Research article

Preformulation studies a view to develop fast release solid dosage form
Rakesh Kumar Sharma¹*, Ezeddin. I. Kolab¹

Abstract:
The purpose of the present investigation was to increase the solubility and dissolution rate of rofecoxib by the preparation of its solid dispersion using Polyethylene glycol 6000 as a hydrophilic carrier in different proportion ranging from 1:2 to 1:12 using solvent evaporation method. Drug polymer interactions were investigated using Fourier transform infrared spectroscopy (FTIR). The solid dispersions prepared were subjected to assay, solubility and in vitro dissolution studies. The obtained results showed that the solubility was increased 5 fold over that of pure rofecoxib with 1:10 ratio of carrier and the dissolution rate considerably enhanced. The drug-to-carrier ratio was the controlling factor for dissolution improvement with maximum dissolution observed with 1:10 solid dispersion. This increase in the dissolution rate was due to improved wettability by the carrier. At higher level (after 1:10 ratio), the negative effect on dissolution appears that may be due to distortion of molecular dispersion structure, which leaves an insoluble drug particle and increased accumulation of carrier molecule in the bulk, to cause a saturation, by which further solubility of rofecoxib is retarded. FTIR spectra revealed no chemical incompatibility between the drug and PEG6000. The optimized 1:10 (RXB: PEG6000) solid dispersion was used in the formulation of tablet using microcrystalline cellulose as superdisintegrant by direct compression. The Flowability and compressibility of the blend was found to be fair for compression. The tablet weight was maintained at nearly 180mg.

Keywords: Rofecoxib, Polyethylene glycol 6000, solid dispersions, FTIR, solvent method

Introduction

Rofecoxib (RXB) is a non-steroidal anti-inflammatory drug (NSAID), acting by inhibition of the synthesis of prostaglandins, by inhibiting the activity of the enzyme, cyclooxygenase-2 (COX-2) [1, 2]. It is 28,000 times more selective for COX-2 than COX-1. Rofecoxib is practically insoluble in water, and peak blood level reaches between 2-3 h after oral administration [3, 4]. Dissolution is the rate-limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/ml at 37°), due to erratic or incomplete absorption from GIT. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates, and consequently, the bioavailability of poorly water-soluble drugs. A number of drugs have been shown to improve their dissolution character, when converted to solid

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dispersions [5-8]. The present investigation was done as an attempt to improve solubility and dissolution of hydrophobic drugs through solid dispersions and formulate into fast release tablets. Rofecoxib was used as model drug. The drug was withdrawn from the market in 2004 by Merck Inc as a result of its cardiac effects.

Materials and methods
Preparation of solid dispersions
Solid dispersions containing Rofecoxib and carrier (PEG6000) in the proportion of 1:1, 1:2, 1:4, 1:6, 1:8, 1:10 and 1:12 were prepared by solvent evaporation method [9-11] using acetone as solvent. The solvent was removed at 45°C under vacuum. The solid residue was dried in a vacuum oven, passed through mesh no 60 and stored in a well closed container.

Drug content analysis
An accurately weighed quantity of solid dispersion equivalent to 20 mg of RXB was taken into a 100 ml volumetric flask and dissolved in acetonitrile. Five ml of the filtrate was diluted to 100 ml with 0.1 N HCL, and assayed for drug content using a double beam UV/Vis spectrophotometer at 245 nm.

Phase solubility study
Solubility studies were performed according to the method described by Higuchi and Connors [12]. An excess amount of rofecoxib was placed into a 25-mL glass flask containing different concentrations of PEG 6000 in 20 mL distilled water. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent loss. The content of the suspension was equilibrated by shaking for 72 hours in a thermostatically controlled water bath at 25°C. After attainment of equilibrium, the content of each flask was then filtered. The filtrate was diluted and assayed spectrophotometrically (Shimadzu UV-110A Japan) for rofecoxib content at 245 nm. The solubility measurements were performed in triplicate.

In vitro dissolution study
The quantity of solid dispersions equivalent to 20 mg of RXB, was filled in colorless hard gelatin capsules by the hand filling method. Dissolution study of capsules was conducted using USP XXIII electrolab 8 basket tab dissolution test apparatus using paddle stirrer, in 900 ml of 0.1 N HCL, maintained at 37±0.5°C at a speed of 50 rpm [13]. Five milliliters of samples were withdrawn at time intervals of 10, 20, 30, 45 and 60 min. The volume of dissolution fluid was adjusted to 900 ml, by replacing each 5 ml aliquot withdrawn with 5 ml of 0.1 N HCL. The concentration of RXB in each sample was determined by using standard curve equation.

Infra red spectroscopy
IR spectra of RXB and solid dispersions were obtained by KBr pellet method using Perkin Elmer FTIR series model 1615 spectrometer in order to rule out drug carrier interaction occurring during the formulation process [14-18].

Preparation of RXB solid dispersion tablets
All the ingredients shown in Table 1 were passed through mesh no 60, evaluated for flow properties, compressibility behavior and compressed on single punch machine with 8 mm flat faced punches. The percentage of each ingredient was optimized. The tablet weight was adjusted to approximately 180mg.

Table 1: Optimized formulation of Rofecoxib solid dispersion tablets

<table>
<thead>
<tr>
<th>S. no</th>
<th>Ingredients</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1: 10 RXB solid dispersion equivalent to 25 mg</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Corn starch</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Micro crystalline cellulose</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Aspartame</td>
<td>0.5</td>
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</table>

Evaluation of RXB solid dispersion tablets
The tablets were evaluated for assay, hardness, friability, disintegration time and dissolution [19-20].

Hardness
It is the tensile strength of tablets expressed in kg/cm². It is the pressure required to break the tablet in to two halves by compression.

Friability
This test is performed to know the effect of friction and shocks on tablets. Preweighed sample of tablets was
placed in the friabilator (Roche friabilator), and operated for 100 revolutions. Tablets were dusted and reweighed. The test complies if tablets not loose more than 1% of their weigh.

**Assay**

Five tablets were crushed and from this, quantity equivalent to 20 mg of RXB was taken into a 100 ml volumetric flask and dissolved in acetonitrile. Five ml of the filtrate was diluted to 100 ml with 0.1 N HCL, and assayed for drug content using a double beam UV/Vis spectrophotometer at 245 nm.

**Disintegration time**

Disintegration time for tablets was determined using USP disintegration apparatus with 0.1 M HCl as the disintegrating medium.

**Dissolution test**

In vitro dissolution study on prepared tablets was performed in 0.1M HCL and Phosphate buffer (pH 6.8) using USP type II (paddle) apparatus operated at 50 rpm (900 ml) for 60 minutes (37 ± 0.5°C).

**Results and discussion**

The percent drug content in all the dispersions contained 100±5% of the drug. The solubility of rofecoxib in distilled water was found to 6mcg/ml (Figure 1).

The obtained results showed that the solubility was increased 5 fold (31mcg/ml) over that of pure rofecoxib with 1:10 ratio of carrier. It can be seen that from figure 2 that dissolution of rofecoxib increases with increases in PEG6000, up to 1:10 drug: PEG6000 ratio. The drug-to-carrier ratio was the controlling factor for dissolution improvement with maximum dissolution observed with 1:10 solid dispersion. This increase in the dissolution rate may be due to improved wettability by the carrier.

**Figure 2. Dissolution of rofecoxib from different solid dispersions in distilled water at 37°C.**

At higher level (after 1:10 ratio), the negative effect on dissolution appears. That may be due to distortion of molecular dispersion structure, which leaves an insoluble drug particle and increased accumulation of carrier molecule in the bulk, to cause a saturation, by which further solubility of rofecoxib is retarded. Figure 3 shows the IR spectra of rofecoxib, PEG 6000, and their formulations.

**Figure 3: FTIR spectra of Rofecoxib-PEG 6000 solid dispersions**
Pure rofecoxib displays a peak characteristic of the C-O bending vibration at 1150.5 cm$^{-1}$ and a band with main strong peak at 1747.4 cm$^{-1}$ indicative of the C=O stretch of the ester group. The spectrum of PEG6000 showed important bands at 2955 cm$^{-1}$ (C–H stretch) and 1655 cm$^{-1}$ (C=O). A very broad band was also visible at 3425 cm$^{-1}$ that was attributed to the presence of water. The FTIR spectra of both physical mixture and solid dispersion still showed peak of the esteric C=O stretch vibration of the drug. Also a C-O vibration peak was still detected at the same position as that of drug. Consequently, the FTIR spectra of both physical mixture and solid dispersion seemed to be only a summation of drug and PEG6000 spectra. This result suggested that there was no interaction between drug and PEG6000 in their combinations. The table 2 shows the directly compressible blend has fair flow and compressible properties. The tablet mean hardness was found to be 2.7 kg/cm$^2$. The tablets disintegrate within two minutes (78sec). The friability and assay was found 0.62% and 101.3%, respectively. The dissolution study was carried out in Purified water, 0.1 M HCL and phosphate buffer pH 6.8 figure 4, yielding about 42%, 45% and 65% drug released respectively in 60 minutes.

### Table 2: Evaluation of optimized directly compressible blend and Tablets

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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<tbody>
<tr>
<td>Angle of repose</td>
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<tr>
<td>Bulk density (gm/cm$^3$)</td>
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</tr>
<tr>
<td>Tapped density (gm/cm$^3$)</td>
<td>0.68</td>
</tr>
<tr>
<td>% compressibility</td>
<td>23.52</td>
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<tr>
<td>Flowability</td>
<td>Fair</td>
</tr>
<tr>
<td>Hardness (kg/cm$^2$)</td>
<td>2.7</td>
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<tr>
<td>Assay</td>
<td>101.3%</td>
</tr>
<tr>
<td>Friability</td>
<td>0.62%</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>78 sec</td>
</tr>
</tbody>
</table>

### Conclusion

The present study showed the suitability of PEG6000 in ratio of 1:10 as a carrier for the preparation of rofecoxib fast release tablets via solid dispersion technique.

### Acknowledgement

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### References


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**Figure 4. Disolution of rofecoxib tablets (1: 10 solid dispersion)**


