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ORIGINAL ARTICLE

Enhanced solubility and intestinal absorption of candesartan cilexetil solid dispersions using everted rat intestinal sacs

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KEYWORDS

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Abstract *Objective:* Candesartan cilexetil (CAN) is a poor aqueous soluble compound and a P-glycoprotein (P-gp) efflux pump substrate. These key factors are responsible for its incomplete intestinal absorption.

Methods: In this study, we investigated to enhance the absorption of CAN by improving its solubility and inhibiting intestinal P-gp activity. A phase solubility method was used to evaluate the aqueous solubility of CAN in PVP K30 (0.2–2%). Gibbs free energy (ΔG^{o}_{tr}) values were all negative. Solubility was enhanced by the freeze drying technique. The in vitro dissolution was evaluated using the USP paddle method. The interaction between drug and carrier was evaluated by Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD) and Differential scanning calorimetry (DSC) studies. Naringin was selected as P-gp inhibitor. Absorption studies were performed using the everted gut sac model from rat jejunum. The drug analysis was performed by HPLC.

Results: FTIR spectra revealed no interaction between drug and PVP K30. From XRD and DSC data, CAN was in the amorphous form, which explains the cumulative release of drug from its prepared systems. We noticed an enhancement of CAN absorption by improving its solubility and inhibiting the P-gp activity. The significant results ($p < 0.05$) were obtained for freeze dried solid dispersions in the presence of P-gp inhibitor than without naringin (15 mg/kg) with an absorption enhancement of 8-fold.

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Conclusion: Naringin, a natural flavonoid, has no undesirable side effects. Therefore, it could be employed as an excipient in the form of solid dispersions to increase CAN intestinal absorption and its oral bioavailability.

1. Introduction

Candesartan cilexetil (CAN) is an antihypertensive angiotensin II receptor blocker, is rapidly and completely biaoactivated by ester hydrolysis at the ester link to form the active candesartan during absorption from the gastrointestinal (GI) tract McClellan and Goa, 1998. Oral administration of CAN shows low bioavailability, approximately 15% in humans, due to its low water (pKa 6.0) solubility (Vijaykumar et al., 2009) and efflux by drug resistance pumps in the gastrointestinal tract, limiting the oral absorption (Zhang et al., 2012; Lee et al., 2009; Kamiyama et al., 2010; Zhou et al., 2009). To overcome these problems, a solid dispersion approach can be utilized to increase the permeability (Shaikh and Avachat, 2011) and the dissolution rate of highly lipophilic drugs thereby improving their bioavailability (Arias et al., 1994; Zerrouk et al., 2001; Palmieri et al., 2002; Lee et al., 2005). Usually, solid dispersions are two-component systems in which the drug is incorporated in the hydrophilic carrier. The drug within the hydrophilic carrier may be dispersed molecularly or occur as amorphous components. The improved dissolution of the drug can be attributed to (i) enhanced solubility owing to its amorphous state or nano-particles (Kelvin's law) Yonemochi et al., 1997; Yonemochi et al., 1999; Mura et al., 2002; Dai et al., 2007 (ii) increased surface area of nano particles of the drug for drug dissolution (Kubo and Mizobe, 1997; Purvis et al., 2006) and (iii) improved wetting caused by the hydrophilic carrier (Kawashima et al., 1975; Chow et al., 1995). Among all hydrophilic carriers, Polyvinylpyrrolidone (PVP) is the most often studied hydrophilic polymeric carriers (Janssens et al., 2008; Shah et al., 2009; Gupta et al., 2004).

Interaction of various sartans with PVP K30 was investigated in solution and in solid state. For example, solid dispersions with PVP K30 were found to improve the solubility and enhance the dissolution rate of valsartan, compared with β-CD and hydroxypropyl β-CD inclusion complexes. Freeze-dried valsartan/PVP K30 (1:5 M ratio) solid systems offer rapid dissolution profiles in comparison with the profiles of valsartan and its physical mixture with PVP K30 (Mahapatra et al., 2011). The effect of water-soluble polymers (PEG 4000 or PVP K-90) as a third component on the complexation of irbesartan with β-CD was investigated. The study revealed that the binding and the solubility were enhanced in the presence of the third component (PVP K-90 at 5%) in comparison with the binary system of irbesartan and β-CD (Rajashree et al., 2009).

Intestinal absorption is another key factor for the bioavailability of oral dosage forms (Chillistone and Hardman, 2011). It is well-known that influx and efflux transporters such as P-glycoprotein (P-gp) expressed on the membrane of epithelial intestinal cells have a substantial impact on drug absorption. Influx transporters facilitate drug absorption, whereas efflux transporters prevent the drug absorption (Scherrmann, 2009).

P-gp alters intestinal permeation of hydrophobic compounds by averting the influx into cells and facilitates drug efflux from intestinal cells back into the lumen. Inhibiting P-gp may improve drug absorption across intestinal barriers (Ishikawa et al., 2004; Linardi and Natalini, 2006; Kim, 2002). P-gp inhibitors act as high avidity substrates (e.g. verapamil, quinidine) or block its function by binding to it (e.g. sulfhydryl-substituted purine) (Föger, 2009).

These two key factors (poor water solubility and P-gp efflux pumps) are well known for incomplete absorption of orally administered drugs and thus limit their bioavailability (Streubel et al., 2006; Dahan and Amidon, 2009).

Therefore; still it is a real problem to improve the intestinal absorption and the oral bioavailability of candesartan cilexetil though Nekkanti et al. and Gao et al. reported that the oral bioavailability of candesartan was improved about 1.5-fold and 10-fold by nanosuspension (Nekkanti et al., 2009) and nanoemulsion (Gao et al., 2011) respectively until today. However, no reports showed the use of naringin as a pharmaceutical excipient in the presence of candesartan solid dispersions to increase candesartan intestinal absorption and therefore its oral bioavailability till today.

This study was intended to investigate the influence of the manufacturing process used to prepare glassy materials on the physicochemical properties of the products. Parameters of particular importance were product homogeneity, dissolution, physical stability, and drug/polymer interactions. The following study constraints were applied to allow comparisons to be made between manufacturing techniques. Only one polymer, poly(vinylpyrrolidone) K30 (PVP), was selected for use with all three manufacturing techniques. PVP was selected as it has high aqueous solubility, a high glass transition temperature, is miscible with a range of poorly soluble drugs, and forms hydrogen bonds with certain drugs (Forster et al., 2001). Hydrogen bonding is widely recognized as an important mechanism to increase amorphous stability (Matsumoto and Zografi, 1999). All products were prepared at a drug/PVP ratio of 1:2 (w/w) as this was suitable for processing using all three manufacturing techniques. The poorly soluble compound selected was candesartan cilexetil (Patterson et al., 2005). Therefore, in this study an attempt was made to enhance candesartan cilexetil intestinal absorption by improving its solubility as solid dispersions with hydrophilic carrier (PVP K30) using different pharmaceutical interventions and inhibiting the intestinal efflux transporters, P-gp using naringin. Permeability studies were conducted using the in vitro everted sac technique.

2. Materials and methods

2.1. Materials

Candesartan cilexetil (purity more than 99%, melting temperature = 163 ± 0.5 °C) was kindly donated as a generous gift by Dr. Reddy's Labs, (Hyderabad, India). Polyvinyl pyrrolidone K30 (PVP-K30) was supplied by SD Fine Chem. Ltd., Mumbai, India. Naringin, Na_2HPO_4, KH_2PO_4, NaOH, KCl, citric acid