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ORIGINAL ARTICLE

Physicochemical characterization and *in vitro* dissolution studies of solid dispersions of ketoprofen with PVP K30 and D-mannitol

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Abstract Aim of the present study was to improve the solubility and dissolution rate of poorly water soluble, BCS class-II drug Ketoprofen (KETO) by solid-dispersion approach. Solid dispersions were prepared by using polyvinylpyrrolidone K30 (PVP K30) and D-mannitol in different drugs to carrier ratios. Dispersions with PVP K30 were prepared by kneading and solvent evaporation techniques, whereas solid dispersions containing D-mannitol were prepared by kneading and melting techniques. These formulations were characterized in the liquid state by phase-solubility studies and in the solid state by Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) spectroscopy, X-ray diffraction (XRD) and Scanning Electron Microscopy (SEM). The aqueous solubility of KETO was favored by the presence of both carriers. The negative values of Gibbs free energy illustrate the spontaneous transfer from pure water to the aqueous polymer environment. Solid state characterization indicated KETO was present as fine particles in D-mannitol solid dispersions and entrapped in carrier matrix of PVP K30 solid dispersions. In contrast to the very slow dissolution rate of pure KETO, dispersions of drug in carriers considerably improved the dissolution rate. This can be attributed to increased wettability and dispersibility, as well as decreased crystallinity and increase in amorphous fraction of drug. Solid dispersions prepared with PVP K30 showed the highest improvement in dissolution rate of KETO. Even physical mixtures of KETO prepared with both carriers also showed better dissolution profiles than those of pure KETO.

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1. Introduction

Poorly water-soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability (Amidon et al., 1995; Leuner and Dressman, 2000). Nearly 40% of the new chemical entities currently being discovered are poorly water-soluble drugs (Lipinski, 2002; Hu

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et al., 2004). Based upon their permeability characteristics, the Biopharmaceutical Classification System (BCS) categorizes such drugs into two major classes, viz. Class II and IV (Amidon et al., 1995; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf). The BCS class II drugs encompass poorly water-soluble entities with high permeability. Attempts to enhance drug solubility of these therapeutic agents correlate well with enhancement in their bioavailability (Amidon et al., 1995; Leuner and Dressman, 2000; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf). Most formulation strategies for such drugs are targeted at enhancing their dissolution rate and/or solubility by achieving their fine dispersion at absorption level (Leuner and Dressman, 2000; Wyatt, 1999; Craig, 1993). This can be attained by formulating supersaturated systems (i.e., solid dispersion) of the drug employing diverse types of carriers, ranging widely from water-soluble to amphiphilic to lipid-soluble ones (Leuner and Dressman, 2000; Habib, 2001; Serajuddin, 1999; Charman, 2000). Solid dispersion is a group of solid product consisting, generally, a hydrophobic drug and hydrophilic matrix. This approach is useful for the improvement of solubility of poorly soluble drugs.

Ketoprofen is Non-Steroidal Anti-Inflammatory Drug (NSAID) of propionic acid class having analgesic and anti pyretic effects. In BCS, it is categorized in Class II (http://www.tsrlinc.com/resources/services/). Solid-dispersion strategy has been experimented for KETO, and various carriers have been tested (Margarit et al., 1994; Roger and Anderson, 1982; Sheen et al., 1995; Takayama et al., 1982). Here authors have formulated solid dispersions of KETO with some more carriers (i.e., PVP K30 and D-mannitol) by various methods with the objective to improve the solubility of the same.

2. Materials and methods

2.1. Materials

For preparation of solid dispersions the following materials were used: Ketoprofen (Gift sample from Alembic Pvt. Ltd., India); polyvinylpyrrolidone K30 (Gift sample from Sun Pharmaceutical Industries, India): D-(-) Mannitol Extra pure (Loba Chemie Indoaustranal Co., India). Analytical grade of solvents were used.

2.2. Phase solubility studies

Phase-solubility studies were carried out by adding excess of drug (60 mg) in 25 ml of aqueous solution of different (5%, 10%, 15% and 20%) PVP or D-mannitol concentrations. The suspensions were continuously stirred on an electromagnetic stirrer with a hot plate (Remi, India) at 37 °C and 300 rpm for 48 h (this duration was previously tested to be sufficient to reach equilibrium). The suspensions were filtered through a 0.22 μm nylon membrane filter. The filtrates were suitably diluted and analyzed, spectrophotometrically (UV-1700, UV/Vis spectrophotometer, Shimadzu, Japan), for the dissolved drug at 259 nm. All assays were performed in triplicate.

The Gibbs free energy of transfer (ΔG^0_{tr}) of KETO from pure water to the aqueous solution of carrier was calculated as follows:

$$\Delta G^0_{tr} = -2.303RT \log S_0/S_S$$

where S_0/S_S is the ratio of molar solubility of KETO in aqueous solutions of carrier to that of the same medium without carrier.

1:1 complex apparent stability constant (K_a) was determined as follows:

$$K_a = \frac{\text{Slope}}{\text{Intercept}(1 - \text{Slope})}$$

where slope and intercept were obtained from the graph of %w/v of ketoprofen vs. aqueous concentration of carrier (PVP K30 and D-mannitol) in %w/v.

2.3. Preparation of solid dispersion

Solid dispersions were prepared by three different methods and were compared with the drug carrier physical mixture and pure KETO.

2.3.1. Melting method

Three solid-dispersion preparations containing different weight ratios of KETO in D-mannitol (1:1, 1:3, 1:5, and denoted as MMDM 1:1, 1:3, 1:5, respectively) were prepared by the melting method. KETO was added to the melted D-mannitol at 168 °C, and the resulting homogeneous preparation was rapidly cooled in a freezing mixture of ice and sodium chloride and stored in a desiccator for 24 h. Subsequently, the dispersion was ground in a mortar and sieved through 60# sieve. The resulted product was stored in a desiccator until further evaluation.

2.3.2. Solvent evaporation method

Solid dispersions of KETO in PVP K30 containing different weight ratios (1:1, 1:3, 1:5 and denoted as SMPVP 1:1, 1:3, 1:5, respectively) were prepared by the solvent evaporation method as follows. To a solution of weighed quantity of KETO in a minimum amount of ethanol, the appropriate amount of PVP K30 was added. The resulting mixture was stirred for 1 h and evaporated at a temperature of 45–50 °C on water bath until nearly dry and then stored in a desiccator over anhydrous $CaCl_2$, to constant weight. The evaporated product was ground in a mortar and passed through a sieve 60# and stored in a desiccator until further evaluation.

2.3.3. Kneading method

Solid Dispersions of KETO in PVP K30 in different weight ratios (1:1, 1:3, 1:5 and denoted as KMPVP 1:1, 1:3, 1:5, respectively) and D-mannitol in different weight ratios (1:1, 1:3, 1:5 and denoted as KMDM 1:1, 1:3, 1:5, respectively) were prepared by the kneading method as follows. A mixture of PVP K30 and KETO was wetted with water and kneaded thoroughly for 30 min in a glass mortar. The paste formed was dried for 24 h. Dried powder was passed through 60# sieve and stored in a desiccator until further evaluation.

2.3.4. Physical mixtures

Physical mixtures having the same weight ratios were prepared by thoroughly mixing appropriate amounts of KETO and PVP