Formulation and Evaluation of Solid Lipid Nanoparticles of Olanzapine for the Treatment of Psychosis

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ABSTRACT

Solid lipid nanoparticles (SLN) are typically spherical with an average diameter between 1 nm to 1000 nm in range. It is alternative carrier systems to tradition colloidal carriers, such as liposomes emulsions and polymeric micro and nanoparticles. Olanzpine (OZP) is an atypical antipsychotic agent which is used for treatment of Schizophrenia. Its oral bioavailability is around of 40%. OZP is a class II drug so it having low aqueous solubility. To overcome that problem and to increase its bioavailability, the solid lipid nanoparticles of olanzepine are prepared. Formulation batches designed by modifying type of surfactant (Span 80, Tween 80), concentration of surfactant, Concentration of cosurfactant, type of lipid (glyceryl monostearate, Stearic acid), Lipid concentration, speed of stirring and time of stirring using customised design of DOE. The SLN were prepared by high speed homogenization technique, and then characterized by particle size analysis, Drug entrapment efficiency and Drug diffusion study. A formulation containing GMS as a lipid stabilised with tween 80 as surfactant show good drug release, smaller particle size, as compared with other formulations with different lipid and surfactant. The present research findings indicate that OZP loaded solid lipid Nanoparticulate system for delivery of OZP with better efficacy with minimum adverse effects.

Keywords: Olanzpine, SLN, GMS, high speed homogenization and DOE

INTRODUCTION

A drug’s therapeutic efficacy depends on four fundamental pathways of drug transport and modification in the body, absorption, distribution, metabolism and excretion. Failure in therapy includes insufficient drug concentration due to poor absorption, rapid metabolism and elimination, poor drug solubility and high fluctuation of plasma levels due to unpredictable bioavailability. A promising strategy to overcome these problems involves the development of suitable drug colloidal carrier system. Among the colloidal carrier systems the solid lipid nanoparticles have many advantages as compare to other colloidal carrier systems. Solid Lipid Nanoparticles (SLN) recently gained significant attention as potential alternate colloidal drug delivery system for lipids emulsions and liposomes. The advantage of SLN is, it gives more flexibility in controlling to drug release and protects the encapsulated ingredients from the degradation. Also it gives selective bio distribution, in vivo and in vitro drug stability, and better bioavailability.
Olanzapine (approved by FDA in 1996) is a novel antipsychotic agent with broad efficacy, and elicits response in both the positive and negative symptoms of schizophrenia. Clinically, schizophrenia is treated in 3 phases. In the first phase called acute phase, complete hospitalization is a must and lasts for 1-2 months depending on patient’s condition. During this period, maximum doses of drugs are given and these are administered forcefully by registered physician or registered nurse, since patient never co-operates with the treatment 2-5.

As per literature survey various formulations of OZP were reported such as OZP tablets 6, OZP matrix sustained release tablets 7, OZP mouth dissolving tablets 8, OZP matrix pellets 9, OZPs Micro emulsion 9 and OZP chitosan nanoparticles 10. To date, only few attempts have been made to formulate the OZP SLN. So, the aim of present study is to formulate solid lipid nanoparticles with better bioavailability.

MATERIALS AND METHODS

Materials

Olanzapine was obtained from Mylan laboratory, Nasik (India) as a gift sample. Glycerol monostearate, Stearic acid, Polysorbate 80 (Tween 80) and Span 80 were purchased from sigma Aldrich chemicals USA. For formulation double distilled water was used. All the reagents and solvents were used of analytical grade.

Preformulation Studies

Determination of Melting Point:

Open capillary tube method was used for determining the melting point of the drug. This procedure was performed in triplicate and mean of three observations is considered as a melting point.

Solubility Study:

The solubility of the drug was performed by placing of a drug in the conical flask by use of different solvents for 24 hours. This practice was performed thrice and a solvent for analysis of drug was finalized.

FT-IR Spectroscopic Determination:

The drug was characterized by using of Infrared absorption spectroscopy. The Required quantity of drug was taken and mixed with potassium bromide and packed into the compact disk and spectrum was recorded.

Calibration curve of OZP:

10mg of drug was dissolved in 25ml of methanol and then volume made upto 100 ml with distilled water to get concentration100µg/ml. Stock solution was diluted further to get concentration range between 2µg/ml to 12µg/ml and absorbance was measured at 226nm.

Drug Polymer Compatibility Study

A compatibility study was carried out with potential formulation excipients and drug. API and excipients were mixed in specific quantity and placed in sealed vials for 4 weeks at 40°C ± 2/75%±5% RH and 25°C±2/75% ±5% RH. After specific time period sample was withdrawn for FTIR study.

Experimental design

For the formulation of OZP- SLN the High speed homogenization technique was used. With the help of Stat- Ease Design Expert software and customized factorial design the all formulation batches were formed. For that two types of factors were used i.e. Dependent factors and Independent factors. The particles size in nanometer, drug entrapment in percent and drug diffusion in percent study were the dependent variables and concentration of Lipid (2.5% to 7.5%), Concentration of surfactant (1% to 5%), speed of stirrer (10000 rpm to 15000 rpm) and time for stirring (15 minutes to 45 minutes) were the independent factors. Total 34 batches suggested by design of experiment (Table 1).

Preparation of Solid Lipid Nanoparticles

Olanzapine loaded Solid- Lipid nanoparticles were prepared by High speed Homogenization technique. First, lipid was heated 5-10°C above the melting point of the lipid (GMS/ Stearic acid) and OZP was made to dissolve in it. A aqueous phase was prepared by dissolving surfactant (Tween 80/ Span 80) in water and heated to same temperature of oil phase. Hot oil phase was further added to the hot aqueous phase and subjected to high-speed homogenization (10000 rpm- 15000rpm) for specified time (15minutes- 45 minutes) as per DOE (Table no. 1). Thereby produces hot oil in water (O/W) emulsion. The hot nanoemulsion was then cooled down to room temperature, and then lyophilized the sample.

Evaluation of Solid-lipid Nanoparticles

Particle size determination

The particle size distribution was analysed by using of digital electronic optical microscope (Labomed LX-200). One drop of sample was taken from each batch and diluted with 10 ml of dispersion medium (distilled water). Then particle size was determined with the help of digital electronic microscope under the 90X at room temperature. Then average size of fifteen particles of each formulated batch was taken for analysis.

Drug entrapment efficiency

The entrapment efficacy (EE) of Solid lipid nanoparticles dispersion was determined by centrifugation method. The SLN dispersion was centrifuged at 2000 rpm for one hour and then collected the supernatant liquid of that dispersion. Then collected liquid was filtered to measure the free drug concentration after making the dilutions with freshly prepared phosphate buffer pH 6.4. The absorbance was measured at 226 nm. Following formula was used for the calculation of EE:

\[
EE (\%) = \frac{\text{Amount of drug in NP (mg)}}{\text{Amount of drug added (mg)}} \times 100
\]

In vitro drug release

In vitro drug release of OZP SLN was determined using Franz-diffusion cell. The cellophane membrane was mounted between the donor and receptor compartments. The receptor compartment was filled with phosphate buffer (pH 7.4) at 37°C. The solution was stirred at 100 rpm. The OZP SLN was placed on cellophane membrane and the compartments were clamped together. One ml of sample was withdrawn at predetermined time for 24 hours, from receptor compartments and immediately replaced using phosphate buffer after filtering through 0.45µm filter and appropriate dilutions, the sample were analyzed for drug content at 226nm.
Table 1: Batches generated by DOE

| Run | Factor 1       | Factor 2       | Factor 3   | Factor 4     | Factor 5     | Factor 6     | Factor 7     |
|-----|----------------|----------------|------------|--------------|--------------|--------------|--------------|
|     | A: Surfactant conc. | B: Co- surfactant | C: Lipid conc. | D: Time for Stirring | E: Speed for Stirring | F: Type of Surfactant | G: Type of lipid |
| 1   | 2.55           | 0.625          | 4.82       | 35.25        | 11700        | Span 80      | Steric acid  |
| 2   | 1              | 0.25           | 7.5        | 45           | 15000        | Tween 80     | Steric acid  |
| 3   | 1              | 1              | 7.5        | 15           | 10000        | Span 80      | GMS          |
| 4   | 2.77           | 0.30           | 6.37       | 15           | 10300        | Tween 80     | Steric acid  |
| 5   | 1              | 0.25           | 7.5        | 15           | 10000        | Tween 80     | GMS          |
| 6   | 2.5            | 1              | 7.5        | 17.25        | 14000        | Span 80      | Steric acid  |
| 7   | 1              | 0.25           | 2.5        | 45           | 10000        | Tween 80     | GMS          |
| 8   | 2.99           | 0.25           | 2.5        | 45           | 12947        | Tween 80     | GMS          |
| 9   | 3              | 1              | 7.5        | 15           | 10000        | Tween 80     | GMS          |
| 10  | 1              | 1              | 2.5        | 45           | 10000        | Span 80      | GMS          |
| 11  | 3              | 1              | 2.5        | 15           | 10000        | Span 80      | Steric acid  |
| 12  | 1              | 1              | 2.5        | 15           | 10000        | Tween 80     | GMS          |
| 13  | 1              | 0.53           | 4.7        | 24.45        | 13050        | Tween 80     | Steric acid  |
| 14  | 3              | 0.25           | 2.5        | 15           | 15000        | Tween 80     | Steric acid  |
| 15  | 1              | 0.25           | 7.5        | 45           | 10000        | Span 80      | GMS          |
| 16  | 1              | 1              | 7.5        | 45           | 10000        | Tween 80     | GMS          |
| 17  | 1              | 1              | 7.5        | 45           | 15000        | Span 80      | GMS          |
| 18  | 3              | 0.25           | 7.5        | 15           | 15000        | Span 80      | Steric acid  |
| 19  | 1              | 1              | 7.5        | 15           | 15000        | Tween 80     | GMS          |
| 20  | 1              | 1              | 7.5        | 45           | 10000        | Span 80      | Steric acid  |
| 21  | 3              | 0.25           | 2.5        | 15           | 10000        | Span 80      | GMS          |
| 22  | 1              | 1              | 2.5        | 45           | 10000        | Tween 80     | Steric acid  |
| 23  | 3              | 1              | 2.5        | 15           | 15000        | Span 80      | GMS          |
| 24  | 1              | 1              | 7.5        | 15           | 10000        | Tween 80     | Steric acid  |
| 25  | 1              | 1              | 2.5        | 45           | 15000        | Tween 80     | GMS          |
| 26  | 1              | 1              | 2.5        | 15           | 15000        | Span 80      | Steric acid  |
| 27  | 3              | 1              | 7.5        | 45           | 10000        | Span 80      | GMS          |
| 28  | 3              | 0.25           | 2.5        | 45           | 15000        | Tween 80     | Steric acid  |
| 29  | 1              | 0.25           | 2.5        | 15           | 15000        | Span 80      | GMS          |
| 30  | 3              | 0.25           | 7.5        | 45           | 10000        | Tween 80     | Steric acid  |
| 31  | 1              | 0.25           | 2.5        | 15           | 10000        | Tween 80     | GMS          |
| 32  | 3              | 0.25           | 7.5        | 45           | 15000        | Span 80      | Steric acid  |
| 33  | 2.77           | 0.93           | 2.5        | 37.5         | 15000        | Span 80      | GMS          |
| 34  | 3              | 1              | 7.5        | 45           | 15000        | Span 80      | Steric acid  |

RESULT AND DISCUSSION

Preformulation studies

Melting point determination

The melting point of OZP API was found to be 188 ± 2°C.

Solubility study

OZP was practically insoluble in water, slightly soluble in Chloroform and freely soluble in Methanol and Ethanol.

FTIR study of OZP

From the FTIR study characteristics of OZP, amine group obtain at 3229 cm⁻¹, C-H stretching at 2844 cm⁻¹ and C=N stretching at 1633 cm⁻¹, C-N stretching at 1258 cm⁻¹.

Calibration curve of OZP

![Calibration curve of OZP](image)
**API Compatibility study**

Table 2: API compatibility study

| Ingredients   | Ratio | Parameters | Initial   | 40°C ± 2°C/75%±5% RH | 25°C ± 2°C/75%±5% RH |
|---------------|-------|------------|-----------|----------------------|----------------------|
| API           | 1     | Appearance | Solid Yellow powder | As initial           | As initial           |
|               |       | Color change | No        | No                   | No                   |
| API + GMS     | 1:1   | Appearance | Solid Yellow powder | As initial           | As initial           |
|               |       | Color change | No        | No                   | No                   |
| API + Stearic acid | 1:1 | Appearance | Solid Yellow powder | As initial           | As initial           |
|               |       | Color change | No        | No                   | No                   |

The compatibility studies between the drug and polymer was evaluated using FTIR spectrophotometry. There was no any significance interaction in IR spectra of drug and excipient.

**DOE Results**

Table 3: Evaluation parameters of batches suggested by DOE

| Run | Response 1 | Response 2 | Response 3 |
|-----|------------|------------|------------|
|     | % Entrapment ± S.D | Particle size ± S.D | Drug diffusion ± S.D |
| 1   | 66.93 ± 0.51 | 715.25 ± 4.10 | 69.81 ± 0.55 |
| 2   | 65.68 ± 0.65 | 825.83 ± 5.25 | 61.66 ± 0.69 |
| 3   | 63.35 ± 0.48 | 894.33 ± 3.65 | 63.58 ± 0.54 |
| 4   | 67.32 ± 0.87 | 792.13 ± 3.25 | 61.05 ± 0.29 |
| 5   | 66.64 ± 0.64 | 912.41 ± 3.15 | 64.38 ± 0.35 |
| 6   | 62.80 ± 0.24 | 792.29 ± 6.25 | 64.62 ± 0.98 |
| 7   | 72.59 ± 0.69 | 768.88 ± 4.25 | 69.33 ± 0.65 |
| 8   | 79.53 ± 0.35 | 631.63 ± 4.15 | 79.66 ± 0.15 |
| 9   | 72.58 ± 0.18 | 775.06 ± 5.32 | 72.31 ± 0.66 |
| 10  | 69.40 ± 0.98 | 756.90 ± 5.15 | 71.63 ± 0.78 |
| 11  | 66.85 ± 0.88 | 712.20 ± 5.36 | 70.45 ± 0.49 |
| 12  | 63.03 ± 0.48 | 850.70 ± 4.35 | 64.65 ± 0.56 |
| 13  | 66.68 ± 0.81 | 855.97 ± 1.36 | 59.32 ± 0.51 |
| 14  | 67.80 ± 0.75 | 725.84 ± 2.35 | 68.97 ± 0.36 |
| 15  | 70.91 ± 0.18 | 812.61 ± 3.25 | 69.35 ± 0.34 |
| 16  | 70.36 ± 0.59 | 818.75 ± 1.22 | 66.57 ± 0.15 |
| 17  | 70.07 ± 0.46 | 797.85 ± 3.15 | 68.78 ± 0.35 |
| 18  | 67.03 ± 0.49 | 767.57 ± 2.15 | 67.90 ± 0.95 |
| 19  | 65.80 ± 0.83 | 894.66 ± 2.36 | 60.90 ± 0.98 |
| 20  | 62.83 ± 0.75 | 816.28 ± 2.15 | 62.24 ± 0.65 |
| 21  | 72.93 ± 0.68 | 710.62 ± 2.36 | 75.66 ± 0.46 |
| 22  | 63.51 ± 0.61 | 778.46 ± 2.15 | 63.22 ± 0.85 |
| 23  | 73.09 ± 0.48 | 687.86 ± 2.65 | 75.09 ± 0.75 |
| 24  | 58.56 ± 0.74 | 924.89 ± 2.48 | 55.17 ± 0.36 |
| 25  | 70.75 ± 0.84 | 753.12 ± 3.25 | 68.85 ± 0.34 |
| 26  | 58.07 ± 0.64 | 828.69 ± 3.36 | 58.95 ± 0.65 |
| 27  | 77.85 ± 0.94 | 685.35 ± 2.36 | 78.29 ± 0.65 |
| 28  | 71.98 ± 0.38 | 628.14 ± 2.15 | 74.95 ± 0.55 |
| 29  | 65.15 ± 0.64 | 837.12 ± 4.65 | 65.16 ± 0.66 |
| 30  | 72.46 ± 0.39 | 703.33 ± 4.45 | 71.17 ± 0.54 |
| 31  | 57.91 ± 0.48 | 856.35 ± 5.15 | 59.52 ± 0.69 |
| 32  | 79.70 ± 0.55 | 684.10 ± 5.15 | 76.81 ± 0.67 |
| 33  | 70.23 ± 0.54 | 670.80 ± 5.14 | 70.65 ± 0.65 |
| 34  | 72.62 ± 0.62 | 685.58 ± 5.25 | 70.60 ± 0.66 |
**Particle size analysis**

The effect of lipid (GMS and Stearic acid) and surfactant (Tween 80 and Span 80) concentration on particle size distribution on OZP loaded SLN was showed in Table 3. The particle size was ranged between 625 nm to 925 nm.

**Influence of Surfactant, lipid concentration and speed of stirring on particle size**

OZP SLN was prepared using Tween 80 as surfactant showed smaller particle size than span 80. This may be due to higher molecular weight and higher HLB value of the Tween 80. When the lipid concentration was above 5%, it requires high speed and more time to break the lipid particles. So, the particle size is increased by using high concentration of lipid content.

**Drug diffusion**

The drug diffusion of OZP from various SLN formulations is shown in table no.3. The drug diffusion of OZP was found in the range of 55% to 80% at the end of 24 hours.

**Influence of type of lipid, conc. of lipid and time for stirring on drug diffusion**

Formulations containing GMS as a lipid matrix shows higher drug release as compare to stearic acid (GMS>Stearic acid). Stearic acid produced less order crystals than GMS leading to lower drug expulsion from the imperfect lattice. To enhance drug diffusion lipid concentration should be below 5%, and time for stirring above the 20 minutes. When the conc. of lipid increases that time increases conc. of surfactant to increase the lipid matrix and entrapment of drug.

**Percent drug entrapment**

In order to attain optimal entrapment efficiency, several factors are varied, including type of lipid, speed of stirring and time for stirring. The EE of all the prepared batches are shown in table No. 3. The EE of SLN dispersions was found in the range of 57% to 80%.

**Effect of surfactant on drug entrapment**

All batches formulated with higher surfactant concentrations shows good entrapment efficiency. Formulations containing Tween 80 as a surfactant shows good entrapment efficacy as compare to Span 80 as a surfactant (fig. 5). This could be due to lower HLB value of Span 80.
Effect of speed and time of stirring on EE

When the speed of stirring above the 12000 rpm and time above the 30 minutes it was showed good entrapment efficacy. As the time and speed of stirring was decreases then entrapment efficacy also decreased.

DOE data of 34 formulation batches were obtained based upon that data, F8 batch was found to be significant and finalized as optimized batch and their further evaluation was done.

Optimization of Batch

The Design-Expert software was used in order to find the optimized conditions for desired formulation. The desirability criteria set in design-expert for optimized formulations were minimum particle size, maximum entrapment efficiency and maximum drug content. The results were obtained significant, when the concentration of Tween 80 2.99% and Lipid as GMS with concentration 2.5%, speed of stirring 12900 rpm and stirring time 45 minutes. This was showed desired particles size with better drug diffusion and entrapment efficiency for improved nose to brain targeting drug delivery.

Evaluation of optimized batch

The evaluation of optimized batch gave particle size approximately 625 nm to 635 nm (Figure no. 6) which can easily cross blood brain barrier. Drug diffusion was found in the range of 75% to 80% (Figure no. 7) which is greater than oral dosage forms. The percent entrapment of optimized dosage form was found in the range of 76% to 80%.
CONCLUSION

Olanzapine was successfully encapsulated into solid lipid nanoparticles by high speed homogenization technique. Various formulations of OZP loaded SLNs were prepared using various process variables. The prepared formulations were evaluated for drug entrapment efficiency; formulation F8 registered highest entrapment of 79% to 80%. The particle size of F8 formulation found in between 630nm to 635nm. The in-vitro drug release of F8 formulation was found to be 79% to 80% over 10 hours in controlled manners; hence the present study was a successful attempt to formulation of OZP by SLN system. Further study is necessary to investigate the exact mechanism related to findings of the study.

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