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DESIGN AND EVALUATION OF SOLID DISPERSED TADALAFIL TABLETS

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ABSTRACT

Tadalafil (TD), a PDE-5 inhibitor, belongs to BCS class II. It is poorly soluble in water and requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. In the present investigation, solid dispersed systems of tadalafil with poloxamer$_{188}$ and sodium starch glycolate were prepared using solvent evaporation technique. The dissolution rate of the drug and poloxamer$_{188}$ based solid dispersion was significantly higher than the sodium starch glycolate (SSG) based preparations and pure drug which reaches closer to the dissolution profile of marketed product. This was due to an increase in surface area of drug available for dissolution. Characterization of binary systems with FTIR studies demonstrated the presence of strong hydrogen bonding interactions, a significant decrease in crystallinity and the possibility of existence of amorphous entities of the drug. In the binary systems tested, 1:0.5 proportion of Tadalafil/poloxamer$_{188}$ showed rapid dissolution of tadalafil (*DE*30 56.68 %). In the binary systems, tested (1:0.5) proportion of tadalafil/poloxamer$_{188}$ showed rapid dissolution of tadalafil. In contrast, higher proportion of polaxmer$_{188}$ (1:1) offered no advantage towards dissolution enhancement of the drug, indicating altered rheological characters of the polymer at its higher concentration, which might have retard the release rate of tadalafil. The tablets were prepared for the optimized formula of solid dispersion, by wet granulation technique. The solid dispersion tablets were evaluated and compared with tadalafil marketed product.

INTRODUCTION: Solid dispersion techniques can be used to increase dissolution and absorption of several insoluble drugs [1-2].

To date, a number of drugs are not showing complete therapeutic effect because of their poor solubility and dissolution, which in turn leads to poor bioavailability of the drug [3-4]. So, in the modern days, top most importance is given for increasing the dissolution rate of poorly soluble drugs, which enhances their bioavailability.

The rate and extent of absorption of class II compounds is highly dependent on the performance of the formulated product. These drugs can be successfully formulated for oral administration, with formulation design to ensure consistent bioavailability [5]. Solid dispersions are one of the most promising strategies to improve the solubility and dissolution rate of poorly water-soluble drugs [6]. By reducing the drug particle size to the absolute minimum, and hence, thereby improving drug wettability, bioavailability may can be significantly improved. They are usually presented as amorphous products.

Recently, surfactants have been included to stabilize the formulations; thus avoiding this avoids drug recrystallization, thereby and potentiating their solubility [7, 8]. The term "'solid dispersion'" has been utilized to describe a family of dosage forms, whereby the drug is dispersed in a biological inert matrix, usually with a view in order to enhancing the oral bioavailability. More specifically, Chiou and Regelman (1971), defined these systems as "the dispersion of one or more active ingredient in an inert matrix at solid-state prepared by the melting (Fusion), solvent or melting solvent method" [9, 10].

A number of poorly soluble drugs have been shown to improve their dissolution characteristics, when converted to solid dispersions. Tadalafil (TD) is widely used in the treatment of erectile dysfunction. It is a PDE-5 inhibitor. The inhibition of PDE5 by TD enhances erectile function by increasing the amount of CGMP. TD is a white or almost white powder and it is poorly soluble in water. Since the dissolution rate of the drug from surface is affected by the carrier has an ultimate influence on the dissolution of the dispersed drug. Hence hydrophilic carriers like SSG and polaxmer$_{188}$ were used as carriers for converting TD into solid dispersions in this study.

EXPERIMENTAL:

MATERIALS AND METHODS: Tadalafil was obtained as gift sample from Rakshith chemicals Hyderabad, A.P, SSG and polaxmer$_{188}$ from Loba Chemie, Mumbai, methanol from Finar chemicals,Ahmedabad,PVPK-30 from M/s B.A.S.F., starch, lactose, microcrystalline cellulose, dicalcium phosphate from Colorcorn Asia. Magnesium stearate, talc from DOW chemicals.

Preparation of Solid Dispersions of Tadalafil: Solid dispersions were prepared by solvent evaporation technique. Accurately 200 mg of Tadalafil (for 10 doses i.e 20 mg/dose)was weighed and dissolved in 50 ml of methanol. Accurately carrier corresponding to different drug: carrier ratio (as shown in **Table 1**) by weight was weighed and dispersed in the drug solution. The solvent was allowed to evaporate on water bath under occasional stirring at temperature of 40-50^{o}C in a protected environmental condition containing an exhaust system. The dried mass was pulverized and was passed through a #100-mesh sieve. The powder was subsequently dried at 40^{o}C for 3 hours in a hot air oven. The powders were stored in desiccators for further studies.

TABLE 1: DRUG: CARRIER RATIO

Drug	Carrier	code	Drug: carrier ratio
Tadalafil (TD)	Sodium starch glycolate	SD1	1:0.5
		SD2	1:1
	Poloxamer$_{188}$	SD3	1:0.5
		SD4	1:1

Fourier Transform Infrared Spectroscopy (FTIR): Infrared spectra were recorded on a Perkin-Elmer Spectrum-one FTIR spectrometer (Shelton, USA) using KBr disks. The scanning range was 4000 to 400 cm^{-1}.

Evaluation of prepared Solid Dispersions:

1. **Assay:** Accurately weighed powdered samples equivalent to 20 mg of drug was taken in a 100 ml of volumetric flask; 40 ml of methanol was added and sonicated for 20 min to dissolve the drug. The volume was made to 100 ml with 0.1 N HCl buffer. The dispersion was filtered using Whatmann filter paper. A 10 ml aliquot of the above solution was taken and diluted to 100 ml with 0.1 N HCl buffer. The absorbance of sample solution was determined at 218 nm against buffer blank. The results are given in **Table 2**.

TABLE 2: ASSAY OF TD SOLID DISPERSIONS

S. No.	Assay (%w/w)
SD_1	98.89
SD_2	97.98
SD_3	99.73
SD_4	99.25

2. ***In vitro* Dissolution studies of Tadalafil Solid Dispersions:** Dissolution rate of tadalafil as such, marketed product and from solid dispersions was studied using ElectroLab India, 8 stage dissolution rate testing apparatus, with a paddle stirrer. The dissolution fluid was 900ml of 0.1N HCl. Dissolution studies [5-6] were carried out by taking solid dispersions equivalent to 20mg of TD, a speed of 50 rpm and a temperature at 37±1.0^{o}C were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted and assayed for TD by measuring absorbance at 218nm.

The dissolution experiments were conducted in triplicate and results are shown in the **figs. 1-4** and dissolution parameters are given in **Tables 3, 4** [11, 12, 13].

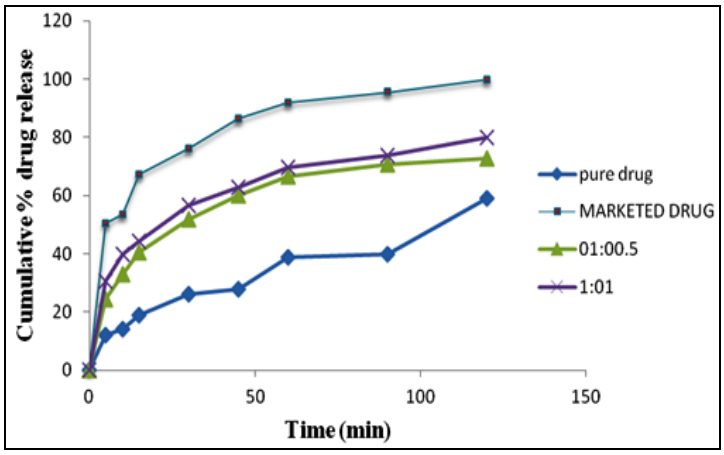

FIG. 1: DISSOLUTION PROFILE OF TADALAFIL AND THEIR SD'S WITH SSG (ZERO ORDER)

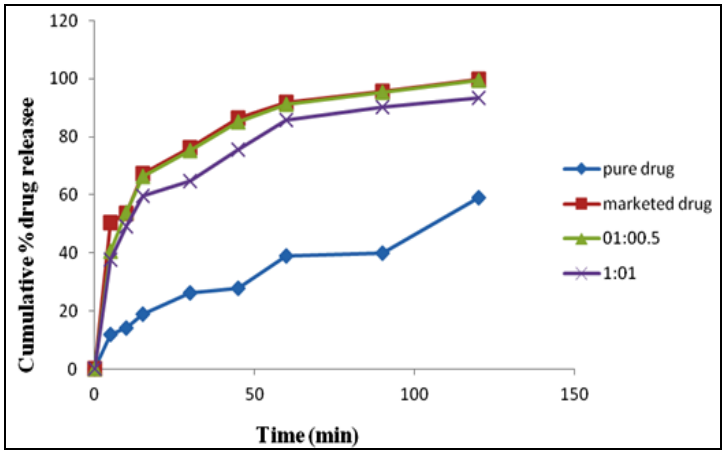

FIG. 2: DISSOLUTION PROFILE OF TADALAFIL AND THEIR SD'S WITH POLOXAMER$_{188}$ (ZERO ORDER)

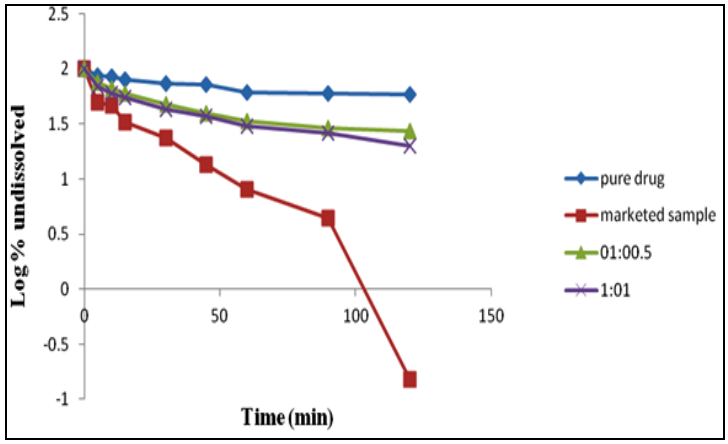

FIG. 3: FIRST ORDER DISSOLUTION PROFILE OF TADALAFIL AND THEIR SD'S WITH SSG

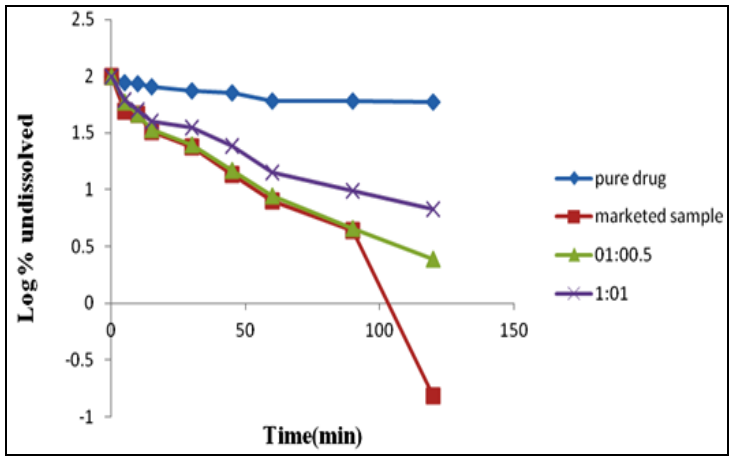

FIG. 4: FIRST ORDER DISSOLUTION PROFILE OF TADALAFIL AND THEIR SD'S WITH POLOXAMER$_{188}$

KINETICS OF THE SOLID DISPERSIONS WITH RESPECT TO PURE AND MARKETED PRODUCT

TABLE 3: ZERO ORDER RELEASE PARAMETERS FOR SOLID DISPERSIONS, PURE DRUG AND MARKETED PRODUCT

Product	Slope	K_0 (mg/hr)	$T_{1/2}$ (min)	DE_{30}%	R^2
SD_1	0.504	0.504	19.8	35.90	0.855
SD_2	0.514	0.514	19.4	40.74	0.848
SD_3	0.620	0.620	16.1	56.68	0.802
SD_4	0.596	0.596	16.7	50.57	0.828
Pure drug	0.3092	0.309	32.3	17.10	0.898
Marketed product (Megalis)	0.595	0.595	16.8	58.80	0.786

TABLE 4: FIRST ORDER RELEASE PARAMETERS FOR SOLID DISPERSIONS, PURE DRUG AND MARKETED PRODUCT

Product	Slope	K_1(min^{-1})	$T_{1/2}$(min)	R^2
SD_1	-0.004	0.01	69.3	0.929
SD_2	-0.005	0.011	63.0	0.948
SD_3	-0.017	0.039	17.7	0.978
SD_4	-0.009	0.021	33.0	0.973
Pure drug	-0.0018	0.0041	169.0	0.919
Marketed product (Megalis)	-0.019	0.044	15.7	0.958

Formulation of Tadalafil Tablets: Tablets each containing 30mg of TD were formulated employing TD co-evaporate of polaxmer$_{188}$ (1:0.5) along with the usual tablet excipients.

The formula of TD tablets is given in Table 2. TD tablets were prepared by conventional wet granulation method as per formula given in **Table 5.**

TABLE 5: FORMULA OF TADALAFIL SOLID DISPERSION TABLETS

INGREDIENTS	F1	F2	F3	F4
Solid dispersion	30mg	30mg	30mg	30mg
DCP	205.5	193 mg	---	---
MCC	---	---	193mg	---
Lactose	---	---	---	193mg
PVP (3%) solution	q.s	q.s	q.s	q.s
Starch	12.5mg	25 mg	25mg	25 mg
Talc	1 mg	1 mg	1 mg	1mg
Magnesium stearate	1mg	1 mg	1mg	1mg
Total weight of the tablet	250mg	250mg	250mg	250mg

Tadalafil dispersions were taken in mortar and pestle along with suitable diluents and mixed constantly until a dry is mix obtained (before mixing both the diluents and dispersions were allowed to pass through # 22 mesh). The binder was dissolved in hot purified water and stirred constantly until the complete PVP K-30 goes into solution (PVP 3% i.e 3 gms of PVP is dissolved in 100 ml water). Binder solution was added to above dry mix and mixed slowly.

Extra water was added till required consistency of mass is obtained and sifted through #22 mesh to obtain granules. Granules were dried in hot air oven and sifted through #24 to obtain uniform sized granules. The sifted granules were taken in blending cover and blended with Talc and disintegrant for 10 min. Magnesium stearate was sifted and added to above blend and lubricated for 5 mins. The blend was compressed into tablet using punches and suitable dies with a tablet weight of 250 mg.

Evaluation of Tadalafil Tablets: Compressed tablets were then evaluated for hardness, thickness, weight variation, disintegration, content uniformity, friability and drug content as shown in **Table 6**. Hardness was measured by Monsanto type hardness tester. One tablet was placed in each tube of disintegration apparatus and the test was carried out using 0.1NHCl as disintegrating media at 37^{o}C.

Friability was determined in Roche friabilator by taking ten tablets. For drug content analysis, twenty tablets were accurately weighed and finely powdered. The quantity of powder, equivalent to 20mg of tadalafil was taken in a 100mL volumetric flask. 40 ml of methanol was added and sonicated for 20 min to dissolve the drug. The volume was made to 100 ml with 0.1 N HCl buffer. The dispersion was filtered using Whatmann filter paper. A 10 ml aliquot of the above solution was taken and diluted to 100 ml with 0.1 N HCl and assayed for drug content at 218 nm, using UV/Vis Spectro-photometer.

TABLE 6: POST COMPRESSION PARAMETERS OF SOLID DISPERSIONS TABLETS

Evaluation tests	Results			
	F1	F2	F3	F4
Average weight (mg)	24.19	24.26	25.2	23.54
Thickness (mm)	3.02	2.93	2.95	2.99
Hardness (kp)	1.12	1.53	1.36	1.29
Friability (%)	1.10	0.28	0.55	0.32
Wight variation (mg)	245	243	256	251
Disintegration Time (min)	15	10	11	13
% Drug content	101.48	99.62	100.74	98.88
Content uniformity (%)	99.07	99.22	102.85	97.42

***In vitro* Dissolution study of Tablets:** *In vitro* dissolution study of tablets was conducted using USP dissolution apparatus II (ElectroLab) at 50 rpm, using 0.1NHCl maintained at 37±0.5^{o}C. Samples were withdrawn at various intervals, filtered through 0.45µm membrane filtered, diluted and assayed at 218nm, using UV/Vis spectrophotometer. The results are shown in the **figs. 5, 6** and dissolution parameters are given in **Tables 7, 8.**

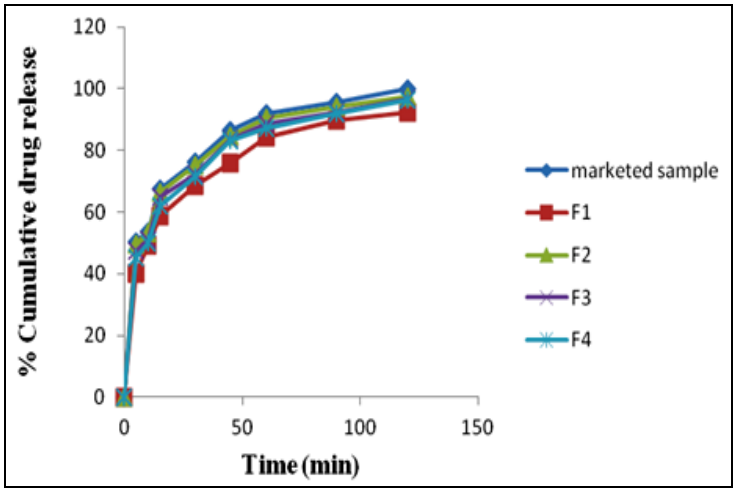

FIG. 5: DISSOLUTION PROFILE OF TADALAFIL AND THEIR SD TABLETS (ZERO ORDER)

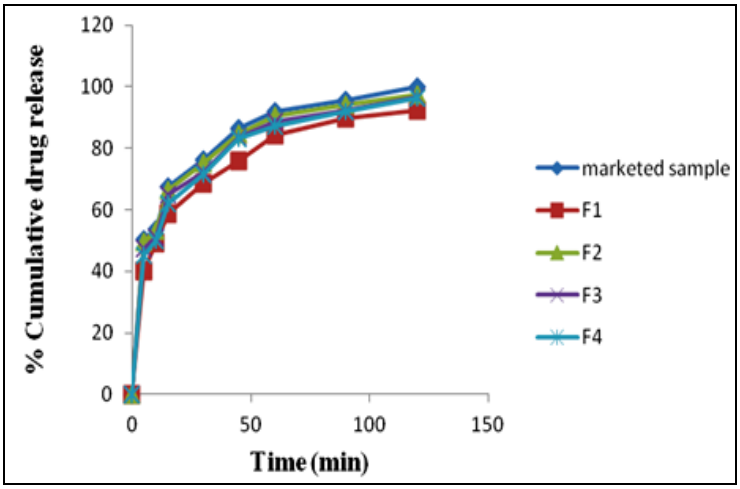

FIG. 6: FIRST ORDER DISSOLUTION PROFILE OF TADALAFIL AND THEIR SD TABLETS

KINETICS OF THE FORMULATIONS WITH RESPECT TO PURE AND MARKETED PRODUCT

TABLE 7: ZERO ORDER RELEASE PARAMETERS FOR SD TABLETS, PURE DRUG AND MARKETED PRODUCT

S. no.	Product	Slope	K_0 (mg/hr)	$t_{1/2}$ (min)	DE_{30}%	R^2
1.	F_1	0.577	0.577	17.33	51.70	0.815
2.	F_2	0.578	0.578	17.30	58.12	0.779
3.	F_3	0.583	0.583	17.15	56.03	0.794
4.	F_4	0.590	0.590	16.94	54.41	0.804
5.	Pure drug	0.3092	0.3092	32.34	17.10	0.898
6.	Marketed product (megalis)	0.595	0.595	16.8	58.8	0.786

TABLE 8: FIRST ORDER RELEASE PARAMETERS FOR SD TABLETS, PURE DRUG AND MARKETED PRODUCT

S. no.	Product	Slope	K_1 (min^{-1})	$T_{1/2}$ (min)	R^2
1.	F_1	-0.008	0.019	36.4	0.967
2.	F_2	-0.011	0.027	25.6	0.980
3.	F_3	-0.010	0.023	30.1	0.980
4.	F_4	-0.000	0.021	33	0.973
5.	Pure drug	-0.0018	0.0041	169.0	0.919
6.	Marketed product (Megalis)	-0.019	0.044	15.7	0.958

RESULTS AND DISCUSSION:

FTIR: Fig. 7 shows the FTIR spectra of tadalafil, poloxamer 188, physical mixture and solid dispersion systems. The IR spectrum of tadalafil (**Fig. 7a**) is characterized by principal absorption peaks at 3330 cm^{-1} (N-H stretch, secondary amine), 3061 cm^{-1} (C-H stretch, aromatic), 2905 cm^{-1} (C-H stretch, aliphatic CH_3 *sym*), 1677 cm^{-1} (C=O amide), 1649 cm^{-1} (C=C aromatic), 1437.62 cm^{-1} (C–N stretch), 1041 cm^{-1} (C-O-C stretch *sym*) and 746 cm^{-1} (benzene). The IR spectrum of poloxamer 188 (**Fig. 7b**) is characterized by principal absorption peaks at 2885 cm^{-1} (C-H stretch aliphatic), 1343 cm^{-1} (in-plane O-H bend) and 1112 cm^{-1} (C-O stretch), which were consistent in all binary systems with the drug.

The IR spectrum of 1:0.5 solid dispersion (**Fig. 7c**) shows the presence of all tadalafil peaks with decreased intensity. However, no additional peak was observed in binary system, indicating absence of any chemical interaction between tadalafil and polymer.

***In vitro* Dissolution Studies:** From the dissolution profiles and dissolution parameters, it is clear that there is a greater increase in the dissolution rate (K_1) and DE values of TD: $Poloxamer_{188}$ solid dispersions when compared to TD: SSG solid dispersions and pure TD.

From the evaluated parameters of the formulated tablets, it is clear that all the tablets fulfilled the official requirements of compressed tablets.

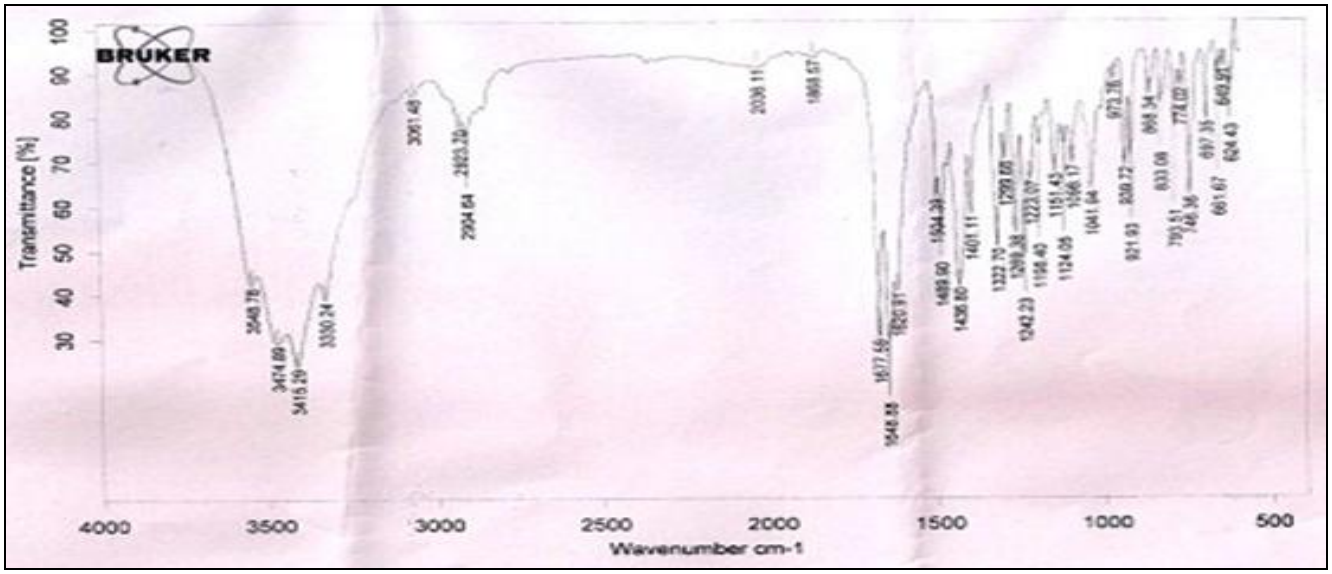

FIGURE 7A: FTIR SPECTRUM OF TADALAFIL

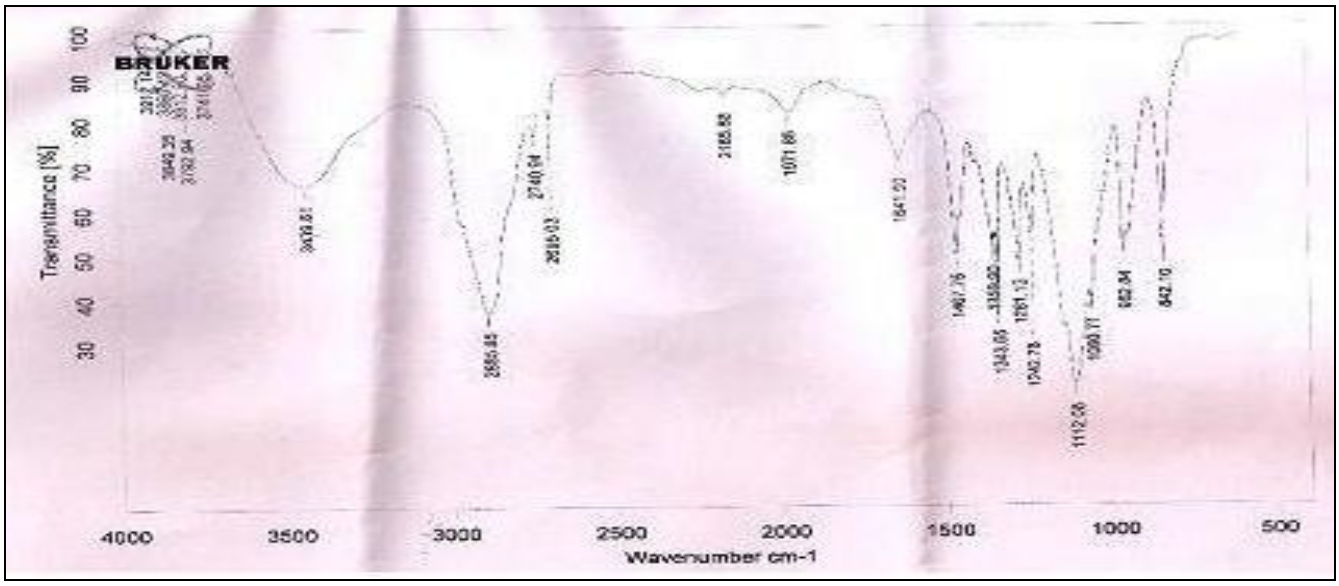

FIGURE 7B: FTIR SPECTRUM OF POLOXAMER$_{188}$

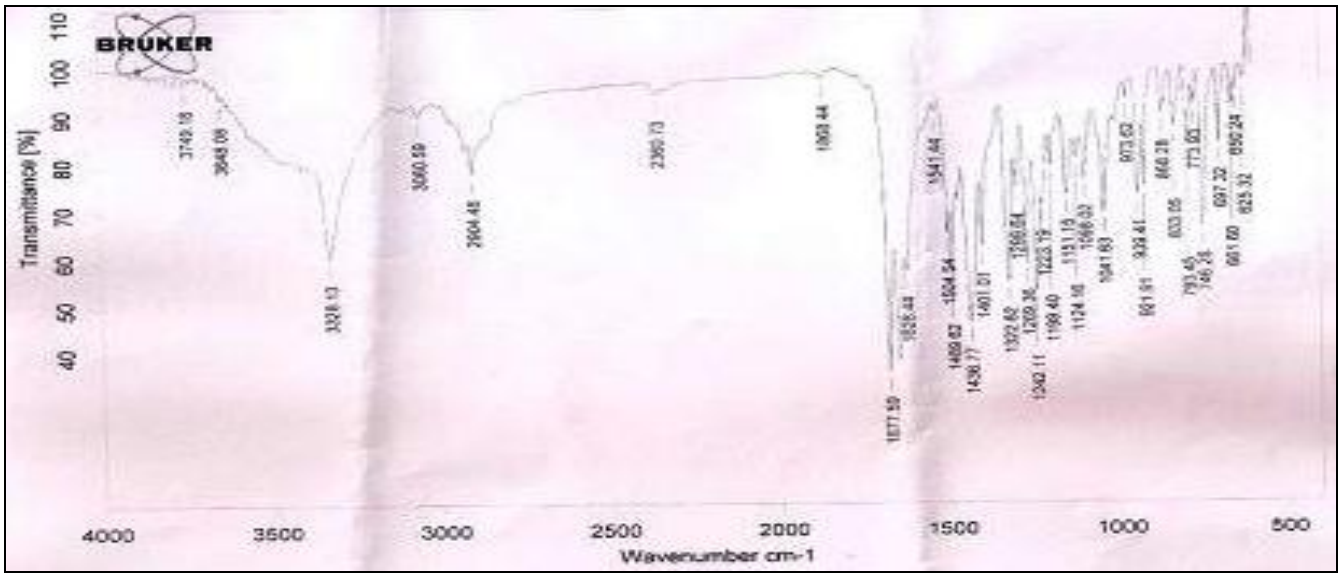

FIGURE 7C: FTIR SPECTRUM OF TADALAFIL + POLOXAMER$_{188}$

From the dissolution profiles and dissolution parameters, it is clear that F_2 formulation showed maximum dissolution.

Suitability of various tablet excipients as carriers for solid dispersions of drugs was studied. Solid dispersions were prepared by solvent evaporation technique using methanol as a solvent. The dissolution profile of prepared dispersion was compared with pure drug and marketed product.

The rank order of dissolution rate improvement on various carriers studied were; Polaxamer 188 **>** Sodium starch glycolate**.** Solid dispersion using drug: poloxamer$_{188}$ (1:0.5) as a carrier was found to be best, which was formulated into tablets. The dissolution studies were carried for the prepared formulations and marketed product. F2 formulation showed drug release similar to marketed product. The optimized formulation showed first order release.

Thus, it can be concluded that the solubility of poorly water soluble drug Tadalafil can be enhanced by formulating as a solid dispersion with optimum concentration of a non ionic surfactant polaxamer $_{188}$ and optimized formula was tableted for administration.

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