Technical Information

October 2009

Soluplus®

BASF
The Chemical Company

Pharma Ingredients & Services

1. Introduction

1.1. General information

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.

2. Specification and properties

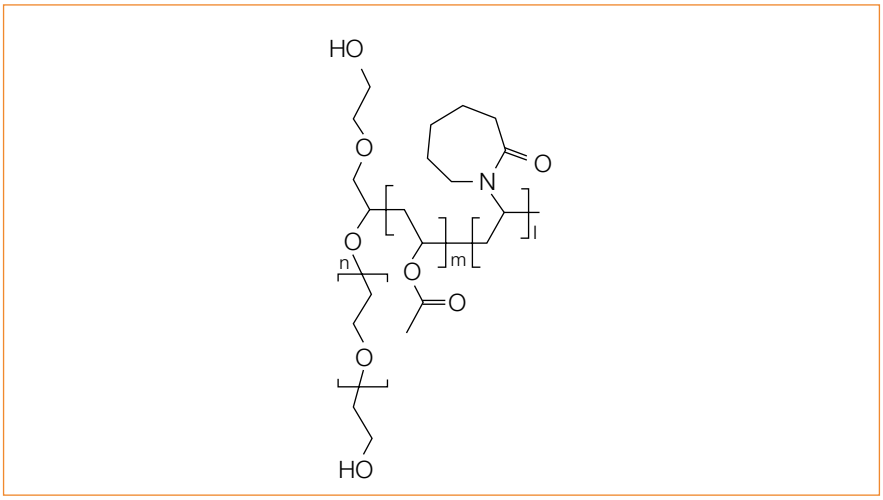
2.1 Description

Soluplus is a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. It is a free flowing white to slightly yellowish granule with a faint characteristic odor and has practically no taste.

2.2 Regulatory status

A DMF is filed in the USA and Japan.

2.3. Structural formula



2.4 Molecular weight

The average molecular weight determined by gel permeation chromatography is in the range of 90 000 – 140 000 g/mol.

2.5 Specification

See separate document: "Standard Specification (not for regulatory purposes)" available via BASF´s WorldAccount: https://worldaccount.basf.com (registered access).

2.6 Sorption isotherm

The sorption isotherm was measured by storing Soluplus over saturated salt solutions.

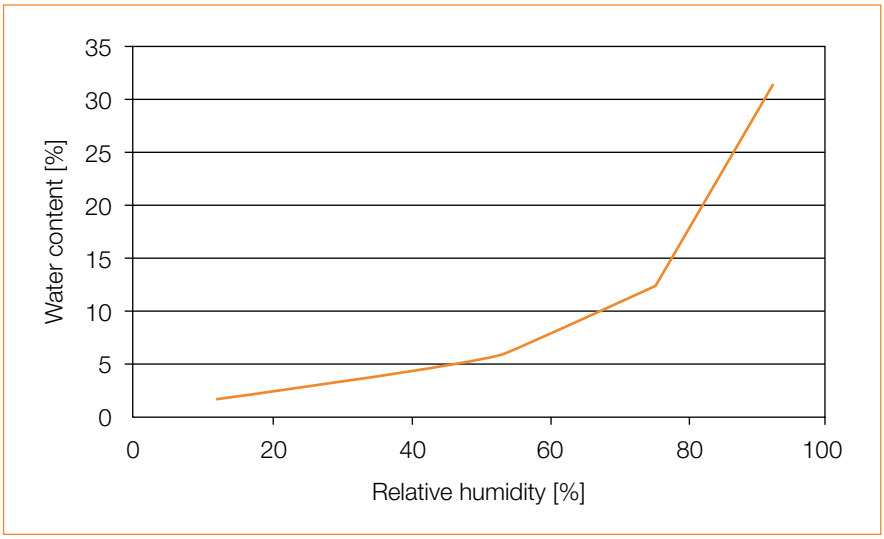


Figure 1: Sorption isotherm of Soluplus

2.7 Critical micelle concentration

7.6 mg/l ~ 7.6 ppm

2.8 Glass transition temperature

Approximately 70 °C

2.9 Minimum ignition energy

According to VDI 2263 the mimimum ignition energy is between 10 – 30 mJ (1.013 hPa, 20 °C).

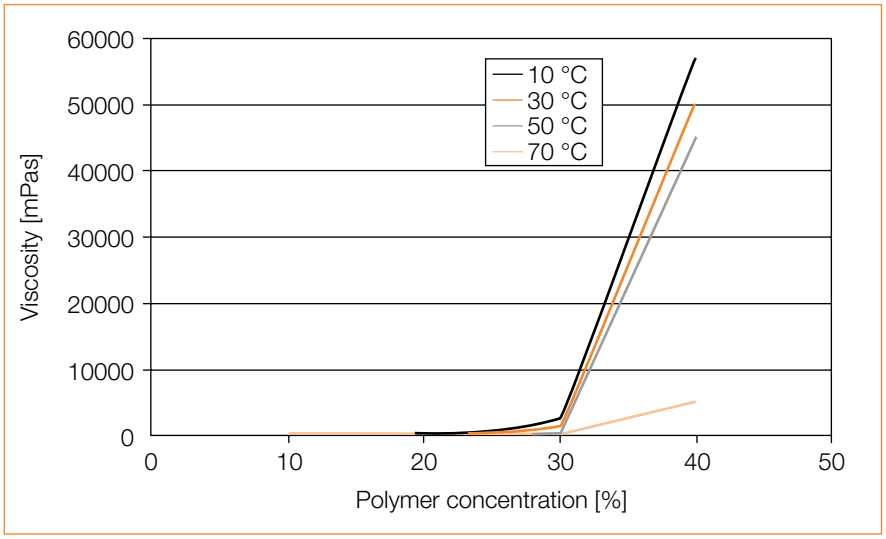
2.10 Solubility

Soluplus is soluble in water in any ratio. Furthermore, it is soluble in acetone (up to 50%), methanol (up to 45%), ethanol (up to 25%) and dimethylformamide (up to 50%). Higher polymer concentration may result in a cloudy or turbid aqueous solution. This is due to formation of colloidal Soluplus micelles.

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.

2.11 Viscosity in water

The values shown in Fig. 2 were determined with a cone-plate viscometer at a shear rate of 100 s^{-1}.



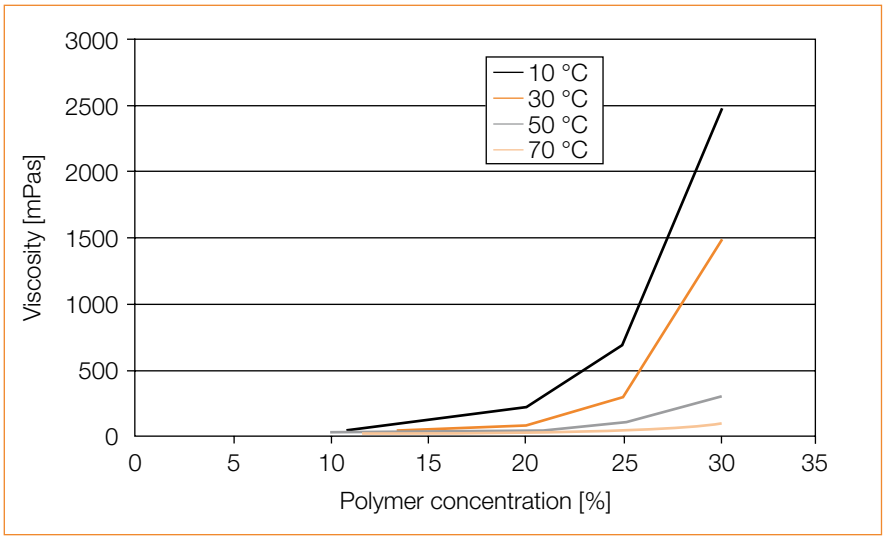


Figure 2: Dynamic viscosity of Soluplus solutions with increasing polymer concentration

3. Application and processing

3.1 Recommendations for pretesting

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

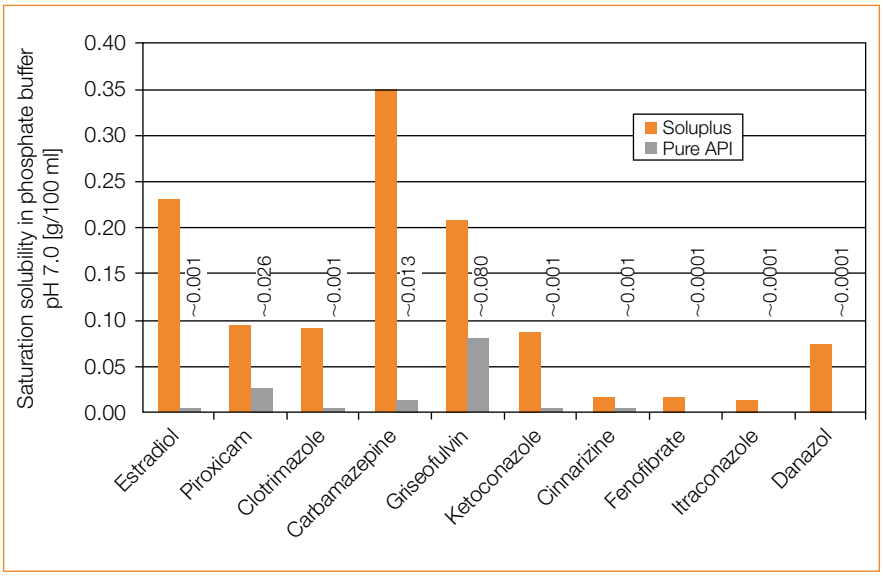


Figure 3: Saturation solubility of various drugs

Capacity for solid solutions

A different approach to test solubilization capacity is the film casting procedure: an appropriate solvent that dissolves the API and also Soluplus has to be chosen (e. g. dimethylformamide). When both substances are dissolved after stirring, the solution can be casted on a glass plate resulting in a thin film. A scraper that leads to a film of 120 µm thickness is recommended as casting device. The thin film (thickness of the dry film <120 µm) enables a fast drying and avoids a recrystallization of the poorly soluble drug due to concentration differences as it is the case within thick films and during slow drying processes. The 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. To analyze the extent of solubilization capacity of Soluplus for a discrete drug, increasing amounts of API should be applied for the film casting method (e. g. 20, 30 and 50%). The higher the incorporable concentration is the higher is the solubilization capacity for a discrete drug. A solid solution becomes obvious in clear and smooth films. Drug crystals can be easily seen after recrystallization resulting also in opaque films.

Drying in a rotating evaporator can take too much time and could lead to recrystallization of the drug within the resulting solid solution. Spray drying is another possible and fast method to form solid solutions.

3.2 Extrusion recommendations

Soluplus with its glass transition temperature of around 70 °C is a well extrudable polymer. The pure polymer can be extruded on a 16 mm twin-screw extruder at temperatures starting around 120 °C up to 180 °C depending on the applied screw configuration. The polymer shows no chemical degradation even after extrusion at 180 °C. Incorporation of a drug can lead to lower temperatures than 120 °C in dependence of the drug melting point.

A solid solution with fenofibrate (melting point ~81 °C) and 20% drug content can be prepared at 100 °C. Higher melting drugs as itraconazole (melting point ~166 °C) with 15% drug content can be extruded with Soluplus at 150 °C. Parameters for a 16 mm twin-screw extruder were 200 rpm and 1 kg/h powder feed rate. The resulting transparent and clear extrudates showed no crystalline amounts of drug determined by x-ray diffraction.

Drug release was tested according to USP, apparatus 2, 50 rpm, 700 ml HCl (0.08 molar) under non-sink conditions. Drug release was determined out of cut extrudates of comparable length (3 mm in length and diameter). API amount was in both cases 100 mg. During dissolution samples were manually taken through a glass drip and immediately diluted in methanol (ratio 1:9). This procedure avoids a recrystallization of API when the sample cools down to room temperature.

Figure 4 shows the dissolution rate of fenofibrate out of a solid solution with Soluplus and the dissolution rate of crystalline substance.

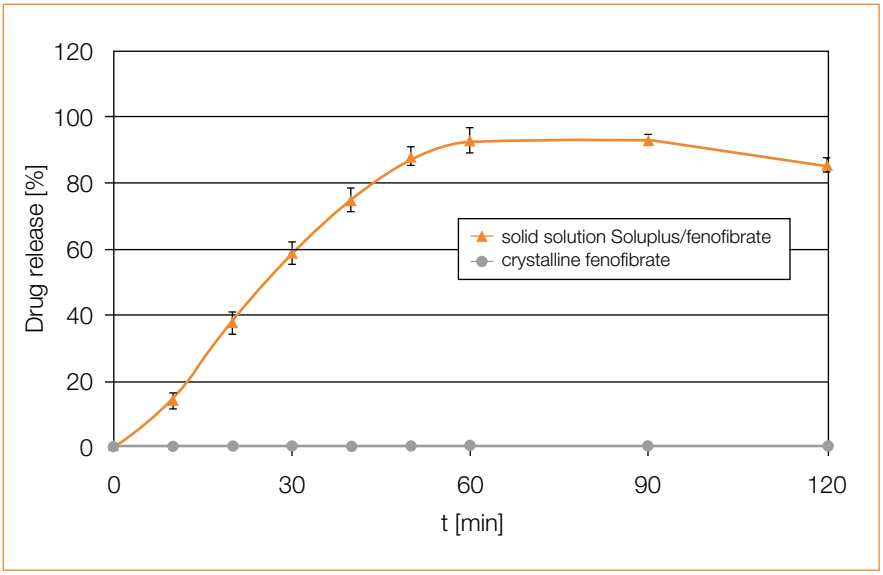


Figure 4: Dissolution rate of fenofibrate

Figure 5 shows the dissolution rate of itraconazole out of a solid solution with Soluplus and the dissolution rate of crystalline substance.

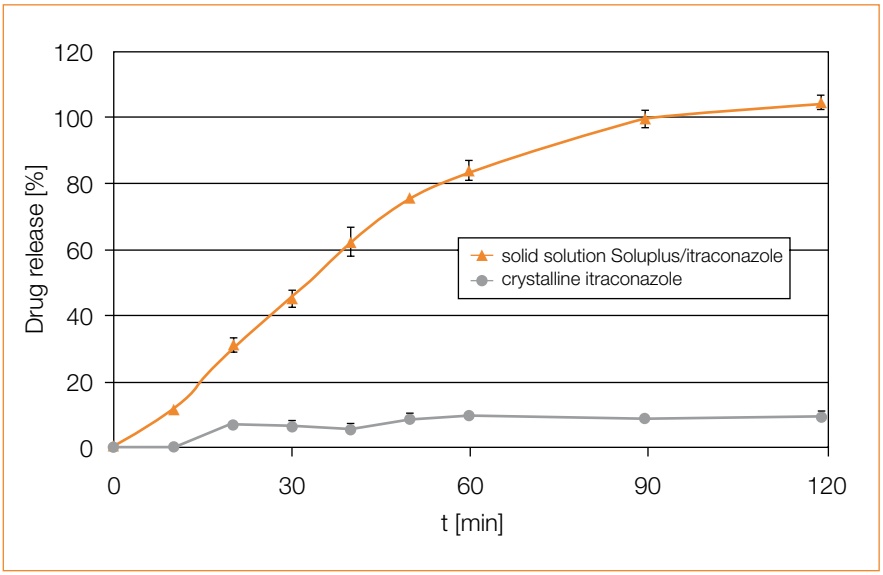


Figure 5: Dissolution rate of itraconazole

3.3 Capsule formulation

Solid solutions can be easily formulated into solid dosage forms, e.g. hard gelatine capsules. The extrudates have to be milled down to an appropriate size for a proper filling of the final capsules. To assure a drug release out of discrete solid solution particles and to avoid lumping additional disintegrant has to be added to the formulation. An effective disintegrant is Kollidon CL in a concentration range of 10 – 15%. Depending on the degree of milling also finer disintegrants as Kollidon CL-F or Kollidon CL-SF are recommendable. Additional water insoluble filler can also be added to the formulation in order to act as a spacer. Microcrystalline cellulose can be used as a potential spacer in concentrations around 15 – 20%.

Capsule formulation:

Solid solution	70%
Kollidon CL	15%
Microcrystalline cellulose	15%

3.4 Tablet formulation

Solid solutions with Soluplus can also be formulated into tablets. Extrudates have to be milled down to an appropriate size and mixed with other excipients of a typical tablet formulation:

Tablet formulation:

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

3.5 Drug layering of nonpareiles

Soluplus can effectively be used in drug layering processes, e.g. in fluid bed granulators with a Wurster insert. Poorly soluble drug and Soluplus have to be dissolved in an appropriate organic solvent, e. g. acetone or ethanol. This solution can be sprayed onto drug free pellets (nonpareiles). In the following example carbamazepine and Soluplus were dissolved in ethanol (ratio drug: Soluplus – 1:2) and sprayed onto sugar pellets. Mass gain of the pellets after layering was approximately 10%.

Figure 6 shows the dissolution rate of carbamazepine out of a solid solution with Soluplus which was coated onto sugar pellets.

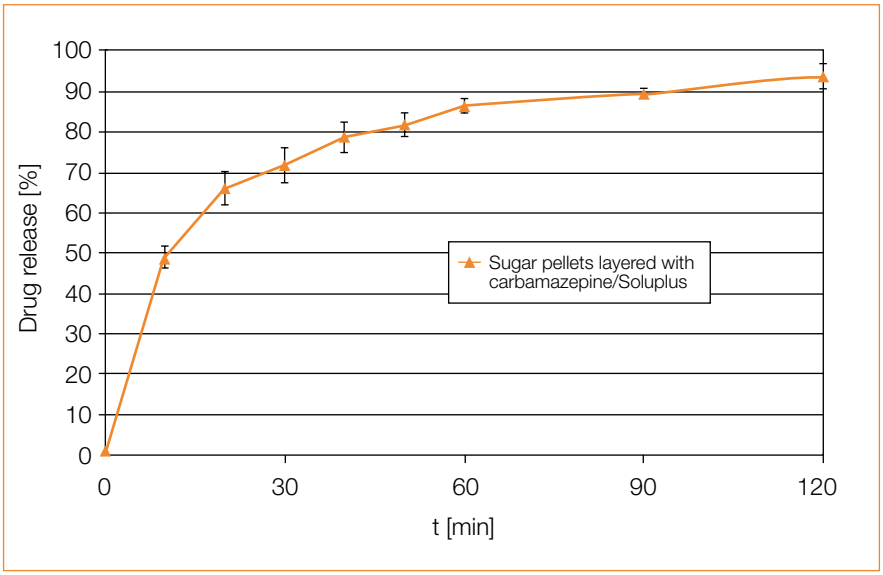


Figure 6: Dissolution rate of carbamazepine

Drug release was tested according to USP, apparatus 2, 50 rpm, 700 ml HCl (0.08 molar) under non-sink conditions. Amount of carbamazepine was 100 mg. During dissolution samples were manually taken through a glass drip and immediately diluted in methanol (ratio 1:9). This procedure avoids a recrystallization of API when the sample cools down to room temperature.

3.6. Other applications

Soluplus can also be used for spray drying out of organic solutions, however, the spray dried powder could show inappropriate properties in terms of the further handling of the powder during the next steps (e. g. compression of tablets, filling of capsules).

Other applications for Soluplus are the use as a binder in wet granulation or a dry binder in direct compression, e. g. for pooly soluble drugs. Thus its solubilization capacity can be used in a simple process method. Furthermore, Soluplus can also be used as a emulsifier in emulsions.

4. Bioavailability

Soluplus can enhance the bioavailability of poorly soluble drugs. Solid solutions were prepared with fenofibrate and Soluplus (ratio 20:80) and itraconazole and Soluplus (ratio 15:85), respectively, and were administered to beagle dogs. For comparison, crystalline substance was administered as well. Each dog received 10 mg API/kg bodyweight in form of hard gelatine capsules. To avoid lumping either of crystalline API or solid solution, a disintegrant was added to the formulations:

Figures 7 and 8 show the blood concentration of API administered to beagle dogs

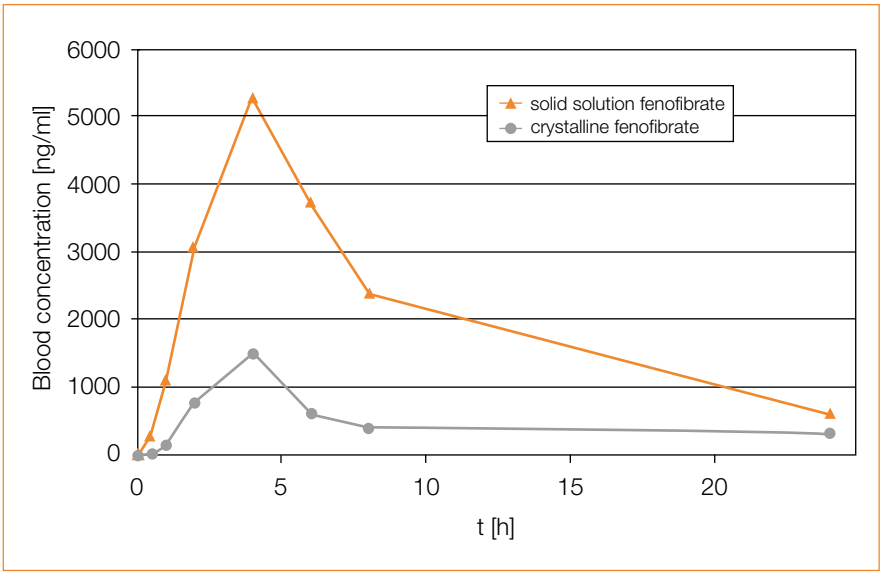


Figure 7: Blood concentration of fenofibrate

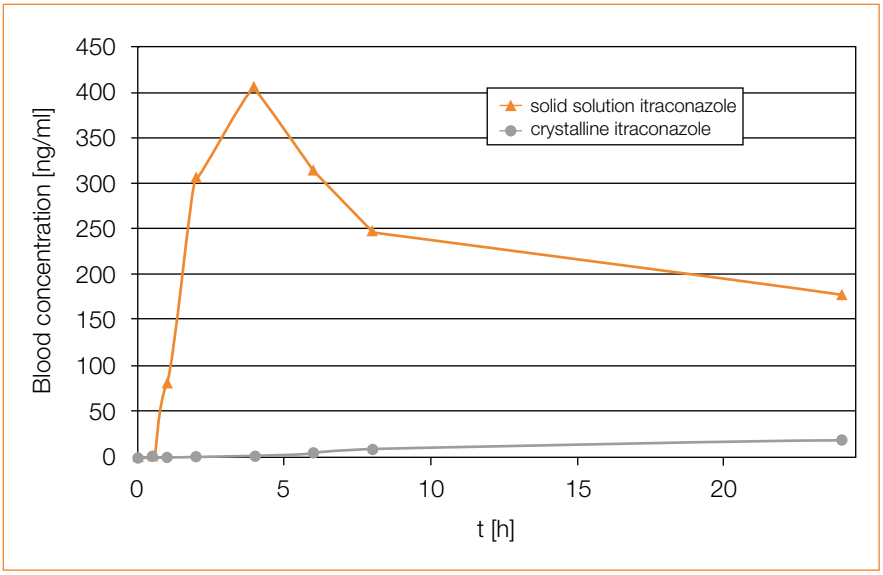


Figure 8: Blood concentration of itraconazole

5. Packaging material

Soluplus is packed into 25 kg cartons with a welded PE/aluminium/Polyester inliner.

6. Retest date and storage conditions

When stored in unopened original containers, the retest period is at least 18 months.

After opening the inliner, it should be stored tightly closed.

7. Safety data sheet

A safety data sheet for Soluplus is available on request.

8. Toxicological Studies

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

9. PRD-No.

30446233

Note

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