Design and *in vitro* Evaluation of Fluvoxamine Nanosuspension using PVA as Stabilizing Agent

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**Abstract**

**Introduction:** Poor aqueous solubility and low dissolution rates are the initial drawback for the majority of upcoming and existing biologically active compounds. **Materials and Methods:** Fluvoxamine (API), other excipients such as PVA, SLS, Tween 80, and methanol. Fluvoxamine is a poorly water-soluble drug and its bioavailability is very low. The present study was to increase the solubility and dissolution rate of Fluvoxamine by formulating nanosuspensions by Emulsification solvent evaporation method. **Results and Discussions:** The formulation nanosuspension was subject to zeta potential, particle size analysis, drug content, and *in vitro* drug release studies. The entrapment efficiency of all the formulations was within 95.78–98.16%, from the drug release studies, The NF6 formulation was optimized and it shows maximum drug release (99.02%) at a shorter period of time than remaining formulations. The average particle size of the optimized formulation was found to be 110 nm. **Conclusion:** The research showed that enhanced dissolution rate by reduced in particle size, which, in turn, increases the dissolution rate and oral bioavailability of fluvoxamine by formulating nanosuspensions. Formulations were found to physically stable with PVA as the stabilizing agent.

**Key words:** Emulsification solvent evaporation, entrapment efficiency, fluvoxamine, nanosuspensions, particle size, PVA

**INTRODUCTION**

Pharmaceutical formulation research is that focus on improving the bioavailability of active agents by improving the solubility and dissolution rate of poorly aqueous-soluble drugs. Various pharmaceutical formulation technologies are used to increase the oral bioavailability of BCS Class II drugs. The main technologies to achieve the enhanced oral bioavailability of drugs with poor aqueous solubility include the use of micronization, nanosizing, solid dispersions, nanosuspensions, crystal engineering, cyclodextrins, solid lipid nanoparticles and, other colloidal drug delivery systems such as micro emulsions, SEDDS, self-microemulsifying drug delivery systems, and liposomes.[1]

Solid oral dosage forms of drug absorption depend on the release of the drug substance from the delivery system, the dissolution of the drug under physiological conditions and the drug permeability across the gastrointestinal tract. Poorly water soluble drugs are expected to have low oral bioavailability, dissolution limited absorption. Increasing the drug solubility may substantially contribute to improved drug absorption and consequently, drug bio-availability. The solid dispersion technique has been used to enhance the dissolution and, oral bioavailability of many poorly soluble drugs.[2]

**MATERIALS AND METHODS**

**Materials**

Fluvoxamine[3] drug is a gift sample from SD Fine Chemicals Pvt Ltd., other excipients such as PVA, SLS, Tween 80, and methanol.

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Methanol were purchased from Sri Krishna Pharmaceuticals, Hyderabad, and in this research work used chemicals were within the analytical grade limits [Table 1].

### Method of preparation of nanosuspension

**Preparation of fluvoxamine nanosuspension by emulsification solvent evaporation method**

Nanosuspension\(^1\) was prepared by the emulsification solvent evaporation technique. Fluvoxamine was dissolved in organic solvent at room temperature (organic phase). This solution is

<table>
<thead>
<tr>
<th>Ingredients/ Formulation code</th>
<th>NF1</th>
<th>NF2</th>
<th>NF3</th>
<th>NF4</th>
<th>NF5</th>
<th>NF6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvaxamine (mg)</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>PVA (mg)</td>
<td>25</td>
<td>50</td>
<td>75</td>
<td>25</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>SLS (mg)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Tween 80 (ml)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Methanol (ml)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Water (ml)</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

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**Table 1: Composition of nanosuspension of fluvoxamine (NF1-NF6)**
followed by its emulsification into water containing stabilizers (PVA), and cosurfactant (SLS and Tween 80) maintained at room temperature. Addition of organic solvents by means of a syringe positioned with the needle directly into stabilizer containing water, and subsequently stirred on magnetic stirrer to allow the volatile solvent to evaporate. Evaporation leads to the precipitation of the drug.⁴

**Evaluation parameters of nanosuspension fluvoxamine**

The nanosuspension was evaluated for various parameters⁵
1. Entrapment efficiency (EE)
2. Particles size analysis
3. Zeta potential

**Entrapment Efficiency**

The freshly prepared Fluvoxamine nanosuspension was centrifuged at 20,000 rpm for 20 min at 5°C temperature using a cool ultracentrifuge. The amount of unincorporated drug was measured by taking the absorbance of the appropriately diluted 5 ml of supernatant solution at 246 nm using UV spectrophotometer against blank/control nanosuspensions. The drug EE was calculated by subtracting the amount of free drug in the supernatant from the initial amount of drug taken.⁶

The EE% could be attained by the following equation:

\[
\% \text{ Entrapment efficiency} = \frac{\text{Drug content}}{\text{Drug added in each formulation}} \times 100
\]

**Particle size and shape**

The average particles size and shape of the formulated nanosuspensions were detected by using Malvern Zetasizer ZS in this water as dispersions medium. The sample was scanned 100 times for detection of particle size [Figure 1].⁷

**Zeta potential**

In zeta potential, there are three ways by which a solid particle (colloid) dispersed in a liquid media can acquire a surface charge. First, the adsorption of ions present in the solution, Second, due to the ionization of functional groups on the particle’s surface, and third, due to the difference in dielectric constant between the particle and the medium. Attention should be paid to the formation of an electric double layer at the solid-liquid interface. The Zeta potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electro-neutral region of the solution. The potential gradually reduces as the distance from the surface increases [Figure 2].⁸

The theory is based on electrophoresis and it can be expressed as:

\[
\mu = \frac{\zeta \varepsilon}{\eta}
\]

Where (\(\mu\)) is the electrophoretic mobility, (\(\varepsilon\)) is the electric permittivity of the liquid, (\(\eta\)) is the viscosity and (\(\zeta\)) as the zeta potential.

**Scanning electron microscopy**

The morphological features of Fluvoxamine nanosuspensions were observed by scanning electron microscopy at different magnifications shown in Figure 3.⁹

![Figure 2: Zeta potential of optimized formulation (NF6)](image-url)
RESULTS AND DISCUSSION

In vitro drug release study

In vitro dissolution study[6] was performed by USP dissolution apparatus-type II using 900 ml of 0.1N HCl as a dissolution medium maintained at 37 ± 0.5°C and stirring speed (50 rpm). The freshly prepared nanosuspensions were added to the dissolution medium, 5-ml samples were withdrawn at specific intervals of time, then filtered through a 0.45 µm filter paper, and analyzed for their drug concentrations by measuring at 246 nm wavelength.

Table 2: Percentage entrapment efficiency of NF1-NF6

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>%Drug content</th>
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<tr>
<td>NF1</td>
<td>98.02</td>
</tr>
<tr>
<td>NF2</td>
<td>96.34</td>
</tr>
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<td>NF3</td>
<td>95.78</td>
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<tr>
<td>NF4</td>
<td>98.16</td>
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<tr>
<td>NF5</td>
<td>97.34</td>
</tr>
<tr>
<td>NF6</td>
<td>97.38</td>
</tr>
</tbody>
</table>

The results of in vitro dissolution of fluvoxamine nanosuspension formulations (NF1-NF6) were fitted into Two models of data treatment as follows:[11]

1. Cumulative % drug release versus time (zero order kinetic model) showed in Figure 4.
2. Log cumulative % drug remaining versus time (first-order kinetic model) showed in Figure 5.

Zero order kinetics

A zero-order release would be explained by the following equation.

\[ A_t = A_0 - K_0 t \]

Where: \( A_t \) = Drug release at time “t,” \( A_0 \) = Initial drug concentration, \( K_0 \) = Zero-order rate constant (h⁻¹).

Figure 3: SEM of optimized formulation (NF6)

Figure 4: Zero-order of optimized formulation (NF6)

Figure 5: First-order of optimized formulation (NF6)

Figure 6: Comparison graphs of in vitro dissolution of fluvoxamine nanosuspension formulations (NF1-NF6)
Table 3: In vitro drug release studies of nanosuspension containing fluvoxamine

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>NF1</th>
<th>NF2</th>
<th>NF3</th>
<th>NF4</th>
<th>NF5</th>
<th>NF6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>5</td>
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<td>46.92</td>
<td>50.63</td>
<td>45.02</td>
<td>50.24</td>
<td>53.02</td>
</tr>
<tr>
<td>10</td>
<td>46.32</td>
<td>52.36</td>
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<td>52.36</td>
<td>56.32</td>
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<tr>
<td>15</td>
<td>52.82</td>
<td>60.25</td>
<td>67.42</td>
<td>59.12</td>
<td>63.25</td>
<td>65.34</td>
</tr>
<tr>
<td>20</td>
<td>58.15</td>
<td>66.43</td>
<td>73.12</td>
<td>68.42</td>
<td>72.35</td>
<td>73.54</td>
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<tr>
<td>30</td>
<td>68.23</td>
<td>72.83</td>
<td>80.26</td>
<td>76.18</td>
<td>83.96</td>
<td>82.69</td>
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<tr>
<td>45</td>
<td>76.35</td>
<td>83.16</td>
<td>91.05</td>
<td>85.24</td>
<td>95.34</td>
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<td>60</td>
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<td>93.65</td>
<td>101.24</td>
<td></td>
</tr>
</tbody>
</table>

When the data were plotted as cumulative percent drug release versus time, if the plot was linear, then, the data obeys zero-order release kinetics, with a slope equal to K0.

**First-order kinetics**

A first-order release would be predicted by the following equation

\[ \log C = \log C_0 - \frac{Kt}{2.303} \]

Where: \( C \) = Amount of drug remained at time ‘t’, \( C_0 \) = Initial amount of drug, \( K \) = First-order rate constant (h\(^{-1}\)).

When the data are plotted as log cumulative percent drug remaining versus time, yields a straight line, indicating that the release follows first-order kinetics. The constant “K” can be obtained by multiplying 2.303 with slope values.

**CONCLUSION**

In the present study, nanosuspension of fluvoxamine was formulated using PVA, SLS, and Tween 80 using the emulsification solvent evaporation method. The study also showed an enhanced dissolution rate by reduced in the particle size. Shows low oral bioavailability of Fluvoxamine due to its poor dissolution and thereby dissolution of fluvoxamine was increased in the form of nanosuspension which, in turn, increases the oral bioavailability of fluvoxamine by formulating nanosuspensions. The preparations were found to physically stable with PVA as stabilizing agent.[12] from the in vitro drug release studies, The NF6 formulation was optimized and it shows maximum drug release (99.02%) at shorter period of time (45 min) than remaining formulations showed in Figure 6. The fluvoxamine nanosuspension used for the depression and obsessive compulsive disorders.

**ACKNOWLEDGMENT**

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**AUTHOR’S CONTRIBUTION STATEMENT**

The author Mr. M. Srinivas confirms sole responsibility for the study conception and formulation design, data collection, methods of preparations, interpretation of results, and manuscript preparation. All the authors verified the results and accepted the final version of the research manuscript.

**REFERENCES**


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