Research Article

Pegylated Solid Dispersions for Enhancement of *In-vitro* Drug Release of Sertraline and Fluoxetine

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ABSTRACT

The main aim of the study was to enhance dissolution rate of Fluoxetine and Sertraline hydrochloride by formulating as solid dispersions using solvent evaporation method. Fluoxetine and Sertraline solid dispersions were prepared using PEG 4000 as polymer. PEGylated conjugates were prepared in the weight ratios of 1:0.5, 1:1, 1:2, 1:3, and 1:4 using solvent evaporation method. Physico-chemical properties were evaluated using solubility studies, FTIR, powder XRD, SEM, dissolution studies. From solubility studies F5, S5 showed highest solubility. From FTIR studies it was proved that there was no interaction between drug and polymer. From SEM and powder XRD studies it was observed that change of polymorphic form of Fluoxetine and Sertraline from crystalline to amorphous form within the solid dispersion. From dissolution studies data it was observed that F5 and S5 showed maximum drug release within 45, 60min respectively, hence they were considered as optimized formulations. Based on the results, it can be concluded that developed solid dispersions was successful to enhance dissolution rate of both the drugs.

Keywords: Solvent evaporation, crystalline, amorphous, melting point, dissolution.

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INTRODUCTION

Fluoxetine and Sertraline are anti-depressants of selective serotonin reuptake inhibitor (SSRI) category. Chemically they are (1S, 4S)-4-(3, 4-dichloro phenyl)-N-methyl-1, 2, 3, 4-tetra hydro-1-napthalene-1-amine hydrochloride, N-methyl-3-phenyl-3-[4-(tri fluoro methyl) phenoxy propan-1-amine of Sertraline and Fluoxetine respectively. They are freely soluble in ethanol and methanol but slightly soluble in water. Daily adult dose of Fluoxetine is 20-60mg/day whereas Sertraline is 50mg/day.[1-4] There is a need to improve aqueous solubility of both the drugs. PEGylation is one of the technique used to improve aqueous solubility of drugs.

The technology of polyethylene glycol conjugation refers to conjugation of drug or drug moiety to polyethylene glycol (PEG) through covalent or non-covalent bonding [5] is called as "PEGylation." PEGylation of a molecule cause changes in Physico-chemical properties such as enhanced hydrophilicity, size and molecular weight, changes in conformation and steric hindrance in intermolecular interaction.[6]

Hence, the aim of the present work is to prepare conjugates of Fluoxetine and Sertraline with PEG 4000, to evaluate the conjugates to find out optimised formulation.

MATERIALS AND METHODS

Pure sample of Fluoxetine HCl was gifted by Strides Shasun, Bangalore. Pure sample of Sertraline HCl was gifted by Aurobindo pharma, Hyderabad. PEG 4000 was purchased from sd. Fine Chem. Pvt. Ltd, Mumbai. All other chemicals and reagents used were of analytical grade.

Preparation of solid dispersions

Solid dispersions of Fluoxetine HCl and Sertraline HCl were prepared utilising solvent evaporation method. The conjugates were prepared using different weight ratios of drugs to PEG were shown in table 1.

Table 1: Formulation codes of Fluoxetine HCl and Sertraline HCl solid dispersions

S. No	Drug : polymer ratios	Formulation code
1	Fluoxetine : PEG 4000 (1 : 0.5)	F1
2	Fluoxetine : PEG 4000 (1 : 1)	F2
3	Fluoxetine : PEG 4000 (1 : 2)	F3
4	Fluoxetine : PEG 4000 (1 : 3)	F4
5	Fluoxetine : PEG 4000 (1 : 4)	F5
6	Sertraline : PEG 4000 (1 : 0.5)	S1
7	Sertraline : PEG 4000 (1 : 1)	S2
8	Sertraline : PEG 4000 (1 : 2)	S3
9	Sertraline : PEG 4000 (1 : 3)	S4
10	Sertraline : PEG 4000 (1 : 4)	S5

Solvent evaporation method

The drug-PEG conjugate was prepared by dissolving accurately weighed physical mixture of drug and polymer (PEG 4000) in minimum volume of methanol.[7-12] The solvent was evaporated later at 50^{0}C until solid film was formed. The film formed was further dried and sieved. Ten

formulations were prepared and their composition showed in table 1.

Evaluation of Fluoxetine HCl and Sertraline HCl solid dispersions [13-16]

Solubility studies

Solubility studies were carried out using shake flask method. Excess of pure drug (Fluoxetine HCl, Sertraline HCl) and its solid dispersions were placed in a test tube containing 10ml of distilled water. The samples were shaken occasionally at room temperature for 48h until equilibrium was achieved. Samples were drawn, filtered, diluted suitably and assayed spectrophotometrically at 226 nm, 275 nm respectively.

Dissolution studies

Dissolution studies of pure drug and all the formulations were carried out in triplicate with the USP XXI dissolution apparatus (basket type) (Electro lab, India) maintained at 50 rpm. Phosphate buffer (pH 6.8) was used as a dissolution medium maintained at 37±1^{0}c. Solid dispersions equivalent to the weight of the drugs (Fluoxetine-20mg, Sertraline-50mg) were added to the dissolution medium. At specified time intervals, 5ml of samples were withdrawn, filtered and assayed for drugs (Fluoxetine HCl, Sertraline HCl) using UV-visible spectrophotometer (Systronics, India) by measuring the absorbance at wavelengths 226nm, 275nm respectively. The initial volume of dissolution medium was maintained by replacing with 5ml of phosphate buffer to maintain sink conditions. Dissolution profile of formulations were analyzed by plotting a graph between % drug release versus time.

FTIR studies

FTIR spectra of pure drugs (Fluoxetine HCl, Sertraline HCl), PEG 4000 and optimized ratios of both drugs (F5, S5) that exhibited highest dissolution rate were obtained on a FTIR spectrophotometer (Perkinelmer 841 model). Samples were prepared by KBr pressed pellet technique. The scanning range was 400-4000cm^{-1}.

Scanning electron microscopy (SEM)

Scanning electron microscopy (JEOL JSM-IT 500, Japan) was used to visualize external and surface morphology of plain drugs (Fluoxetine HCl, Sertraline HCl) and optimized formulations (F5, S5).

Powder X-ray diffraction studies

Powder X-ray diffraction patterns of pure drugs (Fluoxetine HCl, Sertraline HCl), PEG 4000 and optimized formulations (F5, S5) were recorded on the X-ray diffractometer (PANalytical). The samples were analyzed over a range of 0-5^0 at an angle of 2Θ and with a scan rate of 2^0/min.

RESULTS AND DISCUSSION

Solubility studies

Table 2: Solubility data of different formulations of Fluoxetine HCl solid dispersions

Formulation code	Solubility in mg/ml	Volume of solubility of 1mg in ml	Remarks
Pure drug	0.0210	47.6	Sparingly soluble
F1	0.15	6.66	Freely soluble
F2	0.283	3.53	Freely soluble
F3	0.427	2.34	Freely soluble
F4	0.570	1.75	Freely soluble
F5	0.608	1.64	Freely soluble

Table 3: Solubility data of different formulations of Sertraline HCl solid dispersions

Formulation code	Solubility in mg/ml	Volume of solubility of 1mg in ml	Remarks
Pure drug	0.010	100	Slightly soluble
S1	0.0291	34	Sparingly soluble
S2	0.0373	26.8	Soluble
S3	0.0560	17.83	Soluble
S4	0.0843	11.86	Soluble
S5	0.114	8.74	Freely soluble

From the table 2&3, it was observed that pure drugs (Fluoxetine HCl, Sertraline HCl) was sparingly and slightly soluble in water with 0.0210 and 0.010 intrinsic solubility respectively. With the use of carrier PEG 4000 all other formulations showed increase in solubility. Formulations F5 and S5 were considered as optimized formulations with 0.608, 0.114 intrinsic solubility respectively.

DISSOLUTION STUDIES

Table 4: *In-vitro* release data of different formulations of Fluoxetine HCl solid dispersions

S. No	Time(min)	Pure drug	F1	F2	F3	F4	F5
1	0	0	0	0	0	0	0
2	10	9±0.124	14.7±0.159	22.1±0.169	25.8±0.81	27.98±0.54	29.92±0.54
3	20	16.59±0.08	26.5±0.408	33.35±0.122	40.95±0.56	42.41±0.45	49.13±0.16
4	30	39.5±0.405	38.1±0.262	56.5±0.123	68.3±0.12	68.63±0.45	77.83±0.46
5	45	57.15±0.54	51.2±0.163	71.6±0.169	79.5±0.4	83.92±0.17	98±0.23
6	60	71.7±0.19	63.3±0.124	86.92±0.654	89.25±0.20	99.37±0.12	-
7	90	80.6±0.17	81.9±0.169	94.7±0.464	99.8±0.46	-	-
8	120	90.5±0.16	97.5±0.235	-	-	-	-

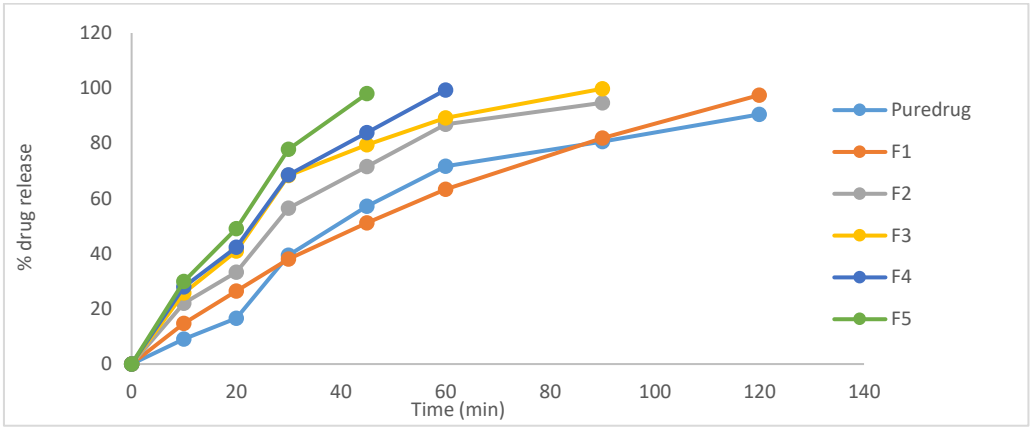

Figure 1: *In-vitro* release data of different formulations of Fluoxetine HCl solid dispersions

Table 5: *In-vitro* release data of different formulations of Sertraline HCl solid dispersions

S. No	Time(min)	Pure drug	S1	S2	S3	S4	S5
1	0	0	0	0	0	0	0
2	10	15.6±0.30	22.86±0.12	24.01±0.08	27.44±0.32	35.1±0.08	42.51±0.40
3	20	28.2±0.12	34.52±0.29	36.25±0.20	40.28±0.16	47.3±0.24	51.8±0.08
4	30	35.32±0.12	48.57±0.40	48.62±0.16	55.55±0.40	55.7±0.12	64.04±0.01
5	45	37.96±0.16	55.92±0.16	59.39±0.24	66.38±0.24	70.8±0.12	85.94±0.08
6	60	49.54±0.20	65.61±0.16	73.69±0.16	84.19±0.08	85.2±0.16	98.7±0.08
7	90	54.76±0.35	75.4±0.30	89.84±0.12	95.3±0.24	98.9±0.08	
8	120	58.28±0.12	85.28±0.12	99.2±0.20			

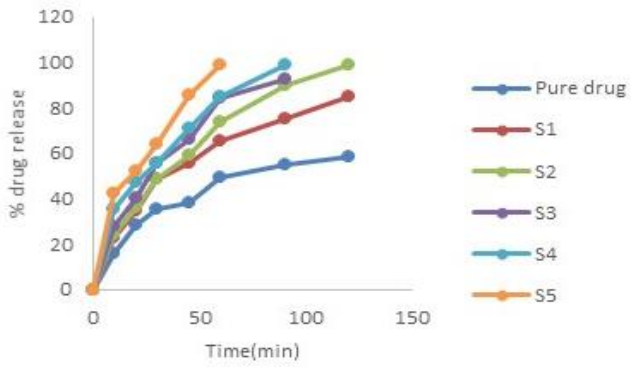

Figure 2: *In-vitro* release data of different formulations of Sertraline HCl solid dispersions

From table 4 and 5, it was observed that the formulations F5 and S5 were found to be optimized with drug release of 98% and 98.9% at 45 min and 60 min respectively.

FTIR studies

Infrared (IR) spectrum of Fluoxetine HCl showed characteristic peaks at 3554, 3177, 1310, 1517 cm^{-1}.

Table 6: IR spectrum indicating functional groups of Fluoxetine hydrochloride

Functional groups	Wave number obtained for Pure drug (Fluoxetine HCl) cm^{-1}	Wave number obtained for formulation (F5) cm^{-1}
Amine stretching vibration (NH)	3554	3553
Halide stretching vibration	1310	1309
Aromatic C-H stretching	3177	3184
C=C stretching	1517	1523

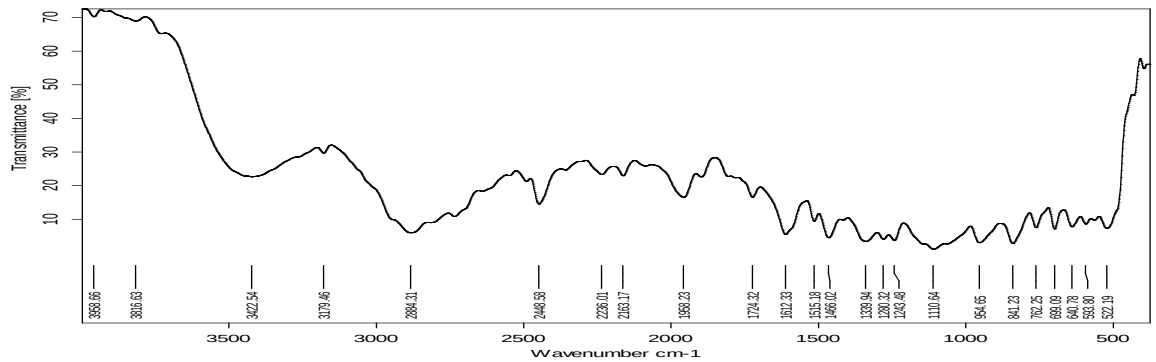

Figure 3: FTIR graph of Fluoxetine (F5) solid dispersion Infrared (IR) spectrum of Sertraline HCl showed characteristic peaks at 3421, 1560, 1354, 1028 cm^{-1}.

Table 7: IR spectrum indicating functional groups of Sertraline HCl

Functional groups	Wave number obtained for Pure drug (Sertraline HCl) cm^{-1}	Wave number obtained for formulation (F5) cm^{-1}
C-OH stretching	3421	3419
Aromatic stretching	1560	1564
C-NH_2 stretching	1354	1351
Aromatic ring stretching	1028	1027

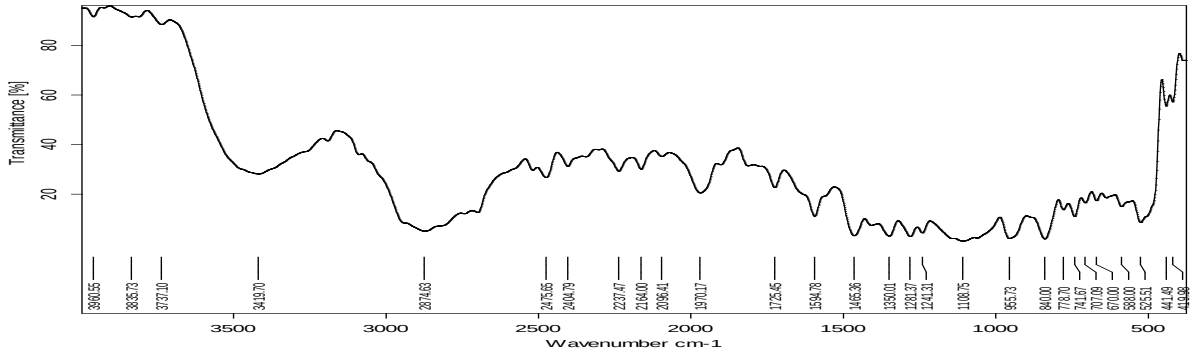

Figure 4: FTIR graph of Sertraline (S5) solid dispersion

Scanning electron microscopy

From the SEM images of optimized formulations (F5, S5), it was found that the surface of solid dispersions was rough with small pores due to sudden loss of moisture from the wet mass.

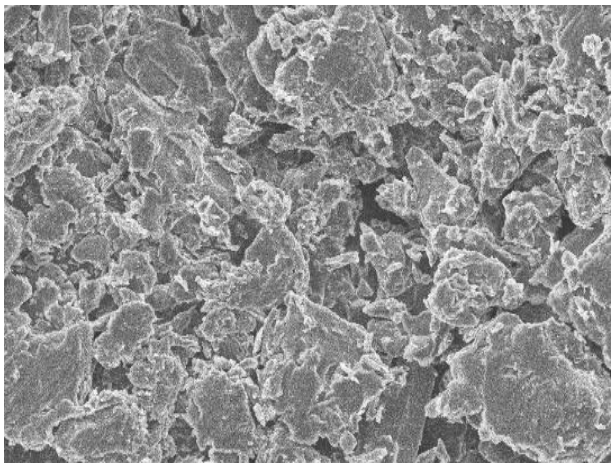

Figure 5: SEM images of Fluoxetine (F5) solid dispersions

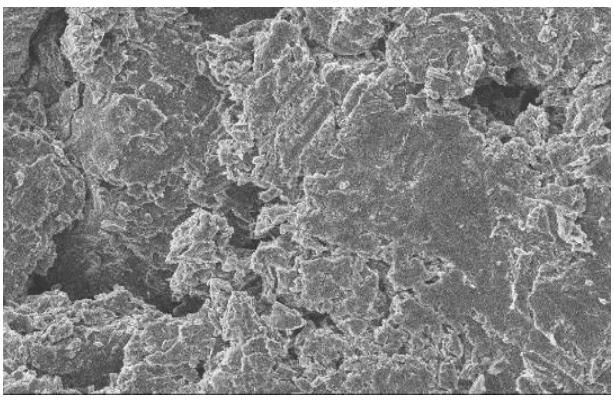

Figure 6: SEM images of Sertraline (S5) solid dispersions

Powder X-ray diffraction studies

The XRD patterns of optimized formulations (F5, S5) were shown in the figure 7&8 respectively. The XRD pattern of pure drugs showed intense and sharp peaks indicating its crystalline nature. A significant reduction in number of peaks in solid dispersions indicates conversion of crystalline nature of both drugs into amorphous form which must be the reason for enhanced solubility and dissolution of both the drugs.

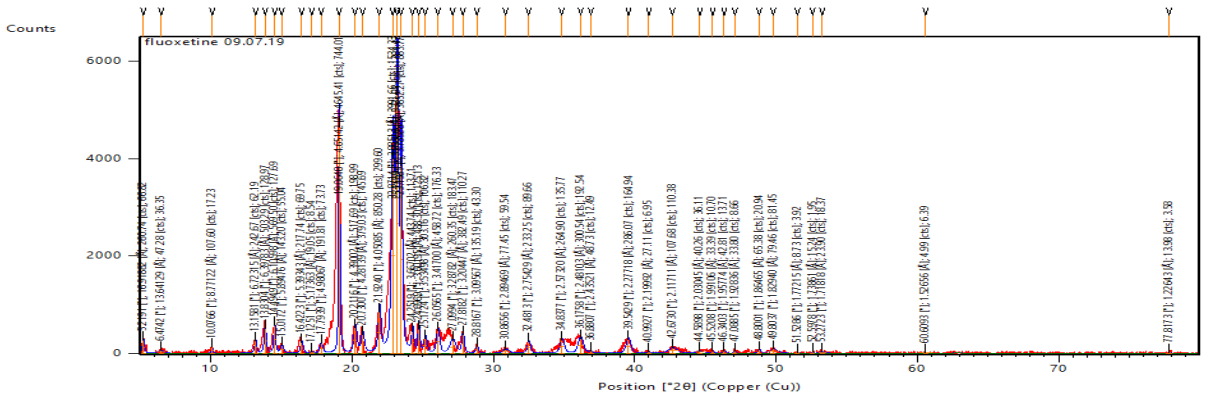

Figure 7: XRD graph of Fluoxetine (F5) solid dispersions

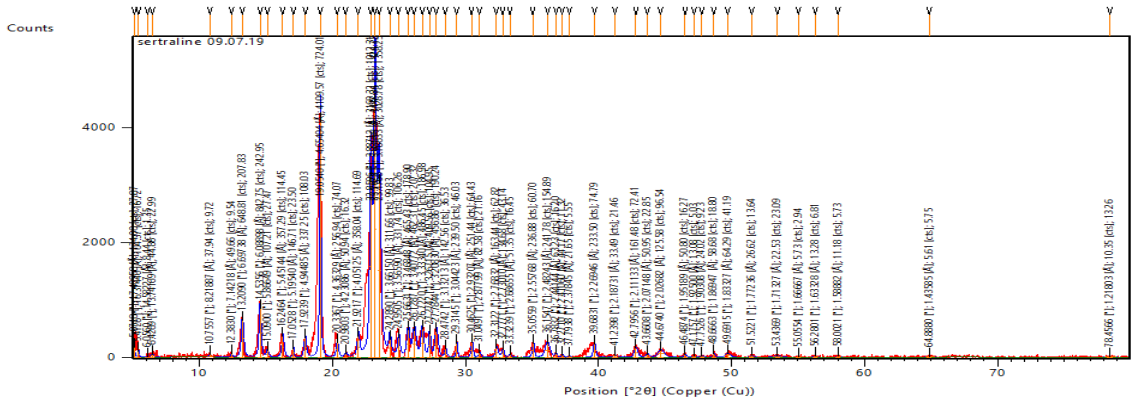

Figure 8: XRD graph of Sertraline (S5) solid dispersions

CONCLUSION

The following conclusions were drawn from results obtained

1. Solubility of Fluoxetine (F1-5), Sertraline (S5) solid dispersions were found to be freely soluble compared to pure forms.
2. From dissolution studies, F5 and S5 were found to be optimized with drug release of 98% and 98.9% at 45 min and 60 min respectively.
3. From FTIR analysis, it was found that there was no incompatibility between drug and polymer.
4. From SEM images, solid dispersions were obtained with rough and porous surface.
5. From XRD patterns, number of peaks decreased in case of solid dispersions with 2 clear peaks indicating conversion from crystalline to amorphous.

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