The Pharmaceutical and Chemical Journal, 2019, 6(3):125-133

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Effect of Poloxamer 188 and Diverse High-Flying Techniques on Crystallinity and Surface Area in Ordered to Enhance Solubility and Dissolution Rate of Sorafenib Tosylate during the Formulation of Solid Dispersions

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Abstract Sorafenib tosylate (SFNt) is an important numerouskinase inhibitor for the curement of cancers. It is commercially available (Nexavar) in the form of SFNt due to its poor aqueous solubility. Studies have been done to further enhance the dissolution property of the form SFNt, which could ultimately reasonable the currently high daily dose and frequency. In the present investigation, SFNt solid dispersions (SFNt-SD) were prepared through methods that combined two industrially well-accepted techniques of physical, melting and solvent evaporation. SFNt was co-mixed, melted and evaporated with hydrophilic polymers (Poloxamer 188). The process enabled the formation of SFNt-SD without using any toxic organic solvents, and the drug/carrier ratio (1:1, 1:3, and 1:5). The solid dispersion was characterised in terms of Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD). The FTIR spectra revealed the drug was found compatible and did not show any interaction with polymer, PXRD spectra showed clear transformation of crystalline to an amorphous form of drug particles. In-vitro dissolution study was performed in dissolution medium i.e. 0.1N HCL (pH 1.2). Cumulative percent drug release from SDs prepared by SE method was faster than from the pure drug, physical mixture (PM) and SDs prepared by MM method. The maximum percent drug release (93.43 ± 0.57) was found with PL 188 in the ratio of 1:5 (w/w). The solubility of drug was increased in concentration dependent manner of polymer and follow linearity order. The enhanced dissolution behaviour of SFNt-NP was possible with an optimized technique of solid dispersions. Solvent evaporation was able to increase the surface area with reduced crystallite size, which accelerated the dissolution of SFNt-SD. This method and drug/carrier combination ratio could be easily extended to other low water soluble active pharmaceutical drug candidates as a handing approach to enhance their solubility and dissolution properties.

Keywords Solubility enhancement, Solid dispersion, Solvent evaporation, Sorafenib tosylate (SFNt), Anticancer

Introduction

Poor water solubility of drugs in gastrointestinal fluid is a rate limiting stage of bioavailability and a challenging task for researchers to enhance the water solubility [1]. SFNt is a weak base and practically insoluble in water. According to Biopharmaceutical Classification System (BCS), SFNt comes under the BCS class II characterized high permeability low solubility drugs [2]. In order to enhance the solubility, numerous techniques have been investigated by the researchers viz. SDs [3], spray drying [4], size reduction [5], salt formation [6], alteration of pH

[7], addition of surfactants [8], inclusion complex formation [9], polypeptide nanocapsule [10], surface modification [11], lipid nanoparticles [12], nanoliposomal formulation [13], self emulsifying [14] electrospraying, lyophilisation using proper hydrophilic carriers in suitable concentrations [15]. In the SDs approaches HPMC E5 LV, PEG 6000 and PL 188 are used most frequently as solubilizing agents. Chemically SFNt is 4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino]phenoxy]-N-methylpyridine-2-carboxamide;4-methylbenzenesulfonic acid, with molecular weight of 464.825 g/mol and pKa of 2.2 basic at 25 °C. It blocks the enzyme RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division, and proliferation; in addition, sorafenib inhibits the VEGFR-2/PDGFR-beta signaling cascade, thereby blocking tumor angiogenesis and is an organosulfonate salt [16]. SFNt is used for the treatment of primary kidney cancer, advanced primary liver cancer, FLT3-ITD positive AML and radioactive iodine resistant advanced thyroid carcinoma. In the few decades, the surface tension reducing agents have been used alone and in combination for SDs formulation. Hydroxypropyl methyl cellulose also known as methocel is low viscosity water soluble polymer. Polyethylene glycol is a polyether and also known as carbowax. PL 188 is a non-ionic polymer containing hydrophilic and hydrophobic cavities, used to increase the solubility of poorly aqueous soluble drugs [17]. Some physicochemical properties of polymers such as biocompatibility, wetability, prevent drug precipitation, prevention of crystal formation, surface area enhancement, and plays vital role to improve the water solubility by SDs method. SDs method has been employed to enhance the solubility and dissolution of many BCS class II drugs. Aqueous soluble surface active agents and synthetic polymers have been introduced, as a solubilising carrier in the SDs formulation. The purpose of this present work was to improve solubility and owing to this, better bioavailability with reduced side effects [18]. SFNt structure shown in Fig. 1.

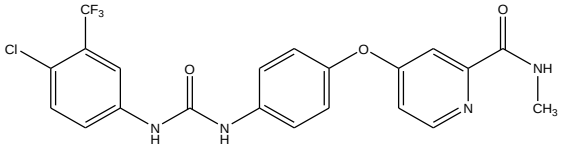

Figure 1: Chemical structure of SFN

Material and Method

Material

SFNt was gifted by Cipla Pharmaceutical Company Mumbai, India, PL 188 from Sigma-Aldrich India. All other reagents were used of analytical grade.

Method

Phase solubility studies

The solubility studies of SFNt and SDs prepared by SE and MM were determined in distilled water, 0.1N HCl (pH 1.2) and phosphate buffer of pH 7.4 at 25°C. For every preparation, excess amount of SDs were added to the 25 ml of distilled water, 0.1 N HCl and phosphate buffer (pH 7.4) in a glass vial (screw capped) respectively. The vials were placed in incubator shaker at 25°C temperature for 24 hrs. The solutions were then filtered through a Millipore membrane filter 0.45 (micrometer), and the filtrates were further diluted and analysed by UV spectrophotometer at λ_{max} of 265 nm [19].

Preparation of physical mixtures

SFNt and PL 188 in the ratio of 1:1, 1:3 and 1:5 triturated in a pestle and mortar for 3 minutes screened by #40 sieve and were stored in desiccators till further use [20].

Preparation of SDs by melting method

SFN and PL 188 in different weight ratio 1:1, 1:3 and 1:5 were heated on oil bath, until it PL 188 melted completely. The SFNt was then dispersed to the melted PL 188. The obtained mixture was immediately cooled on ice cubes, crushed by and mortar pestle then shifted through a #40 sieve [21].

Preparation of SDs by SE method

Weighed accurately SFNt and PL in the ratio of 1:1, 1:3 and 1:5, drug and polymer were dispersed in methanol. Then the solvent was evaporated rapidly by heating up to 45°C with stirring on magnetic stirrer, a uniform solid mass was formed. The prepared solid dispersions were crushed and desiccated for 24 hrs under vacuum, further pulverized, through#40 sieve was screened and stored in desiccators [21].

Table 1: Formulations of SDs of SFNt

Method	**PL 188**		
	Mixing ratio		
	1:1	**1:3**	**1:5**
PM	SPM1	SPM2	SPM3
MM	SMM1	SMM2	SMM3
SE	SSE1	SSE2	SSE3

Characterization of SDs

Drug content

SDs of SFNt equivalent to 10 mg were accurately weighed and dissolved in 10 ml of methanol, in a 100 ml volumetric flask, then the volume was made up with 0.1N HCl, solutions were mechanically shaken for 30 min and filter by 0.45 (micrometer) Millipore membrane filter. Then concentration of 10 µg/ml was prepared and drug content was measured by UV spectrophotometer at λ_{max} of 265 nm [22].

Fourier transform infrared spectroscopy (FTIR)

SFNt, PL 188, PM and SDs were made into fine powder by mortar and pestle, placed into the sample holder of FTIR and recorded FTIR spectra in the spectral range of 4000-400 $cm^{-1}$of FTIR (Alpha II Bruker Germany) [23].

Powder X-ray diffraction pattern (PXRD)

SFNt, PL 188 and SDs were analysed by PXRD diffractogram (Rigaku, Ultima IV, Japan) using Cu-Kα radiation of (40 kV, 320 mA) at 2º/min of analysing speed and 2º/2 cm per 2°θ of chart speed [23].

***In-vitro* drug dissolution studies**

The *in-vitro* dissolution study of Pure drug, SDs prepared by SE method drug equivalent to 10 mg of SFNt was filled into the hard gelatine capsule and performed in 900 ml of 0.1N HCl (pH 1.2) at 37ºC ± 0.5ºC by USP type II dissolution test apparatus, (paddle type) at 50 rpm for 120 min. A 5 ml of aliquots were withdrawn from the vessels, maintaining sink environment with replacement of 5 ml fresh medium at time interval of 0, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 minutes, filtered by Millipore membrane filter 0.45 (micrometer), then filtrates were diluted, and analysed by spectrophotometer (UV1800 Shimadzu, Japan) at λ_{max} of 265 nm; the experiment was repeated three times [13, 15].

Results and Discussion

Phase solubility studies

The profile of phase solubility of SFNt was found to be 1.76±0.24, 2.19±0.11, 1.83±0.45µg/ml in distilled water, 0.1N HCl, and phosphate buffer pH 7.4, respectively. The results strongly suggest for the need to enhance the solubility and dissolution rate of SFNt. The SSE3 SDs prepared by SE method demonstrating maximum solubility in 0.1N HCl (29.77±0.79 µg/ml) and was selected for further dissolution studies.

Table 2: Phase solubility studies data of PM and SDs of SFNt in distilled water, 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4)

S. No.	Formulations	Solubility in distilled water (µg/ml)	Solubility in 0.1N HCl pH 1.2 (µg/ml)	Solubility in Phosphate buffer pH 7.4 (µg/ml)
1	Pure Drug (SFN)	1.76±0.24	2.19±0.11	1.83±0.45
2	SPM1	3.48±0.13	8.15±0.17	8.62±0.11
3	SPM2	3.53±0.67	8.21±0.32	8.70±0.26
4	SPM3	3.76±0.41	9.18±0.87	8.87±0.64
5	SMM1	15.55±0.82	17.79±0.51	15.18±0.74
6	SMM2	16.89±0.44	18.21±0.34	16.22±0.44
7	SMM3	16.63±0.17	18.68±0.42	16.96±0.04
8	SSE1	18.21±0.69	28.72±0.11	17.59±0.66
9	SSE2	20.56±0.71	28.73±0.87	17.78±0.78
10	**SSE3**	21.46±0.01	**29.77±0.79**	20.33±0.56

Data are expressed as mean ± S.D. (n=3)

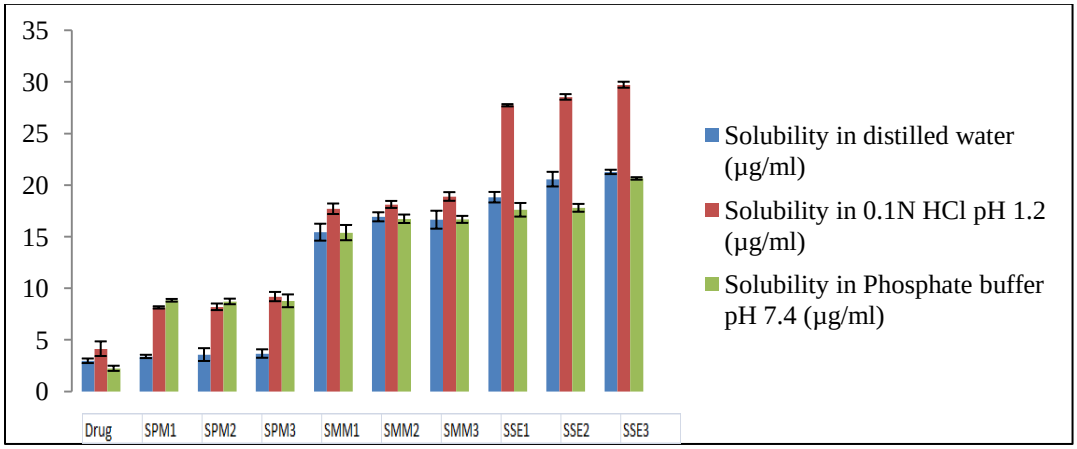

Figure 2: Bar graph of solubility of SFNt, PM and SDs in distilled water, 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4)

Characterization of physical mixtures and solid dispersions

Drug content

Table 3: Drug contents of SDs of SFNt

S. No.	Formulations	% Drug content
1	SPM1	91.26±0.23
2	SPM2	91.58±0.37
3	SPM3	91.71±0.68
4	SMM1	92.91±0.40
5	SMM2	93.23±0.17
6	SMM3	94.36±0.91
7	SSE1	95.89±0.19
8	SSE2	96.36±0.71
9	SSE3	97.76±0.81

Data are expressed as mean ± S.D. (n=3)

The drug content for PM (91.26±0.23 to 91.71±0.68) and SDs prepared by MM (92.91±0.40 to 94.36±0.91) and by SE method (95.89±0.19 to 97.76±0.81) was obtained respectively, given in Table 4.

Fourier transform infrared spectroscopic (FTIR) studies

The FTIR spectra of SFNt indicated presence of 2874 C-H stretching, 1694 C=O stretching, 1540 C=C stretching, 1460 N-H bending, 1099 C-O bending, 948 C- F bending and 674 C-C bending in Fig. 3.

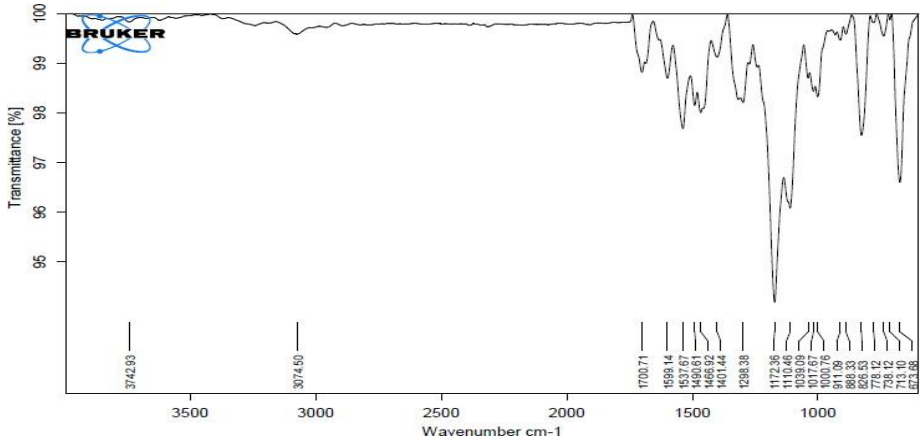

Figure 3: FTIR spectra of SFNt

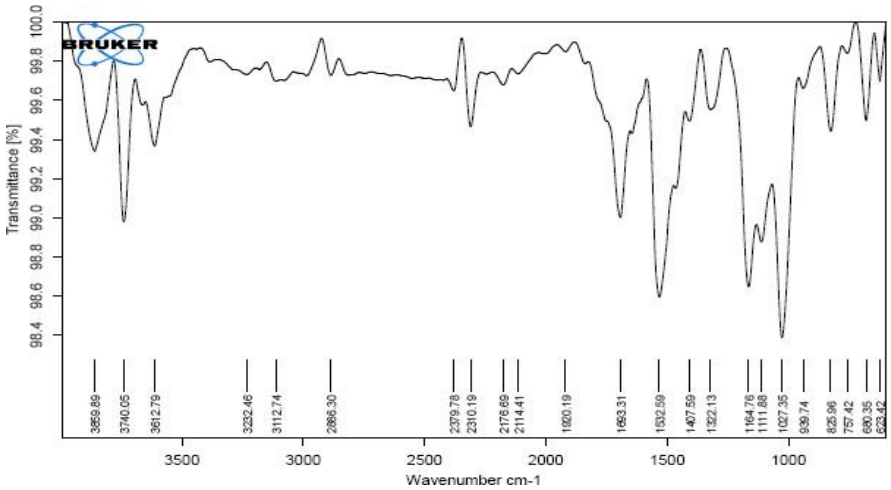

Figure 4: FTIR spectra of SFNt with PL 188, SDs (SE 1:5)

FTIR spectra of SFNt, PL and SDs are presented in Fig. 3 and Fig. 4. The spectra of SFNt exhibit characteristic peaks at The FTIR spectra of SFNt indicated presence of 2886 C-H stretching, 680 C-C stretching, 1027 C-F stretching, 1693 C=O stretching and 1664 C-C stretching, 1532 N-H bending in Fig. 4. were observed. No any interaction between the drug and polymer was seen, and the peaks of the functional groups of SFNt were reserved well in the solid dispersion and intensity of peaks of polymer was increased while intensity of SFNt peaks decreased in the. These findings revealed that excellent compatibility found between the drug and polymer.

Powder X- ray diffraction (PXRD) studies

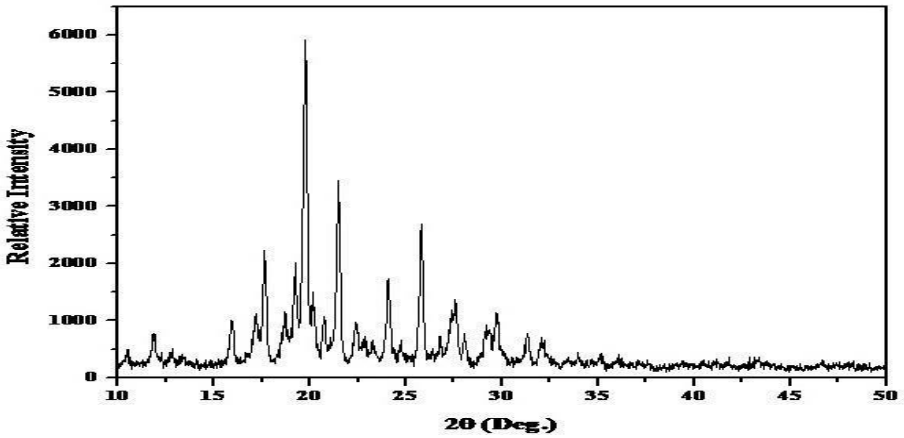

Figure 5: PXRD peaks of SFNt pure

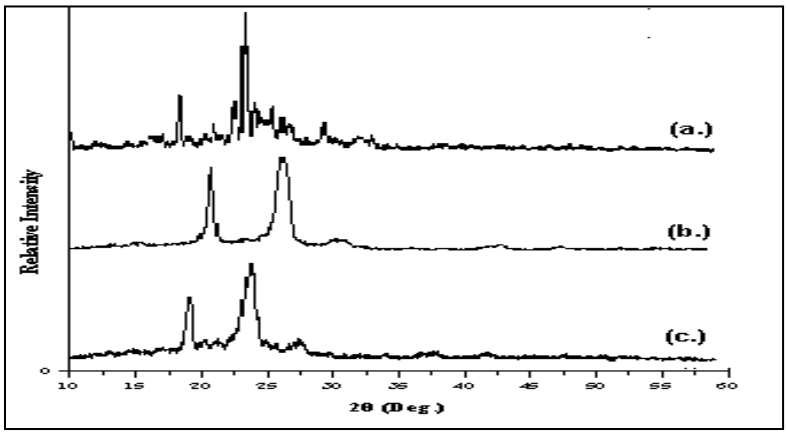

Figure 6: PXRD peaks of (a) SFNt, (b) PL 188, (c) SDs (SM 1:5)

PXRD spectra of SFNt, PL 188 and SDs prepared by SE method are presented in Fig. 6. The PXRD spectrum of the pure drug showed distinct sharp peaks at diffraction angle (2°θ); it confirms that the drug was present in the crystalline form. The PXRD of SDs prepared by SE method indicating the reduction in intensity and number of typical diffraction peaks of SFN. Indicating the reduction in the crystalline nature of core drug. Thus the drug must have been changed from the crystalline state to the amorphous or fine powder in the SDs.

***In-vitro* drug dissolution studies**

Table 4: Dissolution data of SFNt, PM, SDs prepared by MM and SE methods (1:5) in 0.1N HCl (pH 1.2)

Time (min)	Drug	SPM1(1:1)	SPM2 (1:3)	SPM3 (1:5)	SMM1 (1:1)	SMM2 (1:3)	SMM3 (1:5)	SSE1 (1:1)	SSE2 (1:3)	SSE3 (1:5)
0	0	0	0	0	0	0	0	0	0	0
10	3.51± 0.11	5.67± 0.21	5.89± 0.71	6.11± 0.51	4.11± 0.27	5.34± 0.50	6.51± 0.28	5.12± 0.09	6.72± 0.92	7.50± 0.70
20	5.78± 0.22	9.20± 0.72	11.78± 0.89	13.30 ±0.27	13.29± 0.29	16.20± 0.49	18.12±0.20	13.31± 0.67	17.20 ±0.56	18.02 ±0.78
30	8.60± 0.42	11.29 ±0.32	14.02 ±0.59	17.21 ±0.57	17.71± 0.38	20.31± 0.37	23.93±0.68	19.39 ±0.29	20.13 ±0.42	23.79 ±0.20
40	11.12 ±0.40	17.42 ±0.72	19.13 ±0.47	21.31 ±0.60	19.01± 0.24	23.41± 0.27	28.02±0.92	20.31 ±0.36	22.42 ±0.43	25.31 ±0.70

50	15.30 ±0.47	23.51 ±0.29	26.16 ±0.52	29.41 ±0.36	23.31± 0.27	25.61± 0.78	33.52±0.45	25.49 ±0.81	31.72 ±0.03	32.91 ±0.76
60	18.78 ±0.10	38.35 ±0.70	39.78 ±0.25	46.90 ±0.90	33.61± 0.03	38.39± 0.87	44.82±0.49	30.32 ±0.27	39.40 ±0.68	47.82 ±0.08
70	21.12 ±0.39	41.62 ±0.38	44.11 ±0.06	47.66 ±0.76	38.41±0.78	47.51±0.44	54.62±0.03	38.27 ±0.48	49.71 ±0.60	55.62 ±0.33
80	22.20 ±0.28	50.32 ±0.60	53.64 ±0.10	59.61 ±0.58	47.82± 0.25	58.31± 0.40	60.91±0.09	46.91 ±0.40	58.82 ±0.50	61.21 ±0.45
90	23.89 ±0.69	63.41 ±0.19	65.04 ±0.91	66.30 ±0.82	55.72± 0.65	63.41± 0.59	66.32±0.41	58.51 ±0.50	66.41 ±0.31	69.71 ±0.18
100	25.10 ±0.40	69.40 ±0.81	72.47 ±0.06	75.31 ±0.81	58.34± 0.18	69.38± 0.48	70.84±0.50	69.21 ±0.60	75.58 ±0.41	79.08 ±0.90
110	25.45 ±0.29	74.41 ±0.54	75.30 ±0.58	76.48 ±0.28	66.29± 0.37	77.84± 0.39	78.31±0.71	78.09 ±0.69	79.41 ±0.29	82.31 ±0.51
120	25.45 ±0.29	79.38 ±0.38	82.31 ±0.26	83.48 ±0.16	71.31± 0.22	82.69± 0.21	86.62±0.06	80.41 ±0.21	85.69 ±0.44	93.43 ±0.57

Data are expressed as mean ± S.D. (n=3)

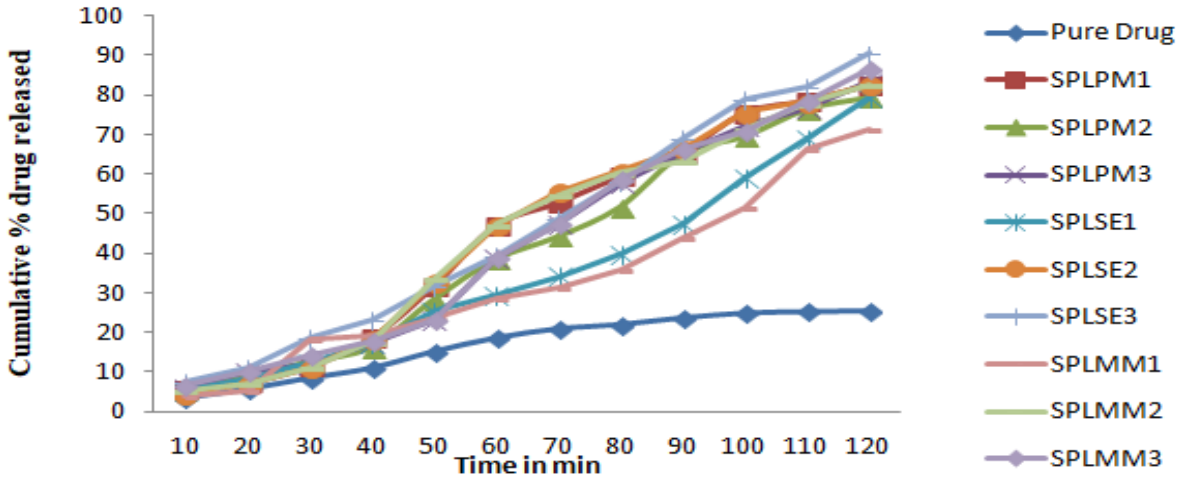

Figure 7: Dissolution profiles of SFNt, PM, SDs prepared by MM and SE methods (1:5) in 0.1N HCl (pH 1.2)

In-vitro dissolution profiles in 0.1N HCl (pH 1.2) of SFNt, PM and its SDs prepared by SE, and MM method with the PL 188 in different ratio were shown in Fig. 8. Pure drug (SFNt) release was found to be only 25.45±0.29 in 120 minutes, result strongly suggest for the need to enhance the dissolution. The results of *in-vitro* cumulative percent drug release indicated that the SE method improved the dissolution rate of SFNt to a great extent. Drug release from SDs prepared by SE method was faster than from the pure drug, PM and SDs prepared by MM method. The drug release from the SDs prepared by SE method (SSE3) was found maximum at 100 minute (79.08±0.90), but after 100 minutes it becomes constant. The maximum Cumulative percent drug release shown by SSE3 formulation was 93.43±0.57 in 120 minutes, this may be due to the molecular and colloidal dispersion of drug in hydrophilic carrier matrix of PL 188. The reduction of crystallinity of drug resulting in improved release (supported by PXRD); reduction of particle size to expand the effective surface area for dissolution solubilizing effect of PL 188.

Conclusion

The aim of present research work was preparation of SDs, by the PM, MM and SE using several combinations (drug: carrier) with PL 188 polymer and found remarkably improved solubility. Among the used techniques, SE method exhibiting maximum increased in solubility and dissolution characteristics as well as *in-vitro* drug release profile. Therefore, it is concluded that the use of the SE method is a promising approach to enhance the solubility

and dissolution rate, it seems that it will be possible to develop a bioequivalent product even with the reduced dose of the of SFNt, which is practically insoluble water drug. Reduction in surface tension, increase surface area and wetting properties was the major mechanism of enhancing the dissolution rate and solubility of SDs made by PL 188.

Acknowledgement

Authors are grateful to Cipla Company, Mumbai, India for providing gift samples of Sorafenib tosylate. I am much thankful to Head, Department of Pharmaceutical Sciences, Physics and Chemistry, University College of Science, Mohanlal Sukhadia University, Udaipur for providing all necessary facilities to carry out this research work.

Conflicts of Interest

I declare that I have no conflicts of interest.

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