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PREFORMULATION STUDIES OF SELECTED SSRI's USED FOR TREATMENT OF DEPRESSION

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ABSTRACT

Pre-formulation studies investigate the physical and chemical properties of an active pharmaceutical ingredient to determine factors that may influence the formulation, development and stability of final product. Overall preformulation parameters contributes in streamlining efficacy, safety and stability of the product and ensures quality drug product to reach the market. Postpartum depression is a mood disorder experienced by mother's post child delivery. It can be treated by antidepressants like Fluoxetine, Sertraline, Amitriptyline and others. **Aim:** The aim of the present work is to study the preformulation parameters of selective serotonin reuptake inhibitors (SSRI's) like Fluoxetine HCl and Sertraline HCl used for the treatment of postpartum depression. **Materials and methods:** Fluoxetine HCl (FLX) exhibits limited solubility in water but dissolves readily in ethanol and methanol. The typical adult dose ranges from 20-60mg/day. Sertraline Hydrochloride (STR) is a slightly water-soluble drug, the minimum effective oral adult dose of Sertraline is 50mg/day in-case of depression. The preformulation studies like solubility profile, FTIR, SEM, dissolution studies and melting point were carried out for both the drugs.

KEYWORDS: SEM, DSC, FTIR, mood disorder, stability, melting point, solubility, preformulation studies.

INTRODUCTION

"The initial stage in developing dosage form for drug substance is known as preformulation studies".[1] The primary objective of pre-formulation testing is to generate data that supports the development of stable, bioavailable and manufacturable dosage forms.[2] Conduction of preformulation studies to active drug molecules discovers the barrier in further development of drug into formulation.[3] The assessment of a drug's physical and chemical properties is crucial, as these factors directly impact manufacturing, storage requirements of the drug.

Fluoxetine (FLX) is a N-methyl-3-phenyl-3-[4-(tri fluoro methyl) phenoxy propan-1-amine, belongs to the class of selective serotonin reuptake inhibitors used as anti-depressants.[4] It is a white powder with 309.33 g/mol molecular weight. It is most soluble in ethanol, methanol while it has limited solubility in acetone, chloroform and water. The initial average dose of Fluoxetine is 20mg orally[5] once a day in the morning which will be increased after several weeks if sufficient clinical improvement is not observed.

Sertraline (STR) is a (1S, 4S)-4-(3, 4-dichlorophenyl)-N-methyl-1, 2, 3, 4-tetrahydro-1-naphthalene-l-amine hydrochloride which belongs to selective serotonin reuptake inhibitors of anti-depressants. It is a white crystalline powder with 306.229 g/mol molecular weight. It shows solubility in dimethyl sulfoxide (DMSO), ethanol, isopropyl alcohol, chloroform and slightly soluble in water.[6] In adults, the starting average dose of Sertraline ranges from 50-100mg taken once a day, with the possibility of increasing the dosage weekly based on the clinical response.[7]

In the present study, preformulation studies were conducted on both the drugs Fluoxetine and Sertraline to investigate the suitability of drug for the further development into formulation.

MATERIALS AND METHODS

Fluoxetine and Sertraline HCl pure samples were gifted by Aurobindo pharma, Chittoor. All the chemicals and reagents used were of analytical grade.

Preformulation studies of FLX and STR

Preformulation characteristics that are investigated are,

a) Powder X-ray diffraction technique.
b) F.T.I.R. analysis
c) Scanning electron microscopy (SEM)

d) Solubility determination of Fluoxetine
e) Melting point
f) *In-vitro* drug release studies

Crystallinity and polymorphism of drugs were carried out to determine crystal habit and internal structure of drug that affects physico-chemical parameters. Crystal habit specifies outer morphology of a crystal. Molecular arrangement within the solid was described by internal structure of drug. Crystallinity and polymorphism assessed by PXRD, FTIR analysis, Scanning electron microscopy.[8,9]

Powder X-ray diffraction technique (PXRD)

The sample was mounted on aluminum frames with adhesive tape and was analyzed in 2Ɵ over a range of 5-40^0 at 20kV and with a scan rate of 2^0/min.[10]

FTIR analysis

FTIR Spectroscopy was performed to determine the structure of the organic compounds and to identify the presence of specific functional groups with in a sample. The interactions between the drug and polymer were identified using the resulting spectra. Sample was added to KBr grounded and converted into transparent discs using pressed pellet technique and spectra were collected. The spectral range was 4000-400cm$^{-1.}$

Scanning electron microscopy (SEM)

Scanning electron microscopy is used to determine surface topography, particle size distribution, morphology of fractured or sectioned surface and texture of particles.[11]

Solubility studies

Solubility studies were carried out using shake flask method.[12,13] Excess of pure FLX and STR were placed in a test tube containing 10ml of distilled water. The samples were agitated at room temperature for 48hr until equilibrium was established and then aliquots were filtered. The filtered samples were diluted and assayed simultaneously using UV spectrophotometer at 226 nm and 275nm respectively.

Determination of melting point

The drugs melting point were assessed through the use of capillary rise method. In this method, capillary tube filled with the drug to a height of 3mm from the sealed end and

introduced into digital melting apparatus. The range of temperature at which drugs melt was noted down.[14]

In-vitro drug release studies

Dissolution studies were carried out for pure FLX and STR 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±0.2^{0}c.[15,16] Fluoxetine and Sertraline in amounts of 20 mg and 50 mg respectively, were incorporated into the dissolution medium. At specified time intervals, 5ml of samples were withdrawn and assayed for drug (FLX and STR) using UV-visible spectrophotometer at[17] 226nm and 275 nm respectively. Dissolution profile of drug was analyzed by plotting a graph between % drug release versus time.

RESULTS AND DISCUSSION

Powder X-ray diffraction technique (PXRD)

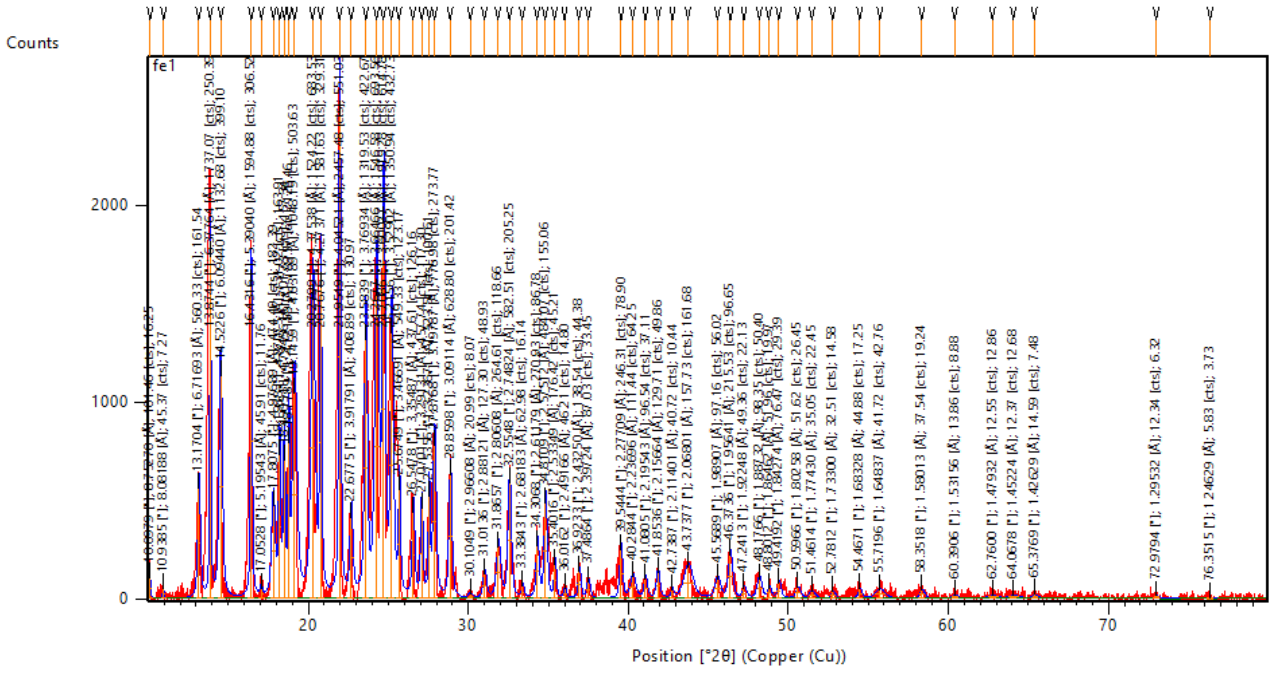

Fig. 1: XRD graph of Fluoxetine HCl Plain Drug.

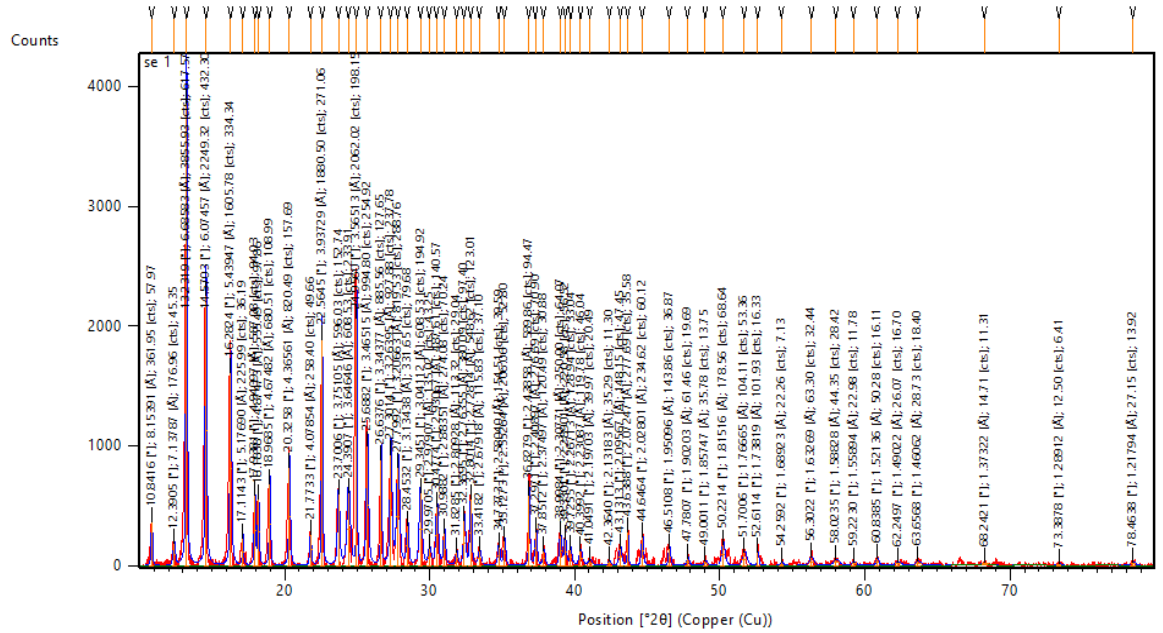

Fig. 2: XRD Graph of Sertraline HCl Plain Drug.

The diffractograms of FLX and STR as presented in **Fig. 1 and 2** revealed highly complexometric peaks indicating the crystalline nature of Fluoxetine HCl and Sertraline HCl.

FTIR analysis

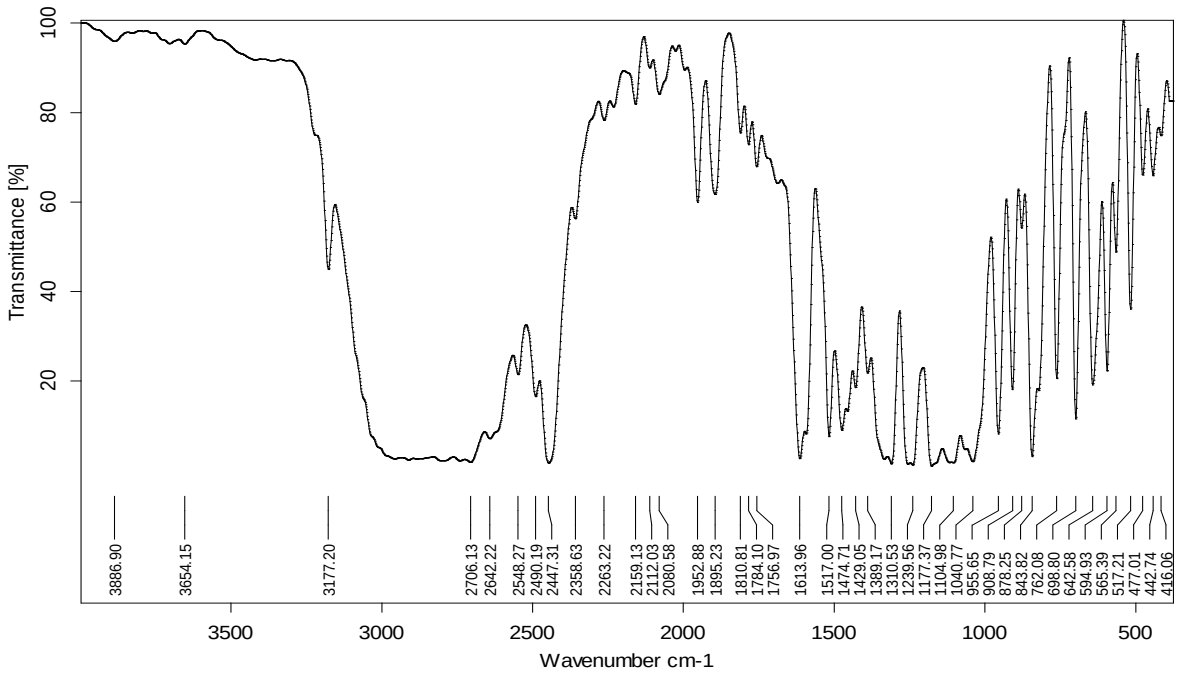

Fig. 3: FTIR Graph of Fluoxetine Plain Drug.

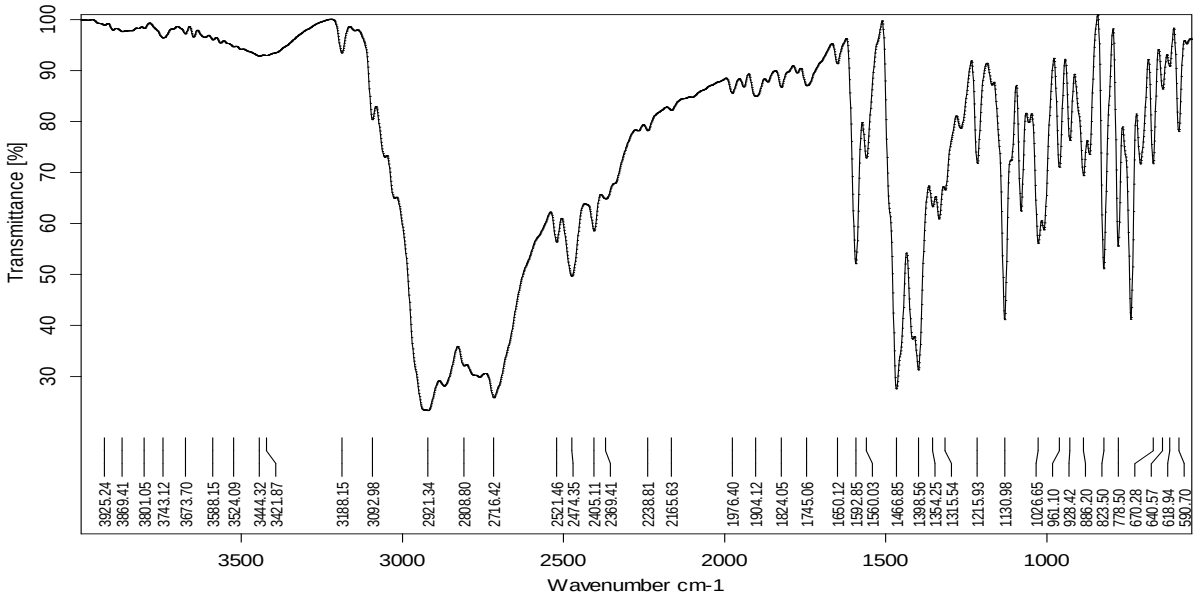

Fig. 4: FTIR Graph of Sertraline Plain Drug.

Infrared (IR) spectrum of Fluoxetine HCl as shown in **Fig. 3** showed characteristic peaks of 3554 cm^{-1} represents amine stretching vibration (NH), 3177 cm^{-1} indicates aromatic C-H stretching, 1310 cm^{-1} indicates halide stretching vibration, 1517 cm^{-1} represents C=C stretching.

Infrared (IR) spectrum of Sertraline HCl as shown in **Fig. 4** showed characteristic peaks at 3421 cm^{-1} represents carbon-oxygen stretching, 1560 cm^{-1} indicates aromatic stretching, 1354 cm^{-1} indicates C-NH_2 stretching vibration, 1028 cm^{-1} represents aromatic ring stretching.

Scanning electron microscopy (SEM)

Fig. 5: SEM image of Fluoxetine HCl.

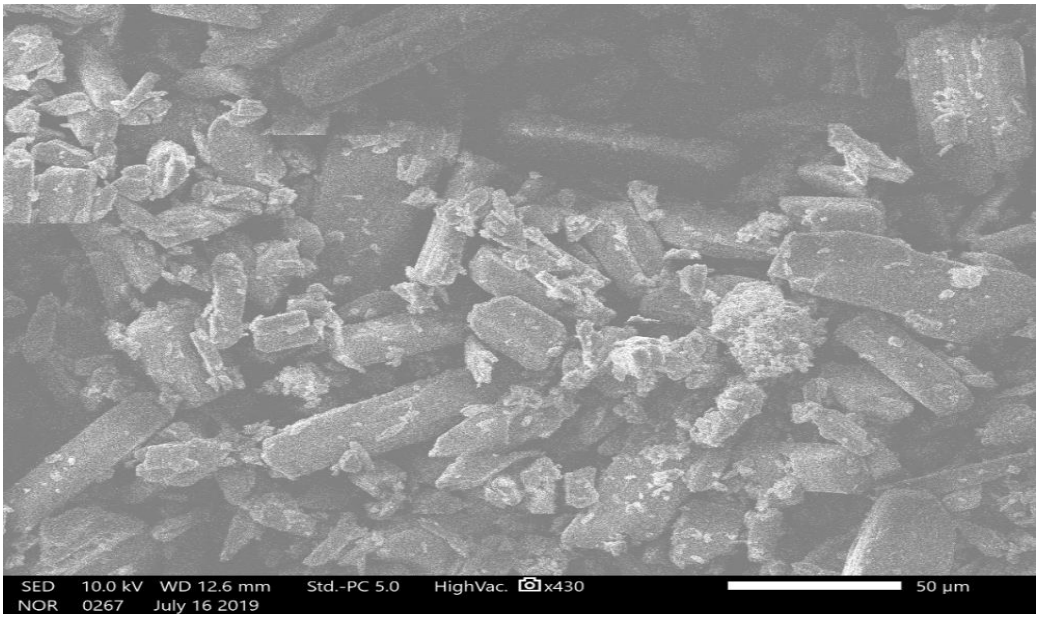

Fig. 6: SEM image of Sertraline HCl.

From the microphotographs of Fluoxetine and Sertraline as shown in **Fig. 5, 6** it was observed that the surface of both the drugs were rough and irregular in texture.

Solubility studies

Table 1: Solubility data of Fluoxetine HCl.

Formulation code	Solubility in mg/ml	Part of solvent required for one part of solute (parts)	Remarks
Pure drug	0.0210 ± 0.02	47	Sparingly soluble

Table 2: Solubility data of Sertraline HCl.

Formulation code	Solubility in mg/ml	Part of solvent required for one part of solute (parts)	Remarks
Pure drug	0.010± 0.01	100	Slightly soluble

The solubility studies of Fluoxetine and Sertraline revealed that they were sparingly and slightly soluble in water as shown in **Table 1, 2**.

Determination of melting point

Table 3: Experimental Vs observed value of melting point of Fluoxetine.

Drug	Experimental value	Observed value
Fluoxetine HCl	161^0c	160.29^0c

Table 4: Experimental Vs observed value of melting point of Sertraline.

Drug	Experimental value	Observed value
Sertraline HCl	246^0c	251.1^0c

Melting point of Fluoxetine and Sertraline pure drug determined by capillary rise method were observed to be 160.29^{0}c and 251.1^{0}c which coincides with the literature value of 161^{0}c and 246^{0}c of both the drugs respectively as indicated in **Table 3, 4.**

***In-vitro* drug release studies**

Table 5: *In-vitro* release data of Fluoxetine HCl.

Time (min)	Plain Fluoxetine
0	0
10	9 ± 2.56
20	16.59 ± 1.47
30	29.5 ± 2.60
45	38.15 ± 1.97
60	57.6 ± 2.45
90	72.8 ± 1.25
120	89.97 ± 0.85

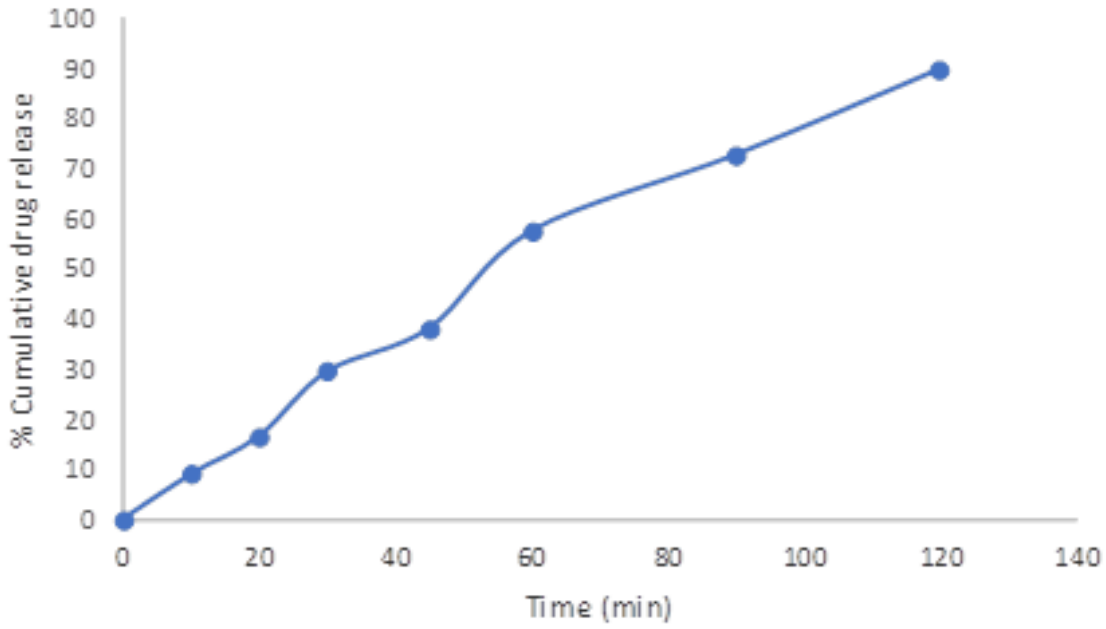

Fig. 7: *In-vitro* release data of Fluoxetine HCl.

Table 6: *In-vitro* release data of Sertraline HCl.

Time (min)	Plain Sertraline
0	0
10	15.6±0.30
20	28.2±0.12
30	35.32±0.12
45	37.96±0.16
60	49.54±0.20
90	54.76±0.35
120	58.28±0.12

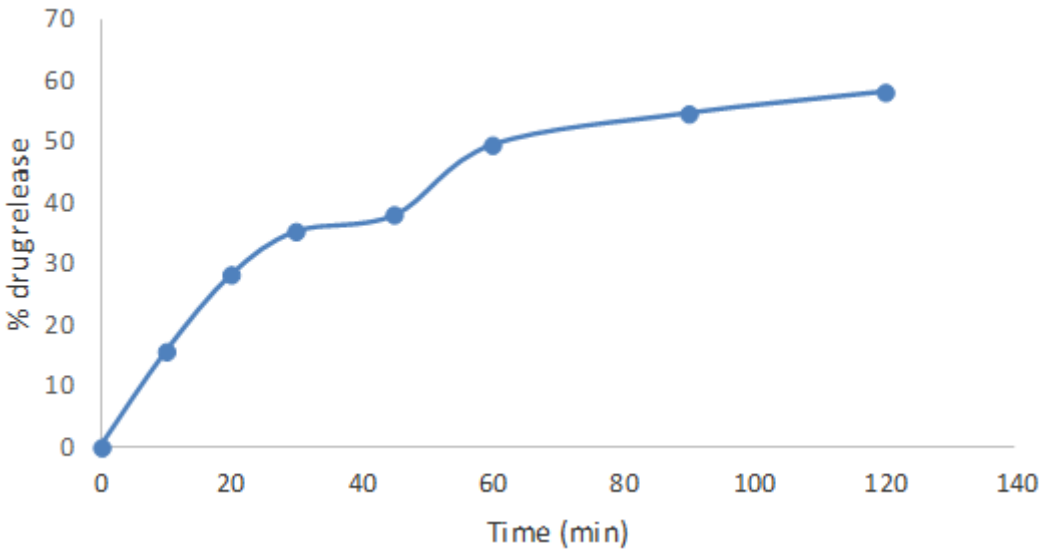

Fig. 8: *In-vitro* release data of Sertraline HCl

As per results indicated in **Table 5, 6 and Fig. 7, 8**, it was found that the pure Fluoxetine and Sertraline showed the rate of dissolution value of 89.97 ± 0.85% and 58.28 ± 0.12% after 2hr respectively.

CONCLUSION

Pre-formulation studies were carried out on both the drugs Fluoxetine and Sertraline revealing the sparingly soluble and slightly soluble nature of drugs confirmed by solubility studies. XRD graphs of FLX and STR confirmed the crystallinity of both the drugs. FTIR graphs showed the characteristic peaks of drugs at different wavenumbers identifying the functional groups. Fluoxetine and Sertraline showed 89.97% and 58.28% drug release for 2 hours respectively. From the results, it was cleared that there is a need to enhance the solubility and dissolution of these drugs by implementing various solubility enhancement techniques for further development into dosage form.

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