**INTRODUCTION**

Drug solubilization has drawn attention in recent years because large numbers of NCEs often fail in development due to their poor solubility and bioavailability. To circumvent these challenges and bring the compounds to the market, the pharmaceutical industry has a desire for novel solubilizers that can provide better opportunities for poorly soluble APIs by (1) lending better solubilization capacity than known solubilizers, (2) having unparalleled safety and toxicological standards, and (3) reducing time and cost in the drug development process.

Classical solubilizers are usually polyethylene glycol-based surfactants that are well suited for liquid formulations (oral, parenteral). In addition, only a selective class of solubilizers has been developed for solid oral dosages. For instance, polyoxyethylene and polyoxypropylene copolymers (Poloxamers) have been used as solubilizers for oral dosage forms, but their application as a matrix (e.g., in solid dispersions) is limited due to their low melting temperatures. Likewise, other polymers, such as povidone, copovidone, and cyclodextrins, have been used in various solubilization technology platforms, but their applications are limited because of poor solubilization capacity of insoluble molecules.

Hot melt extrusion (HME) technology has gained a significant interest in recent years. Even though this technique has been used in the plastics and food industries for decades, it is relatively new in the pharmaceutical industry, and only a few drug products (based on polyethylene glycol or copovidone) are currently available on the market. Hot melt extrusion technology shows numerous benefits over traditional/classical methods, including shorter processing times due to continuous downstream processes, environmental advantages due to elimination of solvents, and increased efficiency in delivery of drugs to the patient.

BASF has introduced a new polymeric solubilizer, Soluplus®, a graft copolymer composed of polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate. Its unique chemistry (Figure 1) coupled with granular and solubilization characteristics are important in the development of solid solutions by hot melt extrusion. Significantly greater lipophilicity in the polymer is a prerequisite for solubilization of poorly soluble molecules in solid solutions as illustrated by complexation of the active with the lipophilic portion of the Soluplus molecule (Figure 2). Soluplus outperforms many of the well-known surfactants and solubilizers for poorly soluble compounds and is potentially applicable to solid oral dosages. The low hygroscopicity and glass transition temperature of about 70°C makes it different from other polymers used as solubilizers.
Germany). Dissolution studies of fresh and stored extrudates, each containing 100 mg of active, were carried out and compared with pure crystalline active. Determination was performed in triplicate using USP apparatus 2 at 50 rpm in 700 mL hydrochloric acid (0.1 molar). The resulting data are mean values ± standard deviation.

Stability of solid solutions was tested at three storage conditions (25°C/60% RH, 30°C/70% RH, and 40°C/75% RH) in glass bottles with a polyethylene lid. After 3 months, the extrudates were analyzed for degree of crystallinity and drug-release profile.

Bioavailability studies were performed in beagle dogs in the fasted state with itraconazole and fenofibrate dosed at 10 mg/kg body weight. For each active, three formulations filled in hard gelatin capsules containing the drug and disintegrant (Ac-Di-Sol®, FMC Biopolymers) were tested. The formulations were (1) crystalline drug substance (95% active, 5% disintegrant), (2) a physical mixture of active and Soluplus (15% active, 80% Soluplus, 5% disintegrant), and (3) solid solution of active and Soluplus manufactured by hot melt extrusion (95% solid solution, 5% disintegrant; 15% itraconazole, 85% Soluplus, 20% fenofibrate, 80% Soluplus).

**RESULTS**

**Solubilization**

For all actives examined, an increase in the saturation solubility was observed with Soluplus (Figure 4). The saturation solubility in 10% solubilizer solution ranged from 0.013 g/100 mL for itraconazole to 0.35 g/100 mL for carbamazepine compared to the saturation solubilities for the pure actives in water that were < 0.08 g/100 mL. In certain cases (e.g., estradiol, danazol, or fenofibrate), the saturation solubility increased > 100-fold in polymer solution.

The impact of pH on solubilization using different buffer media is presented in Figure 5. Soluplus was capable of acting as a solubilizer and increasing the saturation solubility of various actives at all pH values examined. However, actives with basic functionalities, such as clotrimazole, cinnarizine, and ketoconazole, showed an increase in saturation solubility at pH 1.2 due to salt formation in the acidic environment. Likewise, the actives, such as piroxicam among others with acidic functionalities, showed a slightly higher solubility in alkaline condition at pH 9.

The solubilization benchmark in phosphate buffer pH 7 showed a significant solubilization effect with Soluplus for all...
actives examined (Figure 6). In four model drugs studied, Soluplus outperformed the other solubilizers and achieved the best result.

**Extrusion**

The extrusion trials conducted in this study led to transparent and clear extrudates for itraconazole and fenofibrate. Figure 7 shows the solid solution of itraconazole with Soluplus.

X-Ray powder diffraction (XRPD) analysis revealed no crystallinity in the freshly extruded solid solutions of both actives examined. Furthermore, the extrudates stored for 3 months at different storage conditions were clear and transparent, suggesting the drugs were completely miscible in the solid solutions and remained stable under the accelerated conditions (40°C/75% RH) with no apparent crystallization.

**Dissolution**

Dissolution testing of crystalline itraconazole in 700 mL HCl showed about 4% release in 2 hours, which approximates the saturation solubility of active (Figure 8). In comparison, the fresh extrudates showed a complete release and achieved oversaturation in 2 hours. Likewise, the extrudates stored for 3 months under accelerated conditions showed an identical release profile as the fresh extrudates.

Dissolution testing of 100 mg crystalline fenofibrate showed no release of drug in 2 hours in HCl due to the extremely low solubility of fenofibrate (Figure 9). In comparison, the solid solution of Soluplus and fenofibrate showed a complete release and reached several folds higher than
saturation limit in the dissolution media. After storage for 3 months at accelerated conditions, the release of fenofibrate was complete in 2 hours and comparable to fresh extrudates, suggesting the drug remained in the amorphous state and did not change its dissolution profile.

Bioavailability study

The solid solutions of itraconazole and fenofibrate in Soluplus prepared by hot melt extrusion were administered to beagle dogs at 10 mg/kg body weight. In comparison, the APIs as crystalline compounds and as physical mixtures of active and Soluplus were also administered at the same dose levels. Figures 10 and 11 illustrate the plasma concentrations over the time following oral administration of a single dose formulation.

The solid solution of itraconazole in Soluplus led to > 20 to 30-fold increase in the area under the curve (AUC) compared to crystalline or physical mixture formulations. Soluplus in the pure physical mixture did not influence the AUC of itraconazole, and the curve progression was comparable to the progression following the administration of the crystalline active.

Fenofibrate behaved differently than itraconazole. While the formulation with the crystalline active revealed the least concentration of the active in the plasma, the solid solution and physical mixture showed an identical concentration gradient with approximately 5-fold increase in AUC compared to crystalline fenofibrate formulation. Such effect could be related to the lower melting point of fenofibrate, which could help increase the API solubility in the physical mixture. 

DISCUSSION
Soluplus, a polymeric solubilizer with an amphiphilic chemical structure, has been designed and developed for solid solutions. An ideal method for processing this new polymer is hot melt extrusion technology because it is highly extrudable and easily processed due to its low glass transition temperature and thermal stability at higher temperatures.

Soluplus is a polyethylene glycol-polyvinylcaprolactam-polyvinylacetate graft copolymer. Due to its bifunctional character, it is able to act as a matrix polymer for solid solutions and is also capable of solubilizing insoluble drugs in aqueous solution. This is in contrast to classical solubilizers like Cremophor RH40, Solutol HS15, or Tween 80 because Soluplus not only exhibits solubilization properties but also combines the characteristics of a solubilizer and a matrix polymer for solid solutions.

Soluplus is capable of solubilizing various actives bearing a variety of chemical structures with different hydrophobicity and/or lipophilicity. A general trend for solubilization for individual molecules cannot be established because a variety of different drugs were solubilized successfully. Hence, Soluplus can be used as a solubilizer for many poorly soluble molecules with different chemical structures. Soluplus can also be used at a broader pH range because of its non-ionic characteristic without compromising its solubilization capacity.

The poor solubility of drugs often leads to poor or significantly less bioavailability. Soluplus could increase the solubility and enhance the bioavailability of actives in solid solutions.
solutions. Itraconazole and fenofibrate showed a significant increase in the bioavailability with Soluplus. The results also demonstrate that in certain cases, the physical blending or mixing of an active with Soluplus may enhance the bioavailability. Such an effect could be observed with fenofibrate but not with itraconazole. Taken together, the data suggests that for certain individual actives, the physical mixture could be an alternative to the solid solutions to observe an enhanced bioavailability. It is therefore conceivable to use Soluplus as a binder and to achieve the solubilization effects in parallel. Soluplus also possesses appreciable wet and dry binding characteristics like PVP and Copovidone (data not shown).

**CONCLUSION**

Soluplus is especially designed to solubilize poorly soluble APIs and has demonstrated an excellent capability to form solid solutions with many crystalline APIs. Soluplus combines the advantages of solid solutions and solubilization in one, which can help to increase the bioavailability of insoluble actives.

The low hygroscopicity and low glass transition temperature of Soluplus makes it particularly suitable for hot melt extrusion due to its high extrudability at relatively low temperatures. The addition of a plasticizer is not required, and the low extrusion temperature provides the opportunity to extrude actives that are thermally unstable and moisture sensitive. The safety and toxicology of Soluplus have been

**FIGURE 10**

Blood Concentration of Itraconazole in Beagle Dogs

**FIGURE 11**

Blood Concentration of Fenofibrate in Beagle Dogs
demonstrated by comprehensive studies in animal models. The NOAEL value of Soluplus is > 1000 mg/kg.

REFERENCES


BIOGRAPHIES

Dr. Hendrik Hardung is the Technical Product Manager for Soluplus®. The pharmacist by education earned his PhD in Pharmaceutical Technology from the University of Freiburg im Breisgau, Germany. Since joining BASF SE as Manager Global Technical Service Excipients in 2008, he is responsible for technical support for several excipients.

Dr. Dejan Djuric is a Laboratory Manager in the R&D Project Management Excipients at BASF SE focusing on solubilizers and hot melt extrusion processes. As an engineer for pharmaceutical technology, he previously worked in the development for solid oral dosage forms at Abbott GmbH & Co. KG. Dr. Djuric obtained his PhD in Pharmaceutical Technology from the University of Duesseldorf and joined BASF in 2008.

Dr. Shaukat Ali pursued his interest in the pharmaceutical industry and worked at the Liposome Company, Penwest, and Lavipharm before joining the BASF technical team in 2004. He earned his PhD in Chemistry from the City University of New York, NY, and carried out his post-doctoral work at the University of Minnesota and Cornell University. He is an esteemed member of the Editorial Advisory Board of Drug Delivery Technology and a member of panel of experts for Pharmaceutical Technology-Sourcing and Management.