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# IMPROVEMENT OF SORAFENIB SOLUBILITY AND BIOAVAILABILITY USING DIFFERENT SOLID DISPERSION TECHNIQUES

**T. NAGA APARNA[*1, 2] AND A. SAMBA SIVA RAO[3]**

**1:** Research scholar, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad-500085, Telangana

**2:** Assistant Professor, Sri Indu Institute of Pharmacy, Sheriguda, Ibrahimpatnam, Rangareddy District, 501510, Telangana

**3:** Professor, Sri Indu Institute of Pharmacy, Sheriguda, Ibrahimpatnam, Rangareddy District, 501510, Telangana

***Corresponding Author: T. Naga Aparna: E Mail: naga_aparna@yahoo.co.in**

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## ABSTRACT

In this study, solid dispersion (SD) techniques were used to enhance sorafenib (SFN) dissolution and bioavailability. Three different methods were used to prepare the sorafenib SD formulation. The formulations were evaluated for pre-formulation studies, solubility studies, percent practical yield, percent drug content, and in-vitro release. In addition to FTIR, XRD, SEM, and stability studies, the best formulation based on drug release was further characterized. For formulations prepared by surface solid dispersion (SSD1-SSD15), melt granulation (SD1-SD14), or liquid solid compact (LSC1-LSC14), greater than 90% solubility within one hour was reported with comparison to pure drug. Among different formulations of sorafenib, the LSC14 formulation had the best drug release of 99.94 percent, prepared by the liquisolid compact technique. FTIR analysis indicates no noteworthy interaction among the drug and excipients. The XRD and SEM images results indicated the conversion of sorafenib from crystalline to amorphous state on LSC formulation. Stability studies proved that formulation was stable for 3 months. The in vivo bioavailability studies conducted in rats indicate that $C_{max}$ of the sorafenib SD (25.76±1.22 ng/ml) was significant ($p<0.05$) as compared to pure suspension (7.25±1.75 ng/ml). The $T_{max}$ of LSC14 and pure drug was 1.0±0.05 and 1.5±0.2 h,

respectively. $AUC_{0-\infty}$ infinity for sorafenib LSC14 was higher (103.61±1.05 ng.h/ml) than the pure drug suspension 32.4±1.72 ng.h/ml indicating that the optimised formulation was significantly higher ($p<0.05$) as compared to drug suspension formulation.

**Keywords: Sorafenib, Tumour, Solid Dispersions, Solubility, Liquisolid Compact, bioavailabity studies**

## INTRODUCTION

Solid dispersions (SD) are defined as "the dispersion of one or more active pharmaceutical ingredients with a carrier in a solid state" and are an efficient way to improve the dissolution of poorly water-soluble drugs to enhance their bioavailability. Different approaches have been introduced for enhancing the solubility of poor water soluble drugs as it remains one of the most challenging aspects of formulation studies. Currently, only 10-12 percent of new drug candidates have both high solubility and high permeability. Approximately 60-65% of potent drug products are poorly soluble in water. The use of SD has gained considerable interest as a means of enhancing the dissolution rate and thus the bioavailability of various hydrophobic drugs. There are some aspects to consider when preparing solid dispersions, such as the choice of carrier and methods of characterization **[1-5]**.

Sorafenib (SFN), a new bi-aryl urea derivative, has been approved (US-FDA) for treatment of patients with advanced renal cell carcinoma, unresectable hepatocellular carcinoma, and differentiated thyroid carcinoma **[6]**. According to the BCS classification, it is very poorly soluble in aqueous media, at pH ranges from 1.2 to 7.4, which leads to a slow rate of dissolution in the gastrointestinal tract.

As a result, various SD formulation strategies were developed to improve a drug's physiochemical properties andto improve its solubility, dissolution, and bioavailability **[7]**.

## MATERIAL AND METHODS

Sorafenib sample was gifted by Hetero Drugs Ltd, Hyderabad. Pregelatinized starch, SSG, Avicel PH 10, Avicel PH 102 was purchased from Signet Chemical Corp. Pvt. Ltd, Mumbai. Cab-O-sil, Gelucire 50/13 were purchased from Gattefosse, Mumbai. Poloxamer 407 purchased from Hetero Drugs Ltd, Hyderabad. Sterate 6000 WL 1644, PEG 4000, Lactose, Fujicalin, Aerosil 200 purchased from SDFCL, Mumbai. Kollidon CL purchased from BASF, Mumbai.

### Solubility studies of sorafenib

In this study, we assessed sorafenib solubility in various vehicles, as well as sorafenib and carrier (1:1) solubility in

water using the shake-flask method. We added additional amounts of drug to 2 ml of vehicle in each vial and we added physical mixtures to conical flasks containing 10 ml of distilled water. The samples were placed in an orbital shaker at 37°C and 100 rpm for 24 hours to achieve equilibrium. Following centrifugation at 3000 rpm for 10 minutes, the excess drug settled, and the supernatant was collected and filtered through Whatman filter paper no 1. The concentration of sorafenib in filtered solution was determined using a UV-VIS spectrophotometer at 264 nm **[8]**.

**Preparation of sorafenib surface solid dispersion (SSD)**

Sorafenib surface SD were prepared using different hydrophilic carriers, including sodium starchglycolate (SSG), Kollidon CL, Avicel PH 102, pregelatinized starch, and Cab-o-sil. Using the ratios 1:0.5, 1:1, and 1:1.5, surface solid dispersions were prepared. The drug was dissolved in carbinol to form a clear solution followed by addition of carriers. Trituration was used to eliminate the solvent to obtain a dry mass. This mass was further dried at 500ºC for 4 h in an oven. The crude crushed, pulverized and sifted through a 60# sieve. The product was stored in desiccator containing $CaCl_2$ and evaluated **[9]**.

**Table 1: Formulation of sorafenib surface solid dispersions**

| Formulation code | Sorafenib | Ratio of drug: carrier | Pregelatinised starch | SSG | Avicel PH 102 | Cab-O-sil | Kollidon CL |
|---|---|---|---|---|---|---|---|
| SSD1 | 200 | 1:0.5 | 100 | - | - | - | - |
| SSD2 | 200 | 1:1 | 200 | - | - | - | - |
| SSD3 | 200 | 1:1.5' | 300 | - | - | - | - |
| SSD4 | 200 | 1:0.5 | - | 100 | - | - | - |
| SSD5 | 200 | 1:1 | - | 200 | - | - | - |
| SSD6 | 200 | 1:1.5 | - | 300 | - | - | - |
| SSD7 | 200 | 1:0.5 | - | - | 100 | - | - |
| SSD8 | 200 | 1:1 | - | - | 200 | - | - |
| SSD9 | 200 | 1:1.5 | - | - | 300 | - | - |
| SSD10 | 200 | 1:0.5 | - | - | - | 100 | - |
| SSD11 | 200 | 1:1 | - | - | - | 200 | - |
| SSD12 | 200 | 1:1.5 | - | - | - | 300 | - |
| SSD13 | 200 | 1:0.5 | - | - | - | - | 100 |
| SSD14 | 200 | 1:1 | - | - | - | - | 200 |
| SSD15 | 200 | 1:1.5' | - | - | - | - | 300 |

**Note: Methanol was added Qs**

**Evaluation of sorafenib surface solid dispersions**

Solubility studies of sorafenib SSD, % practical yield **[10]**, % Drug content **[11]** were performed accordingly as mentioned in referred procedures.

**In vitro drug dissolution of sorafenib SSD**

*In vitro* dissolution studies were conducted for sorafenib pure drug, marketed formulation (Nexavar) and sorafenib SSD formulations (SSD1-SSD14) was performed using USP dissolution

Apparatus II (Lab India DS 8000, Mumbai, India) using 900 mL of freshly prepared pH 7.4 phosphate buffer at 37 ± 0.5°C and the speed of the paddle was set at 50 rpm . 5 ml of samples were removed using a syringe at predetermined time intervals and immediately replaced with 5 ml of fresh medium maintained at 37°C. After appropriate dilution, samples were analyzed for sorafenib spectrophoto-metrically at 264nm using a UV method. Similarly, studies were also conducted on the dissolution of a pure drug as well as a marketed product. Three independent measurements were taken **[12]**.

**Preparation of sorafenib-loaded SD by melt granulation technique**

To the molten base comprising carrier, sorafenib (200 mg) in the quantities indicated in Table 2 was added. The blend was heated for five minutes at a temperature which is 10°C above the melting point of each carrier. After crushing, the material was ground gently witha mortar and pestle and sieved through a 500-meter mesh. As part of the process of preparing the SD, microcrystalline cellulose was added to the molten solution containing the drug. During continuous mixing for 10 minutes, the final SD obtained **[13]**.

**Table 2: Composition of sorafenib SD'S**

| Formulation code | Sorafe nib | Ratio of drug: carrier | Poloxamer 407 | Sterate 6000 WL 1644 | PEG 4000 | Gelucire 50/13 | Lact ose |
|---|---|---|---|---|---|---|---|
| SD1 | 200 | 1:0.5' | 100 | | | | |
| SD2 | 200 | 1:1 | 200 | | | | |
| SD3 | 200 | 1:1.5 | 300 | | | | |
| SD4 | 200 | 1:0.5' | | 100 | | | |
| SD5 | 200 | 1:1 | | 200 | | | |
| SD6 | 200 | 1:1.5 | | 300 | | | |
| SD7 | 200 | 1:0.5' | | | 100 | | |
| SD8 | 200 | 1:1 | | | 200 | | |
| SD9 | 200 | 1:1.5 | | | 300 | | |
| SD10 | 200 | 1:0.5' | | | | 100 | |
| SD11 | 200 | 1:1 | | | | 200 | |
| SD12 | 200 | 1:1.5 | | | | 300 | |
| SD13 | 200 | 1:1.5 | | | | 300 | 50 |
| SD14 | 200 | 1:1.5 | | | | 300 | 100 |

**Evaluation of sorafenib solid dispersions prepared by melts granulation technique**

The percentage practical yield, % Drug content, in vitro drug dissolution of sorafenib SD were performed in similar manner as mentioned under SSD technique.

**Pre-compression parameters**

The lubricated blend was evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's Ratio as per the referred procedures **[14]**.

**Preparation of Sorafenib Liquid SolidCompacts**

About 200mg of drug was dispersed in200mg of different non-volatileliquids.

The calculated amount of carrier and coating material was added to the dispersion and blended in a porcelain mortar avoiding excessive trituration and particle size reduced. About 40 mg of croscarmellose sodium was added as disintegrants and mixed along with 1% talc **[15]**. The mixture was compressed into tablets manually with the help of multistation rotary punching (RimekMinipress I, Karnavati Engineering Pvt. Ltd., Gujarat, India) **(Table 3)**.

**Evaluation of sorafenib liquisolid compacts [15]**

Average weight, hardness, thickness, friability was recorded as per the referred procedure.

Solubility studies of sorafenib solid dispersions, percentage practical yield, % drug content, in vitro drug dissolution of sorafenib SD.

**In vivo bioavailability**

**Animal preparation [16]**

Eighteen healthy Wistar rats (weighing 150-180 g) were used in this study, and they were all healthy for the duration of the experiment. Whenever possible, the animals have been kept in controlled environments (250 degrees Celsius, 45% relative humidity, 12 hours of alternate light and dark cycles, 100 percent fresh air exchange in animal rooms, uninterrupted power and water supply). Standard diets were provided to the rats, along with water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee.

**Study Design: [17]**

Using randomization, rats were divided into 3 groups of six each. 24 hours earlier, the rats were fasted. Food was reintroduced 4 hours after dosing. First, pure Sorafenib was made suspension in 0.5% methocel; while the second group received a Sorafenib optimized solid dispersion that had been diluted in 0.5% methocel. Control group was the third group. To prevent clotting, 500 mL of blood were collected at intervals of 0, 0.50, 1, 1.50, 2, 2.50, 3, 4, 5, 6, 8, 12, 16, 20, 24 hours after the dose and put into Eppendorf tubes filled with heparin. Plasma was separated from the blood by centrifugation at 5000 rpm in a cooling centrifuge for 5 to 10 minutes, and then stored frozen at −20°C until analysis.

**Table 3: Formulation table of sorafenib liquisolid compacts (LSC'S)**

| Solvents | Formulation code | Sorafenib (mg) | Lf | Avicel PH102 (W) | Fujicalin (W) | Aerosil 200 (Q) | Weight of tablet± |
|---|---|---|---|---|---|---|---|
| PG | LSC1 | 200 | 0.5 | 800 | | 40 | 1155 |
| PEG 200 | LSC2 | 200 | 0.556 | 720 | | 36 | 1062 |
| PEG 400 | LSC3 | 200 | 0.533 | 750 | | 37.5 | 1097 |
| PEG 600 | LSC4 | 200 | 0.588 | 680 | | 34 | 1015 |
| Tween 20 | LSC5 | 200 | 0.593 | 675 | | 34.75 | 1033 |
| Tween 80 | LSC6 | 200 | 0.727 | 550 | | 27.5 | 864 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Transcutol HP | LSC7 | 200 | 0.889 | 450 | | 22.5 | 747 |
| PG | LSC8 | 200 | 0.533 | | 750 | 37.5 | 1097 |
| PEG 200 | LSC9 | 200 | 0.606 | | 660 | 33 | 992 |
| PEG 400 | LSC10 | 200 | 0.567 | | 705 | 35.25 | 1044 |
| PEG 600 | LSC11 | 200 | 0.645 | | 620 | 31 | 945 |
| Tween 20 | LSC12 | 200 | 0.625 | | 640 | 32 | 969 |
| Tween 80 | LSC13 | 200 | 0.870 | | 460 | 23 | 759 |
| Transcutol HP | LSC14 | 200 | 1.212 | | 330 | 16.5 | 607 |

**±Final weight of tablet includes 10% disintegrant croscaramellose sodium and 1%lubricant talc added to it.**
**Lf =weight of liquid formulation/weight of carrier**
**Excipient ratio =W/Q**
**Note: weight of liquid formulation = drug + solvent (200+200)**

## RESULTS AND DISCUSSION

### Solubility studies of sorafenib

**Figures 1 and 2** shows the preliminary solubility analysis of the drug in various solvents and physical mixtures which showed that the pure drug solubility was 0.00021±0.12 mg/ml. We found sorafenib to be highly soluble in buffer acid solution 3.4 pH, at 1.32/0.25 mg/ml, as well as in physical mixtures of the drug and kollidon, at 1.83/0.56 mg/ml.

### Solubility studies of sorafenib SSD

Among the solubility studies of sorafenib solid dispersion formulations with kollidon CL (SSD13, SSD14 and SSD15), SSD15 showed the highest level of solubility at 3.57±0.15 mg/ml **(Figure 3)**.

### Percentage practical yield (PPY) determination and drug content of sorafenib SSD

The PPY for sorafenib SSDs ranged from 95.16±0.27% to 98.92±0.90%. The maximum yield was observed for formulation SSD15 at 98.92±0.90%. The drug content ranges from 95.18±0.32 to 99.23±0.87% for all sorafenib SSDs, with SSD15 having the highest drug content.

### In vitro dissolution studies

As compared to the pure drug (21.27±0.84%) and marketed formulation (95.21±1.09), all formulated SSDs of sorafenib show a significant increase in drug dissolution rate within one hour. In the presence of an increasing carrier concentration, dissolution rates increased, perhaps since polymers have a hydrophilic nature, and that drug particles are adsorbing on the surfaces of the polymer. As the carrier proportion increases, saturated solubility increases as well. This could be due to a greater surface area of contact between the drug and dissolution medium. Formulations containing kollidon CL exhibited greater dissolution than others. In one hour, the SD15 formulation containing high amounts of kollidon CL disintegrated at the highest rate of 98.78±0.47% **(Figure 4)**.

### Sorafenib Solid Dispersions Prepared by Melt Granulation Technique (Figure 5)

### Solubility studies of sorafenib SD

The solubility studies of sorafenib solid dispersion formulations with gelucire 50/13 (SD10 - SD 14) exhibited greater solubility

and SD14 showed highest among all formulations 4.06±0.78mg/ml this may be due to either the reduction in the crystallinity of drug or improved wetting of the drug particles and shown in **Figure 6**.

**Percentage practical yield (PPY) determination and drug content of sorafenib SD**

All formulations met the standard criteria for PPY and drug content. For sorafenib SD's, the PPY ranged from 94.29±0.36% to 98.92±0.24%. For formulation SD14, 98.92.0.24% yield was observed. As a result, the % drug content of all sorafenib SDs lies within 95.02.0.25 - 99.78±0.92%, with SD14 displaying the highest drug content.

**In-vitro dissolution results**

Adding melted granules to a formulation enhances the bioavailability and solubility. As compared to the pure drug (21.27±0.84%) and marketed formulation (95.21±1.09) in one hour, all formulated SDs of sorafenib dissolve at a significantly higher rate. As the polymer concentration increased it was observed that there was increase in the dissolution rate, meltable binder polymer used in the process induces the drug to agglomerate and it reduces recrystallization potential through separation thus improving the solubility and dissolution and among all, formulations containing Gelucire 50/13 as meltable binder exhibited greater dissolution, formulation SD12 containing high amount of gelucire50/13showed more dissolution rate of 98.48±0.36% in one hour. Lactose was used in order to prevent gelucire 50/13 from becoming sticky, and SD14 showed the highest dissolution rate of 98.95±2.41% with more lactose content indicating enhancement of dissolution by using lactose in the formulation **(Figure 7)**.

**Formulation and Evaluation of Sorafenib Liquisolid Compacts**

A liquisolid system with an acceptable flowability, LSC14 has a good flow property of 25.13±0.66. Further studies were undertaken using the formulation with Carr's index of 5.35±0.54 and Hausner's ratio of 1.03±0.10.

Physicochemical tests showed that the mixtures were within the limits

All formulations have within limits variations in weight, and appropriate tablet hardness is necessary for consumer acceptance.

The tablet hardness was measured in each batch for all formulations, i.e., LSC1-LSC14, and were ranged between 6.0 to 8.0Kg/cm$^2$.

The **thickness** of the tablets was found to be almost uniform in all formulations LSC1-LSC14

The thickness of LSC14 was leastand was found to be4.8mm and highest for

LSC1which was 6.78mm, and all the values were according to the tablet weight of the formulations.

The **friability** of all prepared formulation between 0.15-0.21.the friability properties limits are in between 0-1%.

**Percentage practical yield (PPY) determination and drug content of sorafenib liquisolid compact**

The PPY for all sorafenib SDs was between 95.21±0.53% - 99.21±0.46%. Maximum yield of 99.21±0.46% observed for formulation LSC14.

The median drug content of all sorafenib SDs is 95.32±0.64 to 99.65±0.48%, with LSC14 having the maximum drug content.

**In-vitro dissolution studies of sorafenib LSC**

When compared to the pure drug, all formulated LSCs of sorafenib (21.27±0.84%) disintegrate significantly faster. Two carriers (avicel PH102 and fujicalin) were used in the formulation of sorafenib LSC's, formulations containing same solvent but different carrier when compared it was observed that formulations containing fujicalin (LSC8-LSC14) exhibited greater dissolution rate when compared to avicel PH 102 (LSC1-LSC7). The formulation LSC14 containing fujicalin as carrier and transcutol HP as solvent exhibited the highest dissolution rate of 99.94±1.38% in one hour. The increased dissolution rate was found to be for the LSC14, this might be due to the highest solubility of sorafenib drug C., and may be due to the increased wettability of the drug molecules, which reveals the role of liquid vehicle in addition to carrier in liquisolid formulas, the carrier (fujicalin) effect and alsocarrier to coating materialratio (20:1) may be a reason as they adsorb the drug molecules and thus, they make the drug exposed to the dissolution media **(Figure 8)**.

**Characterization of Sorafenib Liquisolid Compacts**

**FTIR spectroscopy**

The characterization of pure drug sorafenib by FTIR studies was shown in **Figure 9**. The spectrum is responsible for the presence of chemical functional groups at different frequencies. The pure sorafenib spectrum showed the main characteristic bonds at 663.53 $cm^{-1}$ (alkene:=C-F Bending) 1033.88 $cm^{-1}$ (alcohol:C-O stretching), 1178.55$cm^{-1}$ (alkyl-halide:C-F stretching), 1284.63 $cm^{-1}$ (carbonyl acid :C-O stretching), 1460.16 $cm^{-1}$ (aromatic:C=C stretching), 1631.83 $cm^{-1}$ (carbonyl amide:C=O stretching), 1691.63 $cm^{-1}$ (alkene:C=C stretching), 1714.77 $cm^{-1}$ (cyclic-ketone:C=0 stretching), 3082.35 $cm^{-1}$ (C-H stretching), 3250.16 $cm^{-1}$ (Alcohol:O-H stretching), 3319.6 $cm^{-1}$ (N-H

stretching), 3375.54 $cm^{-1}$ (Amine:N-H stretching). The FTIR spectrum of optimised formulation of sorafenib solid dispersion LSC14 showed all the peaks for sorafenib suggesting no significant interaction observed between them **(Figure 10)**.

**XRD**

The diffraction pattern of pure sorafenib showed various characteristic 2θ peaks at 13.2°, 17.8°, and 21.5°, revealing a highly crystalline structure and there was reduction in the number of peaks when compared with physical mixture of drug+fujicalin **(Figure 11A And Figure 11B)**. However, these distinctive peaks of sorafenib were absent in the pattern of the sorafenib LSC14 **(Figure 12C)**, the results indicate the conversion of sorafenib from the crystalline state to the amorphous on LSC formulation.

**SEM studies**

**Figure 15A and 12B** show SEM images of sorafenib and its optimised formulation. Despite asmooth surface andirregular shape matrix, the formulation had fine particles with drug deposited on it due to the porous carrier. In SEM studies, the surface morphology of the LSC formulation was described as amorphous.

**Stability Studies**

During the 3-month period, the formulation was stable. Optimized formulation (LSC14) shows no variations in its drug content or in-vitro dissolution profile **(Table 4)**.

**In vivo bioavailability studies**

In comparison with sorafenib pure drug suspension post-single oral administration, plasma drug concentrations following administering the optimised solid dispersion formulation were generally higher than those following administering the pure drug suspension. (**Figure 13A, 13B )**

$C_{max}$ of the sorafenib optimised solid dispersion 25.76±1.22 ng/ml was significant ($p<0.05$) as compared to the pure drug suspension formulation 7.25±1.75 ng/ml. $T_{max}$ of both optimised solid dispersion formulation and pure drug was 1.0±0.05 and 1.5±0.2 h, respectively. The $AUC_{0-\infty}$ infinity for sorafenib optimised solid dispersion formulation was higher (103.61±1.05 ng.h/ml) than the pure drug suspension 32.4±1.72 ng.h/ml **(Table 5)**.

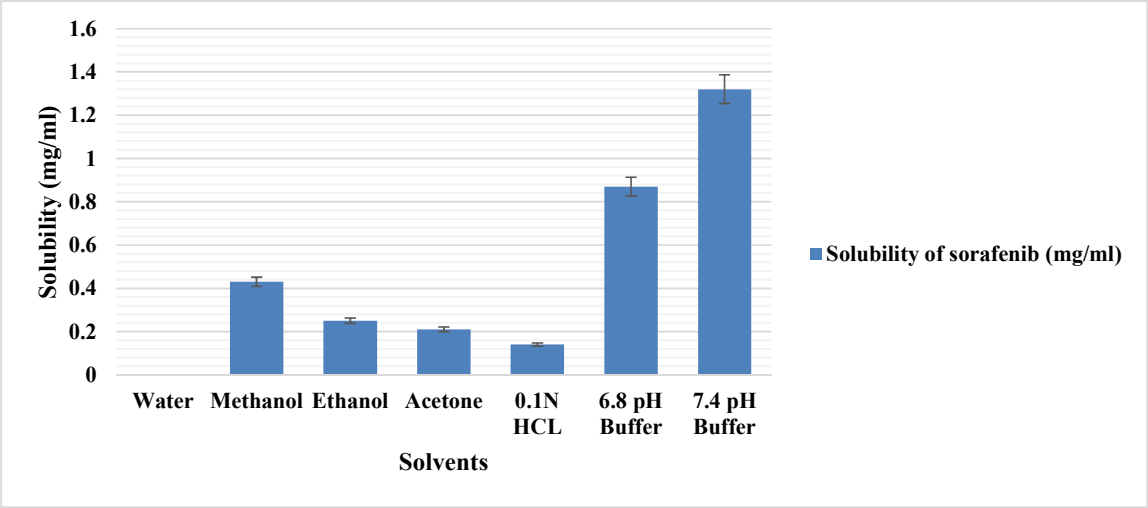



**Figure 1: Solubility studies of sorafenib pure drug in various solvents**
**Above parameters are communicated as Average ± Standard Deviation; (n=3)**

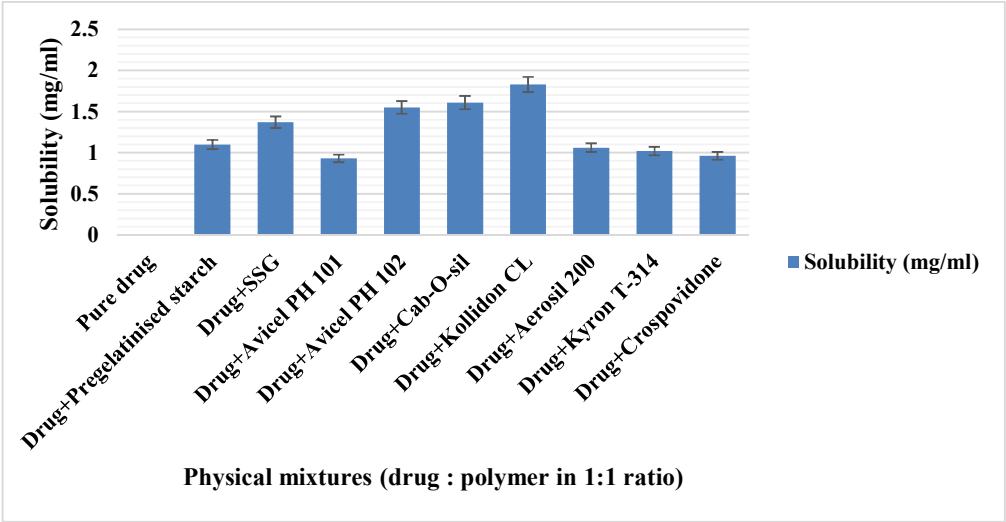



**Figure.2: Solubility studies of sorafenib physical mixture**

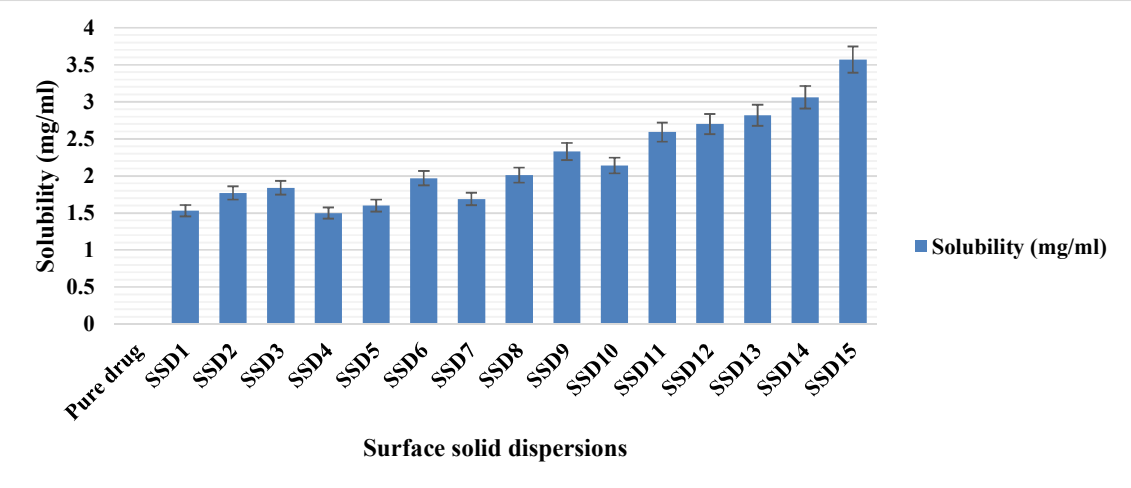



**Figure 3: Solubility studies of sorafenib pure drug and sorafenib solid dispersions (SSD1-SSD15)**

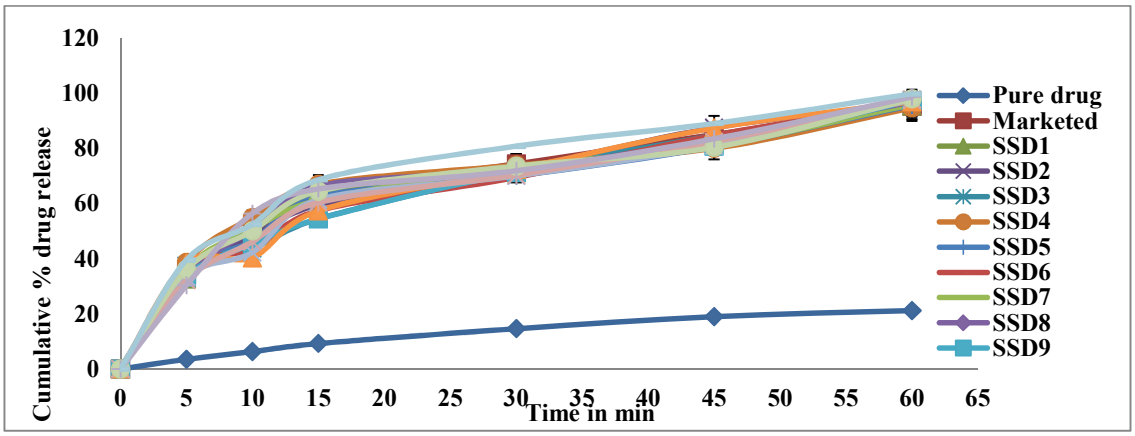



**Figure 4: In vitro drug dissolution of pure sorafenib and sorafenib surface solid dispersions SSD1-SSD15**

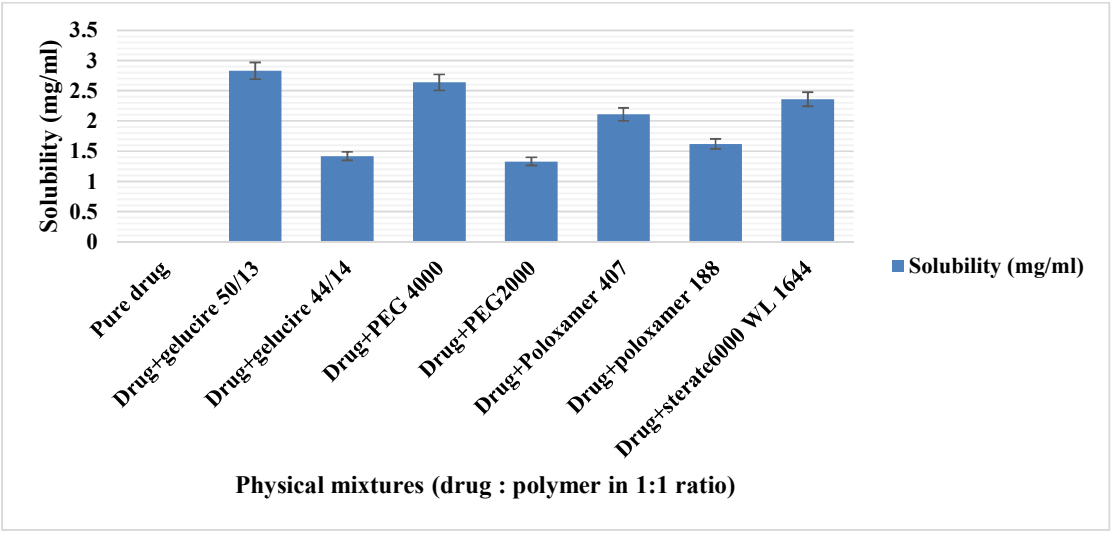



**Figure 5: Solubility studies of sorafenib physical mixture**

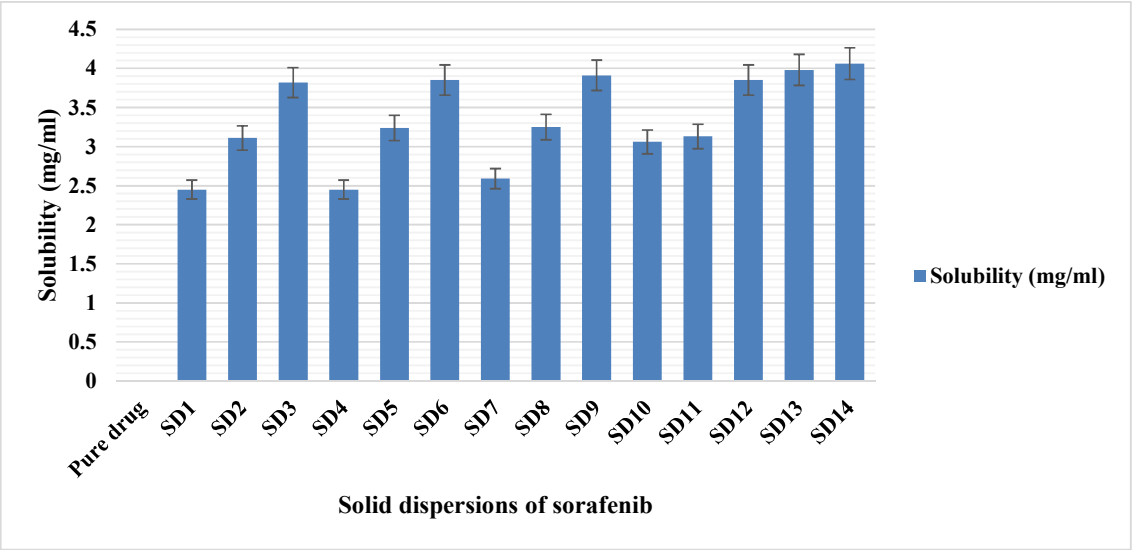



**Figure 6: Solubility studies of sorafenib pure drug and sorafenib solid dispersions (SD1-SD14)**

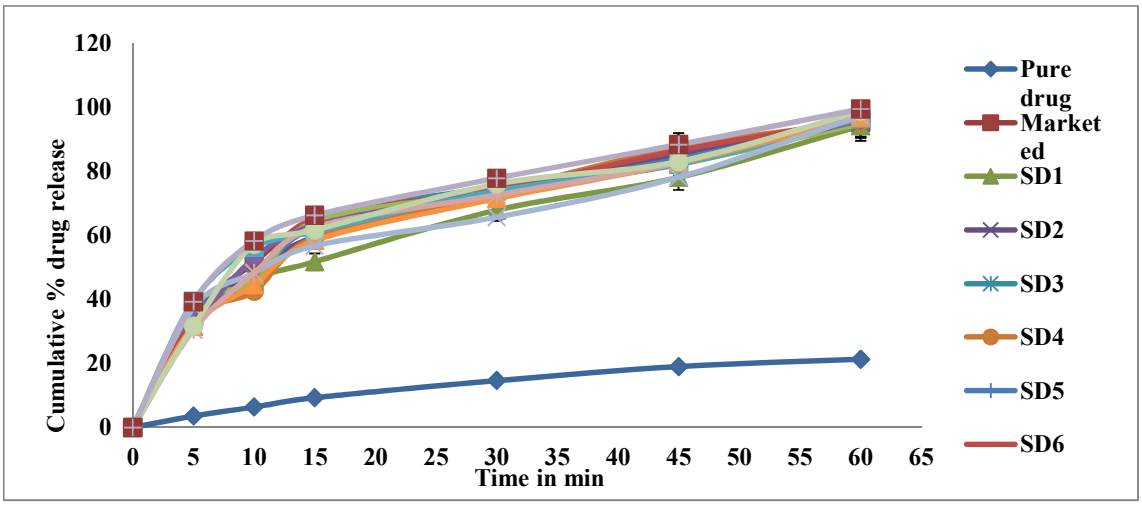



**Figure 7: In vitro drug dissolution of pure sorafenib, marketed formulation and sorafenib solid dispersions SD1-SD14**

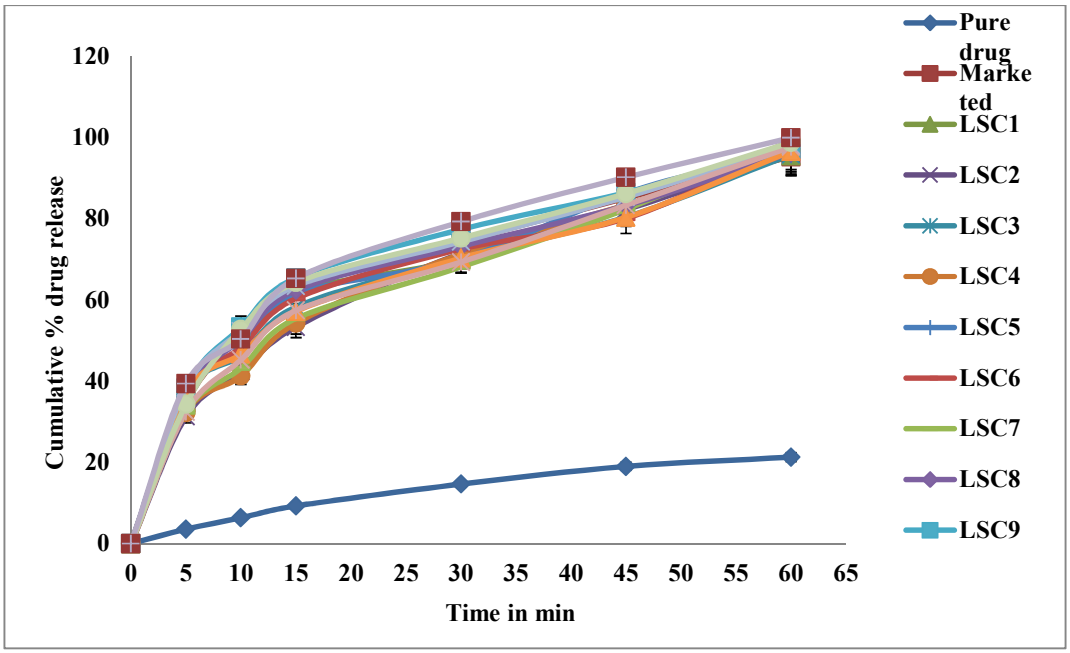



**Figure 8: Comparative dissolution profiles of sorafenib pure drug and sorafenib LSC formulations LSC1-LSC14**

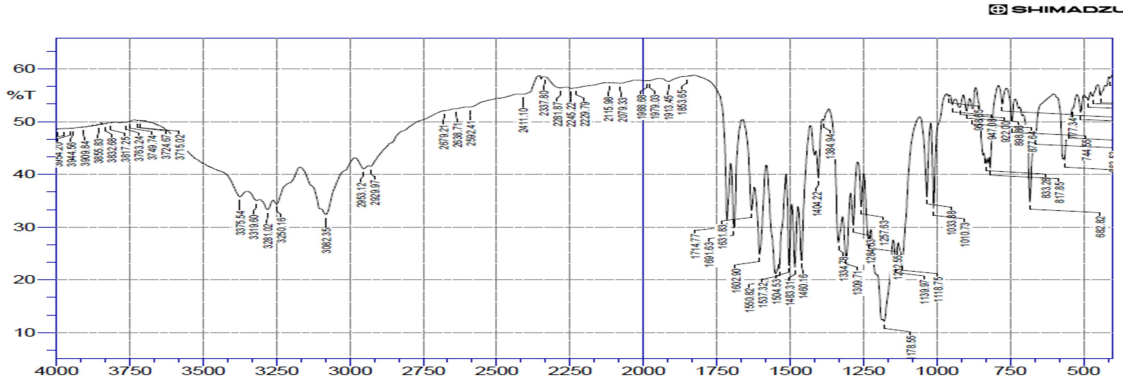



**Figure 9: FTIR Spectroscopy of Sorafenib pure drug**

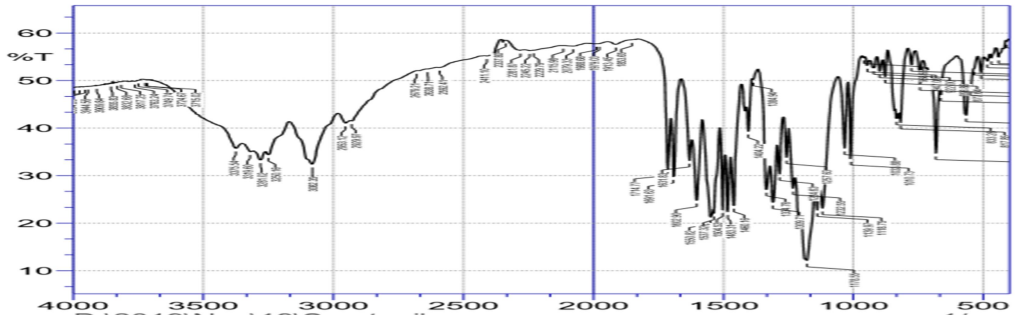



**Figure 10: FTIR spectrum of optimised formulation of sorafenib LSC14**

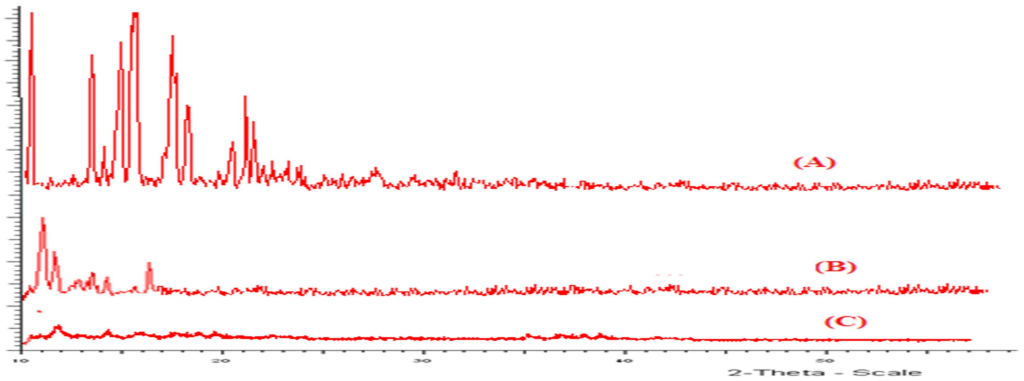
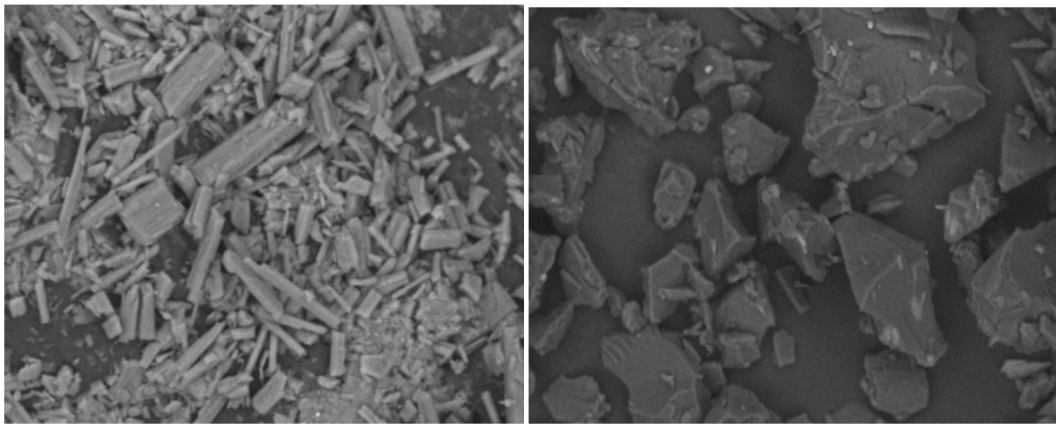



**Figure 11: XRD of (A) Pure drug (B) Physical mixture of drug+fujicalin (C) Optimised formulation of sorafenib LSC14**



**(A) Pure drug (B) Optimized formulation of sorafenib LSC14**

**Figure 12A and 12B: SEM imagesof pure drug and LSC14**

**Table 4: Stability studies of LSC14**

| Retest Time for Optimized formulation LSC14 | Drug content (%) | *In-vitro* drug release profile (%) |
|---|---|---|
| 0 days | 99.65±0.48 | 99.94±1.38 |
| 30 days | 99.24±0.64 | 99.62±1.74 |
| 60 days | 98.77±1.26 | 98.96±1.28 |
| 90 days | 97.63±0.74 | 98.75±0.58 |

**Above parameters are communicated as Average ± Standard Deviation; (n=3)**

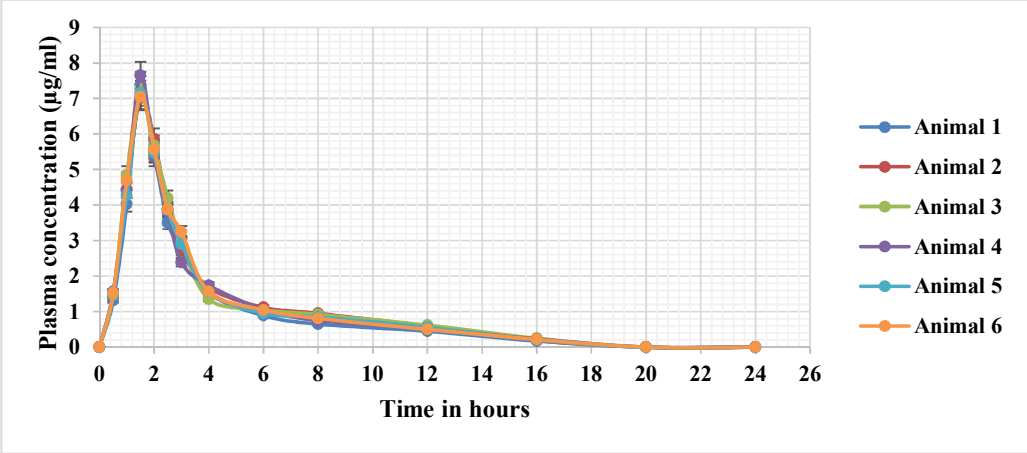



**Figure 13A: Plasma concentration-time profile of sorafenib pure drug in rat plasma**

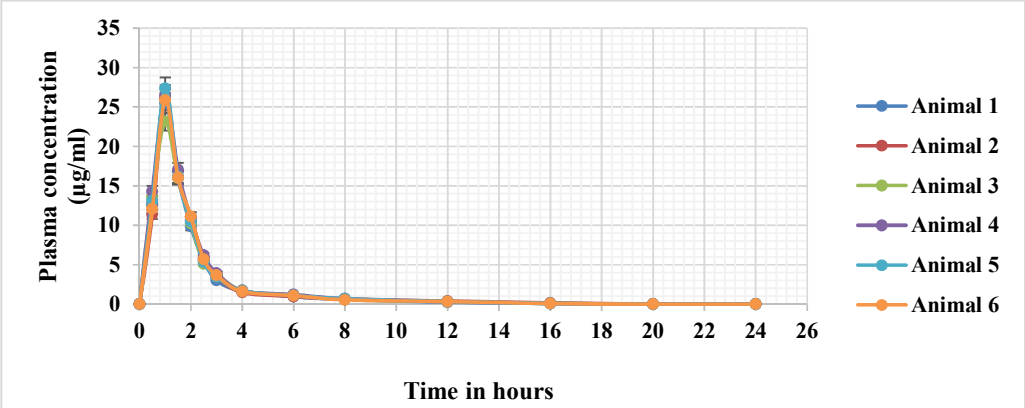



**Figure 13B: Plasma concentration-time profile of sorafenib optimized optimised solid dispersion in rat plasma**

## CONCLUSION

By using three different formulation strategies, the SD approach has been widely applied to enhance solubility and, consequently, dissolve sorafenib. As a result of surface solid dispersion, melt granulation, and liquisolid compact techniques, sorafenib solid dispersions showed improved solubility. Despite minor differences in the release profiles of the three formulations, the sequence for each formulation was as follows: LSC14 > SSD15 > SD14>. Therefore, LSC14 was the best optimised formulation with highest drug release, 99%, and was characterized by FTIR, XRD, SEM, and stability studies, which showed no significant interactions and amorphous nature of the formulation with stability for 3 months. The invivo studies conducted in rats indicated higher amount of drug concentration in blood from the SD formulations indicated better systemic absorption of Palbociclib from LSC14 formulation as compared to the drug suspension formulation. As a result, it can be stated that the study achieved its objective by improving the solubility of sorafenib by using the liquid-solids method, which proved promising for improving the

dissolution of sorafenib, which is poorly soluble.

**Table 5: Pharmacokinetic Parameters of sorafenib optimised solid dispersion formulation and pure drug**

| Pharmacokinetic parameters | Sorafenib pure drug | Sorafenib optimized solid dispersion |
|---|---|---|
| $C_{max}$ (µg/ml) | 7.25±1.75 | 25.76±1.22 |
| $AUC_{0-t}$ (µg.h/ml) | 28.6±1.24 | 92.23±1.18 |
| $AUC_{0-inf}$ (µg.h/ml) | 32.4±1.72 | 103.61±1.05 |
| $T_{max}$(h) | 1.5±0.2 | 1.0±0.05 |
| $t_{1/2}$ (h) | 8.1±0.42 | 6.02±0.04 |

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