Section: Research Paper
ISSN 2063-5346

Effect of Sodium Lauryl Sulfate and Superdisintegrants on Enhancement of Solubility and Dissolution Rate of Simvastatin by Solid Dispersion Approach

Shashikumar Yadav [1]* S. Srinu Naik[2], B. Rajam[2], Vijaya Laxmi. M[3]

1. Department of Pharmacy, University College of Technology, Osmania University, Hyderabad-500007, Telangana, India.
2. Department of Chemical Engineering, University College of Technology, Osmania University, Hyderabad-500007, Telangana, India.
3. Department of Pharmaceutics, Teegala Krishna Reddy College of Pharmacy, Hyderabad-500097, Telangana, India.

***Corresponding Author: Shashikumar Yadav**
shashikumarpharmacy@gmail.com

ABSTRACT

This study focused to investigate the role of Sodium Lauryl Sulfate (SLS) and superdisintegrants in Simvastatin solid dispersions (SSD) using solvent evaporation method in enhancing the solubility and dissolution rate of Simvastatin (SIM). Binary Solid dispersions were prepared at drug to carrier ratio 1:1 with Sodium Lauryl Sulfate (SLS), Crospovidone (CP), Sodium Starch Glycolate (SSG), and Croscarmellose Sodium (CCS) as carriers. Superdisintegrants were incorporated into the SLS binary solid dispersion as the third component to obtain the ternary solid dispersion systems. The prepared solid dispersions were characterized by differential scanning calorimeter, X-ray powder diffraction, and Fourier Transformed Infrared Spectroscopy and dissolution studies. The optimized solid dispersion (SSD9) was formulated into immediate release tablets (F1-F4) by direct compression method and evaluated for its pre and post compression parameters. FTIR spectroscopy showed no interaction between the components in the solid dispersion and XRD and DSC studies indicated a decreased crystallinity of the solid dispersions. In vitro dissolution results clearly showed improved dissolution of drug from the ternary solid dispersion systems when compared with the binary solid dispersion systems and pure drug. This is because of SLS enhances wetting, dispersibility, and inhibition of drug crystallization and Croscarmellose sodium promotes rapid disintegration and dissolution of solid dispersion.

Key words: Solid Dispersion, Simvastatin, SLS, Superdisintegrants, Solubility, Dissolution Rate, Binary, Ternary, FTIR, XRD and DSC.

1. Introduction

In recent years, the development of advanced drug delivery systems has garnered significant attention in the pharmaceutical industry, aiming to overcome challenges associated with poor solubility and bioavailability of various drug compounds (Jiang et al.,

2012). Among these, solid dispersion techniques have emerged as a promising approach to enhance the dissolution rate and oral bioavailability of poorly water-soluble drugs (Leuner & Dressman, 2000; Margulis-Goshen & Magdassi, 2009; Mura et al., 1996. One such drug that falls under this category is Simvastatin, a widely prescribed lipid-lowering agent, which exhibits limited aqueous solubility due to its crystalline nature (Pandya et al., 2008).

Simvastatin, a BCS Class II drug, is known for its limited aqueous solubility, which can result in poor dissolution and reduced bioavailability (Rao et al., 2010; Silva et al., 2010). To address this issue, various carriers such as surfactants and polymers can be employed to create solid dispersions (Sjökvist et al., 1991; Vippagunta et al., 2002). In this study, we focus on utilizing Sodium Lauryl Sulfate (SLS), Crospovidone (CP), Sodium Starch Glycolate (SSG), and Croscarmellose Sodium (CCS) as carriers in binary and ternary solid dispersions with Simvastatin.

SLS, a surfactant, can enhance drug solubility by reducing the interfacial tension between the drug and the dissolution medium (De Waard et al., 2008; Lee et al., 2001; Mura et al., 2005). CP, a superdisintegrant, aids in breaking down the solid dispersion into smaller particles, leading to quicker dissolution. SSG, a disintegrant, promotes the rapid disintegration of the solid dispersion in the gastrointestinal tract, ensuring efficient drug release. CCS, offers the advantages of both polymer stability and drug solubility enhancement (Rao et al., 2010). Among the various methods available for preparing solid dispersions, the solvent evaporation method stands out as an efficient approach (Tachibana & Nakamura, 1965). This method involves the dispersion of a drug and one or more carriers in a solvent, followed by the removal of the solvent through evaporation, resulting in a solid dispersion.

In this research endeavour, we aim to prepare binary and ternary solid dispersions of simvastatin using SLS, CP, SSG, and CCS as carriers. The study will encompass the optimization of carrier ratios, solvent selection, and processing parameters to achieve the desired drug solubility enhancement and dissolution rate improvement. The resulting solid dispersions will be characterized using various techniques (FTIR, DSC, XRD), to evaluate their physicochemical properties, crystallinity, and drug-carrier interactions. Furthermore, the in vitro dissolution profiles of the formulated solid dispersions will be evaluated to assess their potential in improving the drug's dissolution rate and oral bioavailability.

2. Materials and Methods

2.1. Materials

In the present research work, Simvastatin was obtained as a gift sample from Krebs Biochemicals & Industries Limited. Sodium lauryl Sulphate (SLS), Croscarmellose sodium (CCS), Crospovidone (CP), Sodium Starch Glycolate (SSG), Mannitol, Microcrystalline Cellulose (MCC), Magnesium stearate, Talc were purchased from supplier S.D.Fine Chemicals Ltd, Mumbai, India and other chemicals used in the research work were of analytical grade.

2.2. Preparation of Binary Solid Dispersions (SSD1 –SSD6) by Solvent Evaporation method

Solid dispersions (SD) of Simvastatin (SIM) were prepared by solvent evaporation method with four different carriers (Table 1). In this method, accurately weighed carrier was taken into a china dish and added 20 ml of isopropyl alcohol (IPA) (solvent) and mixed with glass rod. Added drug to carrier solution and then mixed well to get complete solubilized solution. Then transferred the china dish to oven to facilitate solvent evaporation. Once the IPA has been evaporated, removed the formed solid dispersion from the china dish and passed through sieve no. 60 and stored in a desiccator to prevent moisture uptake and degradation.

2.3. Preparation of Ternary Solid Dispersions (SSD7 –SSD9) by Solvent Evaporation method

The required quantity of 1500mg SLS carrier was dissolved in 40 ml of IPA and then added 500mg of co-carrier (SSG / CP/ CCS) (Table 1) and 500mg of SIM (Drug:Carrier:Co-carrier::1:3:1 ratio) to carrier solution and thoroughly mixed well to solubilize the drug and co-carrier. Then transferred the china dish to oven to facilitate solvent evaporation. Once the IPA has been evaporated, remove the formed solid dispersion from the china dish and passed through 60 no. sieve and stored in a desiccator to prevent moisture absorption.

2.4. Preparation of Simvastatin Physical Mixtures (SPM1-SPM9)

For Binary physical mixtures drug and carrier and for Ternary physical mixtures drug, carrier, and co-carrier (Table 1) were taken in a poly bag and mixed well for 15min to form a powder blend. The blend was passed through 60 no. sieve and stored in a desiccator.

2.5. Estimation of drug content

Accurately weighed a known amount of the solid dispersion sample equivalent to 20 mg of Simvastatin was dissolved in 100ml methanol and sonicated and analyzed Simvastatin content in the solid dispersions using UV spectrophotometer at wavelength to 238nm. The actual drug content was calculated using the following equation.

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

Table 1. Formulation compositions of Solid Dispersions and Physical Mixtures

Code No. (Simvastatin Physical Mixtures)	Code No. (Simvastatin Solid Dispersions)	Drug: Carrier: Co Carrier Ratio	Drug (mg)	SLS (mg)	SSG (mg)	CP (mg)	CCS (mg)
SPM1	SSD1	1:1	500	500	-	-	-
SPM2	SSD2	1:1	500	-	500	-	-

SPM3	SSD3	1:1	500	-	-	500	-
SPM4	SSD4	1:1	500	-	-	-	500
SPM5	SSD5	1:2	500	1000	-	-	-
SPM6	SSD6	1:3	500	1500	-	-	-
SPM7	SSD7	1:3:1	500	1500	500	-	-
SPM8	SSD8	1:3:1	500	1500	-	500	-
SPM9	SSD9	1:3:1	500	1500	-	-	500

2.6. Aqueous solubility study

Prepared an excess amount of pure Simvastatin and solid dispersions individually in 10ml distilled water and allow it to equilibrate under constant shaking for an extended period 24 hours. Filter the equilibrated solution through a membrane filter and diluted each filtered solution as necessary and measured the absorbance of the solution at 238 nm.

2.7. X-ray Diffraction Study

XRD study for Pure Simvastatin & Solid dispersions samples were performed on an XRD instrument (Shimadzu XRD-7000 Maxima) with a sensitivity of 0.001. The samples were exposed to CuKα radiation a voltage of 40 kV and 50 mA over the 2θ range of 5° to 90° in increments of 0.12°/s every 0.02° (Hou et al., 2013).

2.8. FTIR Spectroscopy Study

FT-IR spectras were obtained by KBr pellet method. The sample was dispersed in dry potassium bromide. The disk was placed in the FT-IR sample holder and the IR spectra were obtained in the region 400 to 4000 cm−1 in transmittance mode.

2.9. Differential Scanning Calorimetry Study

Finely powdered pure Simvastatin & Solid dispersions samples were weighed and sealed in flat-bottomed aluminum pans with crimped-on lids. The scans were obtained in an air atmosphere with DSC instrument (TA instrument USA Model –Q20) by heating from 30°C to 300°C at a rate of 10°C/min under nitrogen gas and the empty pan of aluminum was used as a reference.

2.10. In vitro dissolution study for Solid Dispersion

In vitro dissolution studies conducted for pure Simvastatin drug, Solid dispersions, and Physical mixtures with 900 mL of pH 6.8 phosphate buffer as dissolution media using USP apparatus–II (paddle type) (Lab India DS 8000). Paddle rotation speed was set at 70 rpm, and the temperature was maintained at 37±0.5°C. At predetermined intervals (10, 20, 30, 40, 50 and 60 min) withdrawn 5 mL of sample from each vessel and the same volume of fresh dissolution medium was added simultaneously. The samples were filtered through 0.45-µm membrane filter. The absorbance of each sample was analyzed by UV spectrophotometer at 238 nm. The dissolution rate of the drug was calculated from the slope of the regression line.

2.11. Formulation and Evaluation of Immediate Release Tablets

Immediate release tablets were formulated using solid dispersion (SSD9) equivalent to 20 mg of Simvastatin with Sodium starch glycolate (SSG), Crospovidone (CP), Croscarmellose sodium (CCS), as super disintegrants, Magnesium Stearate as lubricant and Talc as glidant as shown in Table 2 (F1-F4). All materials were shaken well in a poly bag to form a uniform blend and performed Bulk Density, Tapped Density, and Angle of repose, Carr's index, and Hausner's ratio. The blend was compressed by direct compression method and compressed tablets were evaluated for hardness, friability, weight variation, disintegration time and drug content and percent drug release from tablets in pH 6.8 phosphate buffer.

Table 2. Tablet Formulations with Solid Dispersion and Excipients

Ingredients (mg)	F1	F2	F3	F4
Solid Dispersion (SSD9)	100	100	100	100
CCS	---	20	---	---
CP	---	---	20	
SSG	---	----	---	20
Mannitol	100	100	100	100
MCC	48	28	28	28
Mg. Stearate	1	1	1	1
Talc	1	1	1	1

3. Results & Discussions

3.1. Drug Content

The drug content for all prepared solid dispersions were in the range of 99.11 % and 102.06% as shown in Table 3 and it indicates that the uniform dispersion of the drug in the solid dispersions.

3.2. Aqueous solubility studies

The aqueous solubility studies were conducted according to the procedure given in the experimental methodology. The maximum solubility was found to be 0.047±0.001mg/ml in the formulation SSD9. The aqueous solubility of solid dispersions was increased when compared to the solubility of the pure drug 0.024±0.002mg/ml (Alizadeh et al., 2018). The aqueous solubility results are given in Table 3.

Table 3. Solid Dispersions drug content and aqueous solubility

S.No.	Formulation	% Drug Content	Aqueous Solubility (mg/ml)
1	SSD1	101.03±0.38	0.041±0.001
2	SSD2	99.88±0.38	0.032±0.003
3	SSD3	102.06±0.96	0.038±0.002
4	SSD4	100.65±0.38	0.043±0.002
5	SSD5	101.67±0.96	0.044±0.003

6	SSD6	99.11±0.38	0.046±0.001
7	SSD7	101.16±0.96	0.042±0.004
8	SSD8	99.88±1.67	0.044±0.001
9	SSD9	101.3±1.55	0.047±0.001

3.3. X-Ray Diffractometry

The pure Simvastatin XRD shown identical sharp peaks at 9.17, 20.37, 21.63 and 22.37°angles confirming its crystalline nature (Figure 1A). The XRD patterns of Simvastatin SD demonstrated the presence of some crystalline diffraction peak of Simvastatin (Figure 1B). However, the intensity of crystalline peaks of Simvastatin in the solid dispersions was significantly less than that of pure Simvastatin indicating lower crystallinity of Simvastatin in the solid dispersion.

Figure 1A. XRD of pure SIM

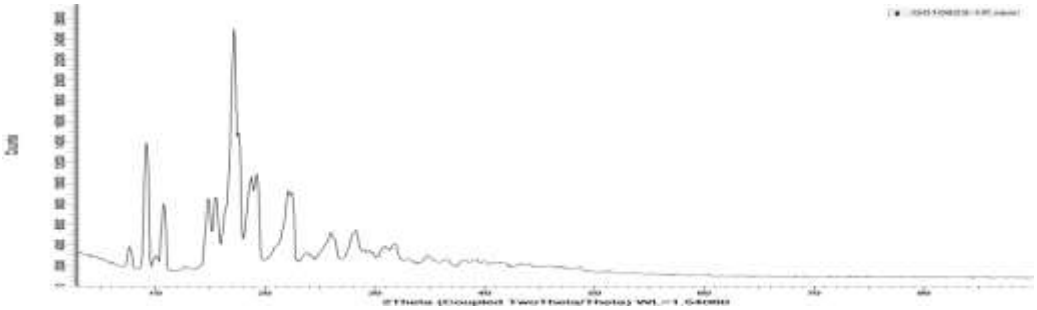

Figure 1B. XRD of Solid Dispersion (SSD9)

3.4. *Fourier Transform Infrared Spectroscopy (FTIR)*

The infrared (IR) spectrums obtained are shown in Figure 2. Pure Simvstatin drug OH stretching appears at 3548 and Aliphatic CH2/CH stretching presents at 2953 & 2870, carbonyl functional stretching peaks at 1695 and 1721, CH bending vibration at 967 & 1466 and CO stretching present at 1071 (Figure 2A). From the optimized solid dispersion (SSD9) IR spectrums, Simvastatin OH stretching present at 3460, CH2/CH peaks at 2955 & 2848 and SLS peaks at 2915. The carbonyl functional stretching peaks of drug at 1695, CO stretching present at 1080 and appearance of intense peak of SLS SO2 stretching at 1215 (Figure 2B).The results from FT-IR spectroscopy showed that all the characteristic bands of Simvastatin molecule remain

unaffected in solid dispersions and no change in the characteristic pattern of absorption bands. Thus FTIR study suggested absence of interactions between Simvastatin and carriers.

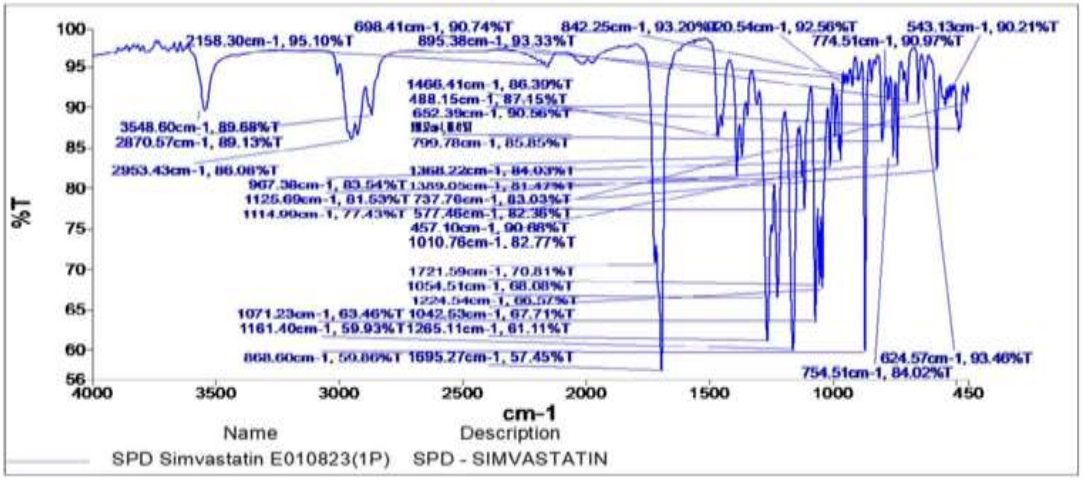

Figure 2A. FTIR spectrum of Pure SIM

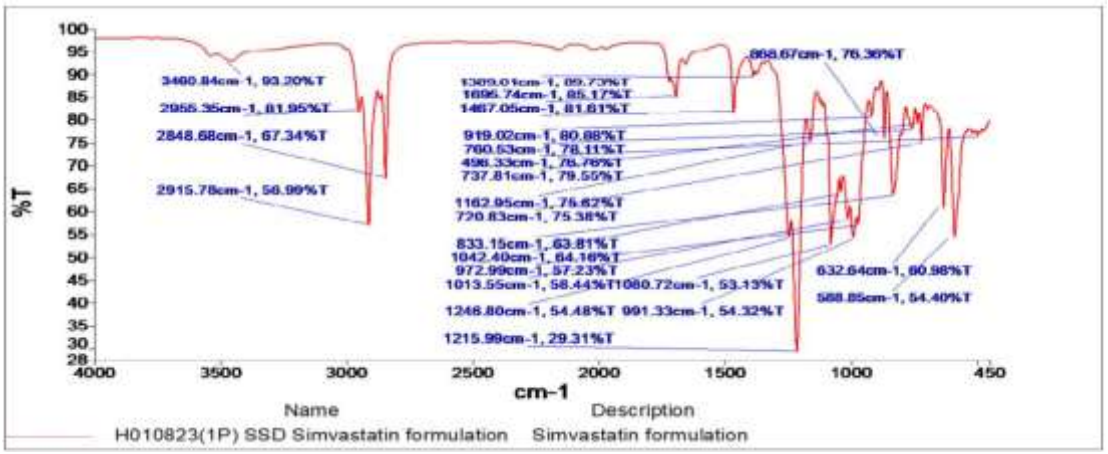

Figure 2B. FTIR Spectrum of Solid Dispersion (SSD9)

3.5. Differential Scanning Calorimetry (DSC)

DSC thermograms of pure Simvastatin shows a sharp melting endotherm at 143.81°C indicating crystalline nature of the drug (Figure 3A) and Simvastatin SD thermogram showed melting peak at 143.33 °C (Figure 3B) it is evident that there was no interaction in between Simvastatin, carriers and co-carriers. The intensity of crystalline peaks was less than that of pure drug, suggesting that lower crystallinity of Simvastatin and conversion from crystalline to amorphous form in solid dispersion.

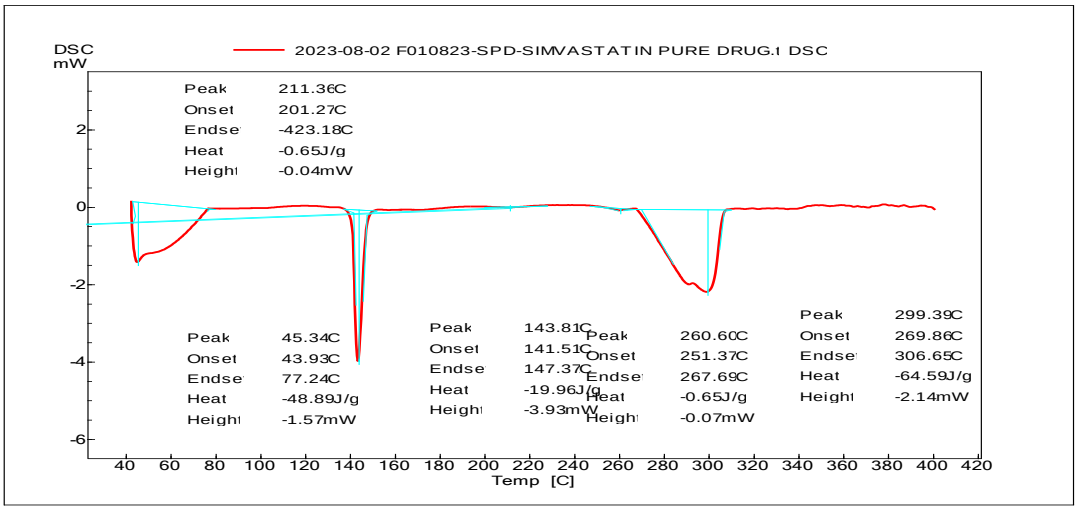

Figure 3A. DSC Thermogram of pure SIM

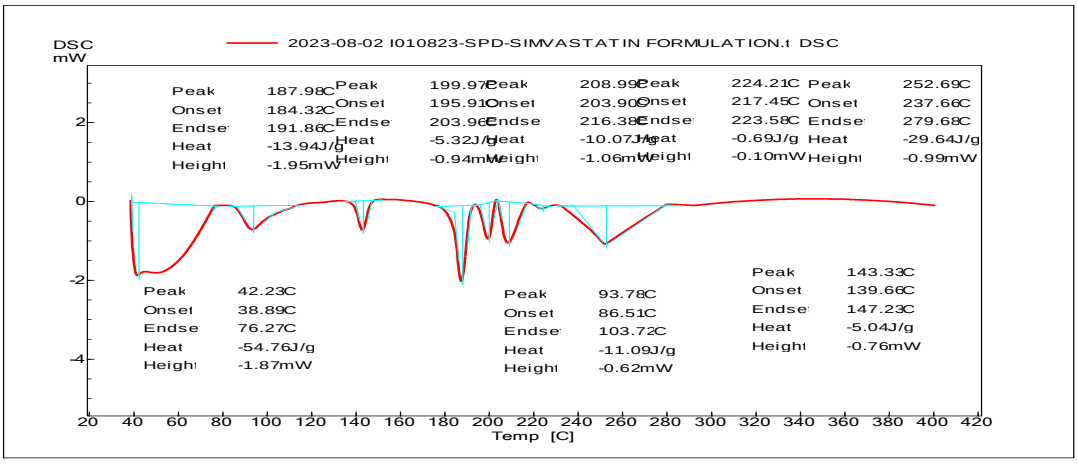

Figure 3B. DSC Thermogram of Solid Dispersion (SSD9)

3.6. In vitro dissolution study of Binary Solid Dispersions

Figure 4 describes the effect of carrier on the dissolution rate of Simvastatin from solid dispersions prepared with 1:1 ratios (SSD1, SSD2, SSD3 and SSD4) and with 1:3 ratios (SSD5, SSD6). The SLS solid dispersion (SSD1) dissolution rate was higher than that of other binary solid dispersions prepared with SSG (SSD2), CP (SSD3), CCS (SSD4), indicating that the SLS solid dispersion system improved the dissolution rate of Simvastatin(Lee et al., 2001) and further developed the binary solid dispersions (SSD5, SSD6) with increased SLS proportions. From the dissolution study, it is observed that percent drug release was increased with increment in amount of SLS from 1:1 to 1:3 (Dave et al., 2012; Dave et al., 2013). SLS can lead to increased solubility and dissolution of Simvastatin in solid dispersions, this might be due to SLS might interact with Simvastatin at the molecular level, altering its crystal structure or forming drug-surfactant complexes and as the ratio of SLS increases in the solid dispersion, more SLS molecules are available to interact

with the drug particles, leading to enhanced solubility through improved wetting, dissolution, and inhibition of crystallization (Mura et al., 2005).

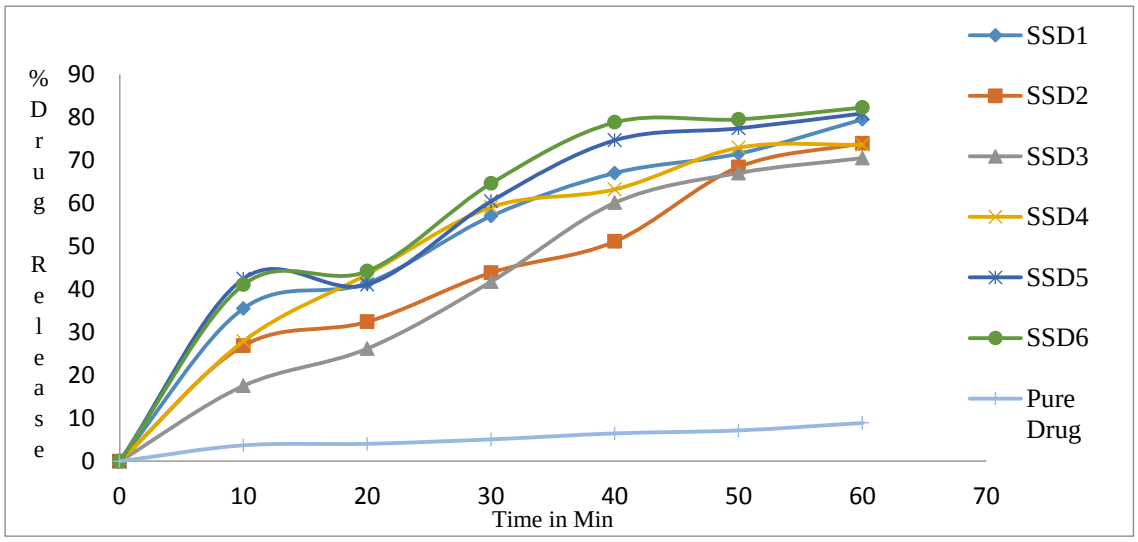

Figure 4. Dissolution of binary solid dispersions and pure SIM

The % drug dissolved of pure Simvastatin powder and SLS binary solid dispersions SSD6 (1:3) was about 8.89% and 82.2% within 60 min, respectively. It describes that the % drug dissolved is increased nine fold compared with that of pure drug powder.

3.7. In vitro dissolution study of Ternary solid dispersions

Dissolution study establishes that the meticulously selected SSD9 1:3:1 ratio of drug, SLS, and Crosscarmellose sodium (CCS) exhibits markedly superior dissolution behavior when compared to other ternary solid dispersions as shown in Figure 5. This effect might be due to 1.SLS can inhibit drug crystallization by preventing drug molecules from aggregating and recrystallizing, thereby maintaining the drug in an amorphous or more soluble state, 2.SLS can improve the wetting properties and dispersibility of SIM, 3.Reduction of interfacial tension between the drug particles and the dissolution medium (Cirri et al., 2007; Jung et al., 2016), and also wetting effect of Croscarmellose sodium (Rao et al., 2010) which absorbs medium and swells and can create voids or channels within the carrier matrix as it swells (Bhowmik et al., 2009) this disruption of the structure of the drug matrix and the SLS carrier can lead to increased exposure of Simvastatin to the dissolution medium, this increased contact area facilitates the transfer of Simvastatin molecules from the solid dispersion to the dissolution medium, thus enhancing its solubility and dissolution rate.

Figure 6, shows the physical mixtures dissolution study, SPM9 (1:3:1) & SPM6 (1:3) ratios showed increased dissolution rate than other physical mixture and pure drug.

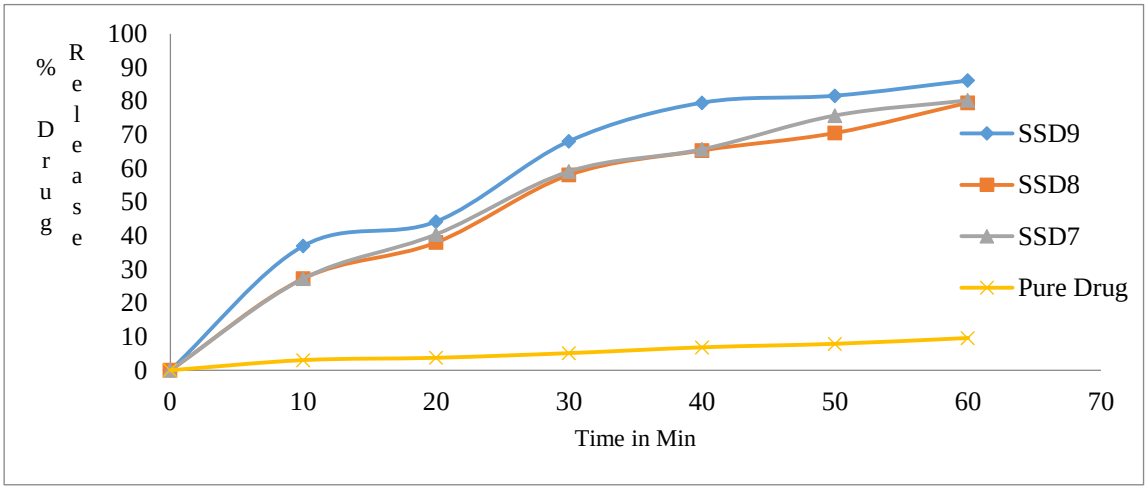

Figure 5. Dissolution of Ternary solid dispersions and pure SIM

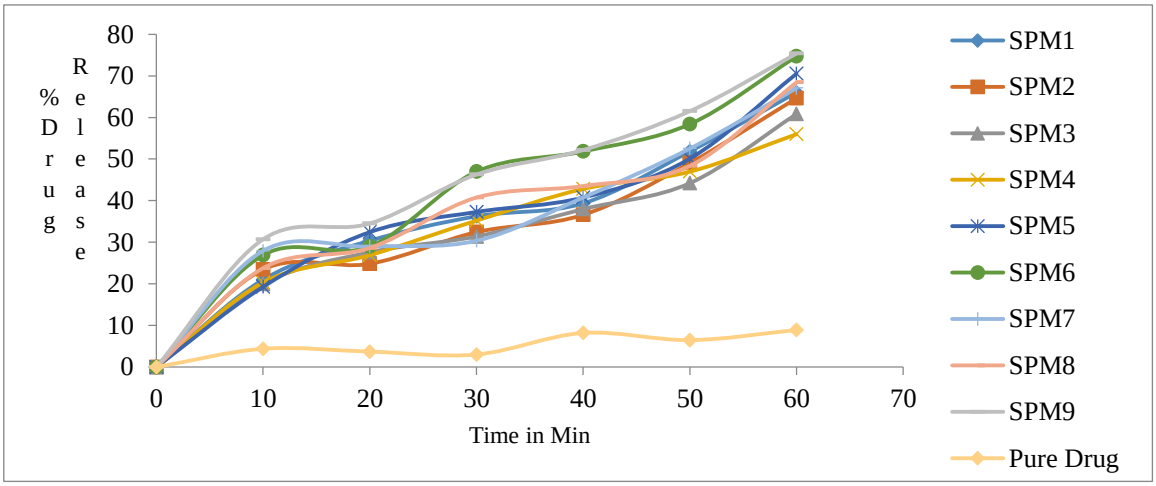

Figure 6. Physical mixtures and pure SIM dissolution study

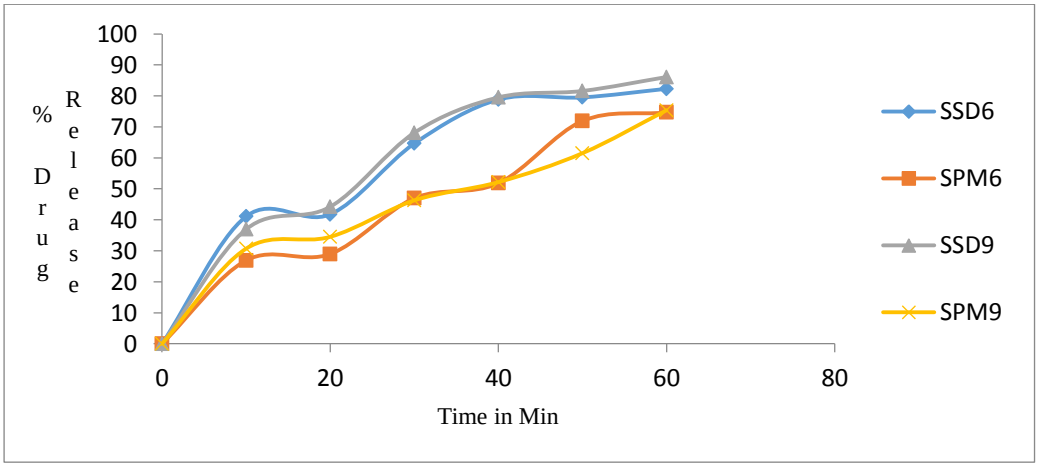

Figure 7. Comparison of dissolution of solid dispersions and physical mixtures.

Figure 7. describes that the solid dispersions showed marked improvement in the dissolution rate when compared to the physical mixtures. This effect might be in solid

dispersions, the Simvastatin was molecularly dispersed within a carrier, which can lead to improved solubility and dissolution rates whereas in a physical mixture, the drug and carriers are simply mixed together without any specific interaction.

3.8. Formulation and Evaluation of Immediate Release Tablets

Blend Evaluation: Well mixed blend of SSD9 with Mannitol, MCC other excipients was evaluated for Bulk Density, Tapped Density, and Angle of repose, Carr's index, and Hausner's ratio and results (Table 4) proved that the excellent flow characteristic of SSD9 blend powder for direct compression method.

Table 4. Pre-compression parameters of SSD9

Formulation code	Bulk density (g/cc)	Tapped density(g/cc)	Hausner's ratio	Carr's index (%)	Angle of repose (degree)
F1	0.832± 0.014	0.932±0.027	1.12±0.052	10.57±4.178	17±1.349
F2	0.842± 0.019	0.939±0.013	1.11±0.019	10.39±1.535	16.7±0.294
F3	0.842 ± 0.018	0.944±0.006	1.12±0.024	10.76±1.941	17.6 ± 0.339
F4	0.833 ± 0.008	0.948±0.010	1.13±0.021	12.07±1.694	17.0 ±0.309

* Table values are expressed as mean Standard Deviation ±n=3

Tablet Evaluation*:* Compressed tablets were checked for hardness, friability, weight variation test, disintegration time and verified results shown in Table 5. Friability of all formulation tablets were found between 0.2 to 0.28% which is well below the standard NMT 1 %. From the disintegration test, the prepared tablets were disintegrated immediately between 26 - 45 seconds.

Table 5. Post-compression parameters of SSD9 Tablets

Formulation code	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Disintegration time in Seconds	Drug content %
F1	3.13±0.078	0.26 ±0.01	245.2±0.748	45 ±1.8	100.8±0.22
F2	2.67±0.078	0.27±0.01	245±0.774	26±0.7	101.3±0.18
F3	2.81±0.07	0.25±0.03	245±0.894	27±1.1	99.9±0.24
F4	2.69±0.083	0.28±0.00	245.2±0.979	33±1.3	100.1±0.30

*Table values are expressed as mean Standard Deviation ±n=3

Tablet drug content: crushed ten tablets and weighed powder equivalent to 20mg of Simvastatin drug and dissolved in 100 ml of Methanol. The solution was filtered and drug content was determined by UV visible-spectroscopy at a wavelength of 238 nm. The obtained results showed in Table 5.

Table 6. % Drug Release of Tablet formulations

Formulation code	% Drug Release in 30 min	% Drug Release in 60min
F1	39.01	80.89
F2	46.97	84.01
F3	43.85	82.28
F4	44.02	80.55

Pure Drug	4.74	10.28

Tablet Dissolution Test: Drug release studies were conducted for four formulation tablets and results are shown in Table 6. From the developed four formulations, F2 showed higher 84.01% drug release at 60 minutes end of the dissolution test than other formulation tablets and pure drug (Figure 8) which might be due to the use of super-disintegrant (CCS) which absorb the medium and swells when exposed to dissolution medium and promote the rapid disintegration of tablets and also MCC and Mannitol prevent the aggregation of solid dispersion particles by coating on them and increase the absorption of dissolution medium and promote the faster disintegration (Zarmpi et al., 2017).

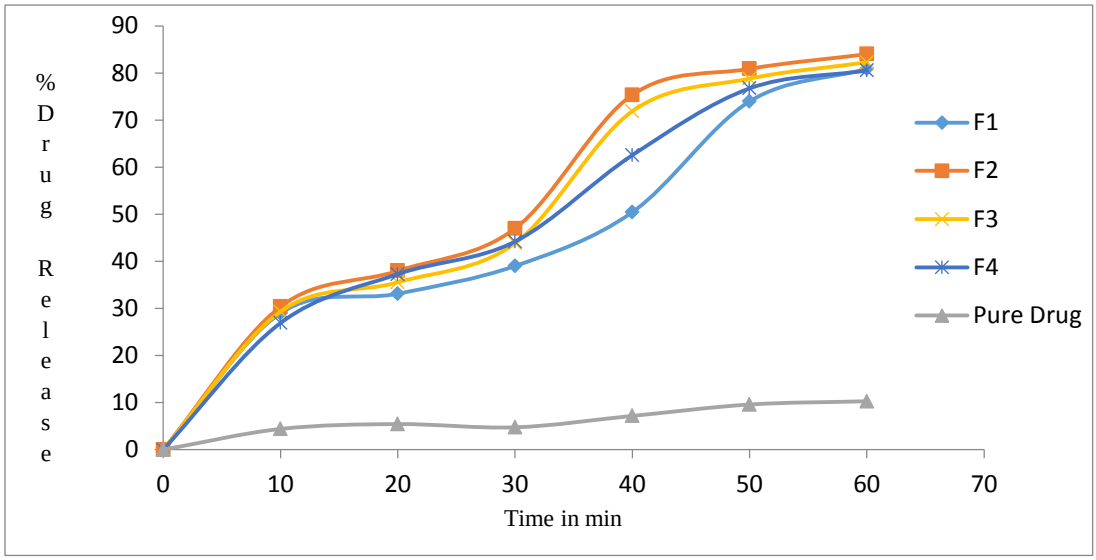

Figure 8. Dissolution profiles of Tablets (F1-F4) and Pure Simvastatin drug.

4. Conclusion

In present work, Solid dispersions (SD) of Simvastatin were prepared by solvent evaporation method with SLS and CCS combinations and evaluated. As per binary solid dispersions dissolution study, SSD6 showed higher dissolution rate compared to other binary solid dispersions and pure drug. Further developed ternary solid dispersions in combination with SLS and CCS. From ternary solid dispersions dissolution results, SSD9 showed fast and higher dissolution rate when compared to other ternary and binary solid dispersions and pure drug which may be due to SLS enhances wetting, dispersibility, and inhibition of drug crystallization and Croscarmellose sodium promotes rapid disintegration and dissolution of solid dispersion. SSD9 is selected as an optimized solid dispersion for the preparation of immediate release tablets (F1-F4) and out of the four prepared formulations, F2 showed better dissolution rate than others. The FTIR, XRD and DSC studies of Simvastatin revealed that the absence of drug and carrier interaction. Hence, it can be concluded that SLS solid dispersions in association with superdisintegrants showed marked improvement in the dissolution rate of Simvastatin using solvent evaporation method. Ternary solid dispersion

dissolution results indicates that the combination of both Sodium Lauryl Sulfate and Croscarmellose sodium effects can lead to a greater increase in simvastatin solubility compared to using either excipient alone or at lower ratios of SLS.

Reference

Alizadeh, M. N., Shayanfar, A., & Jouyban, A. (2018). Solubilization of drugs using sodium lauryl sulfate: Experimental data and modeling. *Journal of molecular liquids*, *268*, 410-414.

Bhowmik, D., Chiranjib, B., Krishnakanth, P., & Chandira, R. M. (2009). Fast dissolving tablet: an overview. *Journal of chemical and pharmaceutical research*, *1*(1), 163-177.

Cirri, M., Maestrelli, F., Corti, G., Mura, P., & Valleri, M. (2007). Fast-dissolving tablets of glyburide based on ternary solid dispersions with PEG 6000 and surfactants. *Drug delivery*, *14*(4), 247-255.

Dave, R. H., Patel, A. D., Donahue, E., & Patel, H. H. (2012). To evaluate the effect of addition of an anionic surfactant on solid dispersion using model drug indomethacin. *Drug development and industrial pharmacy*, *38*(8), 930-939.

Dave, R. H., Patel, H. H., Donahue, E., & Patel, A. D. (2013). To evaluate the change in release from solid dispersion using sodium lauryl sulfate and model drug sulfathiazole. *Drug development and industrial pharmacy*, *39*(10), 1562-1572.

De Waard, H., Hinrichs, W., Visser, M., Bologna, C., & Frijlink, H. (2008). Unexpected differences in dissolution behavior of tablets prepared from solid dispersions with a surfactant physically mixed or incorporated. *International journal of pharmaceutics*, *349*(1-2), 66-73.

Hou, P., Ni, J., Cao, S., Lei, H., Cai, Z., Zhang, T., Yu, F., & Tan, Q. (2013). Preparation and evaluation of solid dispersions of a new antitumor compound based on early-stage preparation discovery concept. *AAPS PharmSciTech*, *14*, 629-638.

Jiang, T., Han, N., Zhao, B., Xie, Y., & Wang, S. (2012). Enhanced dissolution rate and oral bioavailability of simvastatin nanocrystal prepared by sonoprecipitation. *Drug development and industrial pharmacy*, *38*(10), 1230-1239.

Jung, H. J., Ahn, H. I., Park, J. Y., Ho, M. J., Lee, D. R., Cho, H. R., Park, J. S., Choi, Y. S., & Kang, M. J. (2016). Improved oral absorption of tacrolimus by a solid dispersion with hypromellose and sodium lauryl sulfate. *International journal of biological macromolecules*, *83*, 282-287.

Lee, E.-J., Lee, S.-W., Choi, H.-G., & Kim, C.-K. (2001). Bioavailability of cyclosporin A dispersed in sodium lauryl sulfate–dextrin based solid microspheres. *International journal of pharmaceutics*, *218*(1-2), 125-131.

Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *European journal of Pharmaceutics and Biopharmaceutics*, *50*(1), 47-60.

Margulis-Goshen, K., & Magdassi, S. (2009). Formation of simvastatin nanoparticles from microemulsion. *Nanomedicine: Nanotechnology, Biology and Medicine*, *5*(3), 274-281.

Mura, P., Manderioli, A., Bramanti, G., & Ceccarelli, L. (1996). Properties of solid dispersions of naproxen in various polyethylene glycols. *Drug development and industrial pharmacy*, *22*(9-10), 909-916.

Mura, P., Moyano, J., González-Rodríguez, M., Rabasco-Alvarez, A., Cirri, M., & Maestrelli, F. (2005). Characterization and dissolution properties of ketoprofen in binary and ternary solid dispersions with polyethylene glycol and surfactants. *Drug development and industrial pharmacy*, *31*(4-5), 425-434.

Pandya, P., Gattani, S., Jain, P., Khirwal, L., & Surana, S. (2008). Co-solvent evaporation method for enhancement of solubility and dissolution rate of poorly aqueous soluble drug simvastatin: in vitro–in vivo evaluation. *AAPS PharmSciTech*, *9*(4), 1247-1252.

Rao, M., Mandage, Y., Thanki, K., & Bhise, S. (2010). Dissolution improvement of simvastatin by surface solid dispersion technology. *Dissolution Technol*, *17*(2), 27-34.

Silva, T. D., Arantes, V. T., Resende, J. A., Speziali, N. L., de Oliveira, R. B., & Vianna-Soares, C. D. (2010). Preparation and characterization of solid dispersion of simvastatin. *Drug development and industrial pharmacy*, *36*(11), 1348-1355.

Sjökvist, E., Nyström, C., & Aldén, M. (1991). Physicochemical aspects of drug release. XIII. The effect of sodium dodecyl sulphate additions on the structure and dissolution of a drug in solid dispersions. *International journal of pharmaceutics*, *69*(1), 53-62.

Tachibana, T., & Nakamura, A. (1965). A methode for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: dispersion of β-carotene by polyvinylpyrrolidone. *Kolloid-Zeitschrift und Zeitschrift für Polymere*, *203*, 130-133.

Vippagunta, S. R., Maul, K. A., Tallavajhala, S., & Grant, D. J. (2002). Solid-state characterization of nifedipine solid dispersions. *International journal of pharmaceutics*, *236*(1-2), 111-123.

21. Zarmpi, P., Flanagan, T., Meehan, E., Mann, J., & Fotaki, N. (2017). Biopharmaceutical aspects and implications of excipient variability in drug product performance. *European journal of Pharmaceutics and Biopharmaceutics*, *111*, 1-15.