Enhancement of Solubility and Dissolution Rate of BCS Class-II Fluvoxamine Tablets using Solvent Evaporation Solid Dispersion Technique

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Authors' contributions

This work was carried out in collaboration between both authors. The author MS contributed to concept of work, data collection, literature survey and research methodology and the other author AS helped in drafted the manuscript, revised the manuscript and finalized the research work. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: This research work was aimed to formulate Enhancing the solubility of Poorly soluble drug i.e. Fluvoxamine tablets by the solvent evaporation method, Fluvoxamine medicament is a selective serotonin reuptake inhibitor (SSRI) antidepressant agent.

Purpose: The BCS class II drug Fluvoxamine consist low aqueous solubility and low oral bioavailability, for this reason to improve the biological performance of Fluvoxamine drug by solid dispersion mechanism.

Methodology: The drug Fluvoxamine was formulated by using solvent evaporation technique, solid dispersions of Fluvoxamine were prepared with different carriers in different ratios of PEG 6000 & Mannitol (1:1, 1:2 and 1:3).

Results: Results of prepared solid dispersions of Fluvoxamine by solid dispersion method Finally by comparing all the formulations, formulation (SF3) containing Fluvoxamine and PEG 6000 (1:3) shows better results.

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Conclusion: Here we concluded that the poorly soluble drug solubility improving by solvent evaporation solid dispersion mechanism, and also developed six Fluvoxamine formulations (FDF1-FDF6) during this FDF4 shows maximum (98.9±0.8%) drug release at the end of time.

Keywords: Fluvoxamine; antidepressant; PEG 6000; mannitol; solvent evaporation; direct compression method.

1. INTRODUCTION

Various BCS class II drugs of oral bioavailability enhanced through the pharmaceutically verified formulation development technologies [1]. The chosen technologies were Micronization, nanosizing, solid dispersions (SD), Size reduction, cyclodextrians, solid lipid nanoparticles, crystal engineering. These methods were used to improve the oral bioavailability of drug molecules [2]. Anyways, the biggest target with the design of oral dosage forms lies with their poor oral bioavailability. Aqueous solubility, drug permeability, dissolution rate, first-pass metabolism and, presystemic metabolism, these factors which influence the oral bioavailability of drugs. Low solubility and low permeability were the main reasons for low oral bioavailability of drugs. Solubility is the major role for other dosage forms like parenteral formulations as well as other routes of dosage forms. Poorly aqueous soluble active pharmaceutical ingredients generally desired, high amounts of drug in order to reach therapeutic systemic plasma concentrations after oral administration [3].

1.1 Importance of Solubility Enhancement includes

Poorly aqueous soluble drugs frequently require high amount of drugs (doses) and needed high dosage regimens in order to effect therapeutic plasma concentrations after oral administration. Poor water solubility is the biggest drawback, this factor overcomes with formulation development of novel chemical compounds as well as for generic compounds [4].

1.2 Fluvoxamine (API)

Fluvoxamine drug is known as a selective serotonin reuptake inhibitor (SSRI) [5]. Fluvoxamine is used to treat obsessive-compulsive disorder (OCD) and also used to treat depression and social anxiety disorders such as panic disorder. It helps decreasing persistent/unwanted thoughts (obsessions) and urges to perform repeated tasks (compulsions such as hand-washing, counting, checking) that interfere with daily living things. This Fluvoxamine drug works by helping to restore the balance of a certain natural substance (serotonin) in the CNS [6].

1.3 Solid Dispersions

As an effective method to improve the properties of dissolution and the bioavailability of poor water-solution drugs, solid dispersions have historically been used. Since 1961, a number of researchers have investigated poorly water-soluble solid dispersions of drugs with different pharmacologically inert carriers, but only a handful of these mechanisms are commercially useful to improve dissolution and oral absorption of poorly water-soluble drugs. Rapid or immediate drug degradation due to increased wettability, enhanced dispersibility of drug particles, the drug’s presence in an amorphous manner with improved solubility and the lack of aggregation for drug particles was observed. The literature indicates that the solvent system for evaporating solid dispersions has been used to improve dissolution. Previous studies indicate that solid dispersion systems enhance drug dissolution by means of enhanced hydrophilic carrying solubility, weight and dispersibility. In the present work, solid dispersions of Fluvoxamine were prepared using solvent evaporation method. The minimum amount of solvent in dissolving the drug is needed for this approach. In this analysis, we used different polymer carriers [7].

In this solvent evaporation method the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents [8].

1.4 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 50°C 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    | 6.8pH buffer | 0.863±0.04          |
| 4    | 7.4pH 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±0.5°C. 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 | SF1 | SF2 | SF3 | SF4 | SF5 | SF6 |
|------------------|-----|-----|-----|-----|-----|-----|
| %Drug content    | 95.26±0.02 | 90.43±0.09 | 96.84±0.05 | 92.35±0.01 | 93.57±0.10 | 96.14±0.07 |

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

| Time (min) | Pure drug | SF1 | SF2 | SF3 | SF4 | SF5 | SF6 |
|------------|-----------|-----|-----|-----|-----|-----|-----|
| Cumulative percentage drug release (%CDR) | Fluvoxamine: PEG 6000 | Fluvoxamine: Mannitol |
| 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±0.5°C. 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/cm²) | Thickness (mm) | Weight Variation (mg) | %Friability (%) | 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

The present study was performed and compared the in-vitro dissolution studies [14] of Fluvoxamine tablets by direct compression technique using solid dispersions solvent evaporation method with different ratios of drug and carriers PEG 6000, mannitol [15]. From the results of solid dispersion SF3 solid dispersions showed better drug release and, it enhanced the solubility and extent rate of dissolution. Finally Fluvoxamine controlled release tablets developed by using SF3 (equivalent to 50 mg drug SD) and excipients were HPMC K100M, sodium starch glycolate, magnesium stearate and talc. As a result of in-vitro dissolution studies of Formulations (FDF1 to FDF6) in this FDF4 showed 98.9±0.8% better release at the end of 60 mins.

The therapeutic efficacy of a drug product intended for oral administration is determined by how well it is absorbed by the gastro-intestinal tract. Dissolution is also thought to be the rate-limiting step for the absorption by the gastrointestinal tract of drugs of a solid dosage type. When compared to drugs with higher solubility, poorly soluble drugs have been found to be unstable and sluggish to digest. As a result, improving the aqueous solubility, dissolution rate, and bioavailability of these medications from oral solid dosage forms is critical. Difficult to dissolution properties and bioavailability of poorly soluble drugs were improved by PEG 6000 and Mannitol in solid dispersion techniques. The strong dispersion technique has been shown to significantly improve Fluvoxamine dissolution efficiency in this research. From the present research studies, concluded that with further growth of this technology, in the solid dispersions of Fluvoxamine controlled release tablets enormous possibilities in novel drug release dosage forms [16].

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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