Solubility Enhancement of Simvastatin with Use of Novel Polymeric Solubilizer Soluplus®

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Abstract Summary
The study was aimed to improve the solubility of highly insoluble BCS class II molecule, Simvastatin (0.019 mg/mL in water) by use of a novel polymeric solubilizer, Soluplus®. The solubility improvement was nearly 300 fold by just incorporation of Soluplus® (5.54 mg/mL) as a solubilizer and more than 500 folds (9.51 mg/mL), when used in Melt Extrusion process. This clearly indicated that solubility enhancement with Soluplus® was achieved when either used alone or through the process of Melt Extrusion. Further to these when solubilizers were incorporated with Soluplus® in the process of Melt Extrusion the solubility further increased to more than 1400 folds for all the Solubilizers tested. The solubility enhancement with Kolliphor™ TPGS, Kolliphor™ Pluronic and Kolliphor™ P407 were around 28.98 mg/mL, 25.63 mg/mL and 34.62 mg/mL respectively in water. Thus, the novel polymeric solubilizer, Soluplus® is capable of giving very good solubility enhancement for a model BCS class II molecule studied like Simvastatin; alone and/or in melt extrusion.

Introduction
It has been estimated that 40-60 % of drugs in development have poor bioavailability due to low aqueous solubility. This percentage is likely to increase in the future with the increased use of combinatorial chemistry in drug discovery targeting lipophilic receptors. Poor bioavailability results in increased development times, decreased efficacy, increased inter- and intra-patient variability and side-effects, and higher dosages that reduce patient compliance and increase cost. Thus, the ability to improve drug solubility and hence bioavailability through formulation and process technology is critical to improving a drug product’s efficacy and safety and reducing its cost. Solid solution formulated by hot melt extrusion technology, where the API is dispersed at the molecular level as an amorphous material within a solid matrix, is a proven and highly effective technique for improving drug solubility [2-3]. Soluplus® is a polymeric solubilizer with an amphoteric chemical structure, which was developed for preparation of solid solutions. Due to its bifunctional character, its able form matrix polymer for solid solutions on one hand, while capable of solubilizing poorly soluble drugs in aqueous and other media, [4] the aim of the study was to enhance the solubility of poorly soluble BCS class II molecule, Simvastatin with use of novel polymeric solubilizer, Soluplus®.

Experimental Methods
For melt extrusion, Simvastatin and Soluplus® were sifted separately through sieve aperture of 425 microns and blended in cone blender for minutes and again sifted through sieve aperture of 425 micron. Melt extrusion of drug and polymer blend was performed on HAAKE Minilab Micro-Compounder (Thermo Scientific, Germany) consisting of twin screws and has a single heating zone. The formula for melt extrusion is given in table 1. The melt extrusion was carried out at a feed rate of 25.0 rpm and at a constant twin screw rate of 75 rpm. The temperature of the zone was maintained at 135°C. The extrudates were collected at room temperature in the tray at humidity condition of 50% RH. The collected extrudates were milled and sifted through sieve aperture of 425 micron. These extrudates were stored in a double polybag with a desiccant before further processing. Saturation solubility was determined by the shake-flask method. Simvastatin or melt extrudes equivalent to about 1 g of simvastatin were filled in glass vials and around 10 mL of either 0.1 N HCl, acetate buffer, pH 4.5 or phosphate buffer, pH 7.0 was added. The vials were placed in an orbital shaker at 37°C and 100 rpm until for 48 hours. The aliquots were filtered through Whatman filter paper grade 1 (pore size = 11 microns). The filtrates were diluted appropriately using appropriate medium and assayed spectrophotometrically at λ max 238 nm.

Results and Discussion
The solubility of Simvastatin at pH 7.0 was around 8 mg/mL, which was highest among all other medium tested indicating that it showed a pH dependent solubility. With incorporation of plain Soluplus® the solubility enhancement was more than 300 folds in 0.1 N HCl, pH 4.5 and water. The solubility of Simvastatin was also found to increase in presence of other solubilizers such as Kolliphor™ TPGS (9.54 mg/mL), Kolliphor™ P 188 (8.42 mg/mL) and Kolliphor™ P 407 (9.88 mg/mL) in water as shown in figure 1. The Melt Extrudates of Simvastatin showed enhanced solubility of more than 500 folds indicating the usefulness of Soluplus in Melt Extrusion technology. The extrudates showed higher solubility in all media other than phosphate buffer pH 7.0. This can be attributed to the initial high solubility of Simvastatin at pH 7.0. The increase in the solubility of API can be attributed to amorphophic nature of Soluplus®, which gives rise to hydrophilic head and lipophilic tail. The lipophilic tail entraps the insoluble pharmaceutical active and the hydrophilic head helps it to solubilize in the aqueous media. The solubility of the drug was further enhanced by synergistic effect and incorporation of other solubilizers in Melt Extrusion process using Soluplus®. The solubility of Simvastatin was found to be highest with use of Kolliphor™ P 407 in water (34.62 mg/mL), phosphate buffer, pH 7.0 (42.42 mg/mL). This can be attributed to two reasons; formation of the amorphous form of the pharmaceutical active, which was confirmed from XRD studies (Fig. 2) and DSC (Fig. 3) studies, which showed only one Tg for the extrudates. Secondly this was also due to the amphiphilic nature of Soluplus® leading to formation of lipophilic cavity, which took up these amorphous pharmaceutical active and helped in formation of solid solution.

Conclusion
The novel polymeric solubilizer, Soluplus® is capable of enhancing the solubility of a BCS class II molecule Simvastatin. The solubility can be further improved by incorporation of Soluplus® in the process of Melt Extrusion.

References

Table 1: Formula for melt extrusion (%)

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<tr>
<th>Solubilizer</th>
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<th>Soluplus®</th>
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Figure 1: Solubility enhancement with different process and solubilizers

Figure 2: XRD with of Simvastatin and other extrudates prepared with different solubilizers

Figure 3: DSC of Simvastatin and other extrudates prepared with different solubilizers