An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

FORMULATION AND EVALUATION OF IMMEDIATE RELEASE SORAFENIBTOSYLATE FILM COATED TABLETS

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ARTICLE INFO

Key Words

Immediate release, film coated, aqueous wet granulation, sorafenibtosylate, crosscarmellose sodium and sodium lauryl sulfate.

ABSTRACT

Developing generic versions is essential forpharmaceutical companies to economize the disease management programme. Immediate release formulations area novel type of drug delivery systems which disintegrates rapidly andgets dissolved to release the medicaments after administration.Sorafenibtosylate is kinase inhibitors, used to treat renal cell carcinoma. Presentwork involves the formulation and *in vitro*evaluation studies of immediate release sorafenibtosylate film coated tablets by aqueous wet granulation method. Tablet composition contains microcrystalline cellulose (MCC PH101) as afiller, crosscarmellose sodium (CCS) as superdisintegrant and sodium lauryl sulfate (SLS) as a surfactant. The prepared tablets wereevaluated for pre- and post- compression studies. It was concluded that all the pre-formulation and post compression studies of the formulated sorafenibtosylate film coated tablets met with required specifications. The formulation, F6 (with 10% CCS & 2% SLS) which shows comparably a good rate of dissolution rate like that of a marketed product, NEXAVAR 200 mg is selected as an optimized one. Furthermore, the optimized formulation (F6) passes the test for stability as per ICH guidelines.

INTRODUCTION

Oral dosage form is the physical form of chemical compound used as a drug or medication intended for administration or consumption by oral route. Common oral dosage forms are pills that contain tablets or capsules. The tablet is a solid dosage form which consists of a single dose of one or more active substances with or without excipients usually obtained by compressing uniform volumes of particles. It is essential that the exploration of new market for drugs and coupled with the high cost of disease management programs. Developing generic versions of the marketed formulations is necessary for pharmaceutical companies to economize the treatment plan. Immediate release drug formulation is a novel type of drug delivery system which disintegrates rapidly and gets dissolved to release the medicaments after administration. Recently, superdisintegrants such as sodium starch glycolate (SSG), crosscarmellose sodium (CCS), and crospovidone (CPV) shows good effectiveness at lower concentrations with greater disintegrating power and mechanical strength [1]. Surfactants like sodium lauryl sulphate (SLS) will enhance the dissolution rate of poorly soluble drugs. SorafenibTosylate (SFT), an orally active multikinase inhibitor with effects on tumor-

cell proliferation and tumor angiogenesis, was primarily identified as a Raf kinase inhibitor [2]. SFT prevents tumor growth, primarily by inhibiting angiogenesis [3, 4]. Most patients who had a response to SFT had clear-cell renal-cell carcinoma [5]. The aim of the study was formulation and in vitro evaluation of immediate release (IR) SorafenibTosylate film coated (SFT FC) tablets by aqueous wet granulation method. Further it involves the optimization of conc. of superdisintegrant (CCS) and conc. of surfactant (SLS) in developing the generic version of NEXAVAR 200 mg (marketed product).

MATERIAL AND METHODS:

Materials: SorafenibTosylate (SFT) is obtained as a gift sample from M/s NATCO Pharma Ltd., Hyderabad, India. Croscarmellose sodium (CCS), HPMC E5, microcrystalline cellulose (MCC PH 101), sodium lauryl sulphate (SLS), magnesium stearate was purchased from S.D. Fine-Chem. Ltd., Chennai, India. Advantia prime pink (coating composition) from Advantia chemicals Pvt. Ltd., Hyderabad, India. All the excipients used in study are of pharmaceutical grade. Nexavar 200 mg (marketed product) Bayer Health Care, Germany.

Methods:

Drug-excipient compatibility studies by FT-IR: FT-IR spectra of pure drug and drug: polymer (1:1) physical mixtures were recorded out, in the region of 400-4000 cm^{-1} at spectral resolution of 2 cm^{-1}, by the potassium bromide pellet method using (Shimadzu-1800,Japan) [6].

Calibration curve of SorafenibTosylatein 0.1N HClwith 1% w/v SLS by HPLC method:

Calibration curve of SorafenibTosylate was done in 0.1N HCl with 1% w/v SLS. From the stock solution, calibration standards were prepared by adding different concentration of the SorafenibTosylate solution and volume made with the mobile phase to yield the final respective concentration of 10, 20, 40, 60, 80 and 100 µg/mL. The standard solutions were injected separately and the chromatogram was recorded using a UV detector at 293 nm. The standard graph of SorafenibTosylate was constructed by taking the peak area on Y-axis and conc. on X-axis [6].

Preparation of Sorafeneib Tosylate immediate release tablets by the wet granulation method:

The intra granular ingredients SFT, MCC PH102, CCS and SLS were weighed and co-sift through 40 # mesh, transferred to a polybag and mixed for 10 min. Hypermellose-E5 was dissolved in purified water and used to granulate the dry blend. Wet mass was passed through 10 # mesh and dried in a hot air oven at 60 °C for 1 h. Dried granules were passed through 20# mesh and lubricated with 60 # mesh passed magnesium stearate by mixing in poly bag for 2 minutes and compressed with round, plain and concave 11 mm punches, with an avg. wt of 390 mg and hardness of 6-7 kg/cm^2 [6].

Film coating of SorafeneibTosylate immediate release tablets: Thecoating composition wasprepared by dispersing the advantia prime pink into purified water with constant stirring for 45 min to get a homogenous mixture. The tablets were coated in a coating pan by spraying the coating composition, up to 1% weight gain was attained by each tablet [6].

Pre-compression studies: Directly compressible tablet blends of TG-IR layer and MF-SR layer were evaluated for [angle of repose (θ), bulk density (BD), tapped density (TD), Carr's Index (CI) and Hausner's Ratio (HR)] [6-8].

Post-compression studies: [6-8]

Average weight of tablets: 20 tablets (n=20) were randomly selected from each batch and their weight was determined by an electronic balance(Sartorius, Germany).

Thickness: 6 tablets (n=6) were randomly selected from each batch and their thickness was measured using a verniercalipers (Mitutoyo Corporation, Japan.),

Hardness: 6 tablets (n=6) were randomly selected from each batch and their hardness was measured using a Monsanto hardness tester (Secor, India).

Disintegration time: The disintegration timewas determined by using disintegration test apparatus at 37° C ± 2° C. A tablet was placed in each of the six tubes of the apparatus and a disc was added to each tube. The time taken for the complete disintegration of the tablet with no palpable mass left in the apparatus was noted.

Friability: The friability of the 20 tablets from each batch was tested by a friabilator (Roche Friabilator, Germany) at a speed of 25 RPM for 4 min. The tablets were then de-dusted, re-weighed, and percentage weight loss was calculated by the equation below,

$$\% \text{ Friability} = \frac{(\text{Initial Wt.} - \text{Wt. after friability})}{\text{Initial Wt.}} \times 100$$

Eq. No. 1

% Assay: Accurately weighed 6 tablets from each batch (n=6) were powered and 100 mg drug equivalent powder dissolved in 0.1N HCl with 1% w/v SLS. The volume of the solution made up to 100 mL with mobile phase. Then the solution was filtered and diluted to 100 times and analyzed by HPLC and further calculation carried out to determine drug content per tablet. The assay value is calculated by using the below formula.

%Assay = UA/SA * SW/100 * 2/20 * 200/5 *50/2 * P/100 *100/LA *Eq. No. 2*

Where: UA = peak area response due to unknown impurity, SA= standard peak area response due to SFT, SW = wt. of SFT working standard taken in mg, P = purity of SFT working standard taken as on as the basis and LA=label amount of SFT

***In vitro* dissolution studies:** To optimize the composition of FC tablets, 6 tablets (n=6) were randomly selected from each batch and undergone dissolution in the USP-II (paddle) dissolution apparatus (Lab India DS 8000, India)**,** each flask was filled with 900 mL of 0.1N HClwith1% w/v SLS; speed of paddle was maintained at 50 rpm, the temperature was kept constant at 37°C ± 0.5°C. At time points 0, 5, 10, 20 and 30 min; 5 mL of dissolution media was withdrawn, filtered through 0.45µm membrane filter, suitably diluted and analyzed. The samples were analyzedspectrophotometrically by HPLC and further calculation was carried out to get the % drug release. Each sample withdrawn was replaced with an equal amount of fresh 0.1 N HClwith1% w/v SLS, to keep the volume constant.

***In vitro* drug release kinetic studies:** The *in vitro* drug release data of all batches were fitted into zero order and first order models to ascertain the drug release kinetics [9].

Zero order: $Q_t = Q_0 + K_0 t$ ***Eq. No. 3***

First order: $\text{Log } Q = \text{Log } Q_0 - K_1 t / 2.303$ ***Eq. No. 4***

Further the drug release data were plotted and tested with zero order (Cumulative % released Vs time) and First order kinetics (Log % remained Vs time).

Comparision of dissolution profiles of marketed (Nexavar 200 mg) and optimized formulation (F6): Moore and Flanner [10] proposed a model independent mathematical approach to compare the dissolution profiles using two factors: Difference factor (f_1) and similarity factor (f_2). The similarity factor (f_2) is the simplest and widely applicable.

$$f_1 = \{[\sum_{t=1}^{n} |Rt - Tt|] / [\sum_{t=1}^{n} Rt]\} 100 \quad \textit{Eq. No.5}$$

$$f_2 = 50 \log\{[1+(1/n)\sum_{t=1}^{n}(Rt - Tt)^2]^{-1/2} 100\} \quad \textit{Eq. No. 6}$$

Where: Rt and Tt are the cumulative % dissolved at each of the selected n time points of the reference (Nexavar 200 mg) and test (F6) product, respectively.

Accelerated stability studies on optimized formulation: 20 tablets of optimized formulation (F6) packed in 10 CC HDPE and up to 3 months accelerated stability studies were carried according to International Conference on Harmonization (ICH) guidelines by placing in a humidity chamber (NSW-175, Narang Scientific work, India) maintained at 45°C ± 2°C and 75% ± 5% RH [11]. At the end of every month up to 3 months, the samples were withdrawn and evaluated for post compression studies. The consolidated results of accelerated stability studies of optimized formulation (F6) were tabulated. Comparative *in vitro* dissolution profiles of initial and accelerated stability samples of optimized formulation (F6) were shown diagrammatically. The chemical stability of

drug in the 3M-accelerated stability sample of optimized formulation (F6); which will influence the *in vitro* and *in vivo* dissolution characteristics was investigated using FT-IR studies.

RESULTS ANDDISCUSSION:

Drug and excipient compatibility studies by FT-IR: An interpretation of FT-IR spectrum of SFT (pure drug) reveals that the IR bands of pure drug; drug and excipients show no significant shifts or reduction in intensity of the FT-IR bands. Hence there was no incompatibility problem between the drug and excipients used in the study. The FT-IR spectra and the interpretation of SFT FT-IR spectra were shown in (**Fig.1)** and (**Table 2),** respectively.

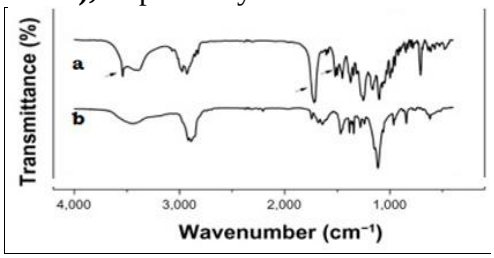

Fig.1. FT-IR spectra of a) SFT and b) SFT+CCS

Calibration curve of SFT in 0.1N HClwith 1% w/v SLS by HPLC method:

λ_{max}ofTG in 0.1N HClwith 1% w/v SLS is 246 nm. The standard curve is following linearity with aregression coefficient of (r^2=0.999). It is obeying the Beer's law in the conc. range of 0-100 µg/mL. Lowerstandard deviation (SD) values ensured reproducibility of the method. As the excipients used in thestudy were not interfering and good % recovery of drug(s) indicates this spectrophotometric method was suitable for the estimation of drug in dissolution studies and % assay of formulations. The standard calibration curve was shown in (**Fig.2)** and the HPLC spectra were shown in **(Fig.3)**.

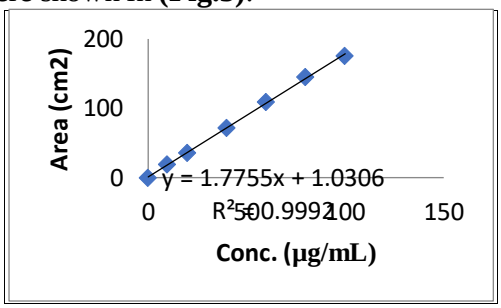

Fig. 2. Calibration curve of SFT in 0.1 N HCl with 1% w/v SLS by HPLC method

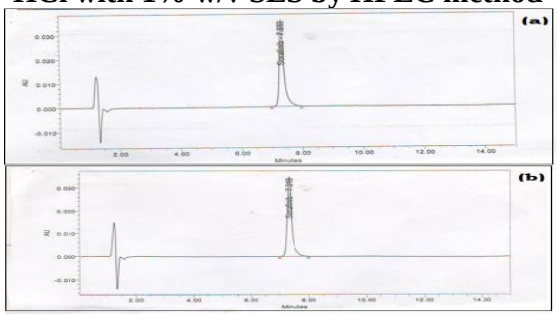

Fig.3. HPLC Chromatograms of a) SFT-pure drug and b) SFT-in formulation

Pre-compression studies: The aqueous wet granulation blends of IR layer of SFT, reveals that the angle of repose was found between 24.52°±0.01to 25.23°±0.02, Hausner's ratio between 1.13 to 1.17and Carr's index between 11.76 to 14.89%. The micromeritic studies indicate a good flow and compression characteristic of all the blends as per USP limits. In these IR tablet blends MCCPH101 [12] is used as diluent, which imparts good flow and compressibility to these blends on aqueous wet granulation with HPMC E5. The consolidated results of pre-compression studies were tabulated in (**Table 3)**.

Post-compression studies: Reveals that the average weight of tablets was found to be 389.11±0.03 to 392.12±0.12 mg. The average thickness of tablets was found to be 5.41±0.10 to 5.45±0.11 mm. The average hardness of the tablets ranges between 8.37±0.01 to 8.43±0.11Kg/cm^2 indicates satisfactory mechanical strength. The % weight loss in the friability test ranges from 0.12 to 0.18 %, which was NMT 1 % as per pharmacopoeia limits indicating a good mechanical resistance of tablets. % Assay all the batches are in 97.4±0.11 to 99.9±0.02% of the labeled amount, indicating the content uniformity of drug. The consolidated results of post compression studies of bilayered tablets are tabulated in (**Table 4**).

***In vitro* dissolution studies:** For the optimization of the composition of IR tablets in comparison with Nexavar 200 mg (marketed product); *invitro*dissolutionstudies were conducted in 0.1N HCl with 1% SLS up to 30 min. Among all the formulations F6 (2% w/w SLS as surfactant and 10% w/w

CCS as superdisintegrant) shows the identical dissolution efficiency at 30 min (DE_{30}) with marketed product. As the concentration of superdisintegrant increases, dissolution rate (DR) of drug increases. *In vitro* dissolution profiles of SFT FC tablets were shown in (**Fig.3)**.

***In vitro* drug release kinetic studies:** Drug release kinetics of the optimized formulation (F6) reveals the first order rate constant (K_1= 0.122 with r^2 =0.996), indicates the film coated immediate release tablets are following first order kinetics.

Comparision of dissolution profiles of marketed (Nexavar 200 mg) and optimized formulation (F6): The similarity factor (f_2) is 74.47 and the difference factor (f_1) is 1.741 on comparing the dissolution profiles of marketed (Nexavar 200 mg) and optimized formulation (F6); indicates their dissolution profiles are identical.

Accelerated stability studies of optimized formulation (F6): As there were no significant differences in post compression studies (**Table 6**) and comparative *in vitro* dissolution profiles of initial and accelerated stability studies (**Fig.5**), of initial and accelerated stability samples of optimized formulation (F6) up to 3 months; it passes the test for stability as per ICH guidelines. Comparative FT-IR spectra of pure drug, optimized F6-Initial and F6-40°C/75%RH-3M accelerated stability samples (**Fig.6**) reveals there is no significant change in the functional groups of SFT due to interaction with excipients in the accelerated stability studies

Table 1. Formulation table of SFT film coated tablets

Ingredients*	F1	F2	F3	F4	F5	F6
Intragranular						
Sorafenib Tosylate	274	274	274	274	274	274
SLS	8	12	16	8	8	8
CCS	40	40	40	56	48	40
MCC PH 101	66	62	58	50	58	66
Aqueous HPMC E5 soln. (q.s.)	8	8	8	8	8	8
Extragranular						
Mg. stearate	4	4	4	4	4	4
Coating composition						
Advantia prime pink	10	10	10	10	10	10
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	400	400	400	400	400	400
*All the ingredients are expressed in mg per tablet						

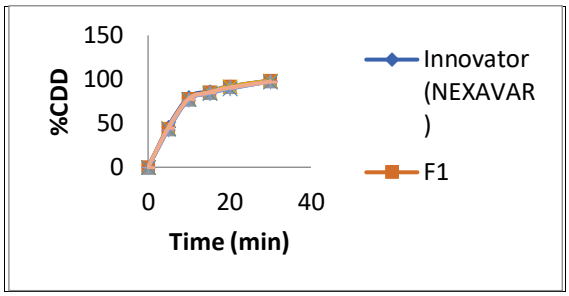

Fig.4. Comparative *in vitro* dissolution profiles of SFT film coated tablets with marketed product in 0.1 N HCl with 1% SLS

Table 2. Interpretation of SFT (pure drug) FT-IR spectra

Functional groups Category	Actual Frequency Range (cm^{-1})	Observed Frequency (cm^{-1})	Type of vibration
Alkene: C=C	1620-1680	1688.85	Stretching
Aromatic: C=C	1400-1600	1485.18	Stretching
Amine: N-H	3300-3500	3327.30	Stretching
Alcohol: O-H	3200-3500	3215.74	Stretching
Alkyl-Halide: C-F	1000-1400	1178.75	Stretching
Alkene: =C-F	675-1000	678.83	Bending
Alcohol: C-O	1050-1150	1036.66	Stretching
Cyclic-Ketone: C=0	1705	1705	Stretching
Carbonyl Amide: C=O	1640-1690	1641	Stretching
Carbonyl Acid: C-O	1210-1320	1262	Stretching

Table 3. Results of pre-compression studies of SFT film coated tablets

F. Code	Angle of repose (°)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio ( )
F1	24.81±0.01	0.45±0.21	0.51±0.41	11.76	1.13
F2	24.71±0.03	0.40±0.11	0.47±0.23	14.89	1.17
F3	24.61±0.01	0.42±0.23	0.48±0.16	12.50	1.15
F4	25.23±0.02	0.42±0.32	0.48±0.11	12.50	1.14
F5	25.14±0.03	0.43±0.15	0.49±0.23	12.24	1.14
F6	24.52±0.01	0.45±0.11	0.51±0.13	11.76	1.13

Table 4. Results of post-compression parameters of SFT film coated tablets

F. Code	Avg. wt. (mg)	Thickness (mm)	Hardness (kg/cm^2)	Disintegration time (min)	Friability (%)	Assay (%)
F1	391.12±0.01	5.45±0.11	8.41±0.12	5.31±0.02	0.15	99.9±0.02
F2	389.11±0.03	5.42±0.12	8.38±0.03	5.26±0.03	0.18	97.4±0.11
F3	390.14±0.02	5.41±0.10	8.43±0.11	5.29±0.11	0.12	98.3±0.03
F4	392.12±0.12	5.43±0.03	8.42±0.05	4.42±0.04	0.14	98.5±0.12
F5	390.16±0.11	5.42±0.02	8.42±0.13	3.45±0.12	0.16	99.7±0.04
F6	391.14±0.04	5.44±0.11	8.37±0.01	5.15±0.02	0.15	98.8±0.13

Table 5. *In vitro* drug release kinetics of SFT film coated tablets

F. Code	Zero order		First order	
	K_0	r^2	K_1	r^2
F1	1.918	0.872	0.131	0.991
F2	1.931	0.865	0.133	0.990
F3	1.894	0.868	0.133	0.991
F4	1.874	0.869	0.122	0.986
F5	1.896	0.868	0.119	0.989
F6	1.826	0.863	0.122	0.996

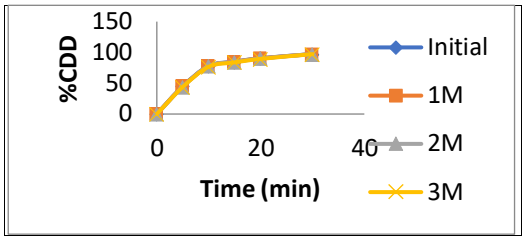

Fig.5. Comparative *in vitro* dissolution profiles of accelerated stability samples of optimized SFT film coated tablets in 0.1 N HClwith 1% SLS (F6)

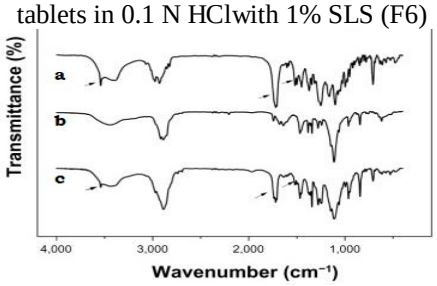

Fig.6. Comparative FT-IR spectra of a) SFT (pure drug), optimized SFT film coated tablets b)F6-Initial & c) F6-40℃/75%RH-3M accelerated stability sample

Table 6. Results of accelerated stability samples of optimized SFT film coated tablets (F6)

Parameter	Initial	1 Month	2 Month	3 Month
Description	Complies	Complies	Complies	Complies
Moisture content (%)	2.20±0.11	2.51±0.12	2.66±0.13	2.72±0.08
Avg. wt. (mg)	391.14±0.04	392.11±0.11	392.23±0.10	392.25±0.08
Thickness (mm)	5.44±0.11	5.45±0.06	5.47±0.08	5.50±0.09
Hardness (kg/cm^2)	8.37±0.01	8.35±0.03	8.32±0.11	8.27±0.13
DT (min)	5.15±0.02	5.12±0.04	5.08±0.12	5.04±0.13
Friability (%)	0.15	0.17	0.19	0.23
Assay (%)	98.80±0.13	98.61±0.11	98.22±0.12	98.23±0.08

CONCLUSION:

In the view of above findings, optimization of conc. of superdisintegrant, CCS to 10% w/w and conc. of surfactant, SLS to 2% w/w in the formulation had significant effect on in having the release profiles identical with the Nexavar 200 mg (marketed product). The optimized formulation (F6) passes the test for stability as per ICH guidelines. Hence a generic version of Nexavar 200 mg (i.e. SorafeneibTosylate film coated tablets) was formulated and evaluated.

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