Application of Central Composite Design for Development of Celecoxib Loaded Lipospheres: Formulation and in-vitro Characterization

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ABSTRACT

Background: This study was initiated to develop celecoxib lipospheres to provide controlled release. It demonstrates the use of central composite design for optimization of liposphere formulation with less number of experiments. The development of formulation is primarily based on poor water solubility, low bioavailability and side effects associated with prolonged administration of celecoxib. Methods: Lipospheres were developed by melt dispersion technique and the effect of amount of ethyl oleate and phospholipon 80H on % entrapment in-vitro drug release was studied using central composite design. Additionally the lipospheres were evaluated for percentage yield, particle size and zeta potential. Differential scanning calorimetry, x-ray diffractometry and scanning electron microscopy was used to identify the melting state, internal structure and surface morphology. Results: Entrapment efficiency of 73.63% was obtained while about 82.51% drug was released. The average particle size was 35µm with homogeneously dispersed particles. Celecoxib was found to be completely miscible in lipids with disappearance of crystallinity. The lipospheres were spherical in shape with smooth outer surface. Conclusion: Prolonged release celecoxib lipospheres were developed using central composite design.

Key words: Celecoxib, Phospholipon 80H, Lipospheres, Central composite design, Melt dispersion.

INTRODUCTION

Celecoxib is a selective cyclooxygenase 2 (COX-2) inhibitor widely used in the treatment of rheumatoid arthritis and osteoarthritis.1,2 It is evident from the literature that celecoxib is 10-20 times more selective to COX-2 inhibition than COX-1 and its use effectively reduces gastrointestinal disturbances as compare to the NSAIDs. It is well reported that celecoxib is lipophilic, poorly water soluble drug (BCS class II) having 40% oral bioavailability and long term use of its may produces severe gastrointestinal side effects.3,4 By taking into consideration the aforementioned problems it is essential to develop such a drug delivery system that can prolong the drug release and improve the bioavailability with reduction in side effects. Number of drug delivery systems has been developed to improve dissolution, bioavailability and therapeutic efficacy which include microspheres,5 nanoemulsions for transdermal use,6 nanostructure lipid carrier based gel,7 solid dispersions,8 amorphous nanoparticles,9 nanosuspensions,10 and self-nano emulsifying drug delivery system.11 However, along with other approaches lipidic carrier system i.e. lipospheres have gained much more attention for delivery of hydrophobic agents because of ability of lipids to increase solubility of drug and also drug release in controlled fashion.12 These are made of solid hydrophobic triglycerides and liquid lipid. The drug is either dissolved or dispersed in a solid fat matrix and can be prepared by solvent emulsification.
evaporation, melt dispersion, double emulsion and high pressure homogenization. Lipospheres are appropriate for oral, parenteral and topical drug delivery system. In this study we utilized central composite rotatable design (CCRD) approach to predict the response of independent variable with minimum runs hence; it could be cost effective and time saving. Therefore, the objective of this work was to develop lipospheres of celecoxib lipid materials as carriers by CCRD approach.

**MATERIALS AND METHODS**

**Materials**

Celecoxib was received as a gift from Glenmark Pharmaceuticals, Baddi. Phospholipon 80H was provided by Lipoid GmBH (Germany). Cetostearyl alcohol, ethyl oleate, oleic acid, stearic acid were purchased from Thomas Baker, Mumbai. Glyceryl tristearate was provided by Estelle Chemicals, Ahmednagar. Arachis oil and olive oil were purchased from Research Lab Fine Chemicals, Mumbai. Chemicals used for analysis including potassium dihydrogen phosphate, hydrochloric acid, sodium hydroxide were of analytical reagent grade and purchased from the Thomas Baker, Mumbai. Methanol was purchased from S. D. Fine Chem. Ltd. Mumbai.

**Methods**

**Screening of lipid excipients**

Liquid lipids (oils) were selected depending on their ability to solubilize the drug. Small amount of drug was added to solid lipid e.g. cetostearyl alcohol (m. pt. 48-55°C), stearic acid (m. pt. >54°C) and glyceryl tristearate (m. pt. 54-73°C) and the mixture was melted. The miscibility of celecoxib in the solid lipid was assessed by smearing the molten lipid onto filter paper followed by observing the presence or absence of drug crystals to determine suitable lipid for encapsulation of high amount of drug. In case of liquid lipid (ethyl oleate, oleic acid, arachis oil and olive oil), excess amount of drug was added in the vials containing 3 ml of liquid lipid. The vials were continuously stirred to reach equilibrium for 48 hr at 25°C in orbital shaker. After that mixtures were centrifuged at 5000 rpm for 30 min at room temperature. The supernatant was separated, dissolved in methanol (oleic acid), in ethanol (ethyl oleate) and in isopropyl alcohol (arachis oil and olive oil). The solubility of celecoxib was estimated by UV spectrophotometer at 252 nm. All the experiments were performed in triplicate.

**Development of lipospheres**

Central composite rotatable design was used for the development and optimization of celecoxib lipospheres using Design Expert® software (V 11.0 Stat-Ease Inc.). Two factors coded as X1 (concentration of ethyl oleate in total lipid) and X2 (concentration of Phospholipon 80H) were used at three levels (+1, 0 and -1) keeping the quantity of water and celecoxib constant. The amount of total lipid (solid and liquid) was kept constant and considered as one variable (i.e. 5 g) for development of lipospheres. Variations were made in the ratio of solid and liquid lipid as it was reported that the use of solid lipid only lead to low drug loading and expulsion of drug with time. Entrapment efficiency (Y1) and percentage drug release (Y2) were the responses. The model was further investigated through coefficient of regression, analysis of variance and percent coefficient variance. Total 13 runs were generated having 4 factorial points, 4 axial points and 5 center points. The description of factors, their level and runs are given in Table 1. Briefly, Different quantities of solid (cetostearyl alcohol) and liquid lipid (ethyl oleate) as stated in Table 1 were melted in previously heated (70°C, above their melting points) vessel and emulsified into a hot external aqueous phase already maintained at 70°C containing varying amount of Phospholipon 80H; which was used as a emulsifier and consists of natural and hydrogenated lecithin fractions and phospholipids either from soyabean, rapeseed or sunflower. The emulsion was stirred by mechanical stirrer (1000 rpm) and the temperature was maintained at 70°C. Further the emulsion was rapidly cooled to about 20°C by immersing into ice bath with agitation to yield uniform dispersion of lipospheres. The lipospheres were collected by filtration, dried overnight at room temperature in a vacuum desiccator over silica gel and stored until its use.

**Evaluation of lipospheres**

**Percentage yield and entrapment**

The amount of lipospheres obtained was used to calculate % yield by considering the total amount of lipid and celecoxib used for development. For determination of entrapment efficiency about 100 mg of dried lipospheres were dissolved in 10 ml methanol and sonicated for 30 min for complete extraction of celecoxib. The resulting solution was filtered through Whatman filter paper no. 41; dilutions were made with methanol and assayed spectrophotometrically at 252 nm. The experiments were performed in triplicate.
The entrapment efficiency was determined using the following equation:

\[
% \text{EE} = \left( \frac{\text{Total amount of drug} - \text{Free drug}}{\text{Total amount of drug}} \right) \times 100
\]

### Particle size and zeta potential
Particle size and polydispersity index (PDI) of the lipospheres was determined by particle size analyzer (ZS 90, Malvern). The dried lipospheres were suspended in water. The obtained homogenous suspension was examined to determine the mean diameter, polydispersity index and zeta potential.

### Differential scanning calorimetric (DSC) analysis
The DSC thermograms of celecoxib, cetostearyl alcohol and celecoxib loaded lipospheres were recorded with a differential scanning calorimeter (DSC 3, Mettler Toledo, India) using aluminum crucible at the heating rate of 10°C/min, under nitrogen environment with sample amount of 5 mg. The temperature range used was 40–240°C.

### Fourier transform infrared (FTIR) spectroscopy
The FT-IR spectrums of celecoxib, ethyl oleate, cetostearyl alcohol, Phospholipon 80H and optimized formulation were recorded using FTIR spectrophotometer (FTIR Affinity-1, Shimadzu, Japan). Samples were prepared by mixing the components with potassium bromide (KBr), triturating in glass mortar and finally placing in the sample holder. The spectrums were scanned over a frequency range 4000 – 400cm⁻¹.

### Surface morphology by SEM
Morphological examination of optimized lipospheres formulation was carried out with a scanning electron microscope (JEOL, Japan). The spheres were vacuum dried, coated with a thin gold-palladium layer with a sputter coater unit and observed microscopically at an accelerating voltage of 10 kV.

### X-ray powder diffraction (XRD) analysis
Powder X-ray diffractometer (PANalytical Xpert PRO) was employed for the powder X-ray diffraction analysis of celecoxib, cetostearyl alcohol and lipospheres. Cu K-alpha (wavelength 1.5406A°) radiation was used as
X-ray source. Samples were placed in the glass sample holders and scanned from 10° to 89° with a scan of 2°/min. XRD pattern was measured using a voltage of 45kV and a current of 40 mA.

**In-vitro release study**

The in-vitro release studies of formulations were carried out using USP dissolution (Type II) apparatus at a rotation speed of 100 rpm maintained at 37±0.5°C. The Lipospheres were filled in empty hard gelatin capsules; transferred to dissolution medium i.e. phosphate buffer (pH 7.4) and aliquots were withdrawn at selected time intervals and filtered through Whatman filter paper no. 41. The filtrates were then analyzed by a UV spectrophotometer at 252 nm. The volume removed was replaced by fresh volume of dissolution medium to maintain sink condition. The study was conducted for 12 hr.22 Experiments were performed in triplicate for each formulation batch.

**RESULTS**

**Selection of solid and liquid lipids**

Among the solid lipids screened, the maximum miscibility of celecoxib was found in cetostearyl alcohol as compared to glyceryl tristearate and stearic acid as drug crystals were absent in case of cetostearyl alcohol. Generally solubility of lipophilic compounds is less in long chain length fatty acids than short and medium chain length.23 Among the long chain length oils used; solubility of celecoxib was highest in ethyl oleate (9.38 mg/ml) followed by oleic acid (6.34 mg/ml), olive oil (5.92 mg/ml) and arachis oil (6.97 mg/ml).

**Optimization of formulation**

The entrapment efficiency of batches (CD1 to CD13) prepared by using central composite design was ranged from 71.93±0.24 to 83.96±0.27%. The results are depicted in Table 2. These batches were evaluated for % drug release which was ranged from 78.12±0.61 to 92.94±0.57. The %EE and % drug release was affected by the concentration of ethyl oleate and Phospholipon 80H. As ethyl oleate has highest solubilizing capacity for celecoxib; high entrapment of drug was observed when high concentration of ethyl oleate (liquid lipid) and Phospholipon 80H (emulsifier); may be due to formation of mixed micelle.24 Solid lipid had shown inverse relation with drug release. Cetostearyl alcohol is hydrophobic in nature which may have caused the drug to be remained embedded in the matrix and hence; slow diffusion may have observed for up to 12 hr. This is the important characteristics of drug embedded matrix system.3 For optimization of lipospheres formulation; the target value set were 70 to 85% for EE and 75 to 95 for % drug release (using the data of CD1 to CD13) with desirability near to 1. By taking the concentration of ethyl oleate (X1) which was 0.9829g and concentration of Phospholipon 80H (X2); 0.5g, the predicted responses given by the software were 76.27% for EE and 85.43 for % drug release and desirability 1. The actual response observed from the optimized lipospheres formulation was 73.63±0.34 % (EE) and 81.90±0.45 (% drug release) with desirability of 0.92. The drug release data was fitted to zero order, first order and Higuchi kinetics. The comparison of correlation coefficient and applied model demonstrated that the zero order R² was 0.984 and Higuchi kinetic R² was 0.994 indicating zero order release with diffusion mechanism and is independent of drug concentration remained in the lipospheres.

**Data analysis**

ANOVA test was used for determining the significance of the variables on % entrapment efficiency and % cumulative drug release which indicates the significance of the models. Also, the observed p values were found less than the probable F value (0.05) for each coefficients implies the significance of the selected models.

Following polynomial equation was generated by the statistical analysis

\[
\text{%EE} = +81.74 + 1.00A + 0.3702B - 1.92AB - 0.1599A^2 - 4.99B^2
\]

From the polynomial equation of % entrapment efficiency, it was observed that coefficient of

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**Table 2: Evaluation of lipospheres.**

<table>
<thead>
<tr>
<th>Batch</th>
<th>% yield</th>
<th>% entrapment efficiency (mean ± SE)</th>
<th>% drug release at 12 hr. (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD1</td>
<td>75.01</td>
<td>72.42±0.15</td>
<td>79.36±0.25</td>
</tr>
<tr>
<td>CD2</td>
<td>70.46</td>
<td>78.32±0.11</td>
<td>83.67±0.34</td>
</tr>
<tr>
<td>CD3</td>
<td>80.02</td>
<td>76.35±0.21</td>
<td>84.52±0.36</td>
</tr>
<tr>
<td>CD4</td>
<td>79.88</td>
<td>74.58±0.23</td>
<td>78.12±0.35</td>
</tr>
<tr>
<td>CD5</td>
<td>73.79</td>
<td>81.2±0.13</td>
<td>79.98±0.49</td>
</tr>
<tr>
<td>CD6</td>
<td>77.48</td>
<td>83.96±0.15</td>
<td>80.08±0.41</td>
</tr>
<tr>
<td>CD7</td>
<td>83.61</td>
<td>71.93±0.13</td>
<td>79.62±0.27</td>
</tr>
<tr>
<td>CD8</td>
<td>81.00</td>
<td>73.89±0.08</td>
<td>85.42±0.40</td>
</tr>
<tr>
<td>CD9</td>
<td>76.60</td>
<td>80.32±0.20</td>
<td>88.43±0.45</td>
</tr>
<tr>
<td>CD10</td>
<td>75.36</td>
<td>83.12±0.08</td>
<td>89.97±0.29</td>
</tr>
<tr>
<td>CD11</td>
<td>79.84</td>
<td>80.67±0.17</td>
<td>91.23±0.16</td>
</tr>
<tr>
<td>CD12</td>
<td>78.64</td>
<td>83.23±0.19</td>
<td>89.37±0.31</td>
</tr>
<tr>
<td>CD13</td>
<td>76.88</td>
<td>81.34±0.13</td>
<td>92.94±0.32</td>
</tr>
</tbody>
</table>

Values are represented as mean±SE, n=3
concentration of liquid lipid have greater positive value than concentration of emulsifier. Thus, it was concluded that factor X1 imparts more effect on entrapment efficiency than X2.

It was interpreted from the contour plot (Figure 1A) that at low level of ethyl oleate; entrapment efficiency was found minimum, but increases when increasing its concentration.

The polynomial equation for % cumulative drug release (%DR) is given below demonstrated that concentration of emulsifier impart more effect on drug release as compared to concentration of liquid lipid.

\[
\% \text{ DR} = +90.39 - 0.2436A + 0.9730B - 2.68AB - 5.14A^2 - 3.89B^2
\]

Contour plot of emulsifier concentration and concentration of liquid lipid in total lipid on drug release (Figure 1B) showed that at low level of emulsifier and liquid lipid leads to low drug release, but increased concentration of emulsifier and concentration of liquid lipid up to certain level increases drug release. This demonstrated the role of emulsifier and oil. The emulsifier responsible for improved release characteristics due to solubilization of the drug and reduced interfacial tension but as cetostearyl alcohol is hydrophobic in nature; the drug is embedded in the matrix and slow diffusion occurs as conformed by Higuchi model.

**Particle size and zeta potential**

The composition of optimized batch is given in Table 3 which was prepared in triplicate. The optimized batch of lipospheres had shown the distinct particles of 35μm (69.4 % intensity) size with smooth surfaces and polydispersity index of 0.3. The low PDI value is a sign of narrow particle size distribution that may due to optimum quantity of the emulsifier as well as appropriate speed of the stirrer. The high particle size in case of lipospheres could be due to increased viscosity of emulsion because of higher amount of lipid used. Zeta potential is important in determining the stability of colloidal particles during storage. High zeta potential inhibits aggregation of the particles by electric repulsion and hence, electrical stabilization of the dispersion. The zeta potential of optimized lipospheres formulation was 9.46mV indicating stabilization by repulsion between close and similarly charged particles in the dispersion. The other mechanism of stabilization could be steric stabilization.

**DSC study**

The DSC thermograms of celecoxib, cetostearyl alcohol and optimized formulations are presented in Figure 2.

**Table 3: Composition of optimized batch with their predicted and observed responses.**

<table>
<thead>
<tr>
<th>Conc. of ethyl oleate (g)</th>
<th>Conc. of Phospholipon 80H (g)</th>
<th>Entrapment efficiency (%)</th>
<th>Drug release (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Predicted</td>
<td>Observed</td>
</tr>
<tr>
<td>0.9829</td>
<td>0.5</td>
<td>76.27</td>
<td>73.63±0.32</td>
</tr>
</tbody>
</table>

The experimental results are expressed as means±SD, n=3
It can be seen that a sharp endothermic peak (A and B) was observed corresponds to melting of celecoxib at 161.69°C and for cetostearyl alcohol at 54.02°C confirming their purity. In Figure 2C; the endotherm of celecoxib is completely absent. It was also observed that the melting point of cetostearyl alcohol depressed from 54.02°C to 50.55°C due to inclusion of drug in the lipid Hence; it can concluded that celecoxib is completely solubilized in the lipid matrix or present in amorphous form than crystalline one.

**FTIR study**

The FTIR spectrums of celecoxib, with ethyl oleate, cetostearyl alcohol and Phospholipon 80H are presented in Figure 3. The principal peaks of celecoxib were observed in between 1100-1200cm⁻¹; that can be interpreted as C-F stretching. The peaks at 3336, 1346, 3230 cm⁻¹ correspond to N=H stretching, S=O symmetric stretching and -SO₂, -NH₂ vibrations, respectively. These characteristic peaks were identified in a physical mixture of the drug and excipients with no appreciable changes in frequency. Thus, it can be stated that there were no chemical interaction between the celecoxib and excipients used in the formulation.

**X-Ray diffraction (XRD) study**

The sharp peak in the XRD pattern of celecoxib was indicative of the crystalline nature of the drug (Figure 4A). The x-ray diffraction of celecoxib showed sharp peaks at 2θ values of 5.31, 10.68, 13, 14.83, 16.08, 19.63, 21.49, 22.13 and 25.36. Two sharp peaks were observed for cetostearyl alcohol (Figure 4B). Some of the characteristic peaks of the celecoxib was absent in the XRD pattern of formulation (Figure 4C). The reason may be that the peaks of celecoxib overlapped with the noise of the coated lipid. It is also possible that a XRD signal of an encapsulated drug may not be identified, which revealed that the drug is dispersed at a molecular level in the lipid matrix. Also another possibility may be conversion of drug from crystalline to amorphous form.

**Surface morphology by SEM**

SEM analysis with different magnification of optimized batch of lipospheres is presented in Figure 5. The lipospheres under low and high magnification had shown spherical shape with smooth surfaces indicating non-appearance of crystallized drug on the surface of sphere with coating of drug particles by lipid and hence no burst release was observed.

**DISCUSSION**

Lipospheres were prepared by using cetostearyl alcohol, ethyl oleate and Phospholipon 80H which was based upon the solubility and miscibility of celecoxib in the solid and liquid lipids. Central composite design was beneficial to decide the concentration of ethyl oleate, Phospholipon 80H and cetostearyl alcohol and demonstrated that ethyl oleate had increased drug loading in the lipospheres. The composition materials...
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did not show any sort of chemical interaction with celecoxib. It was completely miscible in the mixture of solid and liquid lipid. Because of hydrophobic nature of cetostearyl alcohol; the release of celecoxib was reduced. The release of celecoxib from the lipid matrix was dependent on the concentration of emulsifier and liquid lipid. It had followed Higuchi mechanism indicating diffusion controlled release from porous lipid matrices. Although the size of optimized spheres is high which may be due to viscosity but the results of polydispersity and zeta potential indicated that they were homogenous and well separated from each other. The lipospheres were found spherical in shape and had smooth surface.

**CONCLUSION**

In this investigation we tried to encapsulate celecoxib in lipidic system by using melt dispersion technique through experimental design approach. Formulation variables like concentration of liquid lipid and emulsifier affected the entrapment efficiency and drug release from lipospheres. The drug was encapsulated by solid lipid and hence, release occurs for the period of 12 hr by diffusion mechanism. The formulation components did not show any potential incompatibility with celecoxib. The particle size was within the range and zeta potential exhibited the existence of distinct particles with moderate stability. The disappearance of melting peak of drug as evidenced in DSC of lipospheres formulation confirmed complete miscibility of celecoxib, coating by lipid while XRD indicated absence prominent peaks due to dispersion of drug in the matrix as well as conversion of celecoxib to amorphous form. The lipospheres were spherical in shape with smooth surface without adsorption of drug on the surface. It can be concluded that the lipophilic drugs can be entrapped in lipidic system to prolong drug release and central composite design can be used for design of drug delivery system.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**ABBREVIATIONS**

- **COX-1**: Cyclooxygenase 1; **COX-2**: Cyclooxygenase 2; **NSAIDs**: Non Steroidal Anti-inflammatory Drugs; **BCS**: Biopharmaceutics Classification System; **CCRD**: Central Composite Rotatable Design; °C: Degree Centigrade; **m. pt.**: Melting Point; **ml**: Milliliter; **h**: Hour; **min**: Minute; **UV**: Ultra Violet; **nm**: Nanometer; **g**: Gram; **%**: Percentage; **mg**: Miligram; **EE**: Entrapment Efficiency; **PDI**: Polidispersity Index; **DSC**: Differential scanning calorimetry; **FTIR**: Fourier Transform Infra Red; **KBr**: Potassium Bromide; **cm⁻¹**: Centimeter Inverse; **kV**: Kilovolt; **XRD**: X-ray Powder Diffraction; °: Degree; **USP**: United States Pharmacopoeia; **R²**: R Squared; **mV**: Milivolt; **SEM**: Scanning Electron Microscopy.

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PICTORIAL ABSTRACT


SUMMARY

• This study depicts the development and optimization of controlled release lipospheres of celecoxib using central composite design. The effect of independent variables i.e. amount of ethyl oleate and Phospholipon 80H on \% encapsulation efficiency and \% drug release was studied.

• It was concluded from the contour plot that at low level of ethyl oleate; \% entrapment efficiency was minimum but increases with increasing its concentration. The concentration of emulsifier imparts more effect on drug release as compared to concentration of liquid lipid. At low level of emulsifier and liquid lipid leads to low drug release, but increased concentration of emulsifier and concentration of liquid lipid up to certain level; increase in drug release was observed.

• The lipospheres were stabilized by mixed mechanism i.e. electrical repulsion and steric stabilization and had narrow particle size distribution as reflected by small PDI value. Encapsulation of celecoxib was supported by DSC and XRD study as there was no evidences of peaks of drug and surface morphology by SEM revealed smooth outer surface without adsorption of drug on the surface. These properties make this method and lipospheres as a delivery system suitable for incorporation of lipophilic drugs for controlled release.

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