An Approach for the Improvement of Dissolution Rate of Aceclofenac

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ABSTRACT

Aceclofenac is a BCS (Bio-pharmaceutical classification system) class II drug which exhibits poor aqueous solubility. The objective of the present study is to develop a pharmaceutical technique for the dissolution rate enhancement of aceclofenac. This study concentrates on the preparation of aceclofenac microcrystals and the evaluation of the prepared microcrystals. The use of hydrophilic polymers like polyvinyl pyrrolidine [PVP (k-30)] and polyethylene glycol-4000 (PEG-4000) in the preparation of microcrystals has resulted in the dissolution rate enhancement of the drug. The microcrystals were evaluated for their particle size, solubility, drug content, drug-polymer interaction studies and in-vitro dissolution studies. Various concentrations of the polymers like 0.2% and 0.5% were used in this study. It was found that the microcrystals formulated using 0.5% concentration of the polymers has improved dissolution profiles when compared to that of 0.2% concentration of the polymers.

Keywords: Aceclofenac, Microcrystals, Solvent change method, PVP(k-30), PEG-4000, dissolution rate enhancement.

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INTRODUCTION

Poor aqueous solubility of the drug became a typical issue for pharmaceutical scientists in the process of dosage form development. A report says that nearly 40% of the drugs developed were found to have poor aqueous solubility characteristics [1]. Many approaches have been developed for solubility enhancement of biopharmaceutical class II drugs which are characterized with low solubility and high permeability. Various techniques have been developed to modify the physicochemical, micrometrics and biopharmaceutical properties of the poorly soluble drugs and hence solubility. Among the various dissolution rate enhancement methodologies available for poorly water-soluble drugs like amorphous dispersions as solid dispersions/ inclusion complexes [2], salt formation, surfactant/lipid based excipients addition[3], etc., drug particle size reduction is meeting great interest in drug formulation [4,8].

According to the Noyes–Whitney equation, the use of a drug in a reduced particle size is a promising way to improve the drug bioavailability of poorly soluble substances due to the increased dissolution rate of micron size substances [5]. There are various methods to produce a drug with smaller particle size. Most common methods for size reduction of the drugs are milling, precipitation from supercritical fluid [7] and controlled crystallization [8]. Production of smaller crystals is still a challenge due to the high surface area, which has to be created and stabilized against the tendency of a particle growth. An approach to overcome this obstacle is using high amount of stabilizing agents in order to stabilize the high specific surface area of small particles. This approach can be attained by the method called solvent change technique. This technique is a rapid, easy to handle, and requires common equipment which is readily available [9, 10].

Aceclofenac is a NSAID belonging to BCS class II with good analgesic and anti-pyretic properties. It is chemically known as \(((2\text{-}(6\text{-Dichlorophenyl})\text{ amino}\text{ phenyl})\text{ acetyl}\text{ oxy})\text{ acetic acid. It is used in the treatment of various conditions like rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac exhibits very slight solubility in water and aqueous fluids. It is freely soluble in acetone.}

The objective of the present study is to develop aceclofenac microcrystals using hydrophilic polymers, Polyethylene glycol-4000 (PEG-4000) and polyvinyl pyrrolidine (PVP) (k-30) of various concentrations and to evaluate the microcrystals for drug content, solubility, particle size analysis, drug-polymer interaction studies and drug release characteristics.

MATERIALS AND METHODS

Materials

Aceclofenac was purchased from Chennai Drug House Pvt. Ltd., Chennai. Acetone was purchased from Fischer Chemicals Limited, Chennai, which is of analytical grade. Hydroxy propyl methyl cellulose (HPMC), Polyethylene glycol-4000 (PEG-4000), Polyvinyl pyrrolidine
(PVP) (k-30), were purchased from Central Drug House Pvt. Ltd., Mumbai. Polyvinyl alcohol (PVA) was purchased from SD fine Chemicals Ltd., Mumbai.

METHODS

Preparation of microcrystals

Aceclofenac microcrystals were prepared using anti-solvent precipitation technique. 11.6 g of drug was weighed and it was dissolved in 50 ml of acetone. This solution was added to the aqueous phase i.e., 0.2% w/v and 0.5% w/v solutions of PEG-4000 and PVP (k-30) under constant stirring and the stirring was continued for one hour. The resultant dispersion was filtered using Whatman filter paper and the microcrystals formed were separated. The microcrystals obtained were dried for 48 hours under room temperature [11].

Evaluation

Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR studies were conducted in-order to check the compatibility of the drug with the polymers used in the study. This study was conducted using FT-IR spectrophotometer (Model NP-602378-14,002, instrument serial No.72425). The spectrum was recorded in the region of 4000-400 cm\(^{-1}\). The method opted was potassium bromide pellet technique.

Particle size determination

Particle size of the microcrystals was determined using optical microscopy. The microscope was calibrated using an eye piece and a stage micrometer and then used for the particle size determination. 100 microcrystals were measured for their size individually. From the values obtained, the average particle size of the microcrystals was determined.

The average particle size was calculated using the formula,

\[
\text{Average particle size} = \frac{\sum fx}{\sum n}
\]

Solubility studies

100 mg of the formed microcrystals were taken in a standard flask containing 20 ml of distilled water. The samples were shaken at room temperature for 48 hours and then they were filtered. The filtrate was diluted suitably and then analyzed using UV spectrophotometer at 275 nm.
Drug content studies

100 mg of the prepared microcrystals was weighed and taken into a 100 ml standard flask. The volume was made using pH 6.8 phosphate buffer. Then it was sonicated for 10 minutes. The resultant solution was diluted suitably and then analyzed using UV spectrophotometer at 275 nm.

*In-vitro* dissolution studies

In vitro dissolution studies were carried out using eight station USP type II dissolution apparatus. The release of aceclofenac from the prepared microcrystals was studied using phosphate buffer pH 6.8 as the dissolution medium. 100 mg of the microcrystals were added to 900 ml of the dissolution medium. Dissolution medium was maintained at 37 ± 0.50°C temperature and the paddle was rotated at 75 rpm. After predetermined time intervals, 10 ml of samples were withdrawn and 10 ml of fresh dissolution media was added to maintain the sink conditions. The withdrawn samples were analyzed using UV-Visible Spectrophotometer at 275 nm [12].

**RESULTS AND DISCUSSION**

**Percentage Practical Yield**

The percentage yield of the microcrystals was calculated in order to predict the efficiency of the method that has been chosen for the study. Microcrystals obtained were collected and weighed to determine the percentage practical yield (Table. 1) using the following formula,

\[
\text{Percentage practical yield} = \frac{\text{Practical mass (microcrystals)}}{\text{Theoretical mass (Drug + polymer)}} \times 100
\]

<table>
<thead>
<tr>
<th>Microcrystals</th>
<th>Percentage Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-4000</td>
<td>97.82</td>
</tr>
<tr>
<td>PVP (k-30)</td>
<td>97.73</td>
</tr>
</tbody>
</table>

**Table 1. Practical yield of AceclofenacMicrocrystals**

**Fourier Transform Infrared Spectroscopy (FT-IR)**

IR spectra of the pure drug and the prepared microcrystals are shown in the figure no.1, 2, 3, 4 and 5. The IR spectrum of the pure drug shows characteristic bands at 3318 cm⁻¹, 1771 cm⁻¹, 1717 cm⁻¹, 1150 cm⁻¹, 750 cm⁻¹. The IR spectra of the microcrystals also show the same
characteristic bands. From the results obtained from IR spectra it can be concluded that there is no possibility of any interaction, chemical and functional group change during the processing of the formulation of microcrystals. Intensity of IR peaks of aceclofenac microcrystals were decreased as compared to untreated drug, implying that the change in crystal habit and particle size reduction in microcrystals is responsible for these changes.

Fig. 1. FTIR spectra of the pure drug

![Fig. 1. FTIR spectra of the pure drug](image1)

Fig. 2. FTIR spectra of the microcrystals prepared using 0.2% PEG-4000

![Fig. 2. FTIR spectra of the microcrystals prepared using 0.2% PEG-4000](image2)

Fig. 3. FTIR spectra of the microcrystals prepared using 0.5% PEG-4000

![Fig. 3. FTIR spectra of the microcrystals prepared using 0.5% PEG-4000](image3)
Particle size determination

Particle size determination of the microcrystals was performed using optical microscopy with a calibrated eye piece micrometer and stage micrometer by taking a small quantity of formulation on the glass slide. About 100 microcrystals were measured individually, average was taken and their size range and average mean diameter was calculated and shown in the Table 2. The average particle size of the untreated drug was found to be 62.80 µm. The formulations made using the polymers showed decreased particle size when compared with that of the pure drug. The results indicate that the microcrystals prepared using 0.5% concentration of the polymer found to have less particle size when compared with 0.2% concentration.
Table: 2. Particle Size determination of Aceclofenac Microcrystals

<table>
<thead>
<tr>
<th>Microcrystals</th>
<th>Particle size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td>PEG-4000</td>
<td>39.23</td>
</tr>
<tr>
<td>PVP (k-30)</td>
<td>32.35</td>
</tr>
</tbody>
</table>

Solubility studies

The solubility studies were carried out using distilled water. The solubility of the untreated drug was found to be 0.0718 ± 0.008 mg/ml. The solubility studies indicate that the crystals prepared using 0.5% has showed highest solubility of the drug in water when compared with that of 0.2% (Table. 3). Among the two polymers used, PVP (k-30) showed better solubility in water. All the prepared formulations were found to have better solubility when compared with that of the pure drug. This increase in the solubility is credited to the decrease in particle size by size reduction.

Table: 3. Solubility profile of Aceclofenac Microcrystals

<table>
<thead>
<tr>
<th>Microcrystals</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td>PEG-4000</td>
<td>0.1120 ± 0.007</td>
</tr>
<tr>
<td>PVP (k-30)</td>
<td>0.1226 ± 0.009</td>
</tr>
</tbody>
</table>

Drug content studies

The drug content was found to be good and uniform among the different batches of the prepared samples and ranging from 89.92% - 97.75% (Table. 4). The drug content was found to be high in the case of 0.5% concentration of polymer when compared with that of 0.2%. The microcrystals prepared with PVP (k-30) showed better drug content when compared to PEG-4000.

Table: 4. Drug Content of Aceclofenac Microcrystals

<table>
<thead>
<tr>
<th>Microcrystals</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td>PEG-4000</td>
<td>89.92 ± 0.45</td>
</tr>
<tr>
<td>PVP (k-30)</td>
<td>93.76 ± 1.63</td>
</tr>
</tbody>
</table>
In-vitro dissolution studies

From the results obtained, it is evident that the onset of dissolution of aceclofenac is low, about 71.51% of the drug being dissolved in 60 minutes. The drug microcrystals prepared with polymers exhibited better dissolution rates when compared with that of the untreated drug. The dissolution profile of the pure drug and the polymeric microcrystals explains that the particle size reduction was an effective and versatile option to enhance the rate of dissolution. Microcrystals prepared with PVP (k-30) showed enhanced dissolution rates within 60 minutes compared to that of pure drug and microcrystals prepared with PEG-4000. Among the two concentrations used 0.5% was proved to be more efficient (Table. 5). According to the Noyes-Whitney and Ostwald-Freundlich equations, size reduction is an effective tool for dissolution enhancement of a poorly aqueous soluble drug.

<table>
<thead>
<tr>
<th>Microcrystals</th>
<th>Percentage drug dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td>PEG-4000</td>
<td>92.44</td>
</tr>
<tr>
<td>PVP (k-30)</td>
<td>97.74</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td>PEG-4000</td>
<td>95.27</td>
</tr>
<tr>
<td>PVP (k-30)</td>
<td>99.79</td>
</tr>
</tbody>
</table>

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REFERENCES