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SOLUBILITY & DISSOLUTION RATE ENHANCEMENT OF SORAFENIB 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 99.88%. 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.

Keywords: Sorafenib, Liquisolid compacts, Solubility, Surface solid dispersion, Melt Granulation.

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

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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 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. 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. 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 AND METHODS

Sorafenib Tosylate sample was gifted by Hetero Drugs Ltd, Hyderabad. Pregelatinized starch, Sodium Starch Glycolate, Avicel PH 102 were purchased from Signet Chemical Corp. Pvt. Ltd, Mumbai. Cab-O-sil M5, Gelucire 44/14 were purchased from Gattefosse, Mumbai. Poloxamer 407 and Poloxamer 188 purchased from

Hetero Drugs Ltd, Hyderabad. Neusilin and Fujicalin purchased from Signet Chemical Corp. Pvt. Ltd, Mumbai.

A. Preparation and evaluation of sorafenib surface solid dispersions

Solubility studies of Sorafenib

Solubility studies of Sorafenib in various vehicles (Water, 0.1 N HCl, 6.8 pH phosphate buffer) and solubility of Sorafenib physical mixtures (Sorafenib and carrier in 1:1 ratios) was determined by the shake-flask method. Excess quantity of drug was added to 2ml vehicle each in separate 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 h). Later these vials were centrifuged at 3000 rpm for 10mins, the excess drug gets settled and the supernatant was collected and filtered through a Whatman filter paper no 1. Filtered solution analyzed for the concentration of Sorafenib by UV- VIS spectrophotometer at 264 nm.

Preparation of Sorafenib surface solid dispersions (SSD's)

Surface solid dispersion of Sorafenib were prepared by solvent evaporation method using different hydrophilic carriers such as Pregelatinised starch (PGS), Sodium starch glycolate (SSG), Crospovidone (CPV), Avicel PH102, Kyron T-314, Florite R and Cab – O – Sil M5. Surface solid dispersion 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 (274mg) 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 50ºC for 4 hours in an oven. This product was crushed, pulverized and sifted through a 60# sieve. The obtained product was stored in desiccators containing CaCl2 and evaluated.

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

Evaluation of Sorafenib surface solid dispersions

Solubility studies of Sorafenib SSD, Percentage practical yield [11], % Drug content [12] were performed accordingly as mentioned in referred procedures.

In vitro drug dissolution of Sorafenib SSD

In-vitro dissolution studies of samples were carried out by dispersed powder technique using USP apparatus II paddle method. Accurately weighed samples equal to 274 mg were added to 900 ml of 0.1N HCl containing 1 % SLS at 37 $\pm$ 0.5°C and stirred at 50 rpm. An aliquot of 5ml was withdrawn at different time intervals and filtered through a 0.45 µm syringe filter. An equal volume of fresh dissolution medium was immediately replaced. The filtered samples were assayed spectrophotometrically at 264 nm against acid blank. Dissolution of each sample was performed 6 times and mean (n=6) of all determinations was used to calculate the drug release profile.

B. Preparation and evaluation of sorafenib melt granules

Preliminary solubility studies

Performed as mentioned under SSD

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. 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 500 µm sieve (35 Mesh). The final solid dispersion formulation was obtained by continuous blending for 10 min.

Table 2: Composition of Sorafenib Melt Granule's

Formulation code	Sorafenib (mg)	Ratio of drug: carrier	Poloxamer 188 (mg)	Poloxamer 407 (mg)	Gelucire 44/14 (mg)	Inutec SP 1 (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

Evaluation and characterization of Sorafenib solid dispersions prepared by melt granulation technique
Percentage practical yield, % Drug content, In vitro drug dissolution of Sorafenib MG's, Stability studies, FTIR, XRD, SEM Studies were conducted accordingly as mentioned in referred procedures.

C. Preparation and evaluation of sorafenib liquisolid compacts
Liquisolid powder systems were prepared by the method reported by S. Spireas. The solubility of drug was determined in different non-volatile solvents. Studies were designed to obtain liquisolid systems with a carrier to coating ratio of high liquid loading factor and good flow properties.

Solubility studies of Sorafenib

To select the best non-volatile solvent for dissolving Sorafenib, solubility studies were carried out in different non-volatile solvents like Propylene glycol, Glycerine, PEG 600, Tween 80, Solutol HS, Cremophor EL and Transcutol HP by saturation solubility experiments. Saturated solutions were prepared by adding excess drug to the vehicles. They were placed on a rotary shaker for 48hrs at $25^0C \pm 1^0C$. After this period, the solutions were filtered through a 0.45 μ Millipore filter, diluted with 0.1N HCl and analysed by spectrophotometer, at a wavelength of 264 nm against blank sample. Six determinations were carried out for each sample and its mean along with standard deviation was reported.

Preliminary studies for optimum amount of non-volatile solvents incorporated into carrier

Different carrier systems like Neusilin, Fujicalin and Avicel PH 102 were selected to prepare liquisolid powder systems. Based on the solubility studies, Solutol HS 15, Tween 80 and Cremophor EL were selected as best nonvolatile solvents. Dummy systems using different amounts of carrier were taken i.e., 100mg and 200mg. For each weight of the carrier taken different ratios of carrier to coating material was selected as shown in Table 3.

To optimize the amount of Solutol HS 15 added to each carrier to coating ratio, preliminary experiments were carried out by adding Solutol HS 15 in increments of 0.01ml till the carrier was just wet, with no lump or ball formation. The reproducibility of the results was checked by repeating the experiments 3 times. Preliminary studies revealed optimum results with 100mg of all the carriers. To compare and optimize these values, liquid loading factors as described above was calculated for other solvent systems like Tween 80 and Cremophor EL.

Table 3: Amounts of carrier and carrier to coating ratios for preliminary studies

Carrier	Amount of carrier (mg)	Carrier to coating ratio	Non-volatile solvent
Neusilin	100	5:1, 10:1, 15:1, 20:1	Solutol HS 15, Tween 80, Cremophor EL
	200		

Fujicalin	100	5:1, 10:1, 15:1, 20:1	Solutol HS 15, Tween 80, Cremophor EL
	200		
Avicel PH 102	100	5:1, 10:1, 15:1, 20:1	Solutol HS 15, Tween 80, Cremophor EL
	200		

Addition of coating material

Depending upon the carrier to coating ratio selected for each of the carrier system, optimized amount of non-volatile solvents determined from the earlier experiment was added and mixed. Calculated quantities of coating material were added. The powder blend was mixed again thoroughly until wet blend got converted to dry powder. The prepared formulated systems were subjected to calculation of loading factor and evaluation of flow properties.

Calculation of loading factor

The loading factor (L_f) is calculated for different powder systems by the following formula,

$$L_f = W/Q = \text{Weight of liquid/ Weight of carrier}$$

Where in present study weight of liquid indicates amount of non-volatile solvent added and weight of carrier indicates total amount of powder material.

Evaluation of flow properties

The prepared liquisolid powder systems were evaluated for flow properties by well-established standard methods.

Evaluation of Sorafenib liquisolid powders

Percentage practical yield, % Drug content, In vitro drug dissolution of Sorafenib liquisolid powder systems, were performed in similar manner as mentioned under SSD technique.

RESULTS AND DISCUSSIONS

A. Preparation and evaluation of sorafenib surface solid dispersions

Solubility studies of Sorafenib

The solubility of Sorafenib in various solvents is shown in Table 4. Sorafenib exhibited a very low solubility in water, the solubility was observed to be more in acidic pH than in basic pH. The preliminary solubility analysis of drug in physical mixtures is shown in Figure 1 which indicated that physical mixture of Sorafenib + Florite R shown highest drug solubility i.e., 1.83 ± 0.59 mg/ml.

Table 4: Solubility of Sorafenib pure drug in various solvents

Solvent	Solubility of sorafenib (µg/ml)
Water	1.52±0.44
0.1N HCL	62±0.64
0.1N HCL + 1% SLS	314±0.47
6.8 pH Buffer	51±0.42
7.4 pH Buffer	32 ±0.25

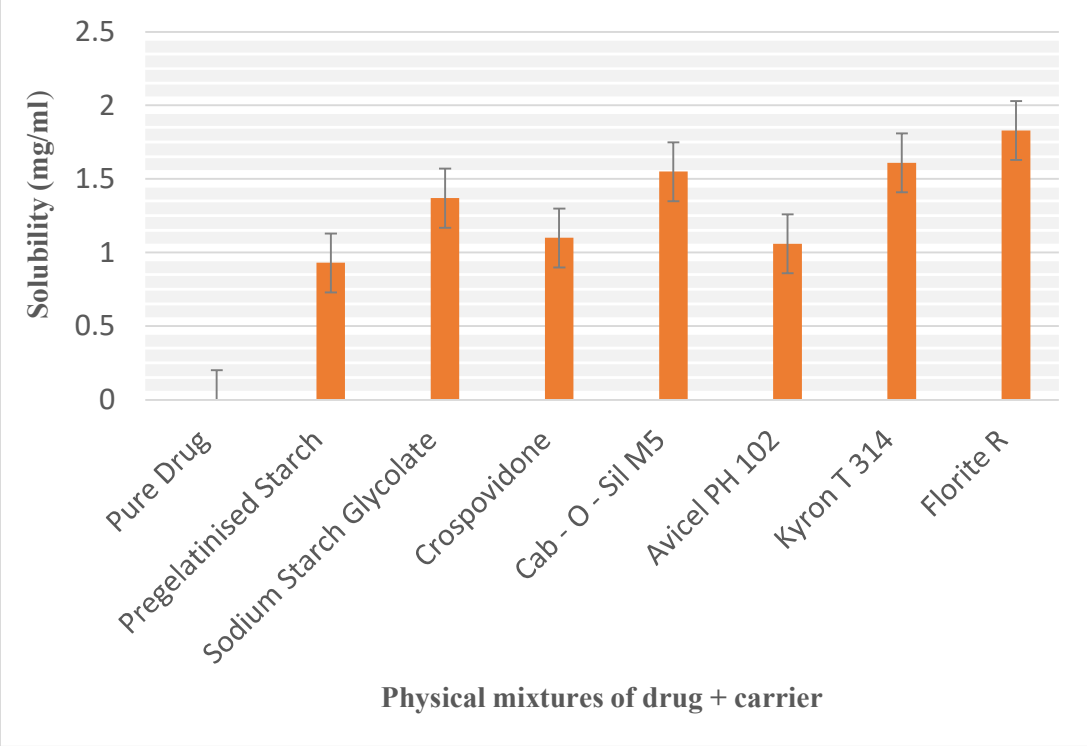


Fig 1: Solubility studies of Sorafenib physical mixtures in 1: 1 ratio

Solubility studies of Sorafenib Surface solid Dispersions

The solubility studies of Sorafenib solid dispersion formulations with Florite R exhibited greater solubility and was shown in Figure 2.

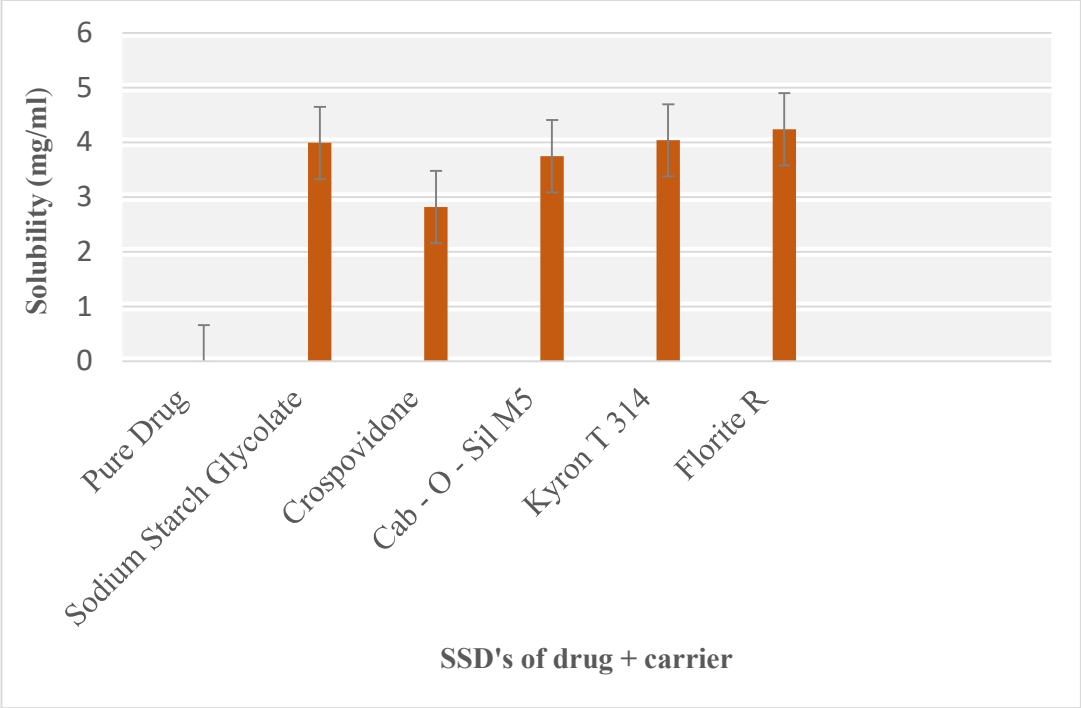


Fig 2: Solubility studies of Sorafenib pure drug and Sorafenib surface solid dispersions

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

All the formulations contained active ingredient within the general limit of 90-110%.

The PPY for all sorafenib SSD's lie within 95.67 ± 0.15% - 99.23 ± 0.85%.

The % drug content of all sorafenib SSD's lie within 96.17 ± 0.82 – 99.31 ± 0.26%

In-vitro dissolution of SSD's of Sorafenib

A significant increase in drug dissolution rate is observed in all the formulated SSDs of sorafenib when compared to the pure drug (11.65±0.65%) in one hour. As the carrier concentration increased it was observed that there was 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±1.02% in one hour.

Florite R has a very fine particle size, hence large surface area. Surface area available for adsorption of drug crystals increases with increase in the concentration of carrier leading to increase in the interfacial area of contact between the drug particles and dissolution media. (Figure 3).

Dissolution rate observed with various carriers were in following increasing order: Crospovidone <Sodium Starch Glycolate< Cab – O – Sil M5 <Kyron T 314 <Florite R.

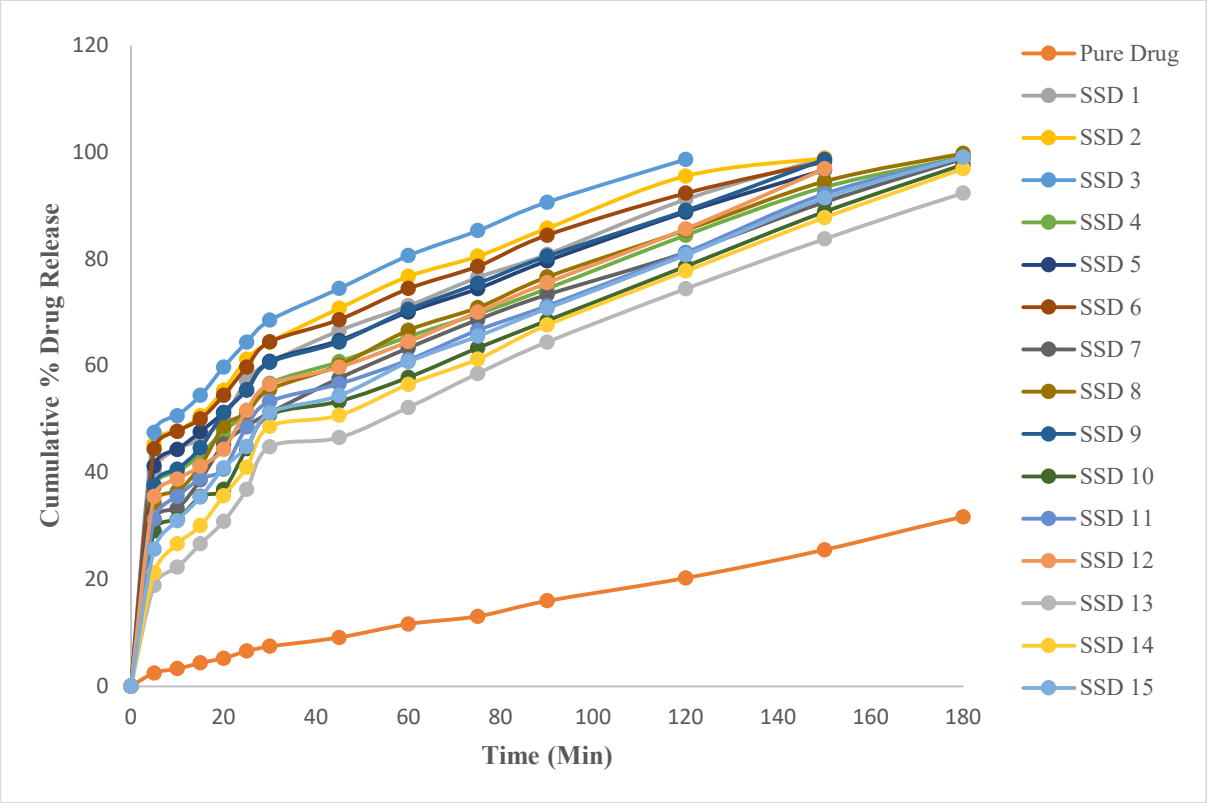


Fig 3: In vitro drug dissolution of pure drug and Sorafenib Surface Solid Dispersions SSD1-SSD15

B. Preparation and evaluation of sorafenib melt granules
Solubility studies of Sorafenib

All the formulations exhibited enhanced solubility compared to pure drug. The solubility of Sorafenib Melt Granule formulations with Poloxamer 188 exhibited greater solubility among all formulations and this may be due to either the reduction in the crystallinity of drug or improved wetting of the drug particles and shown in Figure 4.

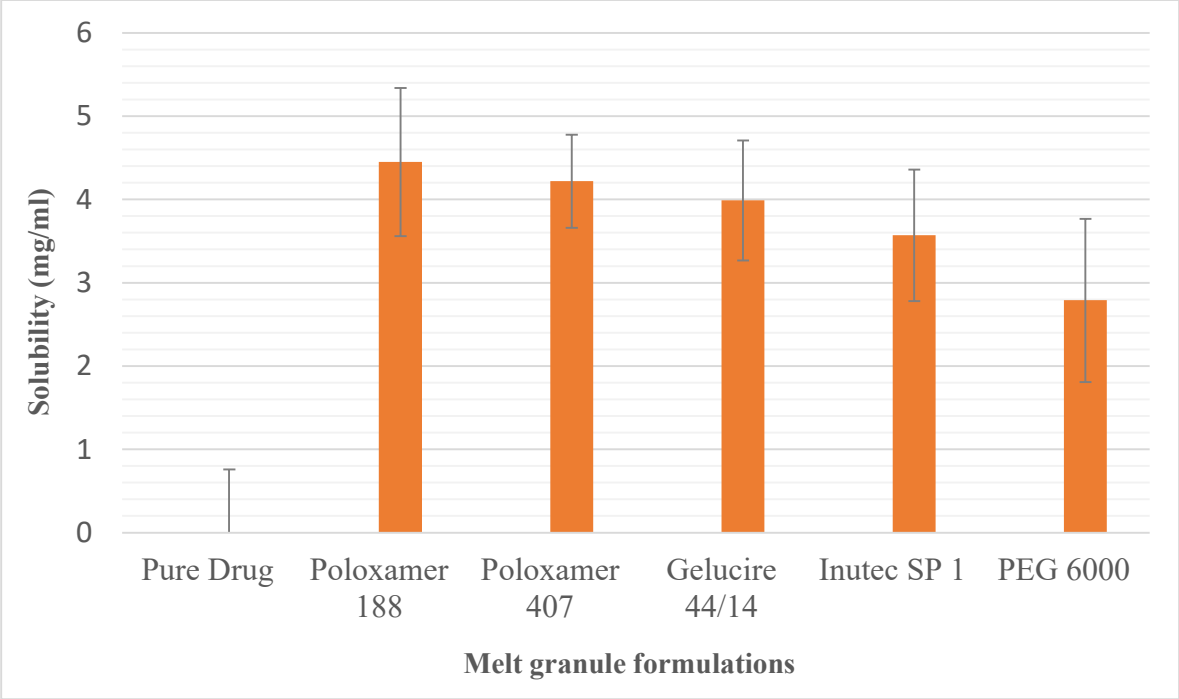


Fig 4: Solubility studies of Sorafenib pure drug and Sorafenib Melt Granules

Percentage practical yield (PPY) determination and drug content of Sorafenib Melt Granules

All the formulations exhibited content uniformity within the IP limits between 90%-110%

The PPY for all Sorafenib Melt Granule's lie within 94.29±0.36 % - 98.94±0.23%.

The % drug content of all Sorafenib Melt Granule's lie within 95.02±0.25 – 99.26±0.27 %.

In-vitro Dissolution studies

A significant increase in drug dissolution rate is observed in all the formulated melt granules of sorafenib when compared to the pure drug (11.65±0.65%) 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. Among all, formulations containing Poloxamer 188 as meltable binder exhibited greater dissolution. Formulation MG 3 containing high amount of Poloxamer 188 showed more dissolution rate of 99.88±1.02% in one hour. (Figure 5).

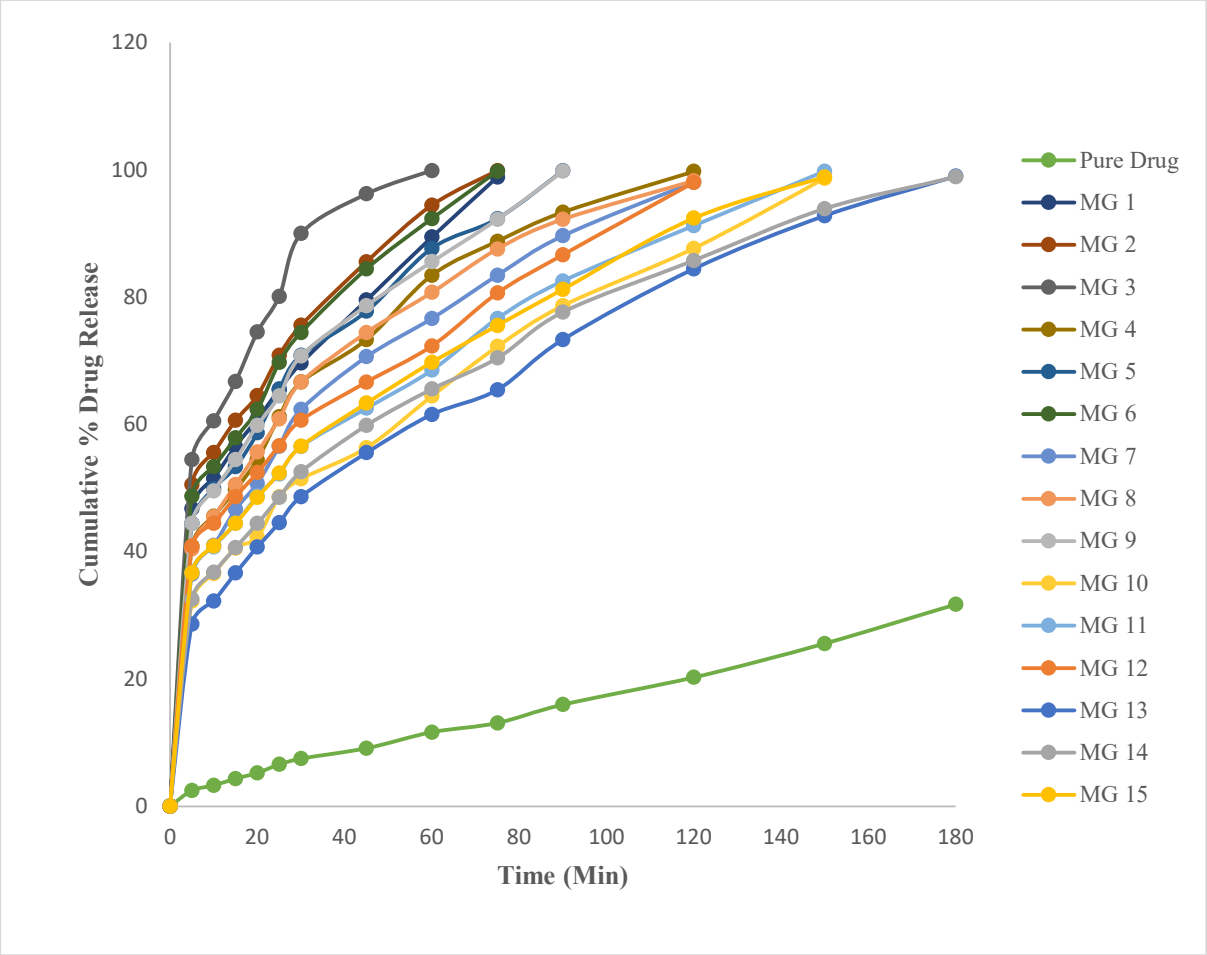


Fig 5: In vitro drug dissolution of pure Sorafenib and Sorafenib Melt Granules MG1-MG15

C. Preparation and evaluation of sorafenib liquisolid compacts

Before preparation of liquisolid compacts of Sorafenib, the solubility studies of the drug in different solvents were conducted (Figure 6), to determine the best non-volatile solvent for dissolving drug. Sorafenib shows maximum solubility in Solutol HS 15.

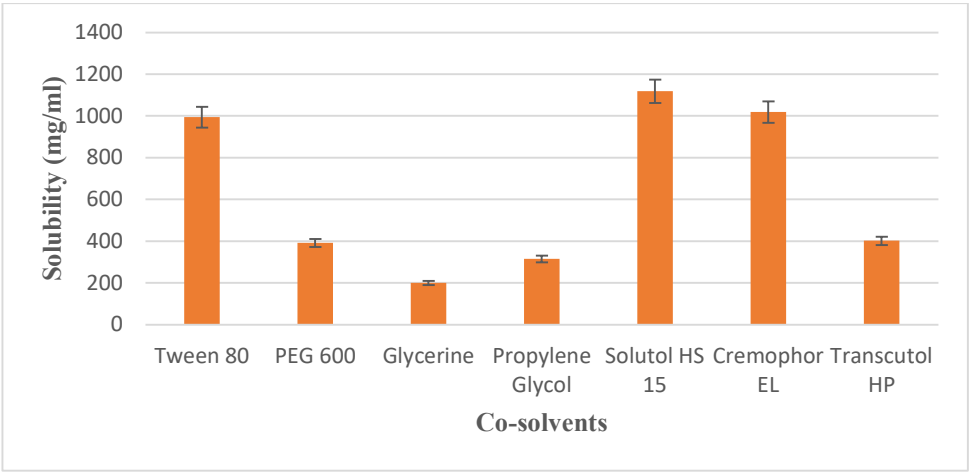


Fig 6: Solubility of Sorafenib in different cosolvents

Preliminary studies for optimum amount of non-volatile solvents incorporated into carrier

For preparation of LSC, Solutol HS 15, Tween 80 & Cremophor EL were selected as the non-volatile solvents for dissolving the drug based on solubility studies performed and Neusilin, Fujicalin and Avicel PH 102 were selected as carrier systems. The optimum amount of non-volatile solvents incorporated into carrier varies with type of carrier, amount of carrier and carrier to coating ratio. Each figure gives comparative study for liquid loading factor for different carriers at same level of carrier material used. As the carrier to coating ratio increases the volume of liquid incorporated decreases as seen in figure 7, 8 & 9. This is attributed to the fact that at higher ratios the amount of coating material is reduced, hence liquid retaining factor is also reduced.

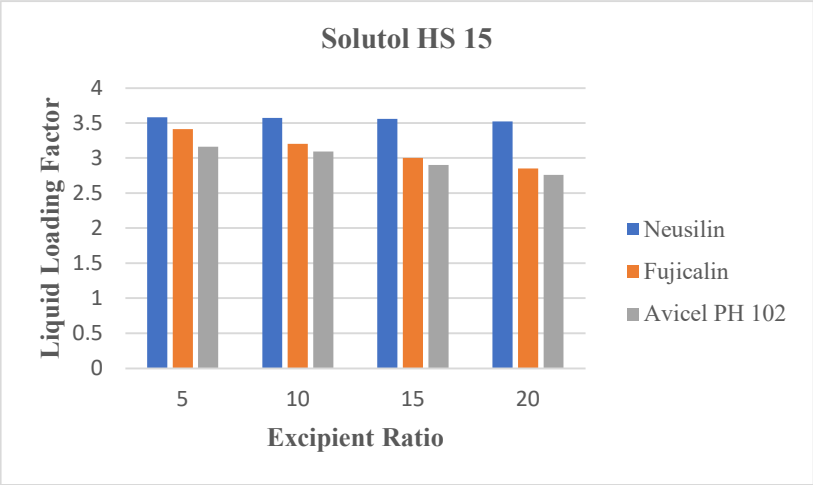


Fig 7: Comparison of Liquid Loading factors of Solutol HS on different carriers

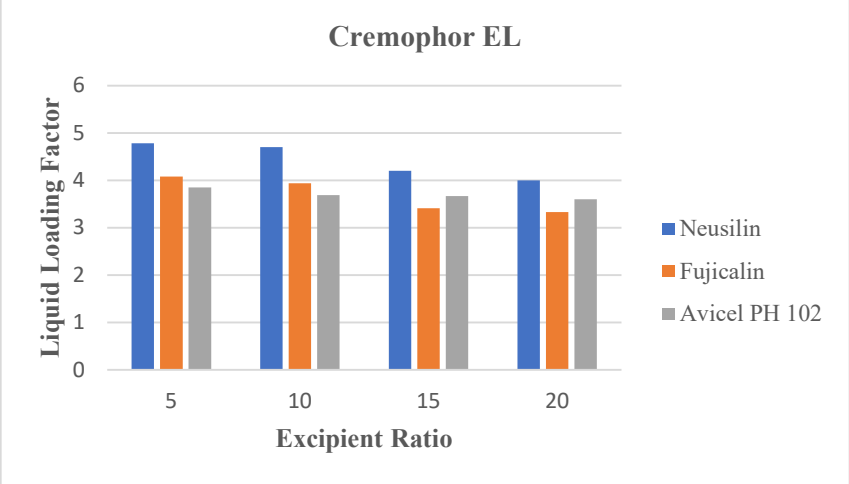


Fig 8: Comparison of Liquid Loading factors of Cremophor EL on different carriers

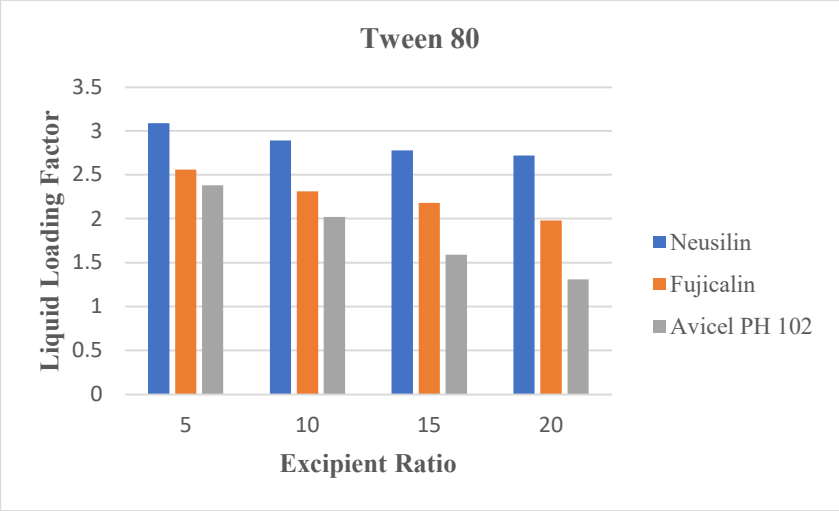


Fig 9: Comparison of Liquid Loading factors of Tween 80 on different carriers

Micrometric Properties of Sorafenib lubricated blend

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 Systems

The PPY for all Sorafenib LSC's lie within 96.69 ± 0.87 % - 99.21±0.53%.

The % drug content of all Sorafenib LSC's lie within 96.90 ± 0.86 – 99.32 ± 0.64%

In-vitro dissolution studies of Sorafenib Liquisolid systems

The dissolution profile of Sorafenib liquisolid powders (LSC1-LSC9) and pure drug is given in Figure 10. A significant increase in drug dissolution rate is observed in all the formulated Liquisolid powders of Sorafenib when compared to the pure drug (11.65±0.65%) in one hour. Among all, formulation LSC1containing Neusilin as carrier and Solutol HS 15 as solvent showed highest dissolution rate of 94.64 ± 0.89% in one hour. The reason was attributed to Sorafenib which is moleculary dispersed in solvent Solutol HS 15 that enhances solubility, and due to the increased wettability of the drug molecules than other solvents, 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. (Figure 10)

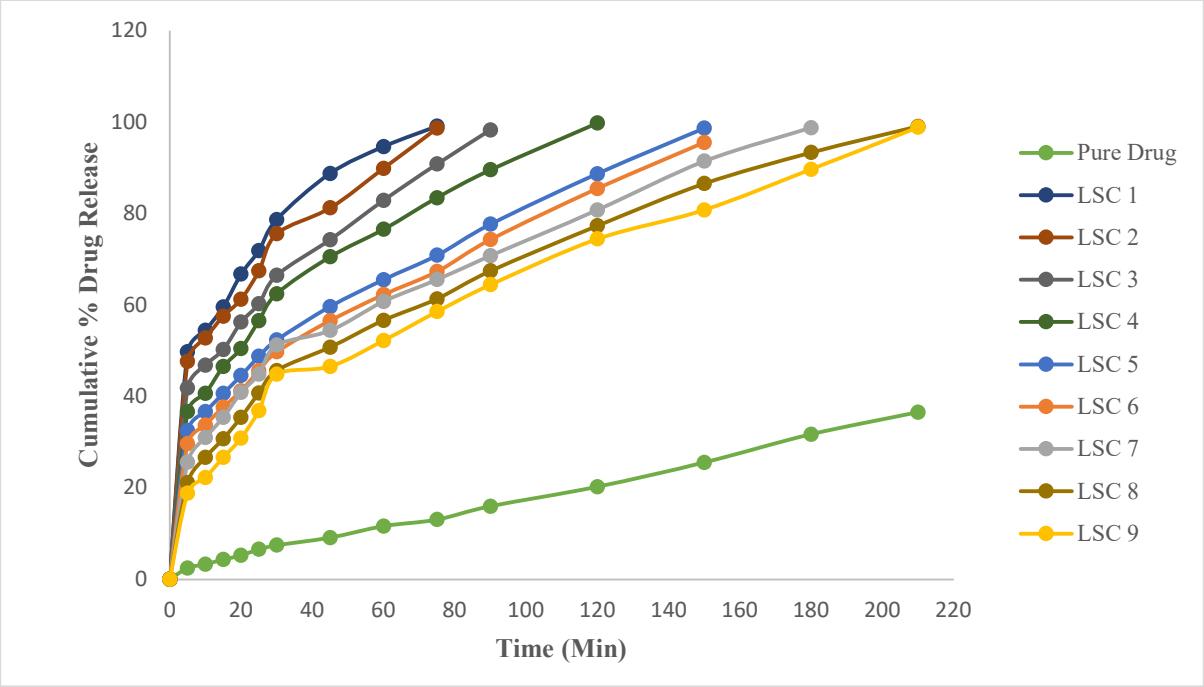


Fig 10: Comparative dissolution profiles of Sorafenib pure drug and Sorafenib LSC formulations LSC 1 – LSC 9

Comparative Dissolution profiles of Optimised formulations of three preparation techniques

The comparison between the dissolution rates of drug was carried out between optimised formulations prepared by Surface solid dispersion, Melt granulation and Liquisolid compacts (**SSD3, MG 3 and LSC1)** to determine the best formulation prepared out of three techniques. Figure 11 depicts the comparative drug release of **SSD 3, MG 3 and LSC 1**. All the three formulations showed good drug release profiles compared to pure drug and of the three techniques sorafenib prepared by Melt granule technique found to be the best formulation (MG 3) with highest drug release of 99.88±1.02%. The overall rank order given for the various formulations was MG 3 > LSC 1> SSD 3.

In conclusion it can be stated that the objective of the study was achieved in improving the solubility of the sorafenib using Melt granule formulation in comparison to other methods.

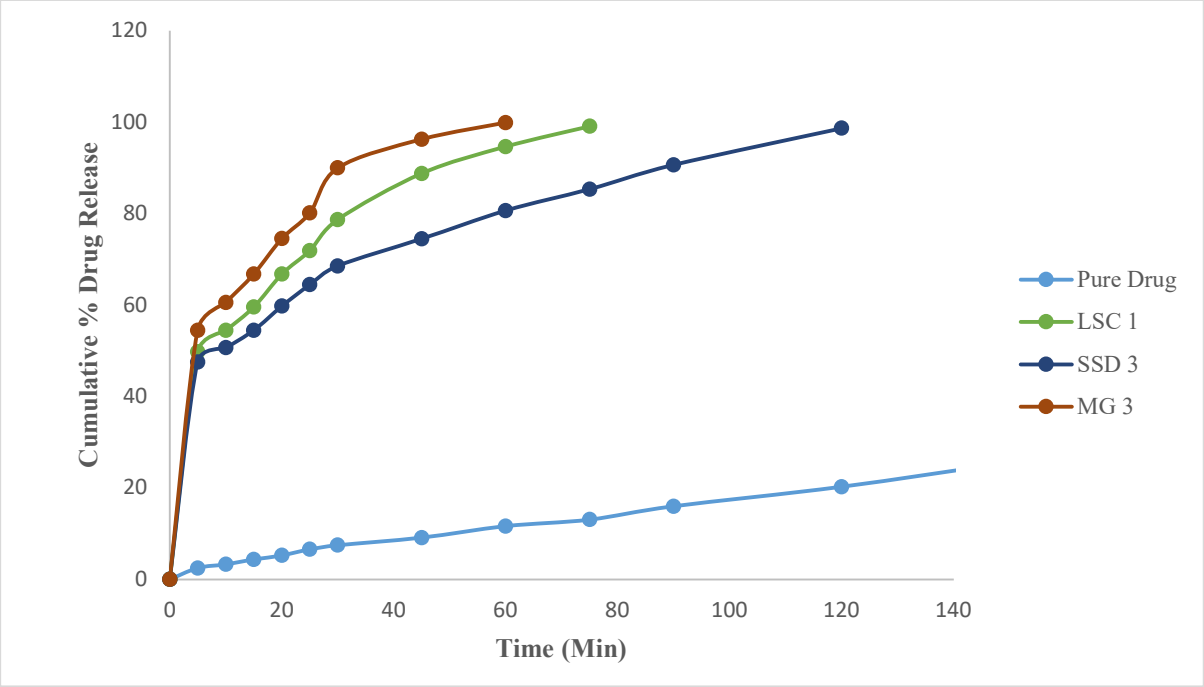


Figure 11: Comparative dissolution profiles of Optimised formulations (SSD 3, LSC 1 & MG 3)

The optimized melt granule formulation MG 3 was prepared into tablets and invitro dissolution studies and stability studies were conducted.

D. Characterization of sorafenib optimised melt granule formulation

Fourier Transformation Infrared Spectroscopy

The characterization of pure drug sorafenib by FTIR studies was shown in Figure 12. 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), 1178.55cm-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 CNFFFcm^{-1} (N-H stretching), 3375.54 cm^{-1} (Amine:N-H stretching). The presence of prominent characteristic peaks confirming the purity of sorafenib as per the established standards (Figure 13).

The presence of prominent characteristic peaks confirming the purity of sorafenib as per the established standards. The FTIR spectrum of optimised formulation of sorafenib Melt granule formulation MG 3 showed all the peaks for sorafenib suggesting no significant interaction observed between them (Figure 13)

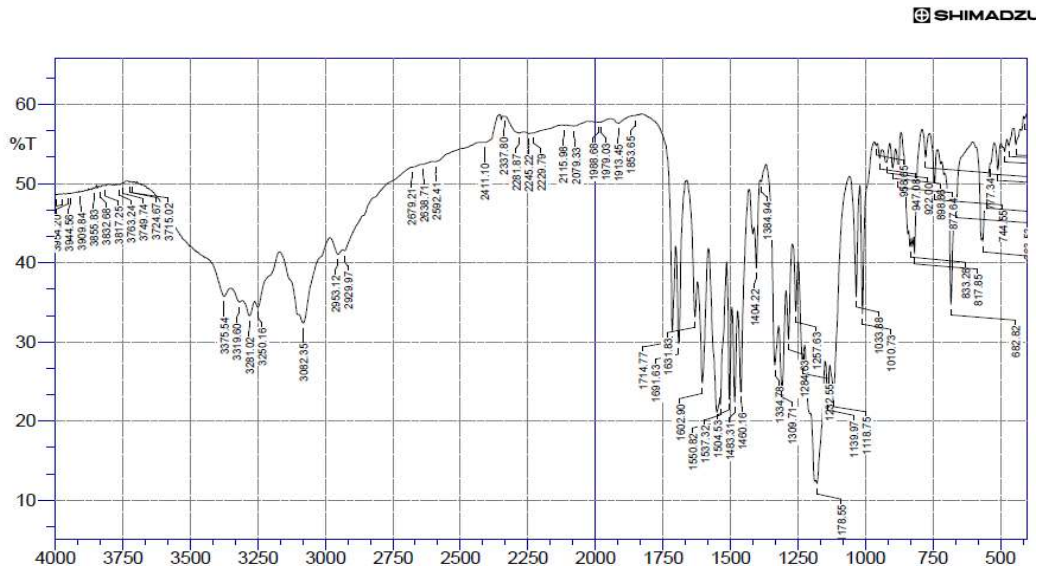
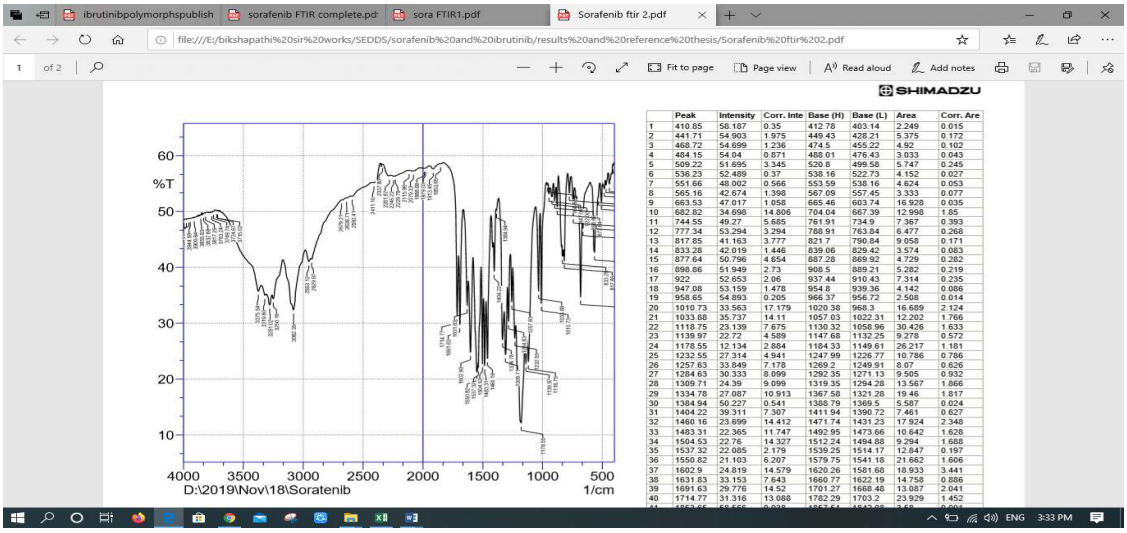


Figure 12: FTIR spectrum of pure drug Sorafenib



	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	410.85	58.187	0.35	412.78	403.14	2.249	0.015
2	441.71	54.903	1.975	449.43	428.21	5.375	0.172
3	468.72	54.699	1.236	474.5	455.22	4.92	0.102
4	484.15	54.04	0.871	488.01	476.43	3.033	0.043
5	509.22	51.695	3.345	520.8	499.58	5.747	0.245
6	536.23	52.489	0.37	538.16	522.73	4.152	0.027
7	551.66	48.002	0.566	553.59	538.16	4.624	0.053
8	565.16	42.674	1.398	567.09	557.45	3.333	0.077
9	663.53	47.017	1.058	665.46	603.74	16.928	0.035
10	682.82	34.698	14.806	704.04	667.39	12.998	1.85
11	744.55	49.27	5.685	761.91	734.9	7.367	0.393
12	777.34	53.294	3.294	788.91	763.84	6.477	0.268
13	817.85	41.163	3.777	821.7	790.84	9.058	0.171
14	833.28	42.019	1.446	839.06	829.42	3.574	0.083
15	877.64	50.796	4.654	887.28	869.92	4.729	0.282
16	898.86	51.949	2.73	908.5	889.21	5.282	0.219
17	922	52.653	2.06	937.44	910.43	7.314	0.235
18	947.08	53.159	1.478	954.8	939.36	4.142	0.086
19	958.65	54.893	0.205	966.37	956.72	2.508	0.014
20	1010.73	33.563	17.179	1020.38	968.3	16.689	2.124
21	1033.88	35.737	14.11	1057.03	1022.31	12.202	1.766
22	1118.75	23.139	7.675	1130.32	1058.96	30.426	1.633
23	1139.97	22.72	4.589	1147.68	1132.25	9.278	0.572
24	1178.55	12.134	2.884	1184.33	1149.61	26.217	1.181
25	1232.55	27.314	4.941	1247.99	1226.77	10.786	0.786
26	1257.63	33.849	7.178	1269.2	1249.91	8.07	0.626
27	1284.63	30.333	8.099	1292.35	1271.13	9.505	0.932
28	1309.71	24.39	9.099	1319.35	1294.28	13.567	1.866
29	1334.78	27.087	10.913	1367.58	1321.28	19.46	1.817
30	1384.94	50.227	0.541	1388.79	1369.5	5.587	0.024
31	1404.22	39.311	7.307	1411.94	1390.72	7.461	0.627
32	1460.16	23.699	14.412	1471.74	1431.23	17.924	2.348
33	1483.31	22.365	11.747	1492.95	1473.66	10.642	1.628
34	1504.53	22.76	14.327	1512.24	1494.88	9.294	1.688
35	1537.32	22.085	2.179	1539.25	1514.17	12.847	0.197
36	1550.82	21.103	6.207	1579.75	1541.18	21.662	1.606
37	1602.9	24.819	14.579	1620.26	1581.68	18.933	3.441
38	1631.83	33.153	7.643	1660.77	1622.19	14.758	0.886
39	1691.63	29.776	14.52	1701.27	1668.48	13.087	2.041
40	1714.77	31.316	13.088	1782.29	1703.2	23.929	1.452

Figure 13: FTIR spectrum of optimised formulation of Sorafenib MG 3

X ray Diffractometry

The diffraction pattern of pure sorafenib showed various characteristic 2θ peaks at 13.2°, 17.8°, and 21.5°, revealing a highly crystalline structure. However, these distinctive peaks of sorafenib were absent in the pattern of the Melt granule formulation, indicating that the drug may be in the amorphous form or molecularly dispersed in the carrier matrix (Figure 14).

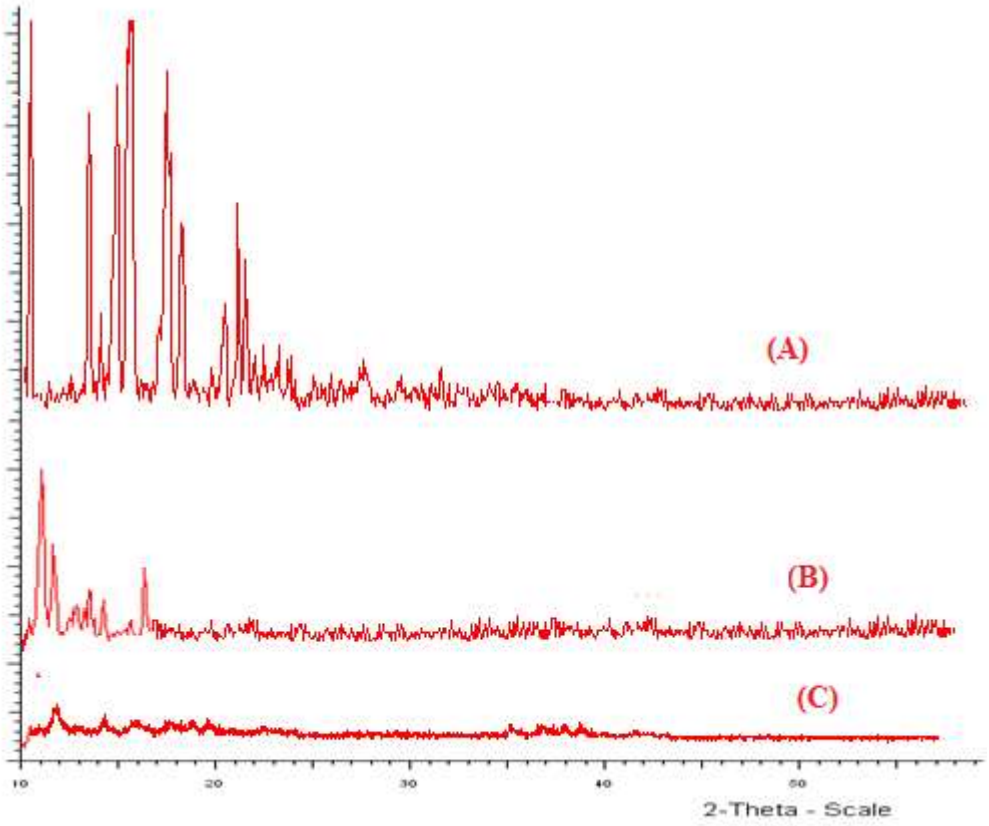
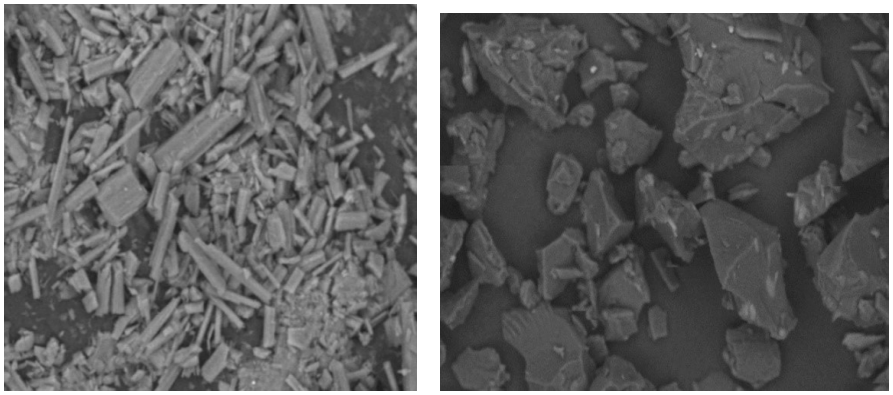


Figure 14: XRD of (A) Pure drug (B) Optimised Liquisolid Formulation LSC 1 (C) Optimised Melt granule formulation MG 3

Scanning Electron Microscopy studies

The scanning electron microscopic pictures of Pure drug and optimised formulation MG 3 are presented in Figure 15. The formulation appeared as spherical and smooth surfaced and Analysis of globule size was in accordance with these results with size of all droplets less than 100 nm.



(A) **(B)**

Figure 15: SEM images of (A) Pure drug and (B) Optimised Melt granule formulation of Sorafenib MG 3

Stability studies

Optimized formulation (MG 3) was subjected to stability study for 90 days at accelerated stability conditions

as per ICH guidelines. 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 5).

Table 5: 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	99.08±1.02
30 days	99.24±0.64	99.02±1.00
60 days	99.23±1.26	98.99±1.01
90 days	99.13±0.74	98.97±0.99

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

The Invitro dissolution profile of prepared tablet with optimised formulation MG 3 was compared with marketed product Nexaver. The release was equal to that of the marketed product as shown in Fig 16.

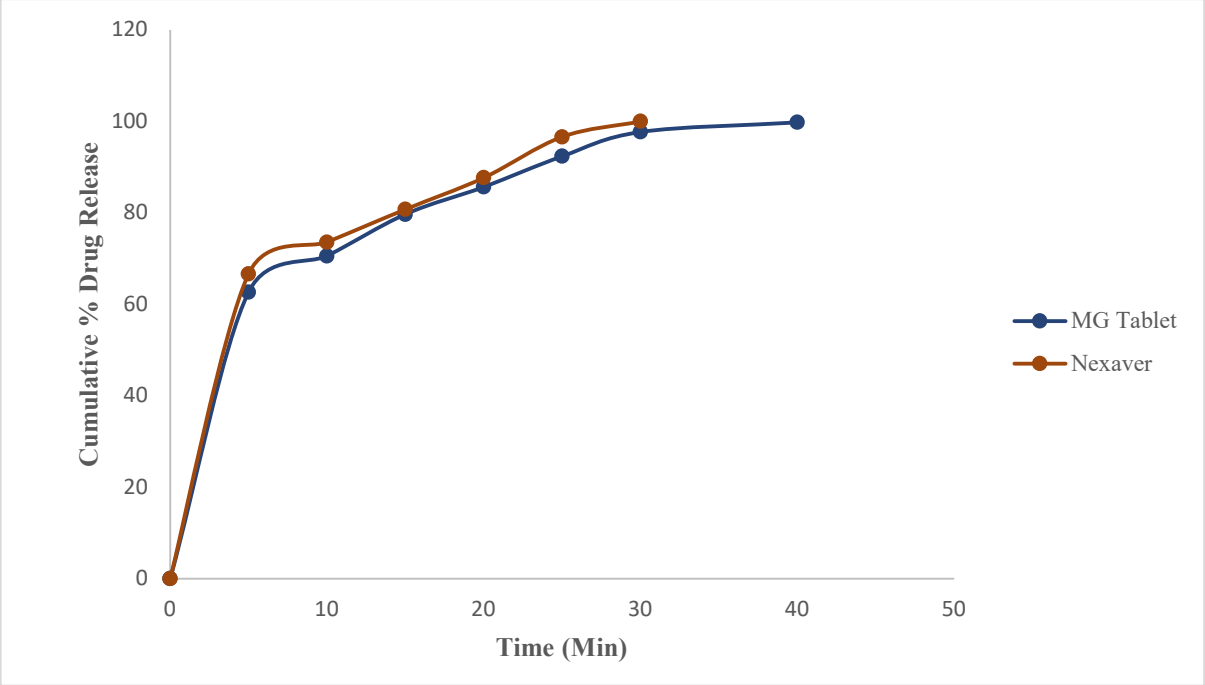


Figure 16: Comparative dissolution profiles of Prepared capsule and Marketed product (Nexaver)

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 99.88% 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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