The aim of this study was to enhance the dissolution rate of Piroxicam using its solid dispersions (SDs) with Polyethylene Glycol (PEG) 6000 and Eudragit RL-100. The SDs of Piroxicam with PEG-6000 and Eudragit RL-100 were prepared at 1:1, 1:3, and 1:5 w/w ratios by solvent evaporation method. Physical mixture and co-grinded mixture of Piroxicam with PEG-6000 (1:3 and 1:5 w/w) and Eudragit RL-100 (1:3 and 1:5 w/w) were prepared also. Evaluation of the properties of the SDs was performed using dissolution, fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD) analysis. The SDs of Piroxicam with PEG-6000 and Eudragit RL-100 exhibited enhanced saturation solubility and dissolution rate of Piroxicam than that of pure drug. The interaction of Piroxicam with the carriers (PEG-6000 and Eudragit RL-100) was studied by differential scanning calorimetry (DSC), fourier-transform infrared (FTIR), and X-ray diffraction (XRD) analysis.

Key words: Piroxicam; Solid dispersion; Physical mixture; Co-grinded mixture; PEG-6000; Eudragit RL-100; Dissolution.

INTRODUCTION

Sufficient aqueous solubility is a prerequisite for effective oral delivery of any therapeutic agent. At this time low soluble and highly permeable drug molecules are gradually becoming prevailing in the development pipelines of pharmaceutical companies. These drug molecules fall into Biopharmaceutics Classification System (Bcs) Class II, for which the dissolution is usually the rate-limiting step for gastrointestinal absorption. The solubility of such drugs can be increased using various techniques that includes solid dispersion, solvent disposition, co-solvents, salt formation, pH control, micronization, co-grinding; however, all these techniques have potential limitations also. All poorly water soluble drugs are not suitable for improving their solubility by salt formation. Decreasing particle size increases solubility, but there is poor wetting and flow. However, solid dispersions can overcome these problems\(^\text{3,5}\). The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly in amorphous particles (clusters) or in crystalline matrix particles. Chiou and Riegelman defined solid dispersions as “the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states”\(^\text{8}\). The SDs of drugs with PEG-6000 may be useful to solve various problems such as stability, solubility, dissolution, and bioavailability\(^\text{3,9}\). Eudragit RL-100 is used as a film coating material and inert carrier for some NSAIDs\(^\text{9,16}\). Piroxicam [4-Hydroxy-2-methyl-N-2-pyridyl-1,2-benzothiazine-3-carboxamide-1, 1-dioxide] is a long acting potent NSAID with good anti-inflammatory, analgesic and antipyretic action and used in the treatment of rheumatoid and osteo-arthritis. But, Piroxicam is a poorly water soluble drug and its absorption is dissolution rate limited. Practically, it is partially soluble in water and aqueous fluid. So, Piroxicam as a suitable drug candidate uses PEG-6000 and Eudragit RL-100 as carriers to improve dissolution characteristic. Piroxicam is an NSAID and belongs to the BCS Class II drugs; therefore, its oral absorption is considered to be dissolution-rate limited\(^\text{16,17}\). In fact, several studies have reported a significant increase in the dissolution rate of Piroxicam solid dispersions over the pure drug formulations\(^\text{16,20}\). This study was aimed at improving the dissolution rate of poorly water soluble drug Piroxicam using two different carriers – PEG-6000 and Eudragit RL-100. In order to characterize the solid dispersions, fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), X-ray diffraction patterns (XRD) as well as saturation solubility and dissolution studies were carried out.

MATERIALS AND METHODS

Piroxicam, PEG-6000, and Eudragit RL-100 were gifted by Sun Pharma; Hydrochloride and Ethanol by Merck Specialities Pvt. Ltd; Magnetic Stirrer (Remi Equipments Pvt. Ltd); UV – Vis Spectrophotometer (Shimadzu UV-1700); Eight Stage Dissolution Apparatus Model TDT-08L (ELECTROLAB).

PREPARATION OF SOLID DISPERSIONS, PHYSICAL MIXTURES, AND CO-GRINDED MIXTURES

1. Solid Dispersions Prepared by Solvent Evaporation Technique

Drug (Piroxicam) and carriers (PEG-6000 and Eudragit RL-100) were weighed according to drug–carrier ratios and they were dissolved in the chosen solvent (Ethanol) with continuous stirring with the help of magnetic stirrer. The solvent was removed by evaporation at 60°C under vacuum and kept for two overnights. Then obtained mass was further dried and kept in desiccators over anhydrous calcium chloride for 24 hrs. The dried product was crushed, pulverized, and sieved through #100. The solid dispersions thus obtained were packed in self sealing pouches and were further stored in well-closed container. The container was kept in desiccators. Solid dispersions were prepared in 1:1, 1:3, and 1:5 w/w ratios.

2. Physical Mixture of Piroxicam with Carriers

Physical mixtures were prepared by simple mixing the accurately weighed drug (Piroxicam) and carriers (PEG-6000 and Eudragit RL-100) in 1:3 and 1:5 w/w ratios with help of spatula for 10 mins.

3. Co-grinded Mixture of Piroxicam with Carriers

Co-grinded mixtures of Piroxicam with PEG-6000 were obtained by co-grinding the drug and carrier in 1:3 and 1:5 w/w ratios for 20 mins in a ceramic mortar and sieved through #100. Similarly, co-grinded mixtures of Piroxicam with Eudragit RL-100 were prepared by co-grinding the drug and carrier in 1:3 and 1:5 w/w ratios for 40 mins in a ceramic mortar and sieved through #100.

IN-VITRO DISSOLUTION STUDIES

In-vitro dissolution studies were carried out on solid dispersion, co-grinded mixture, physical mixture, and pure drug. The in-vitro dissolution studies were carried out using USP XXI Type-II apparatus taking 900 ml of 0.1N HCl as the dissolution medium. The temperature of the medium was maintained at 37°C ± 0.5°C throughout the experiment. Then 80 mg equivalent of powder from each sample was added to dissolution medium and Paddle was used at a stirring rate of 50 rpm. Samples of 6 ml for each formulation were taken from the dissolution medium for absorbance study. For sampling, to maintain the volume of dissolution medium constant the 6 ml of samples were replaced with fresh medium. The samples were analysed for drug content at 334 nm using UV-Visible Spectrophotometer (Genesys-2) against a reagent blank and results were calculated from standard graph.

DIFFERENTIAL CALORIMETRY STUDIES (DSC)

The possibility of any interactions between the drug and the carriers during preparation of solid dispersions were assessed by carrying out DSC (differential scanning calorimetry) study of the drug and solid dispersions in 1:3 ratios for both the polymers (PEG-6000 and Eudragit RL-100) using Perkin-Elmer 7 series thermal analysis system at a rate of 10°C/min in a N₂ (Nitrogen) environment and samples were scanned at 200°C to 3000°C.

X-RAY DIFFRACTION STUDIES

To determine the powder characteristics, X-ray powder diffraction studies of the drug and...
solid dispersions were carried out in 1:5 ratios using both the polymers PEG-6000 and Eudragit RL-100. Samples were scanned from 0–100° angle. X-ray powder diffraction patterns were recorded using Bruker AXS, DH Advance, Germany.

FOURIER TRANSFORMS INFRARED SPECTROSCOPY (FTIR)
Fourier transform infrared (FTIR) spectroscopy was employed to characterize the further possible interactions between the drug and carriers in the solid state using FTIR spectrophotometer (Shimadzu UV-1700) by conventional KBr pellet method. FTIR spectra of pure drug, polymer, physical mixture, co-grinded mixture, and solid dispersion product for both the carriers were obtained. The spectra were scanned over a frequency range 4000–500 cm$^{-1}$.

RESULTS AND DISCUSSION
Solid dispersions of Piroxicam were prepared with Eudragit RL-100 and PEG-6000 respectively. Physical mixture and co-grinded mixture of the drug and carriers were prepared in 1:1, 1:3, and 1:5 w/w ratios for comparison with solid dispersions and stored at similar set of conditions.

IN-VITRO DISSOLUTION STUDIES
The drug release studies were performed on solid dispersions, co-grinded mixtures, and physical mixtures for both the carriers (Eudragit RL-100 & PEG-6000) are shown in Figs. 1–12. The dissolution of pure drug was performed for comparison purpose. The solid dispersions and co-grinded mixtures prepared for different carriers with the drug resulted in fast release of the drug compared to pure drug (see Table 1). Among the solid dispersions of Piroxicam prepared using Eudragit RL-100 and PEG-6000, dispersions with ratio 1:5 for both the carriers gave faster dissolution followed by 1:3 ratio. The order of rates of release of various solid systems found as Solid dispersion > Co-grinded mixture > Physical mixture > Pure drug. The result indicates that there is significant increase in dissolution when dispersed in Eudragit RL-100 and PEG-6000. Although solid dispersion gives better results its implementation in the large scale level is problematic as well as uneconomic also. So, the co-grinded mixture can be considered as an alternative. The prepared solid dispersions and co-grinded mixtures can be easily formulated into various dosage forms.

Table 1. Comparative dissolution profile of piroxicam and its solid dispersion in 0.1N HCl by solvent evaporation method, physical mixture and co-grinded mixture with PEG-6000 and Eudragit RL-100

<table>
<thead>
<tr>
<th>SrNo</th>
<th>Formulations</th>
<th>% of Drug Release</th>
<th>5 Min</th>
<th>10 Min</th>
<th>15 Min</th>
<th>20 Min</th>
<th>30 Min</th>
<th>45 Min</th>
<th>60 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Drug</td>
<td>09.45</td>
<td>13.02</td>
<td>17.21</td>
<td>20.00</td>
<td>21.00</td>
<td>30.00</td>
<td>34.00</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>PM.PEG-6000 (1:3)</td>
<td>11.14</td>
<td>15.00</td>
<td>21.37</td>
<td>27.90</td>
<td>32.52</td>
<td>38.49</td>
<td>39.48</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>PM.PEG-6000 (1:5)</td>
<td>19.68</td>
<td>28.70</td>
<td>36.90</td>
<td>45.08</td>
<td>51.52</td>
<td>54.37</td>
<td>60.11</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>PM.EURL-100 (1:3)</td>
<td>13.00</td>
<td>18.50</td>
<td>24.50</td>
<td>29.00</td>
<td>36.50</td>
<td>39.00</td>
<td>42.00</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>PM.EURL-100 (1:5)</td>
<td>21.00</td>
<td>31.00</td>
<td>41.00</td>
<td>49.00</td>
<td>56.00</td>
<td>64.00</td>
<td>69.00</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>CM.PEG-6000 (1:5)</td>
<td>35.21</td>
<td>48.51</td>
<td>59.00</td>
<td>65.70</td>
<td>70.42</td>
<td>73.85</td>
<td>80.04</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>CM.EURL-100 (1:5)</td>
<td>39.93</td>
<td>54.10</td>
<td>67.38</td>
<td>79.42</td>
<td>83.70</td>
<td>88.27</td>
<td>93.50</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>CM.PEG-6000 (1:3)</td>
<td>32.24</td>
<td>46.80</td>
<td>59.25</td>
<td>64.48</td>
<td>69.56</td>
<td>72.50</td>
<td>79.15</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>CM.PEG-6000 (1:5)</td>
<td>38.64</td>
<td>52.38</td>
<td>65.69</td>
<td>79.05</td>
<td>82.44</td>
<td>87.60</td>
<td>92.54</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>SD.PEG-6000 (1:3)</td>
<td>15.00</td>
<td>29.12</td>
<td>41.65</td>
<td>51.00</td>
<td>55.00</td>
<td>61.00</td>
<td>69.00</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>SD.PEG-6000 (1:5)</td>
<td>21.46</td>
<td>37.35</td>
<td>47.23</td>
<td>57.00</td>
<td>66.12</td>
<td>76.00</td>
<td>83.73</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>SD.EURL-100 (1:1)</td>
<td>18.46</td>
<td>31.77</td>
<td>43.36</td>
<td>52.38</td>
<td>60.11</td>
<td>68.00</td>
<td>75.14</td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>SD.EURL-100 (1:3)</td>
<td>20.61</td>
<td>37.35</td>
<td>47.23</td>
<td>56.67</td>
<td>63.54</td>
<td>74.28</td>
<td>83.73</td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>SD.EURL-100 (1:5)</td>
<td>23.18</td>
<td>35.00</td>
<td>45.00</td>
<td>65.26</td>
<td>72.13</td>
<td>89.00</td>
<td>96.50</td>
<td></td>
</tr>
</tbody>
</table>
Dissolution data of Pure Drug, Physical Mixture and Co-grinded Mixture of Drug with PEG-6000

Dissolution data of Physical Mixture, Co-grinded Mixture and Solid Dispersion of Drug with EuRL-100

Dissolution data of Physical Mixture, Co-grinded Mixture and Solid Dispersion of Drug with PEG-6000 with ratios 1:1, 1:3, 1:5

Dissolution data of Pure Drug, Physical Mixture and Solid Dispersion of Drug with PEG-6000
**DIFFERENTIAL CALORIMETRY STUDIES (DSC)**

Thermograms of the drug (Piroxicam) contained a strong prominent peak at 203.5°C temperature with enthalpy value of 126.6 J/gm, whereas Thermograms of solid dispersion of the drug with carrier PEG-6000 shown peak at 58.7°C with enthalpy value 31 J/gm. Similarly, solid dispersion of the drug with Eudragit RL-100 shown peak at 197.6°C with enthalpy value 101.4 J/gm. From above it is seen peak changes with temperature in prepared solid dispersion product. This confirmed that there is some complexation. From the above study it was concluded that melting point and enthalpy of the drug changed in solid dispersion forms. Drug showed reduced melting point and enthalpy when it is in solid dispersion form. This characteristic referred to formation of an amorphous form of drug.

**FOURIER TRANSFORMS INFRARED SPECTROSCOPY (FTIR)**

FTIR spectrum of Piroxicam, Eudragit RL-100, PEG-6000 and their solid dispersions are shown in Figs. 16–22. From the FTIR study it was found that some of the peaks of the drugs were getting vanished and some new peaks were arisen for solid dispersion form of the drug. The peaks and their characterizations are shown in Table 2.

**Table 2 FTIR of Pure Piroxicam, Eudragit RL-100, PEG-100 and Solid dispersions of Drug with Carriers**

<table>
<thead>
<tr>
<th>Descriptions</th>
<th>Characterizations (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piroxicam</td>
<td>3336.96, 3101.04, 1629.6, 1250.22, 1182.40 and 1039.67</td>
</tr>
<tr>
<td>Eudragit RL-100</td>
<td>1182.4, 3101.04, 1440.87, 1734.06 and 2949.26</td>
</tr>
<tr>
<td>PEG-6000</td>
<td>1064.74, 1240.27, 1614.18 and 2833.68</td>
</tr>
<tr>
<td>PDE (1:5)</td>
<td>3336.96, 3101.04, 1629.90 and 1039.67</td>
</tr>
<tr>
<td>SD Eudragit RL-100 (1:5)</td>
<td>3336.96, 1629.90 and 1182.40</td>
</tr>
<tr>
<td>SD PEG-6000 (1:5)</td>
<td>3336.96, 1629.90 and 1182.40</td>
</tr>
</tbody>
</table>
drug (see Table 2). This was referred to formation of a complex for interaction between the drug and carriers. There was found good complexation in case of drug with Eudragit RL-100 than drug with PEG-6000. Complexation was leading to formation of an amorphous form of drug with Eudragit RL-100 by solid dispersion leading to improve the dissolution rate of drug.

X-RAY DIFFRACTION STUDIES
X-ray diffractogram of Piroxicam, Eudragit RL-100, PEG-6000 and their physical mixture, co-grinded mixture and solid dispersion are shown in Figs. 23–25. The X-ray diffraction of Piroxicam revealed the presence of five well defined Bragg reflections on the 20 scale at different Bragg angles of 9°, 18°, and 27°. This suggests in cases of Piroxicam the extent of crystallinity was less, but with a higher intensity. The X-ray diffractogram of mixture of Piroxicam and PEG-6000 in 1:5 ratio revealed the presence of four prominent reflections at Bragg angles of 9°, 17°, 22°, and 27°. The extent of crystallinity in this case was found increased due to presence of PEG-6000. The X-ray diffractogram of formulation containing Piroxicam and Eudragit RL-100 in 1:5 ratio revealed the presence of three well defined Bragg reflections on the 20 scale at different Bragg angles 9°, 17°, and 27°. At this time the extent of crystallinity was less in comparison to that of solid dispersion of Piroxicam and PEG-6000. This indicates due to solid dispersion technique the extent of crystallinity decreased and probably due to this solubility of insoluble drug Piroxicam may increase.

SUMMARY AND CONCLUSION
The study was performed to improve the dissolution characteristic of Piroxicam, a poorly soluble drug using Eudragit RL-100 and PEG-6000 as carriers. Solid dispersion of the drug and carriers were prepared at various ratios like 1:1, 1:3, and 1:5 w/w. Physical mixtures and co-grinded mixtures were also prepared for comparison. The drug content was estimated in prepared solid-dispersion and it was found to be uniform.

Dissolution studies were performed for pure drug, physical mixture, co-grinded mixture, and solid dispersions in 0.1N HCl media using USP-dissolution apparatus type-2 with paddle stirrer. From the dissolution data it was shown that all solid mixtures gave faster dissolution when compared to pure drug and physical mixture.

From FTIR study using SCHIMADZU apparatus for scanning of solid dispersions of drug with carriers (Eudragit RL-100 and PEG-6000), it was noticed that there was no interaction between the drug and carriers, and complexation occurred. Solid systems for both the carriers were having ratios 1:1, 1:3, and 1:5 w/w – among them 1:5 ratio showed better complexation than other two. Solid system of drug (Piroxicam) with Eudragit RL-100 in 1:5 ratios showed maximum number of peaks of drug than solid system of the drug with PEG-6000. The characteristic peaks of Piroxicam, carriers (Eudragit RL-100 and PEG-6000), and solid dispersions is presented in Table 2.

X-ray diffraction of pure drug and solid dispersions of drug with Eudragit RL-100 and PEG-6000 were carried out, which ensured the amorphous nature of the drug that provides better dissolution rate.

DSC (differential scanning calorimetry) study was performed for pure drug and solid dispersions 1:5 ratio using drug and carriers Eudragit RL-100 and PEG-6000. From the data it was shown that physicochemical properties such as melting point (m.p.) and enthalpy of drug decreased in solid dispersion system. The decrease in melting point and
enthalpy was due to presence of polymer which affected the physicochemical properties of drug. The increase in dissolution rate of solid dispersion system may be due to reduction in particle size, lower melting point, enthalpy of fusion ($\Delta H_f$), and amorphous nature of the drug.

In conclusion, the study showed that Eudragit RL-100 and PEG-6000 could be used as potential carriers for enhancement of dissolution rate of PIROXICAM.

REFERENCES


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