Enhancement of Solubility and Dissolution Rate of Poorly Water Soluble Drug using Cosolvency and Solid Dispersion Techniques

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ABSTRACT: The low aqueous solubility of celecoxib (CB) and thus its low bioavailability is a problem. Thus, it is suggested to improve the solubility using cosolvency and solid dispersions techniques. Pure CB has solubility of 6.26±0.23µg/ml in water but increased solubility of CB was observed with increasing concentration of cosolvents like PEG 400, ethanol and propylene glycol. Highest solubility (791.06±15.57mg/ml) was observed with cosolvency technique containing the mixture of composition 10:80:10%v/v of water: PEG 400: ethanol. SDs with different polymers like PVP, PEG were prepared and subjected to physicochemical characterization using Fourier-transform infrared (FTIR) spectroscopy, X-ray diffractometry (XRD), differential scanning calorimetry (DSC), solubility and dissolution studies. These studies reveals that CB exists mainly in amorphous form in prepared solid dispersions of PVP, PEG4000 and PEG6000 further it can also be confirmed by solubility and dissolution rate studies. Solid dispersions of PV5 and PV9 have shown highest saturation solubility and dissolution rate.

KEY WORDS: celecoxib, cosolvency, solid dispersions, solubility, dissolution.

Introduction

Poor aqueous solubility is a common concern in the pharmaceutical sciences, and there are several established methods reported for increasing the equilibrium solubility of non-polar drugs in aqueous vehicles (Sweetana and Akers 1996, Myrdal et al., 1999). Cosolvency, the addition of water miscible solvents to an aqueous system is one of the most powerful and most popular of these.

Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility while their hydrophobic hydrocarbon regions interfere with water hydrogen bonding network, reducing the overall intermolecular attraction of water, by disrupting waters self-association. Cosolvents reduce the ability of water to squeeze out non-polar, hydrophobic compounds thus increasing solubility. A different perspective is that by simply making the polar water environment more non-polar like the solute, cosolvents facilitate solubilization. Cosolvents are organic compounds that are substantially miscible with water. Cosolvents have small hydrocarbon regions that are nonpolar, do not interact strongly with water, and can reduce the ability of the aqueous system to squeeze out non-polar solutes.

The increase in dissolution rate from solid dispersions can be attributed to one or a combination of the following factors, a reduction of particle size of the drug, solubilizing effect on the drug by the water soluble carrier, enhancement of the wettability and dispersibility of the drug by the carrier material, and the possible formation of a metastable dispersion that has a greater solubility resulting in a faster dissolution rate (Duncan and Craig 2002, Swarbrick 1990, Shargel 1993). Among the popular carriers used in the formation of solid dispersion are polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP), both polymers are freely soluble in water and are available in various molecular weights. The molecular size of both polymers favors the formation of interstitial solid solutions (Van den Mooter et al., 1998).

Celecoxib (CB) was the first specific inhibitor of cyclooxygenase-2 (COX-2) approved by the US FDA in 1998. This clinical introduction of CB has been the result of the important discovery of the COX isoenzymes and the subsequent search for molecules effective in selectively inhibiting COX-2 with little or no effect on COX-1. The major clinical goal was to produce a non-steroidal anti-inflammatory drug (NSAID) that had little or no effect on the gastrointestinal (GI) tract and kidney (Davies et al., 2000), CB is used in the treatment of rheumatoid arthritis, osteoarthritis, and for the management of the pain of these conditions (Simon et al., 1998, Hubbard et al., 1996, Hubbard et al., 1996). Since the pKa of CB is 11.1, the solubility of the CB is also likely to be low at physiological pH (Paulson et al., 2001). Because of its poor water solubility, the oral bioavailability is between 22% and 40% (FitzGerald and Patrono 2001). Thus, it has been selected as model drug to enhance the solubility and dissolution rate thereby to improve its overall oral bioavailability.
Materials and Methods

Materials

Celecoxib (CB) was a gift from Dr. Reddy’s laboratories Ltd, Hyderabad, India. Propylene glycol and Polyethylene glycol 400 were procured from Qualigens (India), Polyethylene glycol (PEG) 4000 and 6000, and Polyvinyl Pyrrolidone (PVP) were purchased from Sd Fine Chemicals (India), Ethanol was purchased from Merck (India). All other chemicals used were of analytical grade. Water used was of double distilled quality.

Determination of saturation solubility of CB in water and water cosolvent media

Solubility separately in water and various volume fractions of water: PEG 400, water: Ethanol, water: Propylene glycol (at ratios 0.1-1.0), and solubility at various percentages [shown in Fig 1-b] of water: PEG 400: ethanol were determined by adding an excess amount of CB to respective solvent media in screw capped vials and maintained at room temp for 24 hr with continuous shaking. The samples were centrifuged after 24 hr and filtered (through 0.45µ membrane filters) the drug content in the filtrate was determined using UV-Vis spectrophotometer (Elico India) at 250 nm.

Solid dispersions

Preparation of solid dispersions

The solid dispersions were prepared using solvent evaporation method. These were prepared with drug: polymer ratios of 1:1, 1:5, and 1:9 w/w. After addition of CB and polymers at various ratios to common solvent the mixtures were homogenized for 5 min. The solvent was removed using rota evaporator (Heidolph Germany) and dried at room temperature, and then samples were pulverized using a mortar and pestle, passed through 150µ(#100 mesh ASTM sieve). Physical mixtures were prepared by light trituration in mortar by taking the required amounts of CB and polymer.

Characterization of solid dispersions of CB

Determination of saturation solubility of CB from solid dispersions

Saturation solubility for prepared solid dispersions was determined as per the procedure described in section 2.2.

FTIR studies

FTIR spectra for CB, physical mixtures and solid dispersions were obtained on Perkin-Elmer FTIR spectrophotometer. Samples were prepared in KBr discs. The scanning range was 4000-400 cm⁻¹ and the resolution was 4.0 cm⁻¹.

XRD studies

XRD patterns for CB, physical mixtures and solid dispersions were obtained using a Siemens D-5000(Germany) with CuKa radiation and scanned at a rate of 2° min⁻¹ over the 20 range of 2° to 70° (λ=1.5406).

DSC studies

DSC studies was performed on a Mettler Toledo DSC 821. Samples (CB, physical mixtures and solid dispersions) were heated in hermatically sealed pans with a heating rate of 10 degrees min⁻¹ under nitrogen atmosphere (gas flow rate 50 ml min⁻¹).

Dissolution studies

The dissolution study was performed using USP-II apparatus, the dissolution medium consisted of 900 ml of phosphate buffer pH 6.8 + 0.25% of sodium lauryl sulphate and the temperature was maintained at 37±1°C at 100 rpm. Samples were filled into capsules by placing 100 mg of CB or its equivalent in PM or SD and dropped into dissolution medium using sinkers. Samples of 5 ml was withdrawn at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered through 0.45µ membrane filter and, amount released was determined spectrophotometrically at 250 nm. CB concentration was calculated and expressed as percentage of CB dissolved.

Results and discussion

Solubility studies

Solubility of CB in water cosolvent media

Solubility in water cosolvent media shows the exponential increase in solubility of CB with increasing concentration of cosolvents, PEG 400, ethanol and propylene glycol (Fig 1-a). The less polar the cosolvent the more effective it is in disrupting hydrogen bonding interaction in water molecules. This in turn reduces the ability of the newly formed solvent (aqueous-cosolvent mixture) to squeeze out
non-polar solutes. As a result, non-polar drugs such as CB can be solubilized most efficiently by PEG 400 and ethanol. Solubility of CB in the mixtures of water, PEG 400 and ethanol is shown in (Fig. 1-b). Increase in CB solubility with increasing percentage of PEG 400 in (water: PEG 400: ethanol) mixture was observed. Highest solubility was observed in the mixture with a composition of 10:80:10 % of water: PEG 400: ethanol.

![Graph showing solubility of Celecoxib](image1.png)

**Fig. 1** Saturation solubility of CB in (a) PEG 400, Ethanol and Propylene glycol (b) Mixture of Water: PEG 400: Ethanol.
Saturation solubility studies from CB solid dispersions

The effect of different carriers on the aqueous solubility of CB is shown in Table 1. The solubility of CB was highest in the presence of PVP (~50 µg/ml) as polymer compared with PEG 4000, and PEG 6000.

FTIR studies

FTIR spectra (Fig.2) was employed to study the interaction in solid dispersions and physical mixtures, between CB and carriers. CB shows the N-H (primary sulphonamides) stretching vibration at 3340-3235 cm⁻¹ and this region of interest showed the evidence of the interaction between CB and carriers via intermolecular hydrogen bonding between NH₂ of CB, C=O group of PVP moiety and with NH₂ group of CB, OH groups of polyethylene glycols.

The most distinct peak in the IR spectrum of PVP was the stretching vibration of the carbonyl group that typically appears around 1715 cm⁻¹ since the carbonyl group is part of a five membered heterocyclic ring with a tertiary amide, the peak for carbonyl stretching appeared around 1654 cm⁻¹. This band is especially sharp, because of the dipolar nature of the N-C=O group. Tertiary amides tend to be hygroscopic, hence absorb moisture resulting in another broad band around 3448 cm⁻¹ that appeared in the IR spectrum of PVP. A very distinctive peak for PEGs was a broad band around 3432 cm⁻¹ that represents the stretching vibration for the OH groups.

An intermolecular hydrogen bonding was suspected, between the hydrogen of NH₂ group of CB and the carbonyl group of PVP. Careful examination of the IR spectrum of the PM and SD of CB revealed insignificant shifts in peaks in the IR spectra for the compounds. It was observed that there was no interaction between the two compounds by FTIR studies.

XRD studies

X-ray diffraction studies have shown that CB is in amorphous form in all forms of solid dispersions. The XRD patterns of CB, physical mixtures and solid dispersions were shown in Fig-3. A diffraction spectrum of pure CB shows that the CB is crystalline indicated by characteristic peaks at 2θ 5°, 11°, 15°, 16°, 21°. In all types of solid dispersions decreased peak intensities were observed when compared with pure CB. Decreased intensity of crystalline peak of CB in solid dispersions indicates its conversions to an amorphous form during the preparation of solid dispersions by the solvent evaporation method.

### Table 1. Saturation solubility of CB, Physical mixtures (PM) and solid dispersions (SD)

<table>
<thead>
<tr>
<th>Samples</th>
<th>CB Code</th>
<th>CB Concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>PVP</td>
<td>09.57±1.22</td>
</tr>
<tr>
<td>SD(1:1)</td>
<td>PV1</td>
<td>41.41±1.76</td>
</tr>
<tr>
<td>SD(1:5)</td>
<td>PV5</td>
<td>50.23±2.62</td>
</tr>
<tr>
<td>SD(1:9)</td>
<td>PV9</td>
<td>52.10±4.57</td>
</tr>
<tr>
<td>PM</td>
<td>P4PM</td>
<td>07.80±0.36</td>
</tr>
<tr>
<td>SD(1:1)</td>
<td>P41</td>
<td>12.50±0.42</td>
</tr>
<tr>
<td>SD(1:5)</td>
<td>P45</td>
<td>37.10±2.12</td>
</tr>
<tr>
<td>SD(1:9)</td>
<td>P49</td>
<td>39.10±0.31</td>
</tr>
<tr>
<td>PM</td>
<td>P6PM</td>
<td>09.24±0.42</td>
</tr>
<tr>
<td>SD(1:1)</td>
<td>P61</td>
<td>19.50±5.21</td>
</tr>
<tr>
<td>SD(1:5)</td>
<td>P65</td>
<td>36.37±2.22</td>
</tr>
<tr>
<td>SD(1:9)</td>
<td>P69</td>
<td>47.35±8.15</td>
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</table>
DSC studies
DSC thermograms of CB, physical mixtures and solid dispersions were shown in Fig-4. CB shown a melting endotherm at temperature 163.32°C. The endothermic peak of CB in SD with PEGs was shifted from higher temperature to lower indicating formation of eutectic mixture. And endothermic peak was absent in SDs with PVP, CB endothermic peak was shifted or absent in all the XRD amorphous solid dispersions, as expected.

Dissolution studies
Effects of different carriers on the dissolution rate of CB from solid dispersions were studied. Fig.5a-c compares the percentage of CB dissolved from PM,SDs containing the
different proportions of three different carriers in the medium. Highest dissolution rate was observed from the SDs containing PVP as a carrier, followed by SDs prepared with PEG 4000 and PEG 6000 (p<0.05). No significant difference was observed between the dissolution of CB from its PM. Particle size reduction and reduced agglomeration may be responsible for increased surface area exposed to the dissolution medium, it has been classically considered to be a result of eutectic or solid solution formation. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition the carriers used for solid dispersions may have some wetting properties; hence it is reasonable to suggest that improved wetting may lead to reduced agglomeration and hence increased surface area.

The dissolution studies of CB from the solid dispersions prepared with PEG 4000 and PEG 6000 revealed that carrier ratio has least effect in increasing dissolution rate.

![DSC Thermograms](image)

**Fig 4.** DSC Thermograms of (a) CB (b) P4PM (c) P45 (d) P6PM (e) P65 (f) PVPM (g) PV5.
Conclusion

It can be concluded from XRD and DSC studies that CB exists mainly in amorphous form in prepared solid dispersions of PVP, PEG. Further this can also be confirmed by solubility and dissolution rate studies. The solid dispersions containing PV5 and PV9 have shown highest saturation solubility (~52µg/ml) and dissolution rate (~98%). When compared with pure CB this was 8-9 fold increase in solubility and 5 fold increase in dissolution rate.

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References


