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Full Length Article

Preparation and characterization of rilpivirine solid dispersions with the application of enhanced solubility and dissolution rate

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ABSTRACT

Rilpivirine (RPV) is a pharmaceutical drug used for the treatment of HIV infection. The drug is characterized with poor aqueous solubility and dissolution rate leading to low bioavailability of the drug. Hence, there is a need for the improvement of the solubility and dissolution of such drugs. In this exertion, enhancement of the solubility and dissolution of the practically water insoluble drug rilpivirine was achieved by solid dispersion (SD) preparation using solvent evaporation method which eventually leads to bioavailability enhancement. SD's were formed using Kollidon VA 64 which is a water-soluble copolymer and varying copolymer ratio to Avicel PH-101, Gelucire 50/13 and lecithin soya. Solubility studies were carried out to establish the solubility-enhancing property of the SD's. To support solubility analysis results, powder dissolution studies were carried out. The SD's were characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, X-ray powder diffraction studies, scanning electron microscopy. It was found that the SD's formed showed the absence of crystalline nature of the drug and its conversion to amorphous state. The solubility and dissolution of the rilpivirine SD's were enhanced. There is a 14.9 fold increase in solubility for Drug: Kollidan VA 64: Gelucire 50/13 (1:4:1). For Drug: Kollidan VA 64 (1:5), Drug: Kollidan VA 64: Lecithin soya (1:4:1) and Drug: Kollidan VA 64: Avicel PH-101 (1:4:1) it was 5.9, 5.4 and 4.2 respectively. In-vitro drug release kinetics was investigated. This study demonstrates the use of solvent evaporation method for the preparation of SD'S in solubility and dissolution enhancement.

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1. Introduction

Rilpivirine, 4-{[4-({4-[(E)-2-cyanovinyl]-2, 6-dimethylphenyl} amino) pyrimidin-2-yl] amino} benzonitrile is a pharmaceutical drug used for the treatment of HIV infection. It is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with higher potency, longer half-life and reduced side-effect profile compared with older NNRTIs, such as efavirenz (Stellbrink, 2007; Goebel et al., 2006). Although rilpivirine has gained acceptance in the treatment of HIV infection, it is characterized with poor solubility which limits its absorption and dissolution rate which delays onset of action (Baert et al., 2009; Sharma and Garg, 2010). The chemical structure of rilpivirine is shown in Fig. 1.

According to the Biopharmaceutical Classification System (BCS), most of the drugs exhibiting insolubility belong to BCS class II. This class includes drugs having low water solubility with high membrane permeability. For this reason dissolution will be the rate-limiting step in drug absorption from the oral solid dosage forms of this class (Amidon et al., 1995). Current statistics report that about 40% of new chemical entities (NCEs) are known to belong to the biopharmaceutics classification systems (BCS) class II type of molecules with poor solubility and high permeability properties (Stegemann et al., 2007; Amidon et al., 1995). Rilpivirine is classified as a BCS class II compound (Anita, 2012). Different solubility and dissolution enhancement techniques are applied such as inclusion complexation (Veiga et al., 1996), drug micronization in to amorphous form (Hancock and Zografi, 1997), prodrug formation (Rautio et al., 2008) and solid dispersion (Porter et al., 2008; Vasconcelos et al., 2007; Chiou and Riegelman, 1971; Serajuddin, 1999; Leuner and Dressman, 2000). Among these methods, solid dispersion technique is most frequently used.

Solvent evaporation method involves preparation of a solution containing both matrix material and drug, and the removal of the solvent resulting in the formation of the solid mass. Nature of the solvent and the rate of evaporation of the solvent are the critical factors which can affect the formed mass (Xie et al., 2009). The most important advantage of this method is that thermal decomposition of the drugs can be avoided as low temperature is required for the evaporation of the organic solvents. Preparation of solid dispersions using solvent evaporation method has been utilized successfully for the improvement of dissolution rate and stability of SDs of poor aqueous soluble drugs (Leuner and Dressman, 2000; Patel and Patel, 2006; Sethia and Squillante, 2004; Jahan, 2011). In the present study Kollidon VA 64 which is a water soluble copolymer is used as matrix material and the solvent system constitutes methanol and ethanol in the ratio 1:1.

The aim of this work was to improve the aqueous solubility and dissolution of rilpivirine using solid dispersion technique using hydrophilic carrier Kollidon VA 64. Powder X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) were used to characterize the solid-state properties of rilpivirine, the physical mixture and solid dispersions. The aqueous solubility and dissolution behaviour of rilpivirine SDs were evaluated further. Surface morphology study was carried out using scanning electron microscopy (SEM).

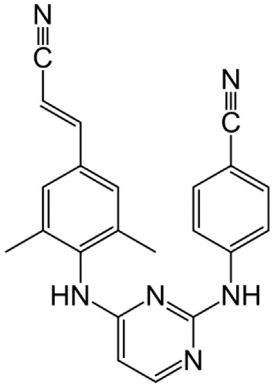

Fig. 1 – Chemical structure of Rilpivirine.

2. Materials and methods

2.1. Materials

Rilpivrine (RPV) was a gift from PharmaTrain (Hyderabad, India). Kollidon VA 64 was procured from BASF (Germany), Soya lecithin was from VWR International Ltd (Poole, England), Avicel PH-101 was from Sigma–Aldrich (Saint Louis, USA), Gelucire 50/13 was provided by Gattefosse (Cedex, France), Ethanol Absolute 99.9% was from Commercial Alcohols (Brampton, Canada) and methanol HPLC grade (merck). All the chemicals used were analytical reagent grade and used without further purification.

2.2. Methods

2.2.1. Preparation of physical mixture

Physical mixtures (PMs) of RPV in the ratio RPV: Kollidan VA 64 (1:5) (PM1), RPV: Kollidan VA 64: Lecithin soya (1:4:1) (PM2), RPV: Kollidan VA 64: Avicel PH-101 (1:4:1) (PM3) and RPV: Kollidan VA 64: Gelucire 50/13 (1:4:1) (PM4) were prepared by blending them by triturating for about 10 min and sieved through 500 micron mesh sieve.

2.2.2. Preparation of solid dispersion

SDs of RPV was prepared by solvent evaporation method. Prepared PMs of RPV were transferred into a beaker containing ethanol and methanol in the ratio 1:1. The solvent was then evaporated under vacuum (Roots vacuum pump-WZJP70, Hyderabad-india) and the resulting solid dispersions were collected and stored in desiccators until they attained constant weight. The solidified masses were crushed, pulverized and passed through size-60 mesh (Retsch, Verder Scientific India Pvt. – India).

2.2.3. Powder X-ray diffraction (XRD)

The XRD patterns of pure RPV, PMs and all binary systems of RPV with Kollidan VA 64 were recorded using a Bruker D8 advance X-ray diffractometer (Bruker AXS GmbH, Germany)