

## STUDIES ON DISSOLUTION ENHANCEMENT OF LOVASTATIN USING SOLUPLUS BY SOLID DISPERSION TECHNIQUE

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### ABSTRACT

For a successful formulation, various formulation parameters that play a crucial role are aqueous solubility; stability at ambient temperature and humidity, photo-stability, compatibility with solvents etc. Among all these, Solubility is the most important property for developing formulations. The present study is an attempt to improve the solubility and dissolution rate using solid dispersion of a poorly soluble drug Lovastatin by using Soluplus as carrier material to enhance the solubility as well as dissolution rate. Six different formulations were prepared using hot melt extrusion technique in different ratios i.e., 1:1, 1:2, 1:3, 1:5, 1:7, and 1:9 and were further characterized by FTIR, DSC, and SEM analysis. The results of FTIR revealed that no chemical interaction between the drug and the polymer exist. DSC studies showed that the drug was in amorphous state completely entrapped by the polymer. SEM studies showed the surface morphology of the solid dispersion. All the formulations showed a marked increase in drug release with the increase in the concentration of soluplus when tested for their in vitro studies. Formulation F6 showed the best release with a cumulative release of 99% in 50 mins when compared to the pure drug, Physical mixture and marketed formulation. Hence, soluplus look to be a promising carrier to improve the solubility of poorly soluble drugs.

**Keywords:** Hot melt extrusion technique, Lovastatin, Solubility, Soluplus, Solid dispersion.

### INTRODUCTION

Presently, there is considerable interest in improving the oral delivery of poorly water-soluble drugs. Compounds exhibiting dissolution rate limited bioavailability are considered as class II drugs according to Biopharmaceutical Classification Scheme (BCS) <sup>1</sup>. Lovastatin is a class II drug. It is a prodrug. After oral administration, the inactive parent lactone is hydrolyzed to the corresponding hydroxyacid form. The hydroxyacid is the principal metabolite and a potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase. This enzyme catalyzes the conversion of hydroxymethylglutarate to mevalonate, which is early and rate-limiting step in the biosynthesis of cholesterol.<sup>2</sup> <sup>4</sup>Low aqueous solubility of the drug leads to inadequate dissolution in gastrointestinal (GI) fluids and hence poor absorption, distribution and target organ delivery. Improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy.

In case of drugs with the dissolution rate limited absorption, reduction in particle size often increases the rate of dissolution and the amount of drug absorbed. The rate of absorption can be further increased using various techniques, which include solvent disposition, cosolvents, salt formation, pH control, Co-grinding, Solid dispersions etc. Most of the poorly water-soluble drugs are not suitable for improving their solubility by salt formation. Decreasing particle size increases solubility but there is poor wetting and flow. Solid dispersions can overcome these problems. The usage of carriers like PEG, PVP,  $\beta$ -cyclodextrin HPMC, Skimmed milk powder, etc have been proved to improve the dissolution of poorly soluble drugs.<sup>5-9, 11, 12</sup> Many carriers used in solid dispersions also cause problems due to their hygroscopic nature. Hence, a continuous search for the new carriers and new techniques is still under progress to overcome the problems. Use of polymers with low viscosity and high swelling capacity offers better alternative for these types of polymers.

Soluplus is a novel amphiphilic polymeric solubilizer, which can be better suited in the solid dispersion technology in improving the solubility of poorly soluble drugs. It is a polyvinylcaprolactam-polyvinyl Acetate-polyethylene glycol grafted copolymer with both hydrophilic and lipophilic properties. This unique structure provides ideal interactions with drugs through hydrogen bonding and leverages stability of the system. It is ideal for formulating novel drug substances<sup>10</sup>

Hence, the present study aimed to improve the solubility and/or dissolution rate of poorly water-soluble drug, Lovastatin through the solid dispersion approach using Soluplus in various ratios in comparison with the plain drug and physical mixtures of the drug and the polymer.

### MATERIALS AND METHODS

Lovastatin and Soluplus was obtained as gift samples from Dr. Reddy's Laboratories, Bachupally, Hyderabad and BASF, The Chemical Company, Germany respectively. All other solvents and reagents used were of analytical grade and used as such.

#### Preparation of Solid dispersion

Solid dispersions of Lovastatin with Soluplus were prepared in the ratios of 1:1, 1:2, 1:3, 1:5, 1:7 and 1:9 using hot melt extrusion technique. The drug and the polymer were accurately weighed and solid dispersions were prepared by incorporating the drug into the melt of Soluplus at a temperature of 115-120°C until a homogenous melt was obtained. This were simultaneously dried by cooling to the room temperature dried under vacuum, pulverized and passed through sieve no: 85. The solid dispersion equivalent to 40 mg of the drug was weighed accurately and compressed to tablets using TDP 1.5 Single punch tablet press and coded as F1, F2, F3, F4, F5 and F6 respectively for 1:1, 1:2, 1:3, 1:5, and 1:9 used for further studies.

#### Preparation of physical mixture (PMs)

The drug and the carrier were weighed accordingly to the specified drug: carrier ratio. The physical mixture was prepared by geometrical mixing of the drug and carrier in a mortar using a stainless steel spatula. Solid mass was pulverized and passed through sieve no: 85 to get uniform sized particles.

#### In vitro Dissolution Studies

The invitro dissolution rate studies were performed in triplicate for all the six formulations i.e., F1, F2, F3, F4, F5, F6, Pure drug, PM and Marketed formulation on a USP -type-I Dissolution test Apparatus (model- Electro Lab TDT-08L) using phosphate buffer of P<sup>H</sup> 7.4 as dissolution medium at 37±0.5° C. at a rotation speed of 50. Aliquots of (5ml) of the dissolution medium were withdrawn at regular time intervals, filtered using a 0.45  $\mu$ m filter (Millipore) and the volume was made up with the dissolution medium. The amount of Lovastatin present in the sample was spectrophotometrically determined at 238nm.

## Characterization of the Solid Dispersion

### Fourier Transform Infrared Spectroscopy (FTIR)

The KBr discs of Lovastatin, Soluplus, and optimized solid dispersion were prepared using electrically operated KBr Press Model SHIMADZU FTIR-5300 Fourier transform spectrophotometer was used to record IR spectra of the prepared discs, to confirm any interaction of Lovastatin with other excipients of dispersion.

### Differential Scanning Calorimetry (DSC)

Lovastatin, Soluplus, physical mixtures and solid dispersions were examined by a differential scanning calorimeter (Universal Thermal Analyzer DSC Q200 V23.12) at a heating rate of 10°C/min from 30°C to 300°C in nitrogen atmosphere.

### Scanning Electron Microscopy (SEM)

The Solid dispersion was examined by Scanning electron microscope to investigate the surface morphology and homogeneity of the particles. The samples of optimized formulation were sputter-coated

with gold at room temperature before examination to render the surface of particles electro-conductive. The SEM analysis of the sample was performed by Jeol JSM-840 (Japan) scanning electron microscope. The scanning range was 450 to 4,000 nm and the resolution was 1 µm.

## RESULTS AND DISCUSSION

### FTIR

Infrared spectra of Lovastatin as well as its solid dispersions are presented in Fig: 1,2,3. Pure Lovastatin spectra showed sharp characteristic peaks at 3532.73, 1706.74, and 1220.66 cm<sup>-1</sup>.

While the FT-IR spectra of soluplus showed peaks at 1621.76, 1242.66, 1144.43, 1100.71 cm<sup>-1</sup>.

The FT-IR spectra of dispersion showed almost all the bands of Soluplus, without affecting its peak position and trends, which indicated the absence of well-defined interactions between the drug and the polymer.

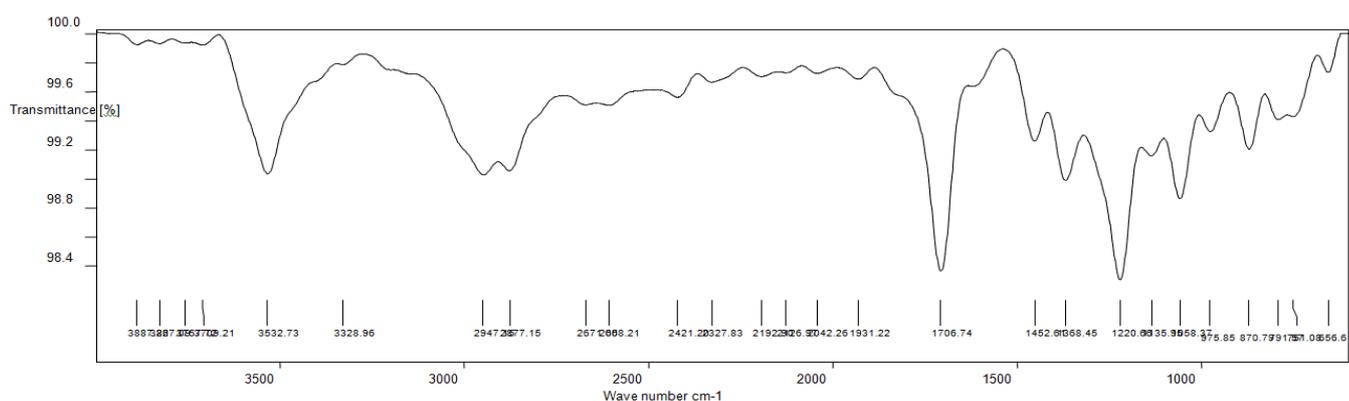


Fig. 1: FTIR Spectra of Lovastatin pure drug

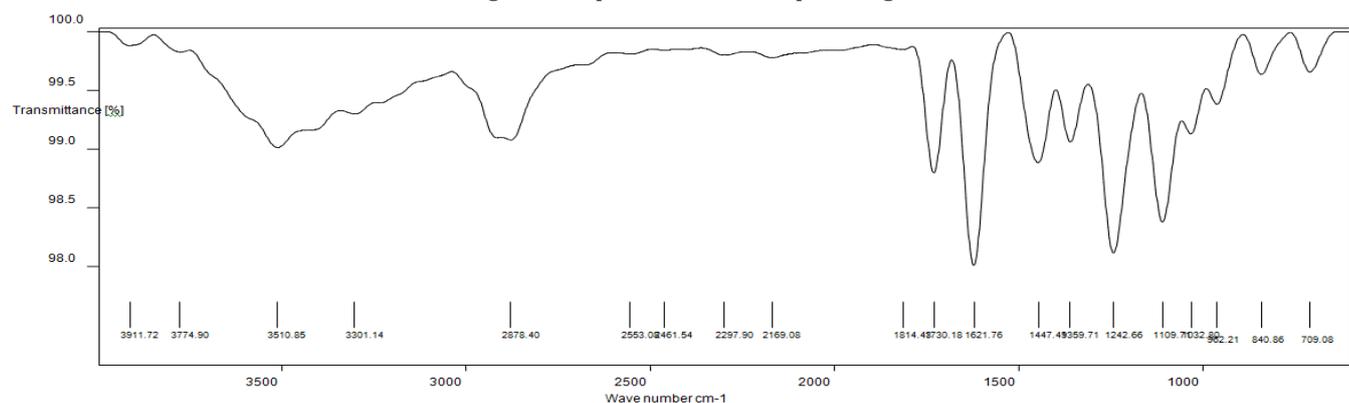


Fig. 2: FTIR Spectra of Soluplus

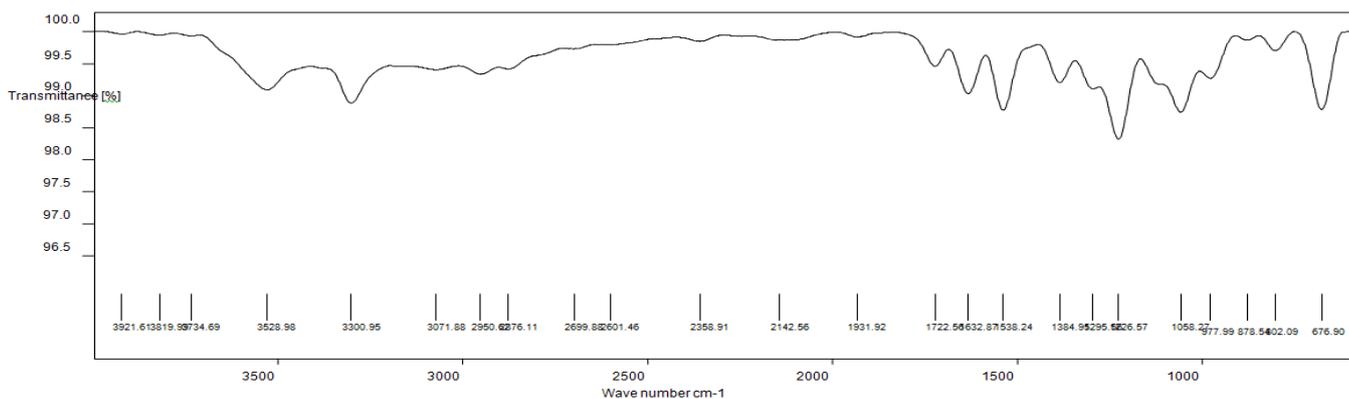


Fig. 3: FTIR Spectra of Lovastatin Solid dispersion

**DSC**

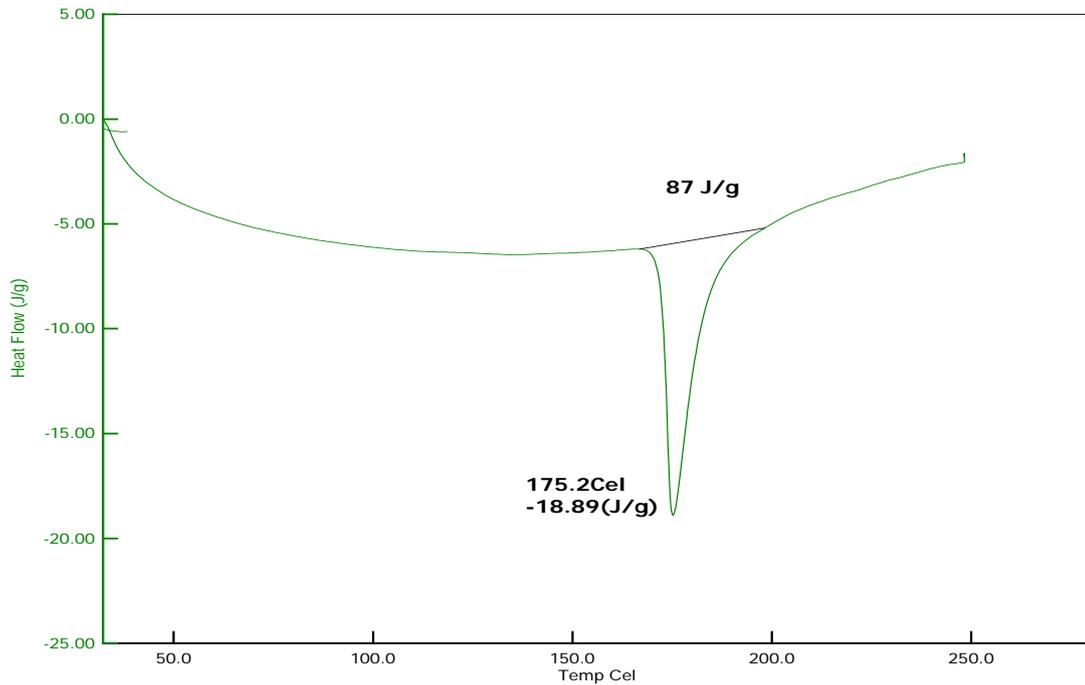
The DSC thermograms of Lovastatin and solid dispersion are shown in Fig: 4 & 5. The thermogram of Lovastatin exhibited an endothermic peak at 175.2 while the solid dispersion exhibited a broad endothermic peak at 173.8 owing to its amorphous nature. The DSC thermograms of physical mixture as well as solid dispersions showed identical peaks corresponding to pure drug but sharpness of the peaks were decreased. Hence the amorphous nature of the drug in the solid dispersion formulation acceding its usage in the improvement of solubility.

**SEM**

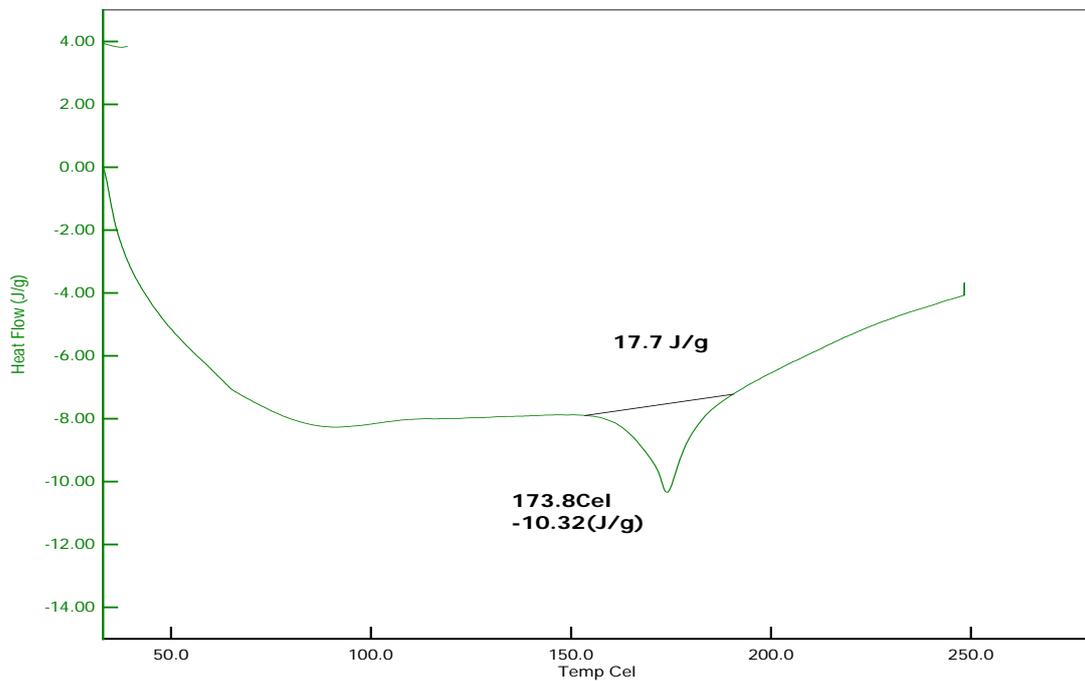
SEM studies as shown in the figure: 7 revealed the surface morphological properties of the solid dispersion indicating that the solid dispersion was in amorphous state.

**SEM**

SEM studies as shown in the figure: 6 revealed the surface morphological properties of the solid dispersion indicating that the solid dispersion was in amorphous state.



**Fig. 4: DSC of Lovastatin**



**Fig. 5: DSC of Solid dispersion**

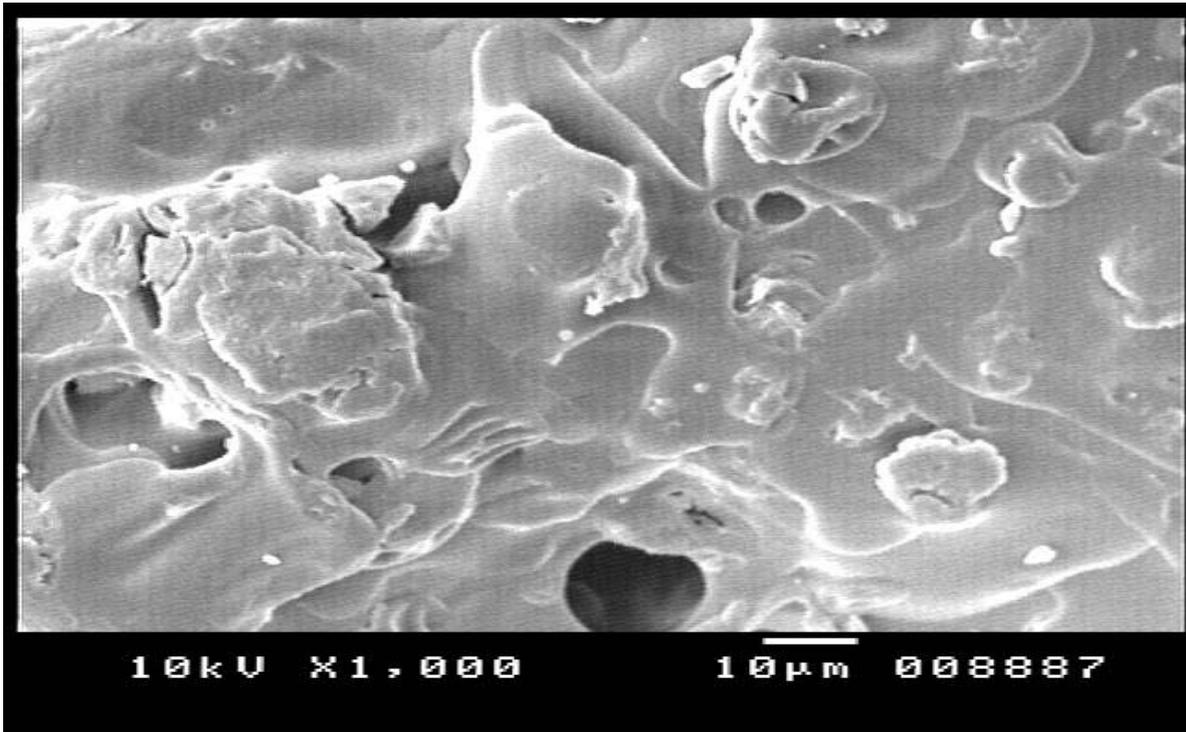


Fig. 6: Scanning Electron Microscopic Photograph of Lovastatin Solid dispersion

**Invitro Dissolution Studies**

Figure: 7 showed the invitro dissolution profile Lovastatin pure drug, PM, Solid dispersion and marketed formulation. From the study, it was observed that as the amount of Soluplus was increased the dissolution rate also increased and dissolution time was decreased. From the study, it was found that F6 has better

dissolution of 99% in 50 minutes when compared to the other formulations. The improvement in the dissolution of the drug may be due to its entrapment within the molten carrier during the melting (fusion technique) process, or due to the molecular dispersed state of the drug in the solid dispersion. The data also suggests that the drug dissolution improvement was due to presence of the drug in amorphous state and the increase of wetting property.

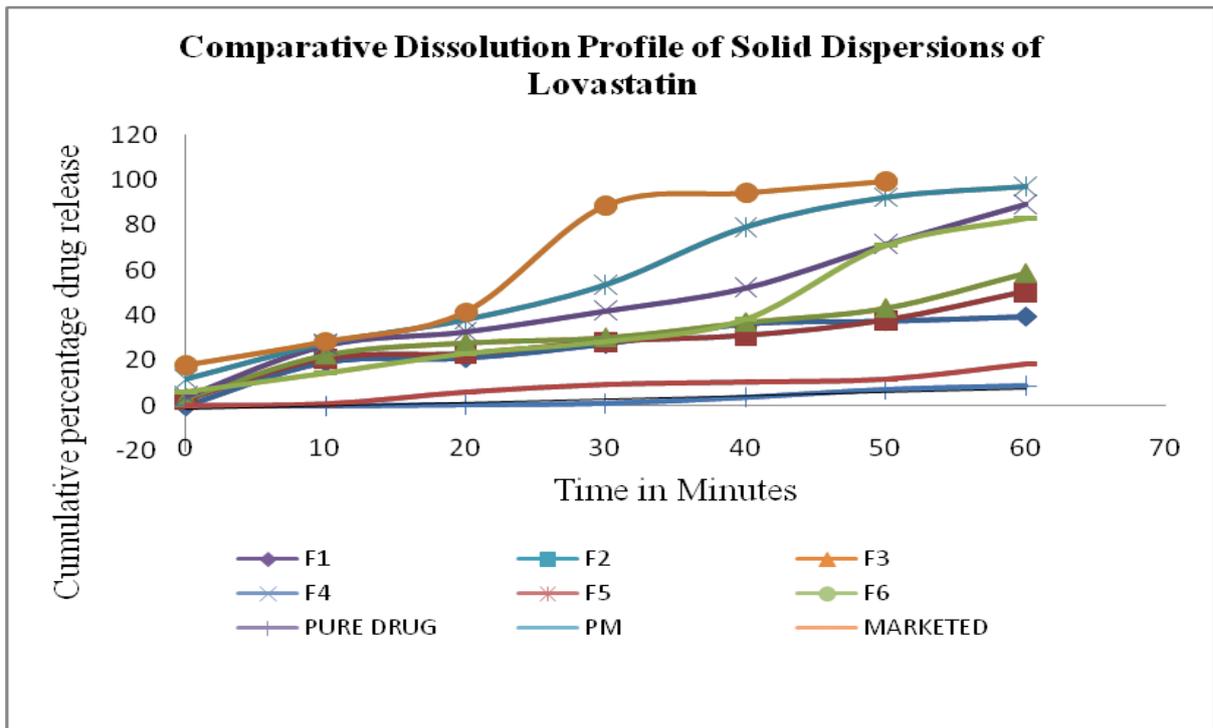


Fig. 7: Comparative dissolution profile of Lovastatin pure drug, Physical mixture, Solid dispersions and Marketed Formulation

**CONCLUSION**

Hence we conclude from our studies that Soluplus could be used as a potential carrier in the dissolution rate enhancement of poorly soluble drugs like Lovastatin using Solid dispersion technique where the drug was in the amorphous state in the molten polymer. The solubility and dissolution rate of a poorly soluble drug, Lovastatin can be effectively enhance by using Soluplus in the form of solid dispersion that imparts good surface adsorbent properties and leaves the drug in amorphous state that increases the surface area, which in turn enhances the dissolution rate.

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