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Research Article

# Improvement of Sorafenib Solubility By Different Solid Dispersion Techniques

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ABSTRACT

The present work aimed to enhance the solubility and dissolution of the poorly water-soluble drug, sorafenib (SFN), by solid dispersion (SD) techniques. Solid dispersions of sorafenib were prepared by three different techniques, namely surface solid dispersions (SSD1-SSD15), melt granulation (MG1-MG15), liquisolid compacts (LSC1-LSC 9). All the formulations were evaluated for pre-formulation studies, solubility studies, percentage practical yield, % drug content, and in-vitro drug release. The best formulation based on drug release was further characterized for FTIR, XRD, SEM and stability studies. The formulations prepared by surface solid dispersions (SSD1-SSD15), melt granulation (MG1-MG15), liquisolid compacts (LSC1-LSC9) exhibited enhanced drug release compared to pure drug. Among all the formulations, sorafenib prepared by Melt Granulation technique (MG 3) showed highest drug release of 99.89%. The order of preference for solid dispersions prepared by different techniques was MG 3 > LSC 1 > SSD 3. The formulation MG 3 was further characterized for FTIR, where no significant changes were observed, suggesting no interactions between drug and excipients. X-ray diffraction studies revealed the conversion of sorafenib from the crystalline state to the amorphous, which was further supported by scanning electron microscopy. Stability studies proved the formulation was stable for 3 months. These findings suggest that the preparation of sorafenib solid dispersions using Melt Granulation technique could be a promising strategy for improvement of solubility and dissolution. Low cost, simple processing and great potentials in industrial production are the main advantages of this approach. In addition to enhancing the dissolution rate of poorly water-soluble drugs, this technique is also a fairly new technique to effectively retard drug release.

## Introduction

Newly discovered chemical molecules have high therapeutic activity but low aqueous solubility, resulting in poor absorption and bioavailability. Many methods were reported for solubility and dissolution enhancement of poorly soluble drug such as micronization, complexation, particle size reduction, etc. However, all these methods have limitations like micronized powder having high energetic surface, which shows poor flow properties and particles often agglomerated. Complexation with cyclodextrin shows low drug load and limitations for drug selection.[1] Salt formation, solubilization and particle size reduction have commonly been used to increase the dissolution rate of the drug, but the desired bioavailability enhancement may not always be achieved. Therefore, several approaches are being explored to enhance the bioavailability of poorly water-soluble drugs. Solid dispersion technique is used in the pharmaceutical field to enhance the solubility and dissolution rate of poorly aqueous soluble drugs. It has been used widely to improve the oral absorption and bioavailability of BCS class II drugs. Solid dispersion is defined as 'a dispersion of drug molecules in an inert carrier or matrix in the solid state. The low oral bioavailability of drug may be due to poor

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aqueous solubility, high first pass metabolism and efflux transport.[2]

One such formulation approach that has significantly enhanced the absorption of such drugs is the melt granulation technique. The advantage of melt granulation technique is that neither solvent nor water is used in this process, fewer processing steps are needed means time-consuming drying steps are eliminated, no requirements for the compressibility of active ingredients. Further advantages are its simple, continuous, efficient, uniform dispersion of fine particles, and good stability at varying pH and moisture levels.[3]

There is widespread interest in melt granulation technique because that offers a means of facilitating the dissolution and the bioavailability of poorly water-soluble drugs when combined with hydrophilic melting binder. This increase in dissolution rate is achieved by a combination of effects. The most significant is the reduction of particle size to the extent that cannot be readily achieved by convention comminuting approaches.[4-6]

Melt granulation process currently applied in pharmaceutical research for manufacturing a variety of dosage forms and formulation such as immediate release and sustained release pellets, granules and tablets.[7-9]

Sorafenib (SFN), a novel bi-aryl urea derivative, strongly inhibits Raf-1, a RAF/MEK/ERK signalling pathway member. SFN targets several serine/threonine kinases and receptor tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, platelets-derived growth factor receptor (PDGFR)-β, Flt-3, and c-KIT, which are related to tumor cell proliferation and angiogenesis.[3] It has been approved by the US Food and Drug Administration (US-FDA) for treating patients with advanced renal cell carcinoma, unresectable hepatocellular carcinoma, and differentiated thyroid carcinoma.[4] According to the Biopharmaceutical classification system (BCS), SFN belongs to BCS class II, characterized by low solubility and high permeability. SFN has very poor solubility in aqueous media at various pH values from pH 1.2 to 7.4. This leads to slow dissolution rate in the gastrointestinal tract, which is supposed to be the rate-limiting step for absorption and, together with the first pass metabolism results in low bioavailability and large inter-subject variability. Therefore, solid dispersion formulation strategies have been developed to enhance the physiochemical properties and improve the solubility and dissolution of the drug.[10]

Low cost, simple processing and great potentials in industrial production are main advantages of this approach. In addition to enhancing the dissolution rate of poorly water-soluble drugs, this technique is also a fairly new technique to effectively retard drug release.

## Materials

Sorafenib Tosylate sample was gifted by Hetero Drugs Ltd, Hyderabad. Pregelatinized starch, SSG, Avicel PH 102 was purchased from Signet Chemical Corp. Pvt. Ltd, Mumbai. Cab-O-sil M5, Gelucire 50/13 were purchased from Gattefosse, Mumbai. Poloxamer 407 purchased from Hetero Drugs Ltd, Hyderabad. PEG 4000, Lactose, Fujicalin, Aerosil 200 purchased from SDFCL, Mumbai. Kollidon CL purchased from BASF, Mumbai

## Methods

### Preparation of Surface Solid Dispersions (SSD) of Sorafenib

#### *Solubility Studies of Sorafenib*

Solubility studies of sorafenib in various vehicles and solubility of sorafenib physical mixtures (sorafenib and carrier in 1:1 ratios) in water was determined by the shake-flask method. Excess drug quantity was added to 2 mL vehicle *each in vial,* and physical mixtures were added in conical flasks containing 10 mL of distilled water. The samples were placed in an orbital shaker at 37°C and 100 rpm until equilibrium was achieved (24 hours). Later these vials were centrifuged at 3000 rpm for 10 min, the excess drug gets settled, and the supernatant was collected and filtered through a Whatman filter paper no 1. Filtered solution was analyzed for the concentration of sorafenib by UV-vis spectrophotometer at 264 nm.[11]

#### *Preparation of Sorafenib Surface Solid Dispersion (SSD)*

Surface solid dispersion of sorafenib was prepared by solvent evaporation method using different hydrophilic carriers such as Kyron T 314, Cab–O–Sil M5, Florite R, SSG and CPV. Surface solid dispersions were prepared with drug to carrier ratios of 1:0.5, 1:1, 1:1.5, as shown in Table 1. The required amount of drug (274 mg) was dissolved in methanol to get a clear solution. Carrier was added to this clear drug solution and dispersed. The solvent was removed by continuous trituration until a dry mass was obtained. The obtained mass was further dried at $50^0$C for 4 hours in an oven. This product was crushed, pulverized and sifted through a 60# sieve. The obtained product was stored in desiccator containing $CaCl_2$ and evaluated.[12]

#### *Evaluation of Sorafenib Surface Solid Dispersions*

Solubility studies of sorafenib SSD, Percentage practical yield,[8] %Drug content[9] 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, and sorafenib SSD formulations (SSD1-SSD15) were performed using USP dissolution Apparatus II (Lab India DS 8000, Mumbai, India) using 900 mL of freshly prepared 0.1N HCl pH 1.2 with 1% SLS maintained at 37 ± 0.5°C and the speed of the paddle

was set at 50 rpm.[10] At pre-determined time intervals, 5 mL of samples were withdrawn using a syringe and immediately replaced with 5 mL of fresh medium maintained at 37 ± 0.5° C. The samples were suitably diluted and analyzed for sorafenib using UV method spectrophotometrically at 264nm. Similar dissolution studies of pure drug and marketed product were also performed for comparison. All measurements were done in triplicate.

## Solubility Enhancement of Sorafenib by Melt Granulation Technique

### *Preparation of Sorafenib-loaded Solid Dispersions by Melt Granulation Technique*

Solid dispersions in various weight ratios of drug to the carrier were prepared by melt granulation method. Sorafenib (274 mg) was added to the molten base comprising carrier with its quantities as listed in Table 2.

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

| *Formulation code* | *Sorafenib (mg)* | *Ratio of drug: carrier* | *Florite R (mg)* | *Kyron T 314 (mg)* | *Cab – O – Sil M5 (mg)* | *SSG (mg)* | *CPV (mg)* |
|---|---|---|---|---|---|---|---|
| SSD1 | 274 | 1:0.5 | 137 | - | - | - | - |
| SSD2 | 274 | 1:1 | 274 | - | - | - | - |
| SSD3 | 274 | 1:1.5 | 411 | - | - | - | - |
| SSD4 | 274 | 1:0.5 | - | 137 | - | - | - |
| SSD5 | 274 | 1:1 | - | 274 | - | - | - |
| SSD6 | 274 | 1:1.5 | - | 411 | - | - | - |
| SSD7 | 274 | 1:0.5 | - | - | 137 | - | - |
| SSD8 | 274 | 1:1 | - | - | 274 | - | - |
| SSD9 | 274 | 1:1.5 | - | - | 411 | - | - |
| SSD10 | 274 | 1:0.5 | - | - | - | 137 | - |
| SSD11 | 274 | 1:1 | - | - | - | 274 | - |
| SSD12 | 274 | 1:1.5 | - | - | - | 411 | - |
| SSD13 | 274 | 1:0.5 | - | - | - | - | 137 |
| SSD14 | 274 | 1:1 | - | - | - | - | 274 |
| SSD15 | 274 | 1:1.5 | - | - | - | - | 411 |

Note: Methanol was added Qs. Sorafenib Tosylate 274 mg equivalent to Sorafenib 200 mg.

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

| *Formulation code* | *Sorafenib (mg)* | *Ratio of drug: carrier* | *Poloxamer 188 (mg)* | *Poloxomer 407 (mg)* | *Gelucire 44/14 (mg)* | *Inutec SP1 (mg)* | *PEG 6000 (mg)* |
|---|---|---|---|---|---|---|---|
| MG 1 | 274 | 1:0.25 | 68.5 | - | - | - | - |
| MG 2 | 274 | 1:0.5 | 137 | - | - | - | - |
| MG 3 | 274 | 1:0.75 | 205.5 | - | - | - | - |
| MG 4 | 274 | 1:0.25 | - | 68.5 | - | - | - |
| MG 5 | 274 | 1:0.5 | - | 137 | - | - | - |
| MG 6 | 274 | 1:0.75 | - | 205.5 | - | - | - |
| MG 7 | 274 | 1:0.25 | - | - | 68.5 | - | - |
| MG 8 | 274 | 1:0.5 | - | - | 137 | - | - |
| MG 9 | 274 | 1:0.75 | - | - | 205.5 | - | - |
| MG 10 | 274 | 1:0.25 | - | - | - | 68.5 | - |
| MG 11 | 274 | 1:0.5 | - | - | - | 137 | - |
| MG 12 | 274 | 1:0.75 | - | - | - | 205.5 | - |
| MG 13 | 274 | 1:0.25 | - | - | - | - | 68.5 |
| MG 14 | 274 | 1:0.5 | - | - | - | - | 137 |
| MG 15 | 274 | 1:0.75 | - | - | - | - | 205.5 |

Sorafenib Tosylate 274 mg equivalent to Sorafenib 200 mg.

The blend was heated 10°C above the melting point of each carrier for 5 min with continuous magnetic stirring. The mass was crushed, ground gently with a mortar and pestle and passed through a Mesh no. 35. The final solid dispersion formulation was obtained by continuous blending for 10 min.[13]

### *Evaluation of Sorafenib Solid Dispersions Prepared by Melt Granulation Technique*

Percentage practical yield, % Drug content, *in-vitro* drug dissolution of sorafenib SD, were performed similarly as mentioned under SSD technique.

## Solubility Enhancement of Sorafenib by Liquisolid Compacts

To select the best non-volatile solvent for dissolving Sorafenib, solubility studies of the drug were carried out in different non-volatile solvents; PEG 600, Tween 80, Solutol HS 15, Cremophor EL, Transcutol HP, Glycerine and Propylene glycol. Saturated solutions were prepared by adding the excess drug to the vehicles and shaking on the incubator shaker for 48 h at 25 ± 1°C. After this period the solutions were filtered through a 0.45 µm Millipore filter, diluted with distilled water and analyzed by double beam UV-Visible spectrophotometer (Systronics, Hyderabad) at a wavelength of 264 nm against blank (blank sample contained the same concentration of specific solvent used without drug).

### *Binding Capacity of Adsorbents for the Solvents*

Binding capacity is defined as the capacity of different excipients (carrier material) to hold liquid and behave like dry powder, determined by a simple technique. The constant weights of (5 g) of the different powder excipients were taken and a non-volatile solvent was added in an increment of 0.01-mL. The mixture was triturated after each addition to helping distributing the liquid throughout the powder particles. The addition of vehicle and the trituration was continued until mortar contents start to look like dry powder.[14]

### *Calculation of Load Factor*

In the liquisolid system, the carrier and coating materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties depending on the excipients ratio. The excipients ratio R (R = Q/q) of powder is defined as the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation. Preparation of a liquisolid system with acceptable flowability and compressibility is possible if a maximum liquid on the carrier material is not exceeded. This characteristic amount of liquid is termed the liquid load factor (Lf). The Lf is defined as the weight ratio of the liquid medication (W) and carrier powder (Q) in the system (i.e., Lf = W/Q). To calculate the loading factor, non-volatile solvent (liquid medication without drug) was added to 10 g of carrier material and blended for 1min. To this coating material was added and triturated.

### *Pre-compression Parameters*

The lubricated blend was evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's Ratio. [15]

## Preparation of Sorafenib Tablets with Optimized Formulation

The optimized melt granule formulation was mixed with other ingredients and the final mixture (Table 3) was compressed into tablets manually using rotary punching machine (Rimek Minipress I, Karnavati Engineering Pvt. Ltd., Gujarat, India). The compression force was adjusted depending on the weight of tablet and ingredients in the formulation. Forty tablets were prepared in a batch for each formulation (Table 3).

### *Evaluation of Sorafenib Tablets*

Tablets were evaluated for following parameters.

### *Physical Properties*

Average weight, hardness, thickness, friability and Disintegration time was recorded.

### *Characterization of Optimised Formulation*

Stability studies and characterization by FTIR studies, X-Ray Diffractometer (XRD), SEM Studies,[16] were conducted as per referred procedures

# Results and Discussion

## Surface Solid Dispersions (SSD) of Sorafenib

### *Solubility Studies of Sorafenib*

The preliminary solubility analysis of physical mixtures is shown in Table 4. From this study, the physical mixture of sorafenib drug with Florite R showed the highest drug solubility, i.e., 1.83 ± 0.56 mg/mL.

### *Percentage Practical Yield (PPY) Determination and Drug Content of Sorafenib SSD*

The PPY for all sorafenib SSDs was within 95.16 ± 0.27% - 98.92 ± 0.90%.

The % drug content of all sorafenib SSD's lie within 95.18 ± 0.32–98.23 ± 0.87% with SSD3 exhibiting maximum drug content.

**Table 3**: Formulation of Sorafenib tablets with Optimised formulation (MG 3)

| *S.no* | *Ingredients* | *Quantity (mg)* |
|---|---|---|
| 1 | Sorafenib + Poloxamer 188 | 480 |
| 2 | Kyron T 314 | 20 |
| 3 | Sodium Lauryl Sulphate | 10 |
| 4 | Magnesium Stearate | 5 |
| 5 | Microcrystalline Cellulose | 25 |
| | Total wt. | 540 |

### *In vitro Dissolution Studies*

A significant increase in drug dissolution rate is observed in all the formulated SSDs of sorafenib when compared to the pure drug (11.65 ± 0.84%) in 1-hour. As the carrier concentration increased, there was an increase in the dissolution rate, this could be due to the hydrophilic nature of polymers and surface adsorption of drug particles on the polymer. It is observed that the saturated solubility increases with an increase in carrier proportion for all the used carriers. This could be attributed to the availability of larger surface area of contact between drug and dissolution medium. Among all, formulations containing Florite R exhibited greater dissolution. Formulation SSD3 containing high amount of Florite R showed highest dissolution rate of 80.64 ± 0.47% in one hour. (Fig. 1).

## Sorafenib Solid Dispersions Prepared by Melt Granulation Technique

### *Percentage Practical Yield (PPY) Determination and Drug Content of Sorafenib SD*

All formulations met the standard criteria for PPY and drug content.

The PPY for all sorafenib MG's found to be between 94.29 ± 0.36% - 98.92 ± 0.24%.

The % drug content of all sorafenib SD's lie within 95.02 ± 0.25– 99.78 ± 0.92% with MG 3 exhibiting maximum drug content.

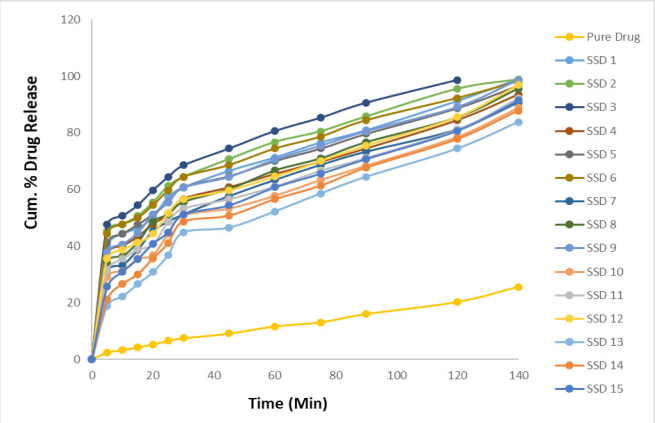


**Fig. 1:** In vitro drug dissolution of pure sorafenib and sorafenib surface solid dispersions SSD1-SSD15

**Table 4**: Solubility studies of Sorafenib Physical mixtures (1:1 ratio)

| *S.no* | *Composition* | *Solubility (mg/ml)* |
|---|---|---|
| 1 | Pure drug | 0.00152 |
| 2 | Drug + Pregelatinised Starch | 0.93 ± 0.33 |
| 3 | Drug + Sodium Starch Glycolate | 1.37 ± 0.34 |
| 4 | Drug + Crospovidone | 1.10 ± 0.56 |
| 5 | Drug + Cab – o – Sil M5 | 1.55 ± 0.89 |
| 6 | Drug + Avicel PH 102 | 1.06 ± 0.84 |
| 7 | Drug + Kyron T 314 | 1.61 ± 0.24 |
| 8 | Drug + Florite R | 1.83 ± 0.56 |

### *In-vitro Dissolution Results*

Melt granulation is a great process for enhancing the solubility and bioavailability arsenal. A significant increase in drug dissolution rate is observed in all the formulated MGs of sorafenib when compared to the pure drug (11.65 ± 0.84%) in one hour. 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 Poloxamer 188 as meltable binder exhibited greater dissolution. Formulation MG3 containing high amount of Poloxamer 188 showed more dissolution rate of 99.89 ± 0.36% in one hour. (Fig. 2).

## Formulation and Evaluation of Sorafenib Liquisolid Compacts

### *Solubility Studies*

The solubility of Sorafenib in different non volatile solvents is given in Table 5. The table shows that the Sorafenib has highest solubility in Solutol HS 15.

### *Binding Capacity of Adsorbents for the Solvents*

The binding capacity of different carrier amounts were evaluated and given in Table 6. From the Table, it is evident

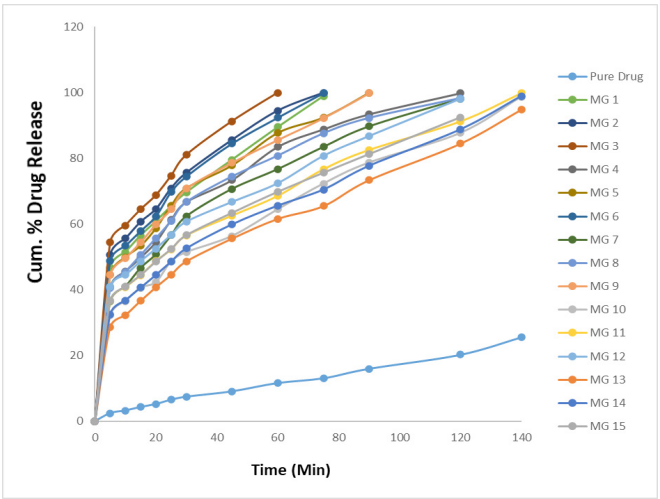


**Fig. 2:** In vitro drug dissolution of pure sorafenib and sorafenib Melt Granules MG1-MG15

**Table 5**: Solubility studies of Sorafenib in non volatile solvents

| *S.no* | *Non volatile solvent* | *Solubility (mg/ml)* |
|---|---|---|
| 1 | Drug + Solutol HS 15 | 1119 ± 0.54 |
| 2 | Drug + Cremophor EL | 1019 ± 0.76 |
| 3 | Drug + Tween 80 | 994 ± 0.84 |
| 4 | Drug + Transcutol HP | 402 ± 0.76 |
| 5 | Drug + PEG 600 | 392 ± 0.81 |
| 6 | Drug + Propylene Glycol | 325 ± 0.95 |
| 7 | Drug + Glycerine | 200 ± 0.48 |

**Table 6**: Determination of optimum concentration of carriers & Loading factors

| *Amount of Carrier 100 mg* | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Solvent* | *Excipient Ratio* | *Volume of liquid consumed* | | | *Liquid loading factors* | | |
| | | *Neusilin* | *Fujicalin* | *Avicel* | *Neusilin* | *Fujicalin* | *Avicel* |
| Solutol HS 15 | 5 | 0.43 | 0.41 | 0.38 | 1.95 | 1.86 | 1.72 |
| | 10 | 0.40 | 0.35 | 0.35 | 1.90 | 1.66 | 1.66 |
| | 15 | 0.38 | 0.32 | 0.31 | 1.83 | 1.54 | 1.50 |
| | 20 | 0.37 | 0.30 | 0.29 | 1.80 | 1.46 | 1.41 |
| Cremophor EL | 5 | 0.41 | 0.35 | 0.33 | 2.60 | 2.22 | 2.1 |
| | 10 | 0.38 | 0.31 | 0.29 | 2.53 | 2.06 | 1.93 |
| | 15 | 0.32 | 0.26 | 0.28 | 2.16 | 1.76 | 1.89 |
| | 20 | 0.30 | 0.25 | 0.27 | 2.04 | 1.70 | 1.84 |
| Tween 80 | 5 | 0.35 | 0.29 | 0.27 | 1.68 | 1.39 | 1.30 |
| | 10 | 0.30 | 0.24 | 0.21 | 1.51 | 1.21 | 1.06 |
| | 15 | 0.28 | 0.22 | 0.16 | 1.43 | 1.12 | 0.82 |
| | 20 | 0.27 | 0.20 | 0.13 | 1.39 | 1.03 | 0.67 |
| *Amount of Carrier 200 mg* | | | | | | | |
| *Solvent* | *Excipient Ratio* | *Volume of liquid consumed* | | | *Liquid loading factors* | | |
| | | *Neusilin* | *Fujicalin* | *Avicel* | *Neusilin* | *Fujicalin* | *Avicel* |
| Solutol HS 15 | 5 | 0.49 | 0.46 | 0.40 | 2.36 | 2.21 | 1.92 |
| | 10 | 0.46 | 0.43 | 0.37 | 2.32 | 2.17 | 1.86 |
| | 15 | 0.44 | 0.40 | 0.35 | 2.25 | 2.05 | 1.79 |
| | 20 | 0.43 | 0.39 | 0.34 | 2.22 | 2.01 | 1.75 |
| Cremophor EL | 5 | 0.47 | 0.44 | 0.33 | 2.99 | 2.8 | 2.1 |
| | 10 | 0.43 | 0.40 | 0.29 | 2.86 | 2.66 | 1.9 |
| | 15 | 0.40 | 0.38 | 0.28 | 2.70 | 2.57 | 1.89 |
| | 20 | 0.37 | 0.37 | 0.27 | 2.52 | 2.52 | 1.84 |
| Tween 80 | 5 | 0.40 | 0.32 | 0.29 | 1.92 | 1.54 | 1.39 |
| | 10 | 0.32 | 0.29 | 0.24 | 1.61 | 1.46 | 1.21 |
| | 15 | 0.29 | 0.27 | 0.20 | 1.48 | 1.38 | 1.02 |
| | 20 | 0.28 | 0.26 | 0.18 | 1.44 | 1.34 | 0.93 |

that as the amount of carrier increases, the amount of liquid that can be loaded onto it decreases. Thus, 100 mg of carrier (Neusilin) was selected for further study at an Excipient ratio of 5:1.

### *Flow Properties of Liquisolid Powders*

The powder mixtures of different formulations were evaluated for angle of repose and Carr's index. The results of angle of repose <30 and compressibility index <15 indicates excellent flow properties of the powder mixture containing Neusilin as carrier material.

### *Percentage Practical Yield (PPY) Determination and Drug Content of Sorafenib Liquisolid Compact*

The PPY for all sorafenib SD's were between 95.21 ± 0.53% - 99.21 ± 0.46%.

The % drug content of all sorafenib SD's lie within 95.32 ± 0.64–99.65 ± 0.48% with LSC1 exhibiting maximum drug content.

### *In-vitro Dissolution Studies of Sorafenib LSC*

A significant increase in drug dissolution rate is observed in all the formulated LSCs of sorafenib when compared to the pure drug (11.65 ± 0.84%) in one hour. Three carriers (Neusilin, Fujicalin and Avicel PH102) and three solvents (Tween 80, Solutol HS 15 & Cremophor EL) were used to formulate sorafenib LSC's. Formulations containing Neusilin (LSC1-LSC3) exhibited greater dissolution rate when compared to Fujicalin and Avicel PH 102 (LSC4-LSC9). Among all, formulation LSC1 containing Neusilin as carrier and Solutol HS 15 as solvent showed highest dissolution rate of 99.94 ± 1.38% in one hour. The increased

dissolution rate was found to be for the LSC1, this might be due to the highest solubility of sorafenib 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 (Neusilin) effect and also carrier to coating material ratio (5:1) may be a reason as they adsorb the drug molecules and thus, they make the drug exposed to the dissolution media (Fig. 3).

## Comparative Dissolution Profiles of Optimized Formulations of Three Preparation Techniques

Fig. 4 depicts the comparative drug release of **SSD 3, MG 3 and LSC 1**. Sorafenib prepared by Melt Granulation technique found to be the best formulation (MG 3) with highest drug release of 99.89 ± 1.38% in 1 hr.

## Evaluation of Sorafenib Tablets

Sorafenib melt granule tablets with optimised formulation MG 3 were prepared by direct compression method. Table 7 reveals that all the prepared tablets have acceptable physical properties according to the IP.

## Characterisation of Sorafenib Melt Granule Formulation

### *FTIR Spectroscopy*

The characterization of pure drug sorafenib by FTIR studies was shown in Fig. 5A. 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 optimized formulation of sorafenib solid dispersion MG 3 showed all the peaks for sorafenib, suggesting no significant interaction observed between them (Fig. 5B)

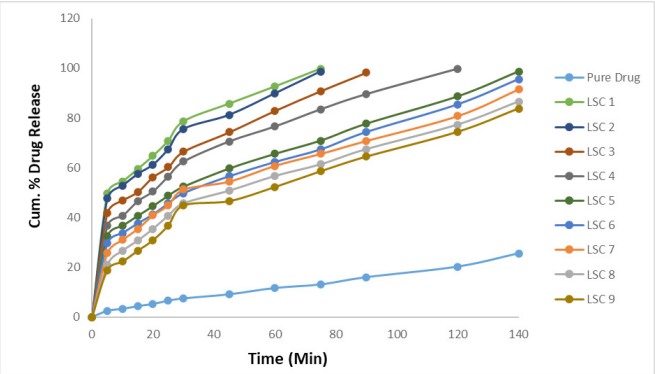


**Fig. 3:** In vitro drug dissolution of pure sorafenib and Liquisolid powders LSC 1-LSC 9

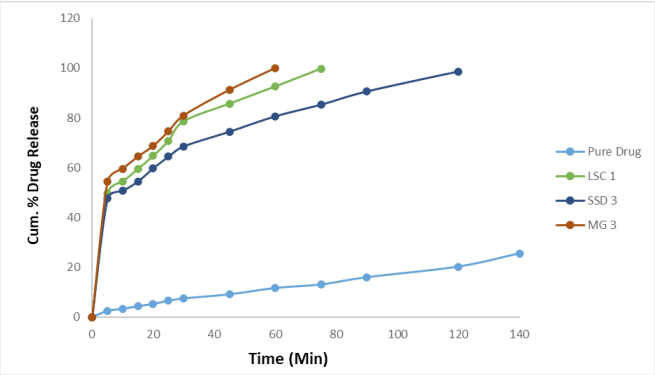


**Fig. 4:** Comparative dissolution profiles of sorafenib pure drug and sorafenib Solid Dispersions

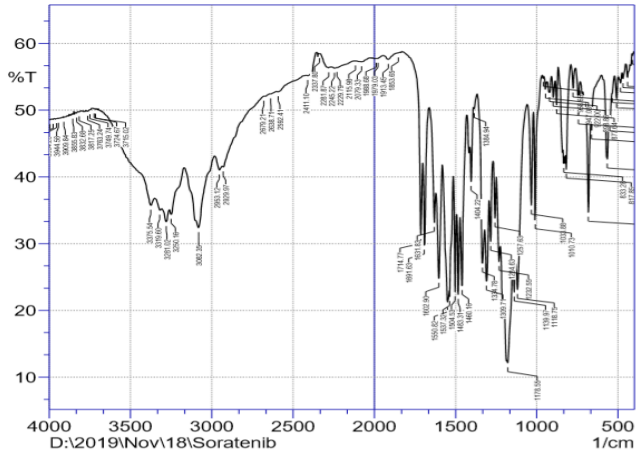


**Fig. 5 A:** FTIR Spectroscopy of Sorafenib pure drug

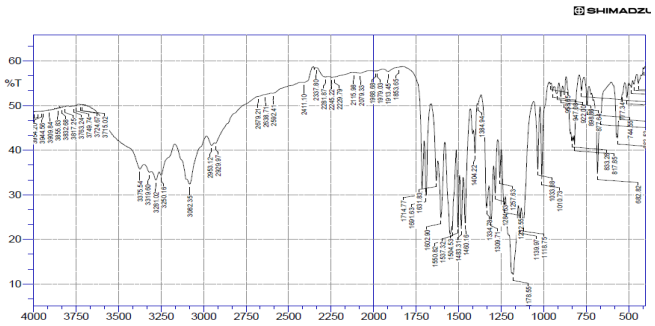


**Fig. 5 B:** FTIR spectrum of optimised formulation of sorafenib (MG 3)

**Table 7:** Evaluation of Prepared tablets & Marketed product

| *S. No* | *Evaluation Parameter* | *Optimised formulation tablet* | *Marketed tablet (Nexaver)* |
|---|---|---|---|
| 1 | Weight Variation (mg) | 535 ± 1.9 | 400 ± 1.6 |
| 2 | Hardness (Kg/cm2) | 4.8 | 5.4 |
| 3 | Friability (%) | 0.51 ± 0.65 | 0.15 ± 0.5 |
| 4 | Disintegration time (min) | 1 ± 0.78 | 2 ± 1.2 |
| 5 | Assay (%) | 99.67 ± 0.56 | 99.99 ± 0.32 |
| 6 | Content Uniformity | 99.87 ± 0.76 | 99.87 ± 0.56 |

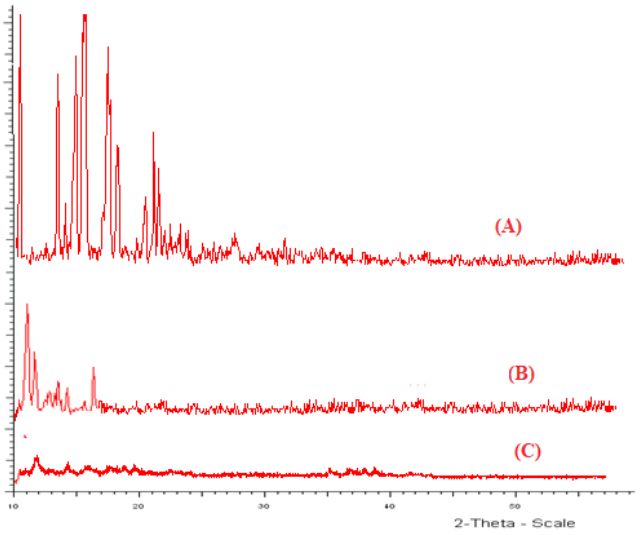


**Fig. 6:** XRD of (A) Pure drug (B) Optimised Liquisolid powder LSC 1 (C) Optimised formulation of Melt granules MG 3

**Table 8**: Stability studies of MG 3 stored at 40 ± $2^0$C /75 ± 5% RH

| *Retest Time for Optimized formulation MG 3* | *Drug content (%)* | *In-vitro drug release profile (%)* |
|---|---|---|
| 0 days | 99.65 ± 0.48 | 99.89 ± 1.38 |
| 30 days | 99.54 ± 0.64 | 99.80 ± 1.74 |
| 60 days | 99.47 ± 1.26 | 99.76 ± 1.28 |
| 90 days | 98.93 ± 0.74 | 99.75 ± 0.58 |

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

### *X Ray Diffraction Studies*

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 in optimised LSC formulation (Fig. 6A and Fig. 6B). However, these distinctive peaks of sorafenib were absent in the pattern of the sorafenib MG 3 (Fig 6C), the results indicate the conversion of sorafenib from the crystalline state to the amorphous on Melt Granulation formulation.

### *SEM Studies*

The scanning electron microscopic pictures of sorafenib pure drug and optimised formulation MG 3 are presented in Fig. 7A and 7B. The formulation appeared smooth surfaced irregular shape matrices due to the porous nature of the carrier with fine particles of the drug deposited on it. SEM studies explained the surface morphological properties of the Melt Granules indicating that the MG formulation is in amorphous state.

### Stability Studies

The optimized formulation was stable during 3 months period. Results indicate that optimized formulation (MG 3) is stable with no variations in its drug content and in-vitro dissolution profile (Table 8).

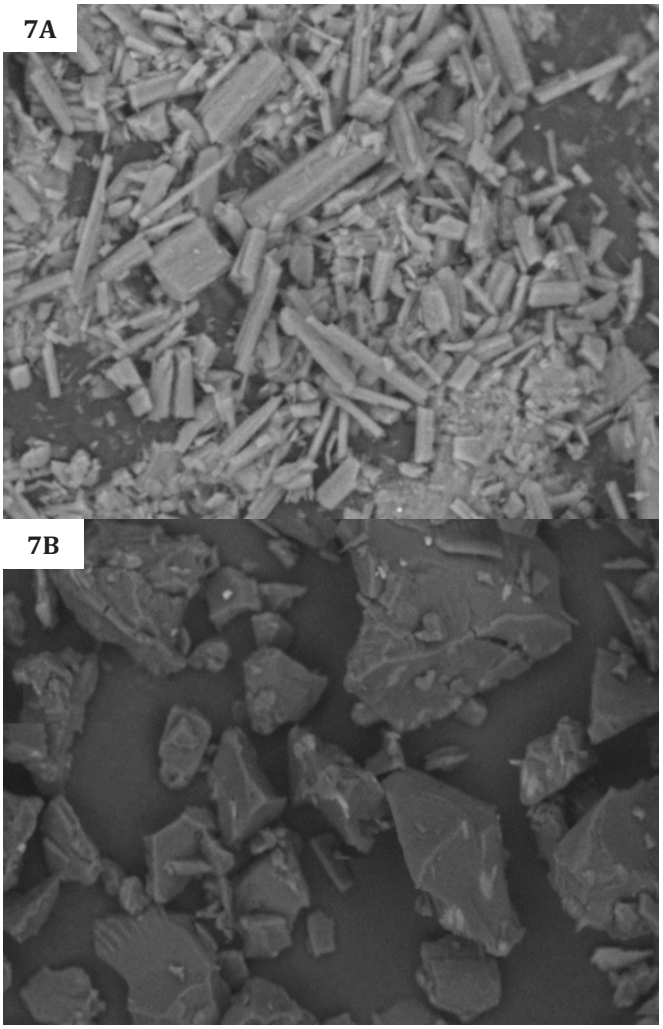


**Fig.7A and 7B:** SEM images of pure drug and optimized formulation of sorafenib Melt granules MG 3

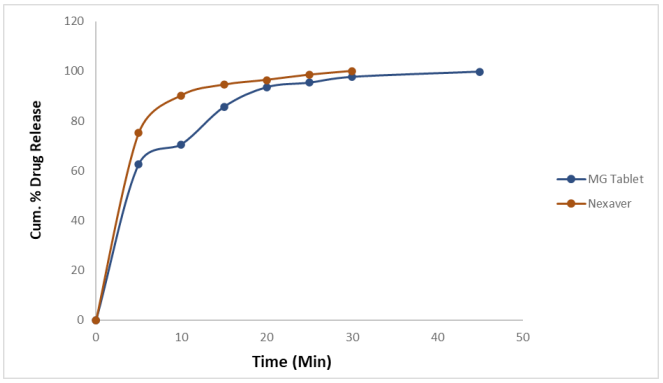


**Fig. 8:** Comparative dissolution profiles of sorafenib Optimised formulation tablet and Marketed Product (Nexaver)

## CONCLUSION

The solid dispersion approach has been widely and successfully applied to improve solubility and consequently

dissolution of sorafenib by three separate formulation methods. Sorafenib solid dispersions were prepared by surface solid dispersion, melt granulation and liquisolid compact methods and exhibited improved solubility. The three techniques showed good drug release profiles, and the sequencing order given for the various formulations was MG 3 > LSC 1> SSD 3. Hence MG 3 was best optimised formulation with highest drug release of 99.89% and was additionally characterized for FTIR, XRD, SEM and stability studies which broadcasted no significant interactions, and amorphous nature of the formulation with stability for 3 months. Thus, in the end it can be declared that the study's objective was achieved in improving the solubility of the sorafenib using the Melt Granulation technique, which was a promising approach for improving the dissolution of a poorly soluble drug like sorafenib.

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