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Enhancement of Solubility and Dissolution of BCS Class II Drugs Using Solid Dispersion Technique

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Abstract:

The purpose of this study was to develop a solvent evaporation technique for improving the solubility of poorly soluble drugs, such as fluvoxamine tablets. Fluvoxamine is an antidepressant medication that is a selective serotonin reuptake inhibitor (SSRI).

The goal is to enhance the biological performance of Fluvoxamine by using a solid dispersion method since the BCS class II medication has poor oral bioavailability and low water solubility. Methodology: The medication Fluvoxamine was created utilizing the solvent evaporation process. Fluvoxamine solid dispersions were made using various carriers in PEG 6000 and mannitol ratios of 1:1, 1:2, and 1:3.

Findings: Findings from Fluvoxamine solid dispersions made using the solid dispersion technique Lastly, a comparison of all the formulations reveals that formulation (SF3), which contains fluvoxamine and PEG 6000 (1:3), performs better.

We came to the conclusion that the solvent evaporation solid dispersion process improves the solubility of poorly soluble drugs. We also produced six Fluvovamine formulations (FDF1–FDF6), and FDF4 exhibits the highest drug release at the end of time (98.9±0.8%).

Keywords: mannitol, PEG 6000, fluvoxamine, antidepressant, solvent evaporation, and direct compression technique.

1. INTRODUCTION

Pharmaceutically validated formulation development strategies have improved the oral bioavailability of some BCS class II medications [1]. In order to increase the oral bioavailability of therapeutic compounds, the following technologies were selected: micronization, nanosizing, solid dispersions (SD), size reduction, cyclodextrins, solid lipid nanoparticles, and crystal engineering [2]. In any case, the low oral bioavailability of oral dose forms is the main aim of their design. The oral bioavailability of pharmaceuticals is influenced by a number of parameters, including water solubility, drug permeability, dissolution rate, first-pass metabolism, and presystemic metabolism. The primary causes of inadequate oral bioavailability of medications were low permeability and low solubility. For various dosage forms, such as parenteral formulations and other routes of dose forms, solubility plays a crucial role. High dosages of medication are often required to achieve therapeutic systemic plasma concentrations after oral administration, and poorly water soluble active pharmaceutical components are typically preferred [3].
1.1 Solubility Is Important Improvement consists of
Drugs that are poorly soluble in water usually need large dosages and high dosing schedules to achieve therapeutic plasma concentrations after oral delivery. The largest disadvantage is poor water solubility, which is addressed in both generic and unique chemical compound formulation development [4].
1.2 API Fluvoxamine
A selective serotonin reuptake inhibitor (SSRI) is the name given to the medication fluvoxamine [5]. Fluvoxamine is used to treat depression, social anxiety disorders including panic disorder, and obsessive-compulsive disorder (OCD). It also helps reduce compulsions, or the need to do repetitive actions, and obsessive-compulsive thoughts, or obsessions.
such as counting, checking, and hand washing) that get in the way of day-to-day activities. This fluvoxamine medication functions by assisting in the restoration of serotonin's equilibrium in the central nervous system [6].
1.3 Dispersions of Solids
Solid dispersions have long been used as a successful technique to enhance the dissolving characteristics and bioavailability of medications with weak water-solution capabilities. A small number of these processes are economically valuable to increase the dissolution and oral absorption of poorly water-soluble pharmaceuticals. Since 1961, many researchers have studied poorly water-soluble solid dispersions of medications with various pharmacologically inert carriers. Increased wettability, greater drug particle dispersibility, the drug's amorphous presence with improved solubility, and the absence of drug particle aggregation were all factors that contributed to the rapid or instantaneous drug degradation. According to the literature, dissolving has been enhanced by using the solvent system for evaporating solid dispersions. According to earlier research, solid dispersion systems improve medication dissolving via increased weight, dispersibility, and hydrophilic carrying solubility. The solvent evaporation approach was used in this study to create solid fluvoxamine dispersions. This method requires the least quantity of solvent to dissolve the medication. We used several polymer carriers in our investigation [7].
The drug and carrier physical combination is dissolved in a common solvent and then evaporated until a transparent, solvent-free film is left behind in this sovent evaporation process. To maintain its weight, the film is further dried. Due to the comparatively low temperatures needed for the evaporation of organic solvents, the solvent method's primary benefit is the prevention of thermal destruction of medications or carriers [8].

1.1 Limitations

The limitations of solid dispersion technology have been a drawback for the commercialization, the limitations include

- Laborious and expensive methods of preparation,
- Reproducibility of physicochemical characteristics,
- Difficulty in incorporating into formulation of dosage forms,
- Scale-up of manufacturing process,
- Stability of the drug and vehicle.

2. MATERIALS AND METHODS

Fluvoxamine (Active Pharmaceutical ingredient) is a gift sample from SD fine chemicals Pvt ltd. Other ingredients Polyethylene glycol 6000, Mannitol, Hydroxy propyl methyl cellulose K100M, sodium starch glycolate, magnesium stearate, talc were purchased from SD Fine chemicals Pvt Ltd in Mumbai. All the excipients used in the research were highest grades of purity [9].

2.1 `Preparation of Solid Dispersions (SD) of Fluvoxamine

2.1.1 Solvent evaporation method

The calculated amount of Fluvoxamine and the employed carriers of PEG 6000 and Mannitol in different drug, & polymer ratios of 1:1, 1:2 and 1:3) are weighed and mixed together in a porcelain dish. Six different formulae were prepared by the solvent evaporation method [10]. Shown in Table 1.

The mixture was dissolved in the least amount of methanol as a common solvent, Then the solvent was evaporated at temperature 50ºC in the oven till complete evaporation. The Fluvoxamine solid dispersions were prepared and pulverized in a mortar than sieved. The powder that passed through 45 µm was stored in a desiccators and used for further investigations purpose.

2.2 Preformulation Studies

Definition: It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

Solubility studies: Solubility of Fluvoxamine was carried out in different buffers. Saturated solutions were prepared by addition excess drug to the vehicles and shaking on the shaker for 24 hrs at 25°C under constant triturate vibration. Filtered samples (1ml) were diluted appropriately with suitable buffer and solubility of Fluvoxamine was determined by UV visible Spectrophotometrically at 246 nm.

2.2.1 Calibration curve of Fluvoxamine in 0.1N HCL: Preparation of stock solution

10 mg of Fluvoxamine was taken in a 10 ml volumetric flask. The solution was made up to the mark with 0.1 Normality HCL to form 1000 µg /ml concentrate preparation. From this stock 1 ml is diluted to 10 ml with, 0.1N HCL to give 100 µg /ml concentration.

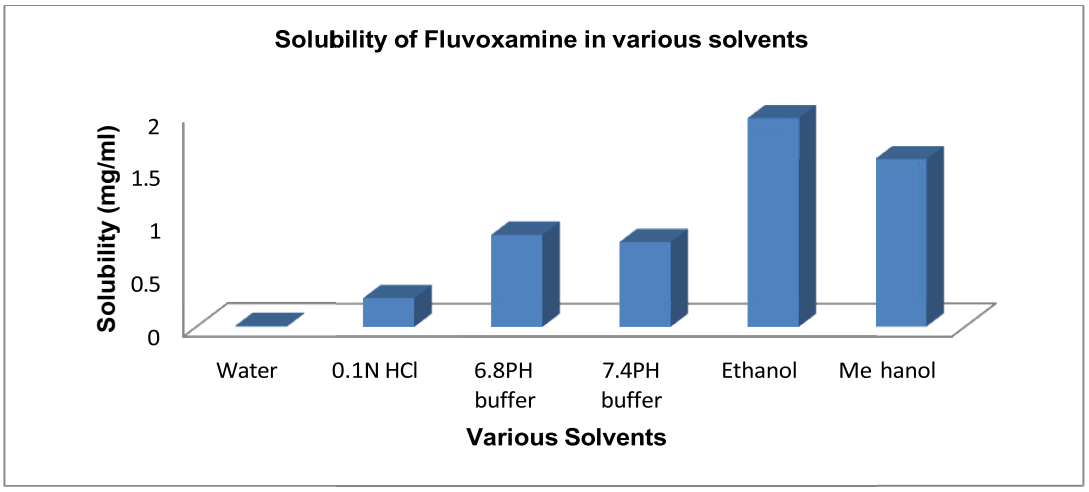
During the above stock solution subsequent dilutions containing 5 to 30 µg/ml solutions were prepared. The absorbance of each test sample solution was measured at λmax i.e. 246 nm of Fluvoxamine in UV Visible spectroscopy against blank.

Table 1. Preparation of Fluvoxamine solid dispersions (SD) using PEG 6000 and Mannitol

Formulation code	Drug : Carrier ratio (Fluvoxamine: PEG 6000)	Formulation code	Drug : Carrier ratio (Fluvoxamine: Mannitol)
SF1	1:1	SF4	1:1
SF2	1:2	SF5	1:2
SF3	1:3	SF6	1:3

Table 2. Solubility studies of fluvoxamine in various solvents

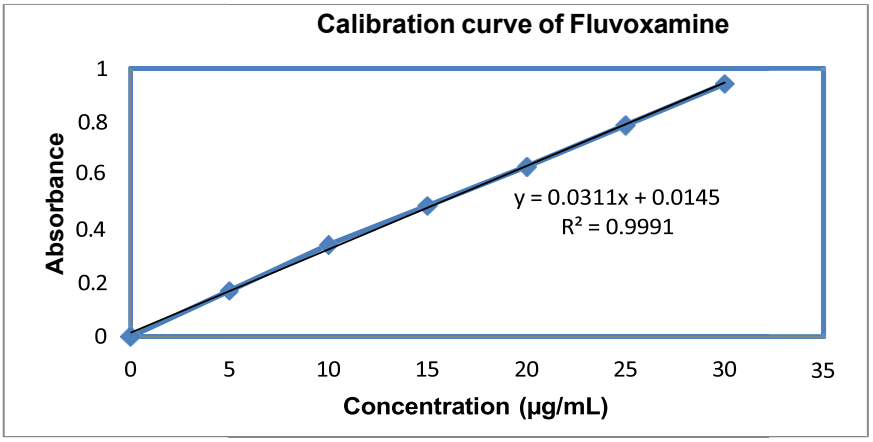
S.NO	Solvents	Solubility (mg/mL)
1	Water	0.0074±0.01
2	0.1N HCl	0.269±0.01
3	6.8P^H buffer	0.863±0.04
4	7.4P^H buffer	0.795±0.05
5	Ethanol	1.958±0.01
6	Methanol	1.568±0.03



Graph 1. Solubility studies of fluvoxamine

Table 3. Calibration curve of Fluvoxamine in 0.1N HCl

S.NO	Concentration (µg/mL)	Absorbance
1	0	0
2	5	0.171
3	10	0.343
4	15	0.488
5	20	0.635
6	25	0.789
7	30	0.943



Graph 2. Calibration graph of fluvoxamine

2.3 Evaluation of Fluvoxamine Solid Dispersions

Prepared polymer drug conjugates were evaluated by

1) Estimation of drug content
2) *In vitro* dissolution studies

2.3.1 Estimation of Drug Content

A quantity which was equivalent to 50 mg of drug was accurately weighed and transferred to 100ml volumetric flask. Then the volume was made up with, 0.1 N HCL buffer and shaken for 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving

standard drug in 0.1 N HCL buffer. For both the sample and standard solutions absorbance was measured at 246 nm for Fluvoxamine in UV-Visible spectrophotometer.

2.3.2 *In vitro* dissolution studies

The prepared solid dispersions by solvent evaporation technique were subjected to *in vitro* dissolution. Dissolution test was carried out using USP type I basket method [apparatus 1]. The stirring rate was 50 rpm (revolution per minute), 0.1 N HCL buffer was used as dissolution medium and this medium was maintained at 37±0.5oC. 5 ml sample solutions were withdrawn at regular intervals of time than filtered and replaced with same (5 ml) quantity of fresh dissolution medium, the dilutions were made wherever needed and were analyzed for Fluvoxamine at 246 nm by using UV-visible spectrophotometer.

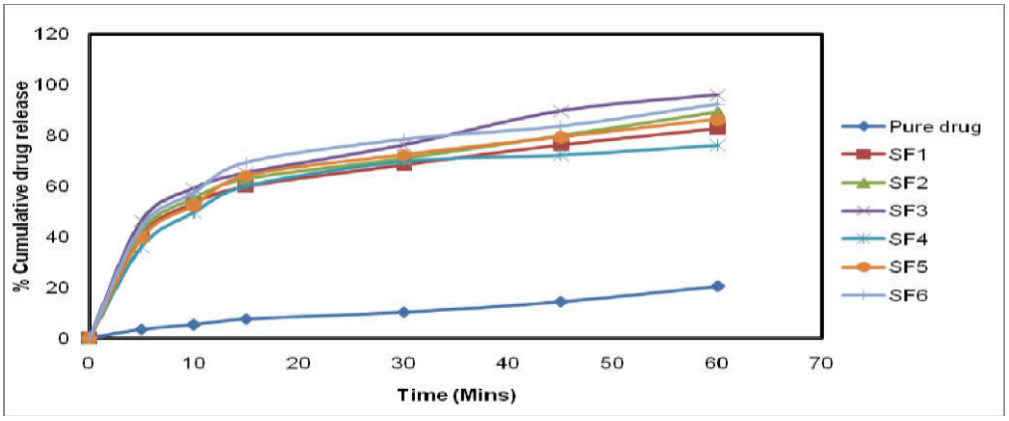
Solid dispersions of Fluvoxamine were prepared with different carriers in different ratios of drug and carrier (1:1, 1:2 and 1:3 by solvent evaporation method. comparing all the formulations, (SF3) formulation containing Fluvoxamine and PEG 6000 (1:3) shows better results by solvent evaporation method at the end of 60 min with maximum drug release (i.e 96.04±1.8%), hence it was selected as the best formulation showed in Table 5.

Table 4. Percentage Drug content of SF1-SF6

Formulation code	%Drug content
SF1	95.26±0.02
SF2	90.43±0.09
SF3	96.84±0.05
SF4	92.35±0.01
SF5	93.57±0.10
SF6	96.14±0.07

Table 5. Cumulative percentage drug release data of (SF1 to SF6) solid dispersions

Time (min)		Cumulative percentage drug release (%CDR)					
		Fluvoxamine: PEG 6000			Fluvoxamine: Mannitol		
	Pure drug	SF1	SF2	SF3	SF4	SF5	SF6
0	0	0	0	0	0	0	0
5	3.4±0.2	40.21±0.9	42.05±1.1	46.32±0.6	36.12±1.1	39.52±3.1	44.01±2.6
10	5.3±0.3	53.29±1.1	55.24±1.4	59.18±0.7	49.63±1.6	52.34±2.9	57.38±3.5
15	7.5±0.5	59.85±1.6	62.85±2.1	65.24±0.9	60.12±2.5	64.12±1.7	69.31±0.4
30	10.2±0.7	68.41±2.1	70.96±2.4	76.24±2.4	69.85±3.2	72.39±2.6	78.42±1.5
45	14.3±0.5	76.24±0.9	79.94±3.2	89.63±3.2	72.34±1.9	79.34±0.4	83.56±2.7
60	20.4±0.6	82.67±2.3	89.24±1.9	96.04±1.8	76.24±2.8	86.34±3.5	92.28±0.7



Graph 3. *In vitro* drug release of fluvoxamine solid dispersions (SF1-SF6)

3. RESULTS AND DISCUSSION

3.1 Preparation of Fluvoxamine Tablets

Preparations of Fluvoxamine tablets were using SF3 formulation (selected as optimized drug release in solid dispersions), in this preparations active pharmaceutical ingredient i.e. Fluvoxamine (equivalent to Fluvoxamine 50 mg) and, other excipients such as HPMC K100M, sodium starch glycolate, magnesium stearate and talc. The Fluvoxamine tablets were prepared with direct compression method [11].

Six formulations of fluvoxamine tablets [12] each one contains 50 mg of Fluvoxamine and various concentrations of excipients were used to prepared 200 mg dose of tablets which were showed in Table 6.

3.2 Evaluation of Fluvoxamine Tablets

Prepared polymer drug conjugates were evaluated by

1) Post compression evaluation studies
2) *In vitro* dissolution studies
3) Drug-polymer compatibility studies
4) *In vitro* kinetic studies

3.2.1 Post compression evaluation studies

The Fluvoxamine tablets formulated by direct compression technique, these prepared tablets were evaluated by various post compression methods such as Weight variation, hardness, %Friability and thickness. As a result of all the post compression parameters were within the IP limits. Which were showed in Table 7.

3.2.2 *In vitro* dissolution studies

The prepared Fluvoxamine solid dispersions were subjected to *in vitro* dissolution studies. Dissolution apparatus test was carried out using USP type II (Paddle method.), The paddle stir rate was 50 rpm (revolutions per minute), 0.1 N HCL (900 ml) buffer was used as dissolution medium and dissolution apparatus maintained at 37±0.5oC. Dilutions were prepared wherever necessary and analyzed for Fluvoxamine tablets at 246 nm by using UV-visible spectrophotometer. Six formulations (FDF1 to FDF6) percentage cumulative drug releases showed in Table 8. From six formulations FDF4 formulation shows 98.9 % drug release at the end of 60 mins, so that comparing with all other formulations FDF4 shows 98.9±0.8% drug release, Hence FDF4 is the best formulation which is showed in graph no 4.

3.2.3 Drug–polymer compatibility studies

FT-IR studies (Fourier transform infrared spectroscopy studies)

In the preparation of tablet formulation, drug and polymer may interact as they're in close contact with one another, which could lead on to the instability of drug. Preformulation studies regard the drug and polymer interactions, so that selection of appropriate polymers is difficult. The employed FT-IR spectroscopy , to determine the compatibility between Fluvoxamine (Active Pharmaceutical Ingredient), and therefore the selected polymers. The pure Active Pharmaceutical Ingredient Fluvoxamine and drug with excipients were separately scanned with FT-IR showed in Fig. 1 and Fig. 2 respectively.

3.2.4 Kinetics of drug release

The Fluvoxamine solid dispersion tablets mechanism of drug release was determined using zero order and first order [13].

In-vitro drug release results profile of Fluvoxamine tablets obtained for optimized formulation (FDF4) was plotted in kinetics of data as follows, which were showed in Graph no 5 and Graph no 6 respectively.

Table 6. Ingredients used for fluvoxamine tablets

Formulation Code/Composition (mg)	FDF1	FDF2	FDF3	FDF4	FDF5	FDF6
Solid Dispersions (SF3) mg	65	65	65	65	65	65
HPMC K100 M	40	35	45	50	15	20
Sodium starch glycolate	60	55	50	45	100	95
Magnesium stearate	10	35	30	25	10	10
Talc	10	10	10	15	10	10

Total tablet weight= 200 mg

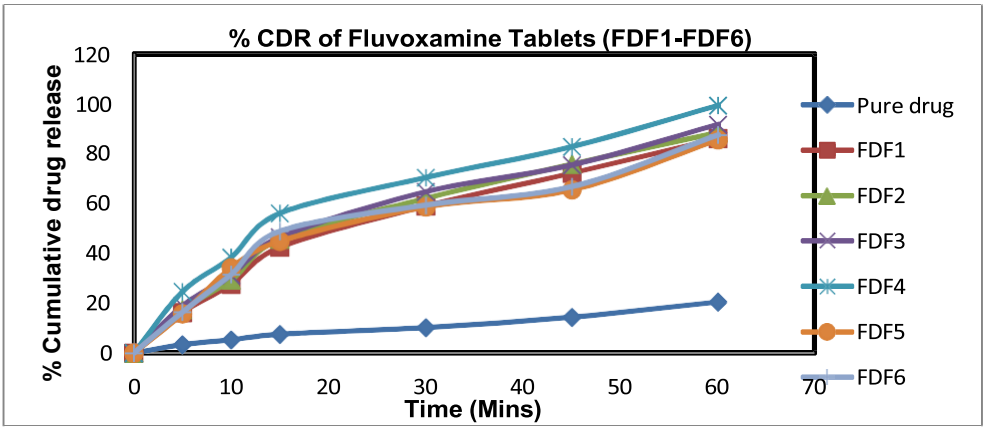
Table 7. post compression parameters of fluvoxamine tablets (FDF1-FDF6)

Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Weight Variation (mg)	%Friability (% loss)	Assay (%)
FDF1	4.1±0.1	2.9±0.02	196.99	0.52	96
FDF2	4.0±0.04	3.0±0.04	204.65	0.60	99
FDF3	3.9±0.4	3.1±0.8	202.13	0.54	98
FDF4	4.0±0.6	2.6±0.2	200.10	0.52	100
FDF5	3.8±0.8	2.8±0.1	199.50	0.50	98
FDF6	4.0±0.4	3.1±0.04	194.50	0.57	97

Table 8. Percentage cumulative drug release

%CDR/Time (mins)	Pure drug	FDF1	FDF2	FDF3	FDF4	FDF5	FDF6
0	0	0	0	0	0	0	0
5	3.4±0.2	16.2±1.2	17.4±0.2	18.9±1.1	24.5±0.7	15.7±0.8	16.4±1.1
10	5.3±0.3	27.5±1.7	29.2±0.9	31.1±2.3	38.2±1.4	34.1±1.5	31.4±1.7
15	7.5±0.5	42.3±2.1	45.6±1.3	46.3±3.6	55.8±2.8	44.7±1.9	48.7±2.5
30	10.2±0.7	58.8±2.4	61.8±2.3	64.4±2,.6	70.1±3.4	58.4±2.5	59.1±0.5
45	14.3±0.5	71.9±3.3	75.5±1.9	75.1±3.4	82.4±2.4	65.2±2.9	66.5±1.4
60	20.4±0.6	85.7±1.3	88.1±1.2	91.3±0.5	98.9±0.8	85.2±1.8	87.1±2.1

%CDR= Percentage Cumulative drug release, ± = Standard deviation values



Graph 4. % Drug release graph of Fluvoxamine tablets (FDF1-FDF6) Versus pure drug

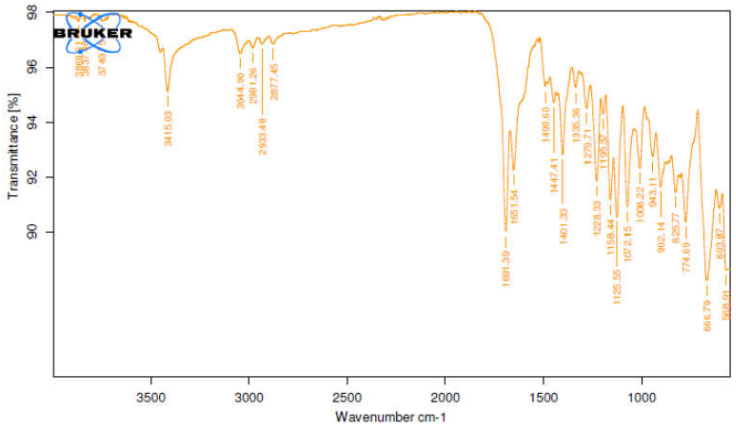


Fig. 1. FTIR of Fluvoxamine pure drug

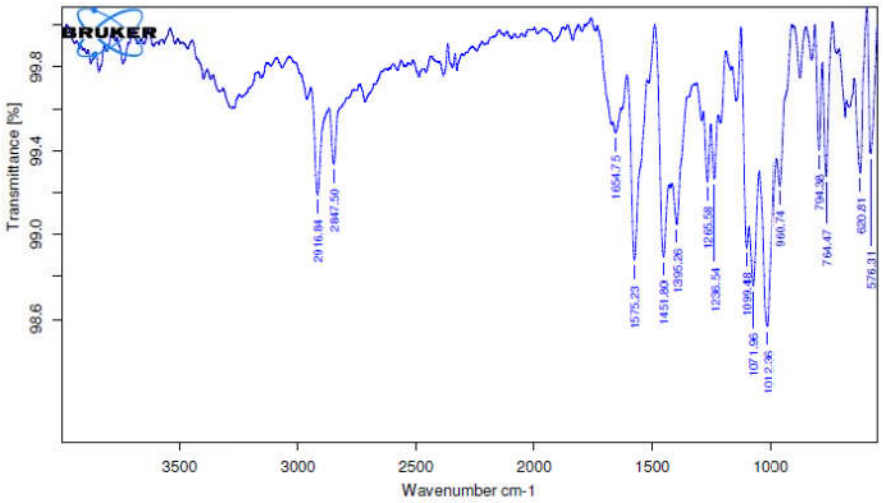
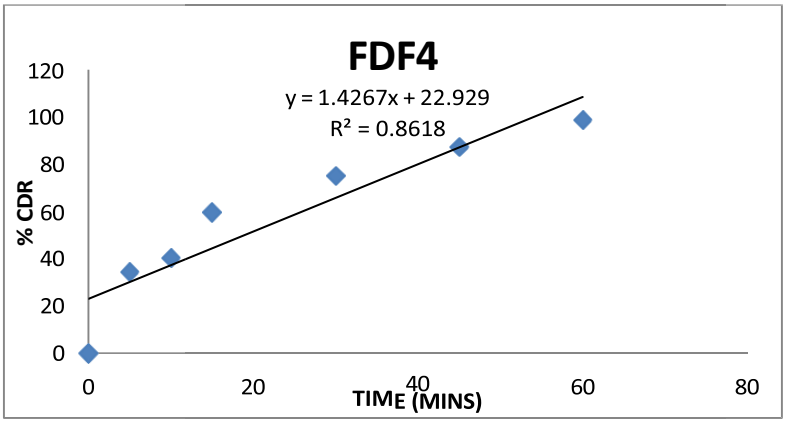


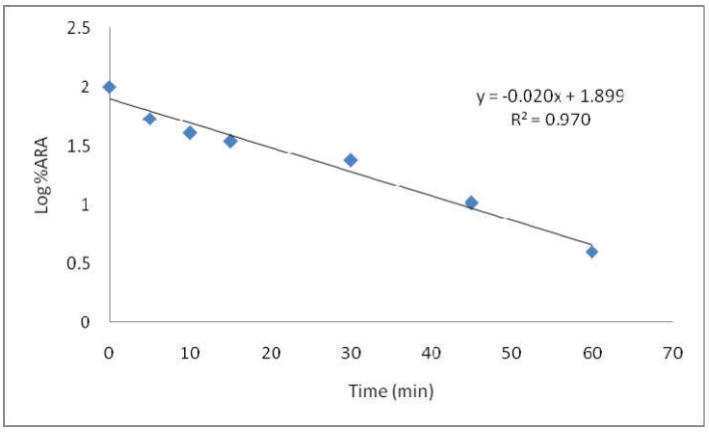
Fig. 2. FTIR of Fluvoxamine + Excipients

1. Zero Order Kinetics



Graph 5. Zero order kinetics of optimized formulation of Fluvoxamine tablets (FDF4)

2. First Order Kinetics



Graph 6. First order kinetics of optimized formulation of Fluvoxamine tablets (FDF4)

4. CONCLUSION

This investigation was conducted utilizing a direct compression approach with solid dispersions solvent evaporation method with varying ratios of drug and carriers PEG 6000, mannitol [15], and compared the in-vitro dissolving tests [14] of fluvoxamine tablets. According to solid dispersion data, SF3 solid dispersions improved drug release and increased solubility and dissolving rate. Lastly, HPMC K100M, sodium starch glycolate, magnesium stearate, and talc were used as excipients in the development of fluvoxamine controlled release tablets, which were made using SF3 (equal to 50 mg drug SD). Formulations FDF1 through FDF6 underwent in-vitro dissolution trials; at the end of 60 minutes, FDF4 had a better release of 98.9±0.8%.

How thoroughly a medication product is absorbed by the gastrointestinal system determines its therapeutic effectiveness when it is meant to be taken orally. It is also believed that the rate-limiting stage for the gastrointestinal tract's absorption of medications with solid dose forms is dissolution. It has been discovered that poorly soluble medications are unstable and slow to digest in comparison to those with greater solubility. Enhancing these drugs' water solubility, rate of dissolution, and bioavailability from oral solid dose forms is thus essential. Mannitol and PEG 6000 in solid dispersion methods increased the bioavailability and difficult-to-dissolve characteristics of poorly soluble medications. In this study, it was shown that the strong dispersion approach greatly increases the fluvoxamine dissolving efficiency. Based on the current study, it was determined that as this technology advances, there will be a great deal of potential for new drug release dosage forms in the solid dispersions of fluvoxamine controlled release tablets [16].

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