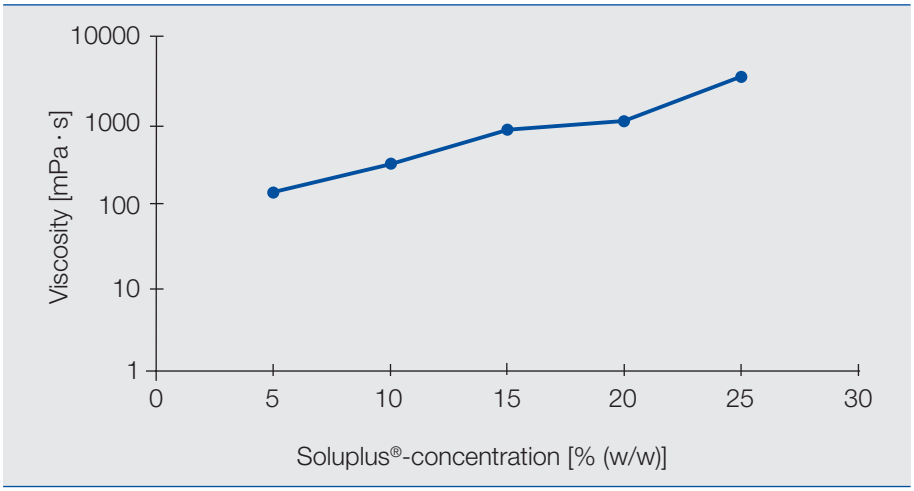


Figure 4: Viscosity of Soluplus®-in-Kollisolv® PEG 400 solution

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

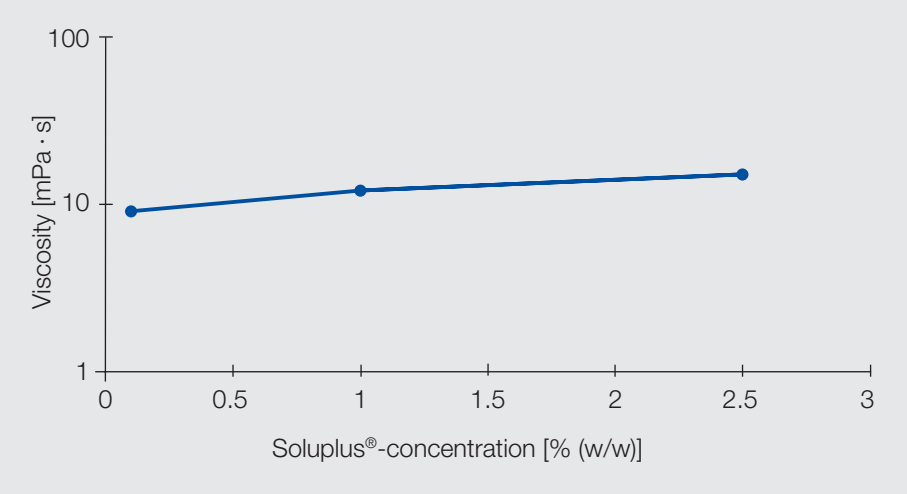


Figure 5: Viscosity of Soluplus®-in-Propylene Glycole solution

Solution Viscosity

Viscosity of Soluplus® is shown in Figure 6 at four distinct temperatures.

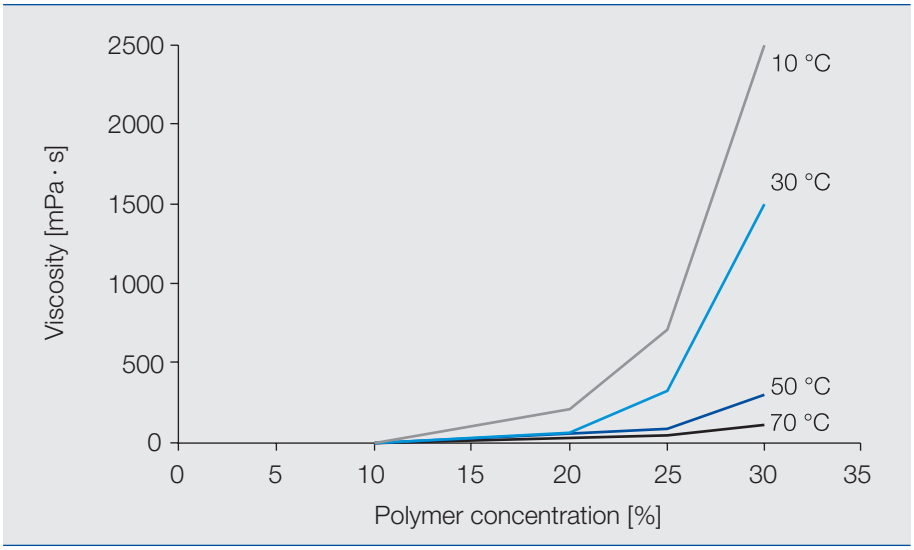


Figure 6: Cone-plate viscosimeter, 100 s^{-1}

Melt Viscosity

The values shown in Figure 7 were obtained on a capillary rheometer.

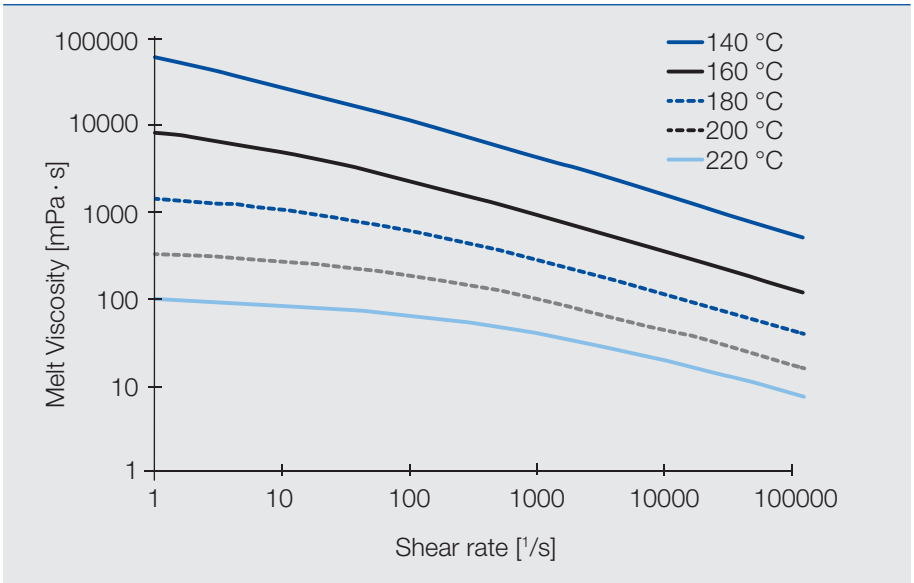


Figure 7

Specific Heat Capacity

The following graph shows the specific heat capacity and the heat enthalpy for Soluplus® in dependency from temperatur.

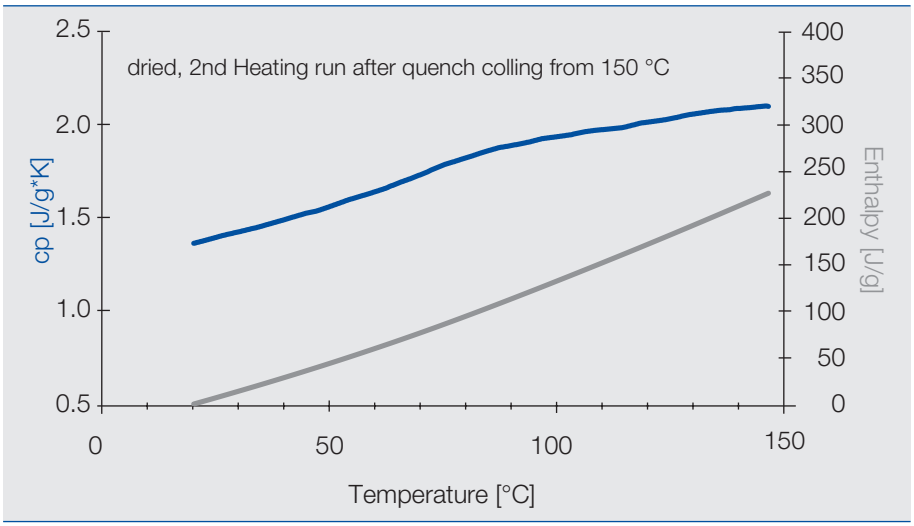


Figure 8

Density

The Density of Soluplus® was determined at room temperature using a helium pycnometer with 1.082 g/cm³.

Angle of Repose

The angle of repose for Soluplus® batch 21819647G0 was determined with the method according to Dr. Pfrengle with 27.5 °.

Particle Size

Soluplus® Granulates are approximately 340 microns in diameter (determined by laser diffraction); images of the granules are shown in Figure 9.

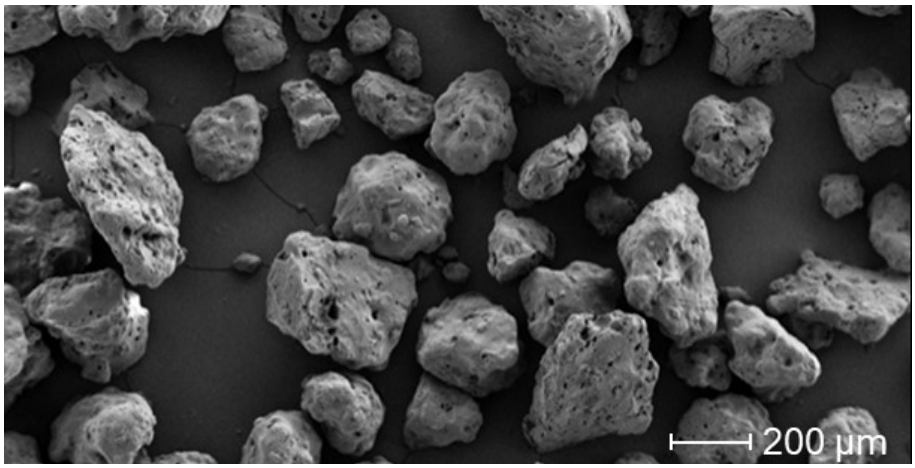


Figure 9

3. Application and processing

Solubilization

A potential affinity between Soluplus® and a poorly soluble drug can be pretested by means of various methods. The solubilization capacity of the amphiphilic polymer is tested by determination of the saturation solubility of a poorly soluble drug in a polymer solution. Phosphate buffer as solvent (e. g. pH 7.0) assures comparable conditions when testing ionic solubilizers or drugs. Thus, solubility effects due to pH shifts can be avoided.

Procedure:

A 10% polymer solution in phosphate buffer is oversaturated with a discrete drug 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 API solubilities in phosphate buffer pH 7.0:

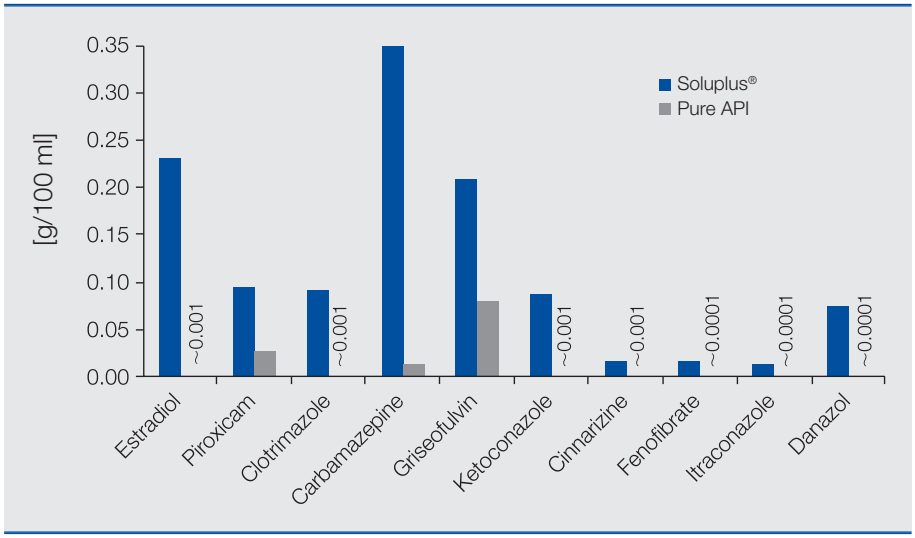


Figure 10: Phosphate buffer pH 7.0; 10% solubilizer solution, saturation solubility detected after 72h stirring

Capacity for Amorphous Solid Solutions

Soluplus® was designed for solubilizing high concentrations of poorly water-soluble APIs in amorphous solid dispersions (ASDs) – these 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 effectiveness, the following procedure is recommended:

Choose an appropriate solvent that dissolves the API and also 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 thin film (thickness of the dry film < 120 µm) enables fast drying and avoids a 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 viewed using polarized light (recommended) or optical microscopy; crystalline API should be visible in ranges beyond the solubility limit. This can be then used as a starting point for designing the formulation. Additional solubilizers (e.g. Kolliphor® RH 40) or plasticizers (e.g. Kollisolv® PEG 1450) can also be incorporated into the solution to test the effect on the solid solution as desired.

Hot Melt Extrusion

Soluplus® exhibits a glass transition temperature of approximately 70 °C and is well extrudable within standard hot melt extrusion devices. As an example, in a standard 16mm twin-screw extruder, temperatures from 120 °C to 220 °C are possible. The polymer shows no chemical degradation even after extrusion at 220 °C. Incorporation of a drug can lead to lower temperatures than 120 °C in dependence on the drug melting point.

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

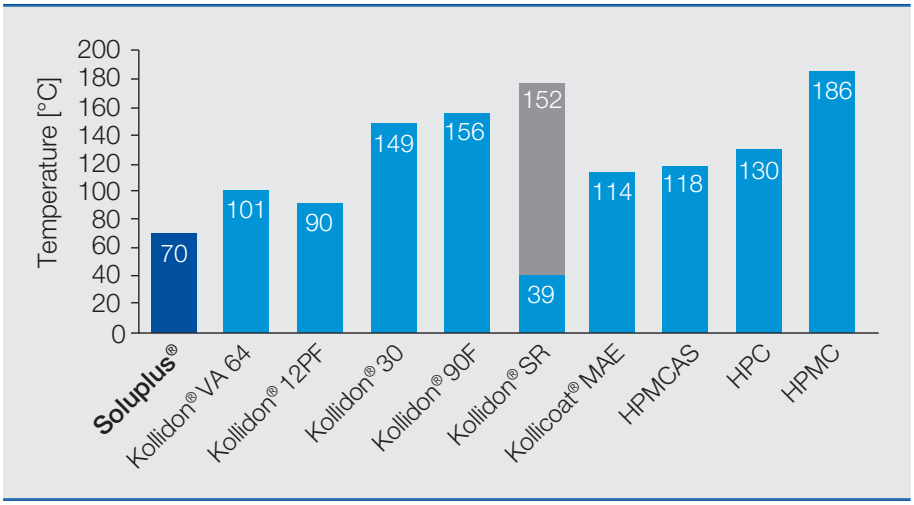


Figure 11

The ability to extrude Soluplus® is further shown by observing the melt rheology of the polymer melt, which is shown to be comparatively low vs. well known extrudable polymers such as Kollidon® VA 64. The comparison is shown in Figure 12.

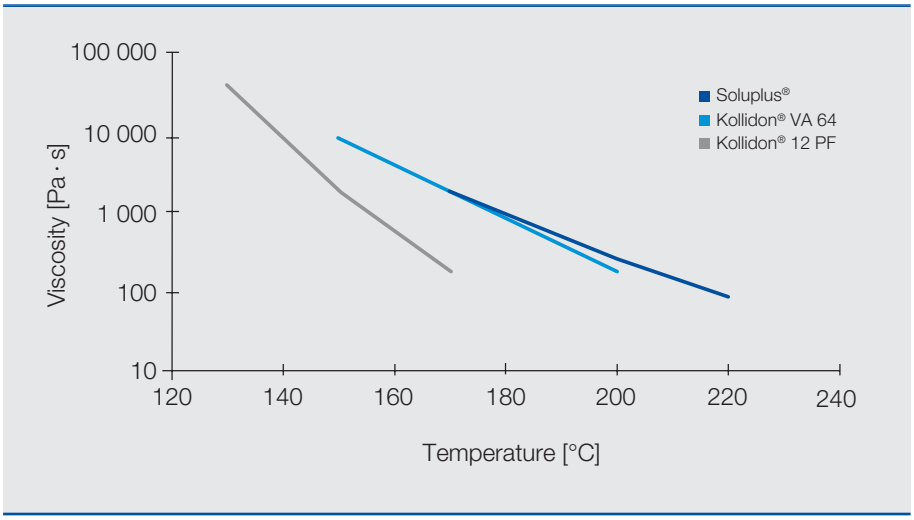


Figure 12: Rotary viscosimeter, plate-plate method, angular frequency: 1.6 rad/s

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

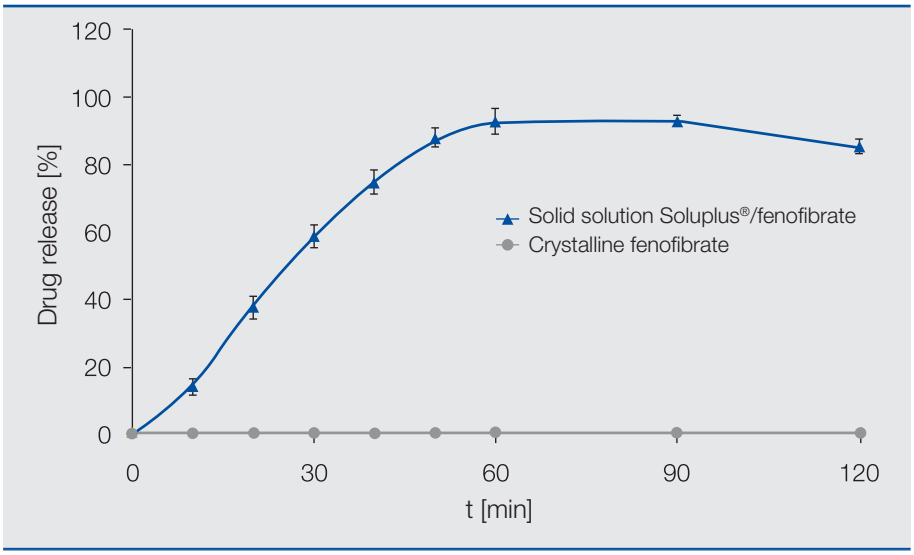


Figure 13

It is important to note that the API does not need to be melted during extrusion in order to produce an amorphous solid dispersion. For example, Itraconazole (melting point ~166 °C) was extruded at 150 °C notably lower than the melting point of the API – in vitro drug release results are shown in Figure 14.

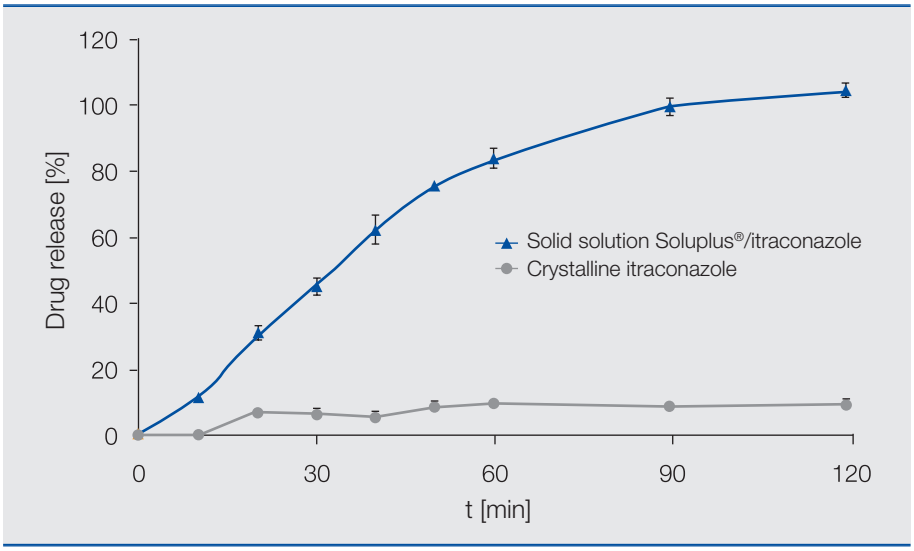


Figure 14

Spray Drying

Soluplus® has a high solubility in common volatile organic solvents used in spray drying, while maintaining also a low viscosity that is needed to process (see section 2 for viscosity). Recommended solvents include methanol, ethanol and acetone. Optimal concentrations for spraying range from 5 to 30% w/w depending on solvent, viscosity, API load and other spray dryer conditions. An example formulation of 20% poorly water-soluble drug Ritonavir at 20% w/w in Soluplus® is shown in Figure 15.

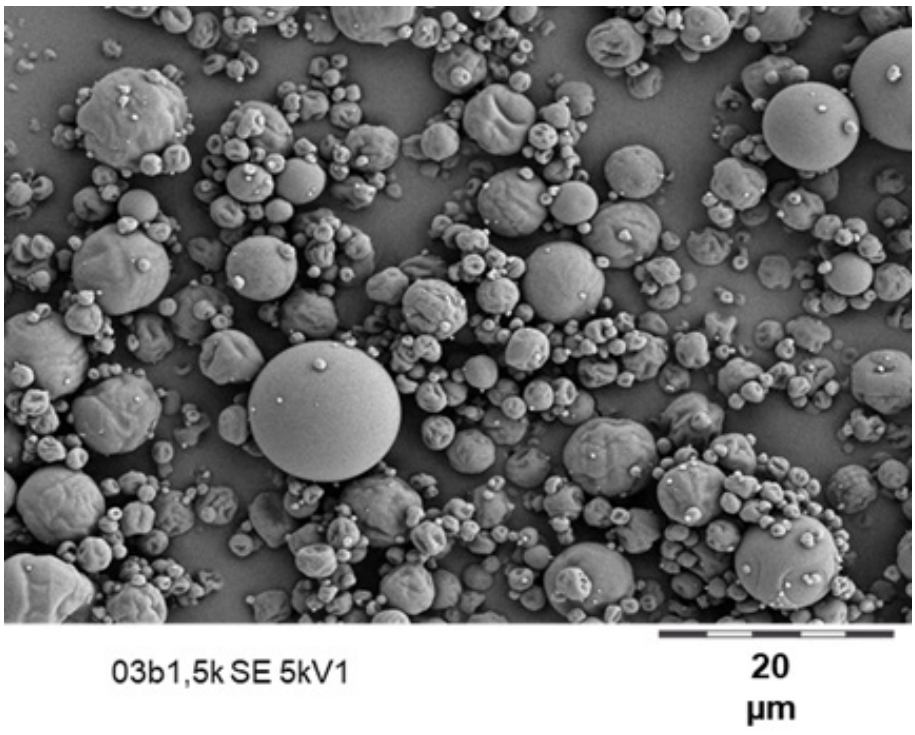


Figure 15

Drug Polymer Layering

Soluplus® can effectively be layered over 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 poorly water-soluble API in a mutually effective solvent (e.g. ethanol, methanol, acetone). Care should be taken to allow coating of the substrate prior to evaporation rather than spray drying of the solution. This is typically controlled with solvent type, solids concentration and temperature profile in the bed. In the following example, poorly water-soluble drug Carbamazepine was spray coated using Soluplus® from an ethanol solution (ratio 1:2 Soluplus®: Ethanol). The mass gain was approximately 10%.

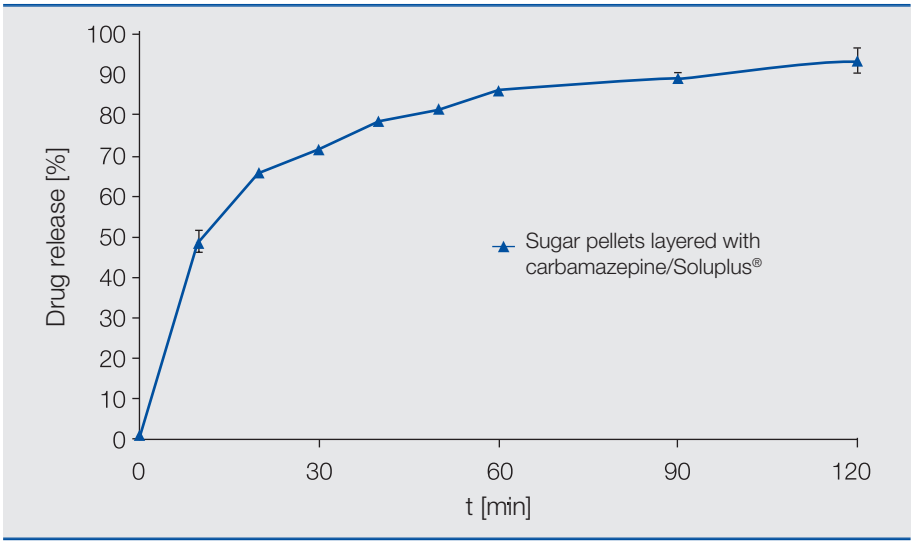


Figure 16: Dissolution rate of carbamazepine

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, mixed with a disintegrant (e.g. Kollidon® CL) at a concentration of 10-15% w/w and any non-soluble filler may also be used (e.g. microcrystalline cellulose). An example formulation is shown below:

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

Tablet formulation

Using a preformed ASD from hot melt extrusion or spray drying, the formulation may be compressed into tablets. It is typically recommended to include 5-10% disintegrant (e.g. Kollidon® CL), lubricant, flowability aid and insoluble filler such as microcrystalline cellulose. 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%

Case Study – Bioavailability

Three poorly water-soluble APIs were used as a case study for Soluplus® bioavailability enhancement. These drugs were administered to Beagle dogs in a fasted state (n=5). The APIs and dose were as follows: Itraconazole (10 mg/kg bw), Danazol (30 mg/kg bw), and Fenofibrate (10 mg/kg bw).

Formulations were compared in three configurations:

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

All formulations were produced using a 16 mm twin screw co-rotating extruder.

Itraconazole ASDs were produced at 1kg/hr, 200 rpm and 150 °C – the results are shown in Figure 17 where a clear increase in bioavailability is only evident for the ASD.

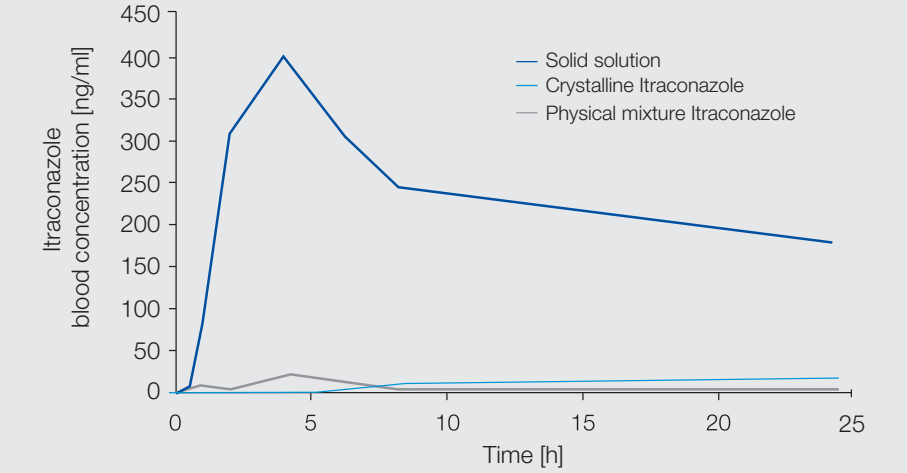


Figure 17: Blood concentration of itraconazole

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):

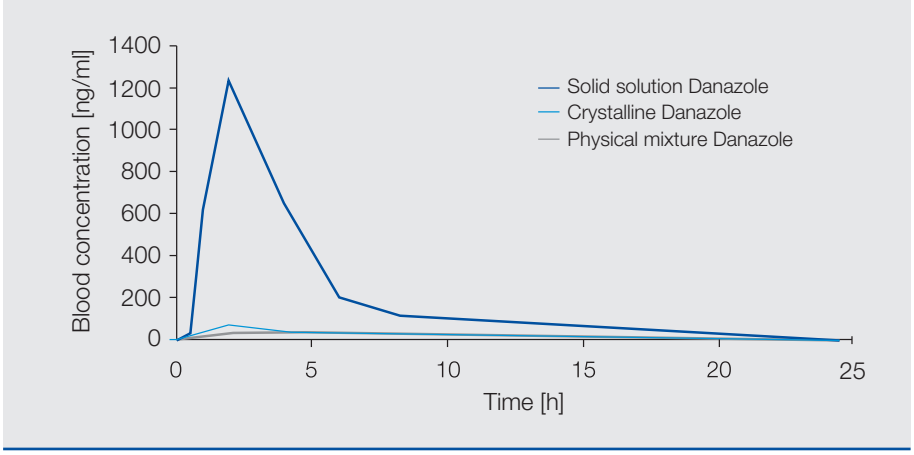


Figure 18: Blood concentration of danazole

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.

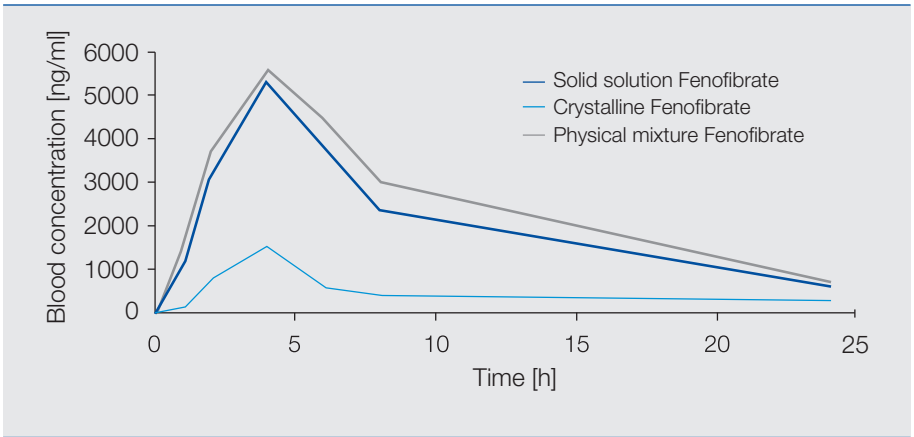


Figure 19: Blood concentration of fenofibrate

4. Handling & Safety

Please refer to the individual material safety data sheet (MSDS) for instructions on safe and proper handling and disposal. Material safety data sheets are sent with every consignment. In addition they are available on BASF WorldAccount* or from your local BASF sales representative.

5. Product Specification

The current version of the product specification is available on BASF WorldAccount* or from your local BASF sales representative.

6. Regulatory & Quality

Please refer to the individual document quality & regulatory product information (QRPI) which is available on BASF WorldAccount* and from your local sales representative. **The QRPI covers all relevant information including retest dates, and storage conditions.**

7. Toxicology

Toxicological studies are available on request. For detailed information and individual reports a secrecy agreement has to be signed in advance.

* https://worldaccount.basf.com

8. PRD and Article numbers

PRD-No.*	Product name	Article numbers	Packaging	
30446233	Soluplus®	50539897	0.5 kg	Plastic bottle
		50101050	2.5 kg	Plastic jerricans
		50477909	12.5 kg	Plastic drums
		52155222	25 kg	Fibreboard boxes

* BASF's commercial product number.

9. Publications

Publications including scientific posters are available on http://pharmaceutical.basf.com/en.html

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