FORMULATION AND CHARACTERIZATION OF PIROXICAM LIQUISOLID TECHNIQUE FOR SOLUBILITY ENHANCEMENT

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ABSTRACT

This present study an attempt was made to formulate poorly water soluble drug i.e., piroxicam to enhance the dissolution rate of piroxicam by liquisolid systems. Based on the solubility studies the polyethylene glycol 400 (PEG400) is chosen as cosolvent, Microcrystalline cellulose (MCC) used as carrier material and Aerosil used as coating material. Liquisolid system is characterized by flow properties, solubility studies in non volatile solvents (hydrophobic carriers), drug content, Fourier transform infra red spectroscopy (FTIR), powder X-ray diffraction (XRD) and in-vitro release evaluation. By using this liquisolid technique, solubility parameter and dissolution rate can be improved. Based on various formulations of liquisolids were prepared by using non volatile solvents or hydrophobic carriers and their effect on dissolution of piroxicam was studied.

Conclusion: The liquisolid systems is a novel technique for solubility enhancement and dissolution improvement of low soluble drugs.

Keywords: liquisolid systems (LS), carriers, low soluble drug and non-volatile solvents.

INTRODUCTION

According to Bio-Pharmaceutical Classification (BCS) system, Piroxicam is class-II drug (i.e., Low Solubility-High Permeability), the rate of oral absorption is controlled by the dissolution rate in the gastrointestinal (GI) tract. Piroxicam is an oxicam derivative. It is not only potent Non-Steroidal Anti-Inflammatory Drug (NSAID) but also used in acute and
chronic musculoskeletal and joint disorders. The liquisolid systems offers various advantages like improvement of bioavailability of an orally administered water insoluble drugs and improvement of dissolution profiles. The bioavailability of Bio-Pharmaceutical Classification (BCS) class-II products is controlled by their solvation rate. Poor water soluble compounds show decreased release rate. Low water soluble drugs also show poor rate and extent of drug absorption. Solubility is the most essential formulation parameter for the formulation development. Solubility is becoming rate limiting factor in the development of new drugs. The improvement of oral bioavailability of poor water soluble drugs remains one of the most challenging aspects of drug development. The liquisolid approach has been successfully applied in release enhancement of low dose poorly soluble drugs. The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability. There are several ways, in which the solubility of a drug can be enhanced includes particle size reduction, solid dispersion, pH adjustment , high pressure homogenization, by complexation, by salt formation, by surfactants and liquisolid technique(powdered solution technology).[1-10]

MATERIALS AND METHODS

MATERIALS

The following materials were used: Piroxicam, Tween 80 (Palmo industries), polyethyleneglycol (PEG 400- Clariant), Microcrystalline cellulose (Asakeshi). Aerosil, Span20 were purchased from Loba chemie and fine chemicals. All reagents used were of analytical grade.

METHOD

Solubility studies

Solubility studies of piroxicam were performed by selecting different nonvolatile or hydrophobic solvents like PEG 400 ,Tween 80, Span 20. 10 ml of each non volatile solvents was taken in 25 ml conical flasks. To each of these flasks excess amount of piroxicam was added. The flasks were stoppered and shaken thoroughly by using vortex mixer for 30 minutes. Then the samples were placed in water bath shaker and continued shaking for 24 hours. The temperature of the bath was maintained at 37°C. After 24 h the contents was subjected to centrifugation. The supernatant was collected and filtered by using 0.45 μ filter. Thus, saturated solutions of piroxicam were prepared by adding excess drug to the vehicles and shaking on the shaker. The samples were diluted and analyzed spectrophotometrically.
using UV-Visible spectrophotometer (Elico SL-191) for piroxicam content at 354 nm. All solubility measurements were performed in triplicate. The data is given in Table 1.

**Carrier Suitability Studies**

The non volatile liquid was adsorbed on to a suitable carrier for converting the liquid system in to a solid system. In the present work we have selected on the solubility studies the polyethylene glycol 400 (PEG400) is chosen as nonvolatile solvent. The systems were prepared by using the above selected solvents alone and in combination at 1:1 ratio. The amount of solid carrier required for converting the liquid system in to a solid system was evaluated by taking 1 ml of PEG 400 in a mortar and pestle. Then the solid carrier material MCC was added and triturated to adsorb the liquid. The solid addition was continued until the powder was free flowing. Same process was adopted for studying the quantity of aerosil by taking 1 ml of PEG 400. It was found that the carrier is required at a ratio of 1:0.85 for aerosil and 1:1 for Micro crystalline cellulose in case of PEG 400.

**Preparation of liquisolid systems**

The liquisolid systems were prepared as per the formula given in Table 2. Initially the 100 mg piroxicam was transferred in to a mortar. Then 5 ml of PEG 400 was added slowly and dissolved the drug by triturating to give the concentration 20 mg/ml. This solution was adsorbed on MCC in mortar by trituration. The addition was continued until the liquid convert in to a free flowing solid system. All the formulae were prepared by using the above described method.

**CHARACTERIZATION**

**Micromeritic properties**

% compressibility index (I)

The bulk densities for the prepared piroxicam liquisolid systems (LS) were determined by the tap method. Weighed quantity (5 g) of powder (w) was carefully introduced into a 25 ml graduated cylinder. The cylinder was dropped onto a hard wood surface 3 times from a height of 2.5 cm at an interval of 2 seconds. The bulk density was obtained by dividing the weight of the sample by volume of the sample contained in the cylinder (V1). Reciprocal of bulk density or the specific bulk volume gave the bulkiness.

Tapped density is the ratio of weight of dry powder to its tapped volume. The weighed quantity of dry powder was taken is a graduated cylinder. The cylinder was placed on the tap
density tester (M/s. Inco) and subjected to 100 taps. The volume of powdered bed is measured. The tapping is continued until the difference of last two volume measurement is zero.

The percent compressibility index (I) of prepared microparticles were calculated using following formula.

\[ I = \left(1 - \frac{V_f}{V_o}\right)100 \]

where, \( V_o \) is initial volume and \( V_f \) is final volume after tapping. The results are shown in Table 3.

**Angle of repose**

Flow properties of prepared LS were determined by determining the angle of repose. Angle of repose was determined by the fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to its axis of symmetry was fixed at a given height (h) above the graph paper placed on a flat horizontal surface. In each case 5 grams of each powder was carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius (r) of the base of the pile was determined and the tangent angle of repose (\(\theta\)) was calculated by following equation

\[ \tan \theta = \frac{h}{r} \]

**Drug content**

Drug content of all the prepared liquisolid systems (LS) was estimated by the following procedure. Accurately weighed 100 mg of the liquisolid systems (LS) powder was taken and transferred into a 100 ml volumetric flask. 50 ml of methanol was added and vigorously shaken for 15 minutes. The solution was then sonicated for 15 minutes. After this the solution was kept aside for 15 min for equilibration and made up to volume with phosphate buffer pH 6.8. The resulted solution was filtered through 0.45 µm filter paper and suitably diluted and the drug content was estimated spectrophotometrically by measuring the absorbance at 354 nm.

**Dissolution studies**

*In vitro* dissolution studies were carried out in 900 ml of pH 6.8 phosphate buffer using USP XXIV type-II (Paddle) dissolution rate test apparatus (Model L6, M/S Electrolab). Sample
equivalent to 20 mg of piroxicam, a speed of 50 rpm and a temperature of 37±1°C were used in each test. A 5 ml aliquot was withdrawn at different time intervals, filtered and replaced with 5 ml of fresh dissolution medium. The filtered samples were suitably diluted whenever necessary and assayed for piroxicam by measuring absorbance at 354 nm. All the dissolution experiments were conducted in triplicate and the mean values are reported. The dissolution studies were carried for the pure piroxicam and for all the prepared LiquiSolid systems.

**Analysis of dissolution data**

The analysis of the mechanism of drug release from pharmaceutical dosage form is an important but complicated problem and is practically evident in case of multi particulate dosage form. The dissolution data obtained was fitted to zero order\textsuperscript{[11]}, first order\textsuperscript{[12,13]}, Higuchi\textsuperscript{[14]} and erosion\textsuperscript{[15]} equation to understand the order and mechanism of piroxicam release from the LiquiSolid systems (LS).

**Zero order release kinetics**

It defines a linear relationship between the fraction of drug released versus time.

\[ Q = k_0 t \]

where, \( Q \) is the fraction of drug released at time \( t \) and \( k_0 \) is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

**First order release kinetics**

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process, suggested that drug release from most slow release tablets could be described adequately by apparent first-order kinetics. The equation used to describe first order kinetics is

\[ \ln (1-Q) = -k_1 t \]

where, \( Q \) is the fraction of drug released at time, \( t \) and \( k_1 \) is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.
**Higuchi equation**
It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

\[ Q = k_2 t^{1/2} \]

where, \( k_2 \) is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation.

**Erosion equation**
This equation defines the drug release based on erosion alone.

\[ Q = 1 - (1 - k_3 t)^{1/3} \]

where, \( Q \) is the fraction of drug released at time \( t \), \( k_3 \) is the release rate constant. Thus, a plot between \([1 - (1 - Q)^{1/3}]\) against time will be linear if the release obeys erosion equation.

The values of correlation coefficient (r) and release constants are given in Table 10.

**Fourier Transform Infrared spectroscopy(FTIR)**
Infrared spectral analysis of piroxicam, LS6 were done using Fourier Transform Infrared Spectrophotometer (FTIR) (PerkinElmer FTIR, Spectrum GX v 5.0.1 software). The IR spectra were done against the KBr background. Averages of 100 scans of each sample were collected at 4 cm\(^{-1}\) resolution over a wave number region of 4000-600 cm\(^{-1}\). The FTIR spectra are shown in Fig. 3 and 4.

**X-ray diffraction**
Predicted PXRD pattern of crystal form shown in figure 5 (pure) and figure 6 (LS6 formulation). By comparing the graphs, each graph showing 100% relative intensity at different 2θ ranges, which showing clearly that the formulated. The PXRD were undertaken to investigate drug sample (pure) and Liquisolid system (LS6Formulation). The study was carried out using X-Ray Diffractometer using Cu kα radiation. The tube operated at position o2 Theta, copper (cu) 40 kV, 20mA and data was collected over an angular range from 5 to 70 .20 of the diffraction angle in continuous scan mode using a step size of 0.02 .20 and a time of 0.2 seconds.
RESULTS

Table 1: Solubility data of piroxicam in various non volatile solvents

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Amount dissolved (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG 400</td>
<td>9.77</td>
</tr>
<tr>
<td>Span 20</td>
<td>2.00</td>
</tr>
<tr>
<td>Tween 80</td>
<td>1.71</td>
</tr>
<tr>
<td>Span 20+ PEG 400</td>
<td>17.66</td>
</tr>
<tr>
<td>Tween 80 + PEG 400</td>
<td>21.73</td>
</tr>
</tbody>
</table>

Table 2: Formulae for the preparation of various Piroxicam liquisolid systems

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Ingredients</th>
<th>LS 1</th>
<th>LS 2</th>
<th>LS 3</th>
<th>LS 4</th>
<th>LS 5</th>
<th>LS 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>PEG 400</td>
<td>1000</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>3</td>
<td>Span 20</td>
<td>-</td>
<td>-</td>
<td>500</td>
<td>-</td>
<td>500</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Tween 80</td>
<td>-</td>
<td>500</td>
<td>-</td>
<td>500</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Microcrystalline cellulose</td>
<td>2000</td>
<td>2000</td>
<td>-</td>
<td>-</td>
<td>2000</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Aerosil</td>
<td>-</td>
<td>-</td>
<td>1000</td>
<td>1000</td>
<td>-</td>
<td>1000</td>
</tr>
</tbody>
</table>

Table 3: Flow properties of various Piroxicam liquisolid systems

<table>
<thead>
<tr>
<th>Liquisolid system</th>
<th>% Compressibility±S.D.*</th>
<th>Angle of repose (°)±S.D.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS1</td>
<td>22.24±0.155</td>
<td>35.26±0.278</td>
</tr>
<tr>
<td>LS2</td>
<td>11.46±0.243</td>
<td>24.15±0.554</td>
</tr>
<tr>
<td>LS3</td>
<td>11.48±0.414</td>
<td>23.16±0.445</td>
</tr>
<tr>
<td>LS4</td>
<td>13.23±0.342</td>
<td>27.87±0.697</td>
</tr>
<tr>
<td>LS5</td>
<td>14.32±0.134</td>
<td>26.89±0.654</td>
</tr>
<tr>
<td>LS6</td>
<td>10.54±0.122</td>
<td>24.32±0.874</td>
</tr>
</tbody>
</table>

*S.D. Standard deviation from mean .n=3

Table 4: Drug Content of various Piroxicam liquisolid systems

<table>
<thead>
<tr>
<th>Liquisolid system</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS1</td>
<td>99.85</td>
</tr>
<tr>
<td>LS2</td>
<td>98.56</td>
</tr>
<tr>
<td>LS3</td>
<td>100.64</td>
</tr>
<tr>
<td>LS4</td>
<td>101.49</td>
</tr>
<tr>
<td>LS5</td>
<td>100.19</td>
</tr>
<tr>
<td>LS6</td>
<td>101.29</td>
</tr>
</tbody>
</table>
Table 5 Correlation coefficient of various Piroxicam liquisolid systems

<table>
<thead>
<tr>
<th>Liquisolid system</th>
<th>Zero order</th>
<th>First order</th>
<th>Hixson crowell’s</th>
<th>Higuchi</th>
<th>Erosion</th>
<th>First order rate (k) (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS1</td>
<td>0.8051</td>
<td>0.9479</td>
<td>0.9406</td>
<td>0.8717</td>
<td>0.9086</td>
<td>0.0447</td>
</tr>
<tr>
<td>LS2</td>
<td>0.7896</td>
<td>0.9995</td>
<td>0.9830</td>
<td>0.8770</td>
<td>0.9814</td>
<td>0.1684</td>
</tr>
<tr>
<td>LS3</td>
<td>0.9823</td>
<td>0.9787</td>
<td>0.9845</td>
<td>0.9611</td>
<td>0.9801</td>
<td>0.0109</td>
</tr>
<tr>
<td>LS4</td>
<td>0.8609</td>
<td>0.9851</td>
<td>0.9461</td>
<td>0.8892</td>
<td>0.9773</td>
<td>0.0236</td>
</tr>
<tr>
<td>LS5</td>
<td>0.8832</td>
<td>0.9095</td>
<td>0.9617</td>
<td>0.9325</td>
<td>0.9011</td>
<td>0.0131</td>
</tr>
<tr>
<td>LS6</td>
<td>0.7796</td>
<td>0.9406</td>
<td>0.9161</td>
<td>0.8435</td>
<td>0.9330</td>
<td>0.0763</td>
</tr>
</tbody>
</table>

Fig 1 Dissolution profiles of Piroxicam liquisolid systems (LS1 to LS3)

Fig 2 Dissolution profiles of Piroxicam liquisolid systems (LS4 to LS6)
Fig. 3 FT-IR spectrum of pure Drug sample

Fig. 4 FT-IR spectrum of LS6 sample

Fig. 5 XRD of Drug sample
RESULTS AND DISCUSSION

The solubility studies of piroxicam in various non volatile solvents is very important for choice suitable solvent system. Hence the solubility studies were conducted using various nonvolatile solvents. The results shown in Table 1 High solubility was observed in 1:1 ratio of Span 20 and PEG 400 (17.66 mg/g) and 1:1 ratio of Tween and PEG 400 (21.73 mg/g). Hence in the preparation of piroxicam liquisolid systems (LS) these solvents alone and in combination were used. The properties such as % compressibility index and angle of repose were observed. The percent drug content (%) of the Piroxicam in liquisolid systems were found to be in the range of 98.56 to 101.49. The high drug content values indicated the suitability of the technique. The release profile of drug from these liquisolid systems (LS) was subjected for zero order, first order, Hixson-Crowell equation Higuchi diffusion and erosion equation and the correlation coefficient (r) values are given in Table 5.

FTIR spectroscopy

FTIR spectra of Piroxicam showed characteristic peaks of aromatic C-H stretching at 3024 cm$^{-1}$, aromatic CH bending at 876 cm$^{-1}$, C-S stretching at 692 cm$^{-1}$, C=O stretching at 1746 cm$^{-1}$, S(=O)2 Stretching at 1145 cm$^{-1}$, secondary amine N-H stretching 3337 cm$^{-1}$ and OH stretching at 3646 cm$^{-1}$. The LS6 showed all these characteristic peaks with minor shifts. This indicated that the drug is not having any chemical incompatibility with the excipients used in liquisolid systems.

X-ray diffraction

X-ray diffraction of piroxicam displayed some sharp peaks at 10, 16 and 24 position of 20 values. This indicated absence of the crystallinity in drug. This also indicated that the drug is
entrapped in the carrier in liquid form by adsorption. The results of the present study clearly indicated the usefulness of liquisolid technique in the improvement of dissolution of poorly soluble drug Piroxicam.

CONCLUSION
The potential of liquisolid systems to improve the dissolution properties of piroxicam was investigated in the present study. The results clearly indicated that the liquisolid systems of piroxicam is converting the drug into liquid form and when adsorbed on to solid carrier the LS were converted into free flowing powders. High drug content and drug release characters indicated the usefulness liquisolid technique for improvement solubility and dissolution of poorly soluble Piroxicam. Hence this technique can be used as a potential tool for design of suitable dosage forms for poorly soluble drugs.

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