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, hydophobic 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 wettablility 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.

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