RESEARCH ARTICLE

Preparation and Characterization of Solid Dispersion of Sorafenib Tosylate for Enhancement of Bioavailability

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ABSTRACT

Solid dispersions have garnered significant attention as an effective strategy for enhancing the solubility and, consequently, the bioavailability of poorly water-soluble drugs. By forming solid dispersions of these drugs with water-soluble carriers, issues related to limited solubility have been mitigated, leading to improved dissolution rates. The core focus of solid dispersion technology revolves around the creation of two-component systems involving the drug and a polymer, where the successful dispersion and stabilization of the drug play pivotal roles in the formulation development process. As a result, this technology is widely acknowledged as a highly valuable approach for enhancing the dissolution properties of poorly water-soluble drugs. In recent years, a substantial body of knowledge has been amassed concerning solid dispersions. Nonetheless, their practical implementation in the commercial sphere remains somewhat limited.

In the current investigation, we embarked on the preparation of a solid dispersion of sorafenib tosylate, with the primary objective of achieving the maximum release of the drug within the shortest possible timeframe. Our aim was to develop and optimize the solid dispersions of sorafenib tosylate in a manner that ensures the successful design and formulation of this system.

Keywords: Solid dispersion, Sorafenib tosylate, Polymeric carriers, Drug release.

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INTRODUCTION

The oral route of drug administration stands as the most common and preferred method for delivering medication due to its convenience and ease of ingestion. From a patient's perspective, taking medication by swallowing a dosage form is a comfortable and widely accepted means of treatment. This, in turn, enhances patient compliance, making it more effective compared to other routes like the parenteral route.[1-3] While the oral route is the preferred option, it can be problematic and inefficient for certain drugs due to several reasons. Limited drug absorption, leading to poor bioavailability, is one of the potential challenges when delivering active agents orally. When a drug is administered orally, it initially dissolves in the stomach's acidic environment and then needs to pass through the membranes of the gastrointestinal tract to enter the systemic circulation. Consequently, a drug with poor aqueous solubility often experiences dissolution rate-limited absorption, while a drug with poor membrane permeability typically faces permeation rate-limited absorption.[4-6]

Two critical areas of pharmaceutical research aim to address these challenges and enhance the oral bioavailability of active agents: improving the solubility and dissolution rate of poorly water-soluble drugs and enhancing the permeability of drugs with limited membrane permeability. Solubility is a crucial factor in determining the rate of absorption. For a drug to exert its therapeutic effect, it must enter the systemic circulation. Modern technologies, such as combinatorial chemistry and high throughput screening (HTS), have led to the discovery of new drugs with promising pharmacological activities. However, a significant proportion (35–40%) of these newly discovered drugs exhibit poor aqueous solubility.[7,8] In the Biopharmaceutical Classification System (BCS), drugs

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with high membrane permeability and low aqueous solubility fall into Class II. This is where solid dispersion technologies come into play, particularly in improving the oral absorption and bioavailability of BCS Class II drugs.[9-11]

Solid dispersion is a pharmaceutical formulation technique used to enhance the solubility and bioavailability of poorly water-soluble drugs. It involves dispersing a drug within a solid matrix, typically a polymer or a combination of polymers, with the aim of improving its dissolution rate and, consequently, its absorption within the body. This technology has gained significant attention in the pharmaceutical industry as it provides a solution to the challenge of delivering drugs with limited aqueous solubility, which is a common issue in drug development. Many pharmaceutical compounds have poor solubility in water, which can hinder their absorption and therapeutic efficacy when administered orally. This low solubility often results in inadequate bioavailability, longer onset times, and inconsistent drug delivery.[12,13] The primary objective of solid dispersion is to increase the solubility of the drug in gastrointestinal fluids, thereby improving its dissolution rate. This enhanced solubility enables more efficient drug absorption and better therapeutic outcomes. Solid dispersion formulations commonly use carrier materials such as polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG), and various copolymers. These carriers play a critical role in stabilizing the dispersion and influencing drug release.[14-16]

Various methods can be employed to prepare solid dispersions, including hot melt extrusion, spray drying, solvent evaporation, and freeze-drying. The choice of method depends on the drug's properties, the carrier material, and the desired dosage form. Sorafenib tosylate (SF) is classified as a BCS Class II drug, characterized by low solubility. It undergoes first-pass metabolism, leading to a reduced bioavailability of 38%. Despite this, SF is an important bi-aryl urea and an oral multikinase inhibitor used to treat hepatocellular carcinoma, a type of liver cancer that cannot be removed surgically.[17,18] In the current study, a solid dispersion of SF was prepared with the aim of achieving the maximum release of the drug in the shortest possible time, contributing to the successful design, development, and optimization of SF solid dispersions.

MATERIALS AND METHODS

Method of Preparation

To create solid dispersions of sorafenibtosylate (SF), three different carriers were used *viz.* Polyethylene glycol 6000 (PEG 6000), polyvinyl pyrrolidone K30 (PVP K30), and Eudragit RL 100. In the vast array of available techniques, we opted for the physical mixture approach to prepare these solid dispersions. The process involved the precise measurement of SF and the selected carriers, followed by their meticulous blending in a glass mortar through trituration. Subsequently, the resulting mixture was passed through a 44-mesh sieve and then carefully stored in a desiccator, where it awaited further examination and analysis.

Experimental Design

In our research, Box-Behnken Design was used to investigate the impact of key independent variables, specifically Polyethylene glycol 6000 (PEG 6000) denoted as X1, Eudragit RL 100 (EUD RL 100) denoted as X2, and Polyvinyl pyrrolidone K30 (PVP K30) denoted as X3. These variables were evaluated with respect to their influence on essential dependent variables, namely the percentage of Cumulative Drug Release (%CDR), designated as Y1, and the time required to achieve a certain %CDR, designated as Y2. Our study involved the exploration of the effects of these independent variables across three different levels. To facilitate our analysis, we appropriately coded the factors and their respective levels. These codifications were instrumental in the design and execution of our experimental approach. We established a polynomial equation to derive meaningful conclusions from our data. This equation allowed us to consider not only the magnitude of the coefficients but also the mathematical signs they carried, whether positive or negative, to better understand and interpret the relationship between the variables. Our criteria for selection primarily hinged on achieving the highest %CDR values, aiming to exceed the 90% mark, and simultaneously striving for the shortest time required to reach %CDR, ideally less than 90 minutes. This meticulous approach guided us in singling out the formulations that best met these stringent criteria, ensuring that they represented the pinnacle of results. Table 1 represents coded factors with their levels and Tables 1 and 2 represent drug and polymer ratio as per BOX Behnken experimental design.

Characterization

Fourier transform infrared spectrometry (FTIR)

FTIR of pure drug SF and PEG 6000, PVP K30 and EUD RL 100 was carried out by using a JASCO FTIR-410, Japan. The spectra were scanned over a wavelength region of 400 to 4000 cm^{-1}, resolution of 4 cm^{-1} and an accumulation of 20 scans were used in order to obtain good quality spectra by making a pellet of the sample with KBr.[19]

Differential scanning calorimetry (DSC)

The phase transition of the pure drug, excipients, solid dispersion formulation batches were studied by thermogram obtained by using a differential scanning calorimeter (Dupont 2000, model SDT- 2960, USA). An empty aluminum pan was used as a reference. DSC measurements were performed at the heating rate of 10ºC/min from 25 to 350ºC using an aluminum sealed pan. Sample weight was kept between 5- 10

Table 1: Coded factors with their levels

Factors	*Levels*		
	Minimum (-1)	*Intermediate (0)*	*Maximum (+1)*
PEG 6000	1:0.5	1:1	1:1.5
EUD RL 100	1:0.5	1:1	1:1.5
PVP K30	1:0.5	1:1	1:1.5

Table 2: Drug and polymer ratio as per BOX Behnken experimental design

Batch	*SF*	*PEG 6000 (A)*	*EUD RL 100 (B)*	*PVP K30 (C)*
F1	1	-1.00	-1.00	0.00
F2	1	1.00	-1.00	0.00
F3	1	-1.00	1.00	0.00
F4	1	1.00	1.00	0.00
F5	1	-1.00	0.00	-1.00
F6	1	1.00	0.00	-1.00
F7	1	-1.00	0.00	1.00
F8	1	1.00	0.00	1.00
F9	1	0.00	-1.00	-1.00
F10	1	0.00	1.00	-1.00
F11	1	0.00	-1.00	1.00
F12	1	0.00	1.00	1.00
F13	1	0.00	0.00	0.00
F14	1	0.00	0.00	0.00
F15	1	0.00	0.00	0.00

mg. During the measurement, the sample cell was purged with nitrogen gas.[20]

X-ray powder diffraction (XRD)

The crystalline nature of pure drug and all solid dispersion formulation batches were examined by studying its X-Ray diffraction patterns by using powder X-Ray diffractometer (PW- 3710 BASED). It was determined whether the obtained formulation after precipitation is a co-precipitate of individual substances or whether it becomes co-crystal. The operating parameters for instrument were Cu filtered K (α) radiations, a voltage of 40 kV, current of 25 mA and receiving slit of 0.2 In. The instrument was operated over 2θ scale. The angular range was 5 to 50° (2θ) and counts were accumulated for 0.8 second at each step.[21]

In-vitro drug release

The *in-vitro* drug release of all the solid dispersion formulations was investigated by dissolution study. An accurately weighed amount of solid dispersion equivalent to 400 mg of SF was added to 900 mL of dissolution medium; of pH 1.2 phosphate buffer solution for the first two hours and pH 6.8 phosphate buffer for the subsequent hours until achieving 100% drug release using the USP rotating paddle dissolution apparatus (Lab India 2000) at 100 rpm and 37.5°C. A percent release study was continued from 5 to 30 minutes. The final volume in all cases was 900 mL. The samples were withdrawn from the dissolution medium at various time intervals. About 5 mL of sample was subjected to UV Spectrophotometric analysis at 264 nm (λ max of SF). All the samples were analyzed in triplicate.[22]

MTT Assay

The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyltetrazolium bromide) assay is based on the conversion of MTT into formazan crystals by living cells, which determines mitochondrial activity.[23,24] MCF7, liver cancer cell lines were cultured in DMEM (Dulbecco modified eagle medium) supplemented with 10% fetal bovine serum (FBS) penicillin (100 IU/mL) and streptomycin (100 µg/mL) (Krishgen Biosystems, Mumbai). The cells were incubated in an incubator containing a humidified atmosphere of 5% CO_2 at 37°C. For toxicity testing, the cells were utilized when they reached 60 to 70% confluency. The cells were diluted as needed and seeded as 5000 cells/ml for MCF7 cells in 200 µL media per well, sequentially plated in flat bottom 96-well plates. This number of cells was selected to avoid potential over-confluence of the cells by the end of the experiment while still providing enough cells for adequate formazan production. After plating, the 96 well plates were then incubated at 5% CO_2 at 37°C and 80% RH for 24 hours in an incubator (New-Brunswick Scientific CO281R) to allow adherence of cells prior to administration of various samples for testing. Different concentrations (160, 80, 40, 20, 10, 5 µg/mL) of samples were treated. The cells were incubated for another 48 hours. The wells were washed twice with phosphate buffer solution (PBS) and 20 µL of the MTT staining solution was added to each well and plate was incubated at 37°C. After 4 hours, 100 µL of DMSO was added to each well to dissolve the formazan crystals, and absorbance was recorded with a 570 nm using a microplate reader. The following equation (Eq. 1) was used.[25]

$$\text{Surviving cells (\%)} = \frac{\text{Mean OD of test compound}}{\text{Mean OD of Negative control}} x100 \ldots\ldots\ldots \text{(Eq. 1)}$$

RESULTS AND DISCUSSION

Characterization

Fourier transform infrared spectrometry (FTIR)

From the above studies, it can be concluded that the peaks obtained in the spectra of each sample correlates with the peaks of drug spectrum. From the FTIR spectra of all the procured samples (Figure 1) and characteristic bands (Tables 3-6), it is found that the spectra obtained by FTIR spectrometry, was concordant with the standard reference of the respective sample. Hence, it was confirmed that the procured drug and excipients samples were authentic.

Differential scanning calorimetry (DSC)

In differential scanning calorimetry (DSC), a comparison of DSC thermograms of drug alone as well as in the presence of polymer give an idea about the glass transition temperature (Tg) of dug in solid dispersions. DSC thermograms of sorafenib, as well as their solid dispersions prepared by physical mixture method, are shown in Figures 2 and 3. Pure sorafenib exhibited a characteristic, sharp endothermic peak at 200.54°C which is associated with the melting point of the drug and indicates the crystalline nature of the drug. However, the characteristic,

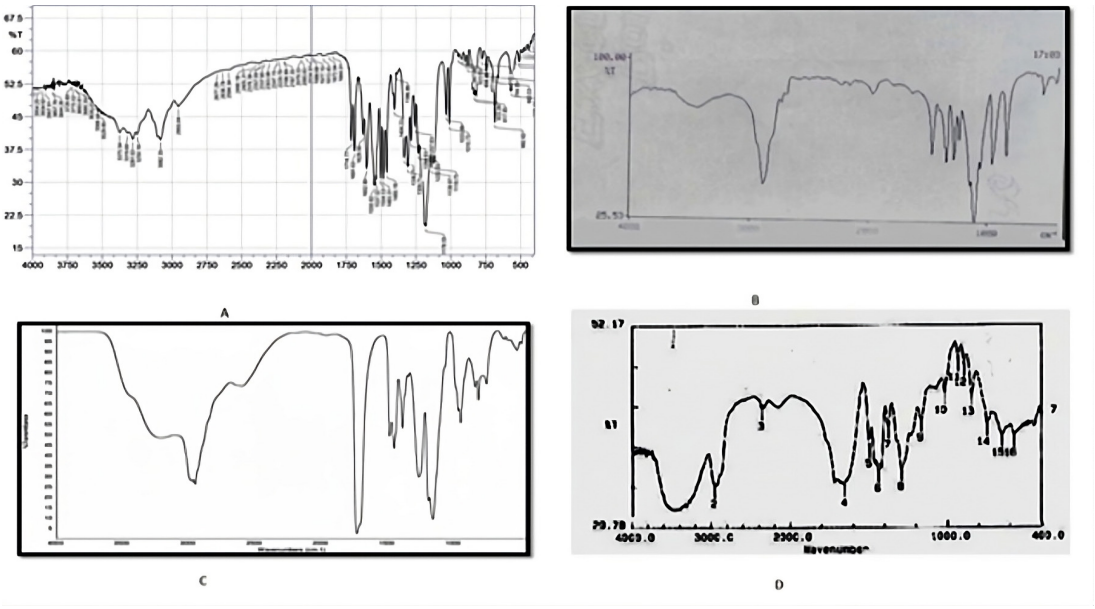

Figure 1 : A. IR Spectra of Pure Sorafenib B. FTIR spectra of procured PEG 6000 C. FTIR spectra of procured EUD RL 100 D. FTIR spectra of procured PVP K 30

Table 3: Authentication of Sorafenib by FTIR spectrometry

Type of vibration and Functional group/structure	*Wave number (cm^{-1})*	
	Reference	*Observed*
Amide	3675.36	3680.3
C-O bond	2353	2357.09
C=C stretching bond of alkynes molecule	2260-2100	2229.79
Diketones	1535-1640	1550.82
Isopropyl group	1368	1336
Ester Carbonyl	1270-1150	1257.63

Table 4: Authentication of PEG 6000 by FTIR spectrometry

Type of vibration and Functional group/structure	*Wave number (cm^{-1})*
O-H str	3447
Alkyl C-H str	2887
C=O str	1723
Alkyl C-H bending	1469, 1431, 1344, 1324, 1282

Table 5: Authentication of EUD RL 100 by FTIR spectrometry

Type of vibration and Functional group/structure	*Wave number (cm^{-1})*
O –H str	3400
Alkyl C-H stretching	2900,3000
C=O Str	1700, 1750
Alkyl C-H bending	1400,1500, 1200,1300
C-O str in ether	1350,1400

Table 6: Authentication of PVP K 30 by FTIR spectrometry

Type of vibration and Functional group/structure	*Wave number (cm^{-1})*
Alkyl C-H stretching	2950, 3000
C=O Str	1600, 1700
Alkyl C-H bending	1200, 1450
C-H out of plane bending	990, 910

The IR spectrum of pure drug, carrier were studied.

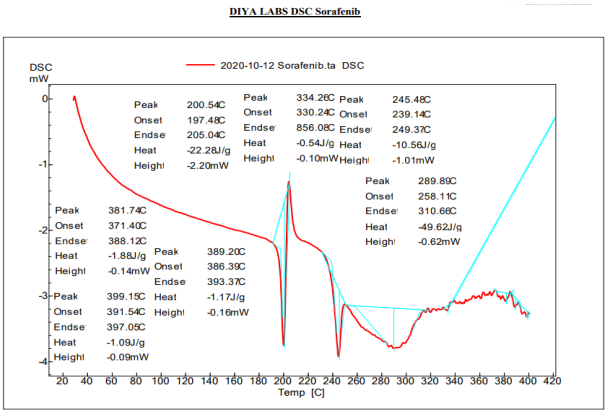

Figure 2: DSC of sorafenib

endothermic peak corresponding to drug melting was broadened and shifted towards a lower temperature with reduced intensity in solid dispersions. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in a polymer.

X-ray powder diffraction (XRD)

The crystalline nature of pure drug and solid dispersion formulation were examined by studying its X-Ray diffraction

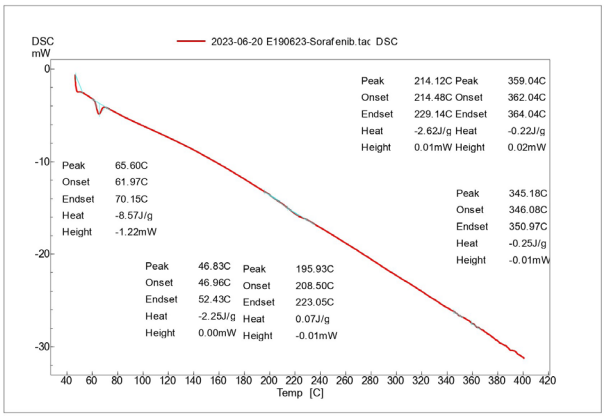

Figure 3: DSC of sorafenib formulation

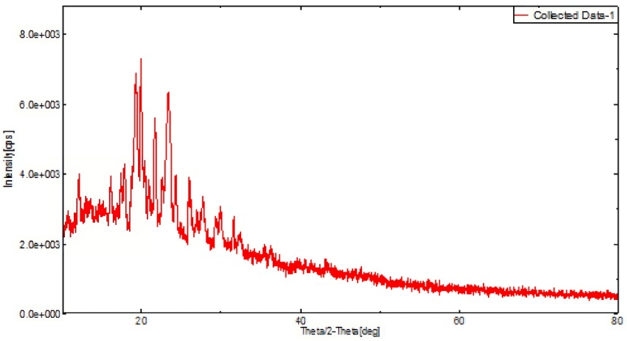

Figure 4: X-Ray Diffraction Study (XRD) of Sorafenib

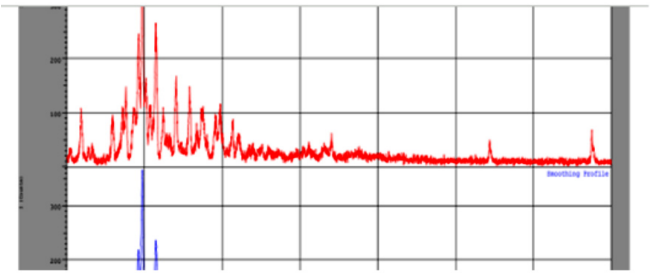

Figure 5: X-ray diffraction study (XRD) of formulation

patterns. The diffraction pattern of pure sorafenib was highly crystalline in nature as indicated by numerous peaks. Three peaks at 19.6770°, 21.4224°, 19.1800° main peaks were particularly distinctive. It is known that the lack of a distinctive peak of a drug in SD systems demonstrates that a high concentration of the drug is dissolved in the solid state. Moreover, a large reduction in characteristic peaks indicates an amorphous state. X ray powder diffraction patterns of pure sorafenib and solid dispersion are showed in Figures 4 and 5, respectively. X-ray diffraction of powder sorafenib showed sharp diffraction peaks, indicating the presence of crystalline form. Reduction of intensity of crystalline peaks was observed in the formulation. These results indicate that Sorefenib is no longer present in crystalline form, and its exits in the amorphous state.

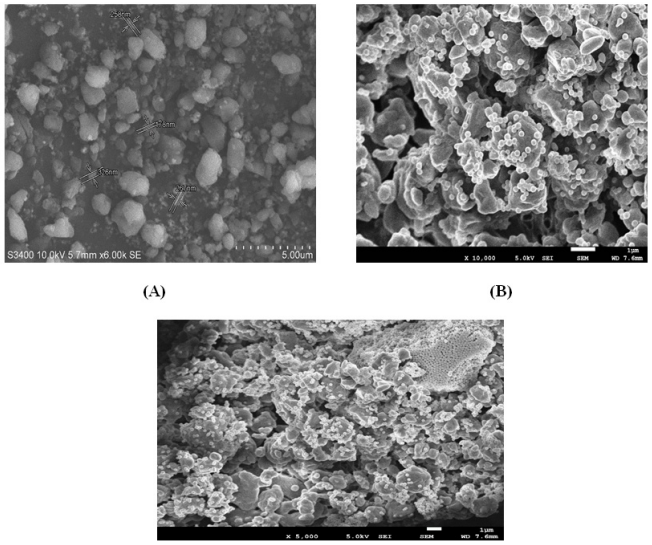

Figure 6: A. SEM of Sorafenib B. SEM of Formulation C. SEM of Formulation

SEM

Scanning electron microscopy (SEM): Scanning electron microscopy is very helpful in studying the change in the surface topography and shape of the particles of pure drug and solid dispersions. The batches of engineered crystals covering extreme polymer concentrations from the entire range of experimental batches were taken for SEM studies. Photomicrographs of the pure drug (Figure 6A) and solid dispersion are shown in Figures 6(B) and 6(C). Photomicrographs of the pure drug and the formulated batches revealed the change in particle shape and surface topography. SEM thus indicates that the polymer has formed a uniform coating over the individual drug particles thus resulting in the formation of spherical particles with improved crystal properties as revealed from later studies 10 structure. Many irregular particles with much fragmentation were observed. The scanning electron micrograph sorafenib solid dispersion showed the powder to be a typical aggregate of amorphous material. Many irregular particles with cluster were observed. This observation was further confirmed by differential scanning calorimetry and X-ray diffraction study.

In-vitro drug release

In-vitro dissolution studies were conducted on all formulated solid dispersions using USP dissolution test apparatus Type II, employing the rotating paddle method at 100 rpm with 900 mL of pH 1.2 phosphate buffer solution for the first two hours and pH 6.8 phosphate buffer for the subsequent hours until achieving 100% drug release. The temperature of the dissolution medium was maintained at 37 ± 0.5°C. The results of the *in-vitro* drug release profiles are depicted in Table 7 and Figure 7. Solid dispersions of sorafenib tosylate (SF) with PEG 6000, EUD RL 100, and PVP K30 in the ratio 1:0.5:1:0.5, respectively, exhibited complete drug release within 30

Table 7: Solid dispersion: Physical mixture method

Time in nin	*% CDR*														
	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*	*F10*	*F11*	*F12*	*F13*	*F14*	*F15*
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	4.24	1.41	20.25	8.95	71.1	0.94	12.24	10.83	4.71	6.12	5.18	19.78	13.65	14.85	17.65
30	41.43	13.65	90.4	28.25	99.41	6.12	57.91	25.9	16.95	81.45	20.72	32.49	43.79	53.71	44.75
45	65.92	27.31	101.12	41.9		57.44	97.46	45.67	26.84	103.11	36.25	76.75	87.58	77.54	76.87
60	68.74	81.45		79.1		59.8	100.76	57.91	47.08		81.93	90.87	91.34	82.24	80.79
75	72.04	81.45		90.87		61.68		57.93	68.27			91.81	88.05	89.15	85.65
90	72.51	85.69		95.58		66.39		102.64	72.51			92.28	88.99	90.55	89.99

Table 8: %Inhibition for sorafenib and formulation by MTT assay

S.No	*Sample*	*Concentration (µL)*	*OD*	*Mean*	*%Inhibition*	*IC_{50}*
	Control		1.340	1.282		
1			1.236			
			1.272			
		10	0.421 0.456	0.429	66.53	
			0.412			
		40	0.312	0.341	73.40	
2	Std.5FU		0.352			39.22
			0.361			
		100	0.287	0.263	79.48	
			0.256			
			0.246			
		10	0.616	0.638	50.23	
			0.640			
			0.659			
		40	0.522	0.521	59.36	
3	Sample-		0.525			38.14
	Plain drug		0.516			
		100	0.430	0.433	66.22	
			0.434			
			0.435			
		10	0.591 0.594 0.591	0.592	53.82	
4	Sample- Formulation	40	0.475 0.422 0.455	0.450	64.89	37.83
		100	0.365 0.330 0.350	0.348	72.85	

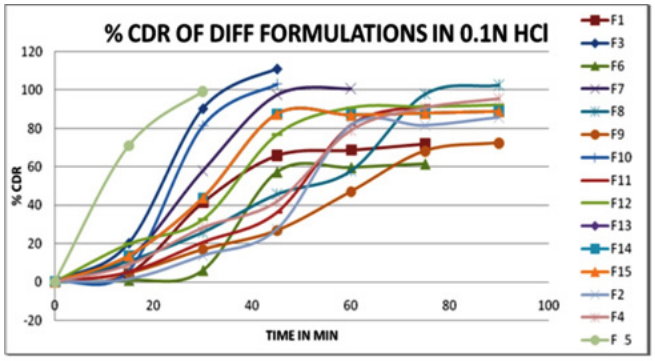

Figure 7: Release profile of all formulations

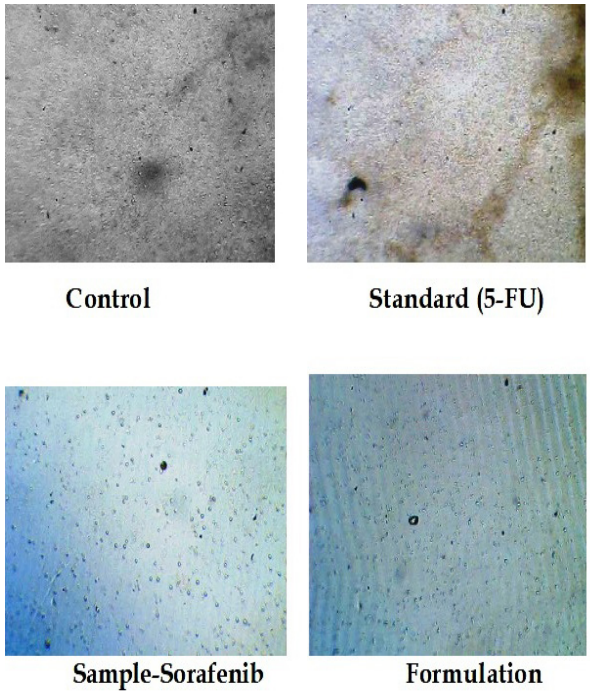

Figure 8: Effects of sorafenib against MCF-7 (Breast Cancer cell line) by MTT assay

minutes, whereas solid dispersions F3 and F10 demonstrated complete drug release by the end of 45 minutes. The solid dispersion granules, composed of sorafenib tosylate with PEG 6000, EUD RL 100, and PVP K30, showed enhanced drug dissolution. The hydrophilic properties of the carriers likely contributed to improved dissolution through increased wetting and reduced interfacial tension between the drug and the dissolution medium. Therefore, dissolution enhancement is correlated with solid dispersion. The studies indicated the drug release-retarding efficiency with the polymer concentration of the formulations.

MTT Assay

The antiproliferative activity of the solid dispersion of sorafenib tosylate was assessed through the utilization of the (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay, as outlined by Mosmann. Cytotoxicity against the MCF-7 cell line was determined by calculating the IC_{50} values for the standard drug 5-FU, plain sorafenib tosylate, and the formulated Sorafenib tosylate, yielding values of 39.22, 38.14, and 37.17, respectively. These results indicated no significant difference between the IC_{50} values. However, the impact of the drug on %inhibition exhibited a concentration-dependent relationship. Various concentrations (10, 40, and 100 µg/mL) were employed for cytotoxicity assessment, revealing a proportional increase in %inhibition with rising concentrations. At 100 µg/mL concentration, the %inhibition for standard 5-FU was 79.48%, plain Sorafenibtosylate was 66.22%, and the formulated Sorafenibtosylate was 72.85%. Notably, a direct correlation between absorbance and %inhibition was observed, further affirming the concentration-dependent nature of the cytotoxicity Table 8 and Figure 8. These findings suggest that the formulated sorafenib tosylate exhibited superior cytotoxicity compared to plain sorafenib tosylate, which demonstrated only moderate cytotoxicity.

CONCLUSION

The focal point of this study was to enhance the solubility of SorafenibTosyate, a representative poorly water-soluble drug. Various excipients, including PEG 6000, EUD RL 100, and PVP K 30, were employed for this purpose. Utilizing a Box Behnken design, the study aimed to analyze the impact of independent variables—PEG 6000, EUD RL 100 and PVP K 30—on dependent variables, namely %cumulative drug release and the time required for cumulative drug release.

Free-flowing, solid dispersion granules were obtained using the physical mixture method. The solid dispersion demonstrated an enhanced dissolution rate from sorafenib tosylate. The results indicated that a combination of various hydrophilic carriers with solid dispersion is a promising approach to enhance the release of poorly water-soluble drugs, such as sorafenib tosylate. The solid dispersions exhibited a linear release rate within 30 minutes in the gastric environment. Thus stable, safe, and effective solid dispersions containing Sorafenibtosylate with enhanced dissolution rate can be formulated successfully.

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