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Profiling biopharmaceutical deciding properties of absorption of lansoprazole enteric-coated tablets using gastrointestinal simulation technology

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ABSTRACT

The aim of the present study was to correlate *in vitro* properties of drug formulation to its *in vivo* performance, and to elucidate the deciding properties of oral absorption. Gastrointestinal simulation technology (GST) was used to simulate the *in vivo* plasma concentration–time curve and was implemented by GastroPlus™ software. Lansoprazole, a typical BCS class II drug, was chosen as a model drug. Firstly, physicochemical and pharmacokinetic parameters of lansoprazole were determined or collected from literature to construct the model. Validation of the developed model was performed by comparison of the predicted and the experimental plasma concentration data. We found that the predicted curve was in a good agreement with the experimental data. Then, parameter sensitivity analysis (PSA) was performed to find the key parameters of oral absorption. The absorption was particularly sensitive to dose, solubility and particle size for lansoprazole enteric-coated tablets. With a single dose of 30 mg and the solubility of 0.04 mg/ml, the absorption was complete. A good absorption could be achieved with lansoprazole particle radius down to about 25 μm. In summary, GST is a useful tool for profiling biopharmaceutical deciding properties of absorption of lansoprazole enteric-coated tablets and guiding the formulation optimization.

1. Introduction

In recent years, the number of new chemical entities (NCEs) increases steadily due to the advances in high throughput screening methods and the introduction of combinatorial chemistry (Kesisoglou and Wu, 2008). Unfortunately, the methodologies have resulted in candidate NCEs with an increase in molecular mass, lipophilicity and a decrease in aqueous solubility. According to the statistics, about more than 40% of marketed drugs are poorly soluble in water (Lindenberg et al., 2004). Obviously, the poor aqueous solubility restricts oral drug bioavailability and is a barrier for oral drug formulation development. Consequently, during the last years, various kinds of methods have been taken to enhance solubility and/or dissolution rate of insoluble drugs by optimizing the active pharmaceutical ingredient (API) chemical (*e.g.*, salt formation) and physical (*e.g.*, particle size reduction through micronization) properties (Juenemann et al., 2010; Jinno et al., 2006; Kesisoglou and Wu, 2008).

Traditionally, preclinical pharmacokinetics of a drug product is firstly obtained by animal study which is time-, cost-consuming, and then is extrapolated the human with uncertain accuracy. With the development of the computer technology, physiologically based absorption modeling has emerged as an active field for new drug development (Jiang et al., 2011). Gastrointestinal simulation method can replace animal model in part and makes new drug development fast and inexpensive (De Buck et al., 2007a, 2007b; Jones et al., 2006; Kuentz et al., 2006; Parrott and Lavé, 2002). The *in silico* prediction tool which can forecast *in vivo* absorption on the basis of physicochemical and pharmacokinetic properties has received much attention over the recent few years (Agoram et al., 2001; Norris et al., 2000; Okumu et al., 2009; Yokoe et al.,

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2003; Yu et al., 1996). Based on the theory of the BCS (Amidon et al., 1995) and gastrointestinal physiology, a semiphysiological absorption model, Advanced Compartmental Absorption and Transit model (ACAT), was developed for *in silico* prediction. The ACAT model was further improved by taking into account the dissolution rate, pH dependent solubility, controlled release, absorption in the stomach or the colon, metabolism or degradation in the gut or the liver, or changes in surface area, transporter densities, and other regional factors within the gastrointestinal tract (Yu et al., 1996). GastroPlus™ is a commercial software integrated ACAT model, and FDA recommends GastroPlus™ to implement quality by design for optimizing drug formulation and process (Zhang et al., 2011). Physiologically based ACAT model has been successfully applied in clinical candidate selection and pharmacokinetic extrapolation to human (Kesisoglou and Wu, 2008; Neil Parrott and Lave, 2008).

A typical BCS class II drug, lansoprazole, was chosen as a model drug in this study. Lansoprazole is a second-generation proton pump inhibitor with antisecretory and antiulcer activities and is converted to active sulfonamide metabolites in the acidic environment of the parietal cells (Horn, 2000). Due to acid-labile lansoprazole, it is usually administered as enteric-coated formulations to prevent gastric decomposition and to increase the oral bioavailability (Kristl and Vrečer, 2000; Tabatar et al., 1992). We intended to use gastrointestinal simulation technology to simulate the *in vivo* performance of lansoprazole delayed-release tablets based on its physicochemical and pharmacokinetic properties and to find out the deciding parameters which have a key impact on the oral absorption *via* parameter sensitivity analysis (PSA).

2. Theoretical considerations

There are three dimensionless parameters, *i.e.*, dose number (D_o), absorption number (A_n) and dissolution number (D_n) that quantitatively describe the characters of oral drug absorption (Oh DM and Amidon, 1993). The three parameters are the combination of drug physicochemical properties and physiological factors in gastrointestinal tract, and can reflect the basic factors influencing drug absorption.

The dose number (D_o) is calculated using the equation (Eq. (1)):

$$D_o = \frac{M/V_o}{C_s} \quad (1)$$

where M is the drug dose, C_s is the solubility and V_o is the volume needed for dissolving the drug and is usually set with the value 250 ml.

The absorption A_n is a basic variable to predict oral drug absorption and can be expressed as follows:

$$A_n = \frac{P_{eff}}{R} \times T_{si} = \frac{T_{si}}{T_{abs}} \quad (2)$$

where P_{eff} is effective permeability, R is radius of the intestine, T_{si} is the residence time in gastrointestinal tract and T_{abs} is the drug absorption time.

The dissolution number D_n is a parameter that reflects the release rate from the formulation. D_n can be calculated by the equation (Eq. (3)).

$$D_n = \left(\frac{3D}{r^2}\right) \cdot \left(\frac{C_s}{\rho}\right) \cdot T_{si} = \frac{T_{si}}{T_{diss}} \quad (3)$$

where D is the diffusion coefficient, r is the initial radius of the drug particles, C_s is the solubility, ρ is the drug density, T_{si} is the residence time in gastrointestinal tract and T_{diss} is the dissolution time.

3. Materials and methods

3.1. Materials

Raw lansoprazole was purchased from Ningxia Kangya Pharmaceutical Co. Ltd. (China). Lansoprazole commercial enteric coated tablets were purchased from Jinan Wutian Pharmaceutical Co. Ltd. (China). The blank plasma was purchased from Shenyang Shengjing Hospital (China). Triethylamine and phosphoric acid were purchased from Bodi Chemical Company (Tianjin, China). Acetonitrile, methanol and anhydrous ether of chromatographic grade were purchased from Concord Technology Co. Ltd. (Tianjin, China).

3.2. Determination of solubility

To determine the content of lansoprazole and to evaluate the solubility, a HPLC method was used. The HPLC system was equipped with methanol–water–triethylamine–phosphoric acid (700:300:5:1.5, v/v/v/v) as mobile phase, and the flow rate was set at 1.0 ml/min. An ultraviolet absorbance detector was used and operated at 284 nm. 10 μL of the samples were injected into Diamonsil® ODS (5 μm, 4.6 mm × 200 mm) column maintained at 30 °C.

Equilibrium solubility was determined in a series of pH 3.0, 5.0, 7.0, 9.0 and 11.0 buffer media by a "shake-flask" method. Excess amount of lansoprazole was add into the conical flask containing 30 ml of buffer media and shaken at 100 rpm for 48 h at 37 ± 0.5 °C. The withdrawn samples were filtered and diluted properly and assayed by HPLC. Each sample was prepared in triplicate.

3.3. Dissolution tests

Dissolution of enteric coated formulations is performed through a two stage test according to the compendia (The Chinese Pharmacopeia 2010). At first, the dissolution is generally proceeded in 0.1 N hydrochloric acid solution, and then is carried out in pH 6.8 buffer media. The acid test stage confirms the integrity of the enteric coating and the buffer dissolution stage demonstrates the release behavior. Dissolution studies of 30 mg generic lansoprazole enteric coated tablets were carried out in basket apparatus at 37 ± 0.5 °C and rotational speed of 100 r/min. At first, the release condition in 1000 ml hydrochloric acid solution was investigated for 2 h. If the tablets did not disintegrate and the release was less than 10%, then the tablets were transferred into 1000 ml pH 6.8 phosphate buffer solution. Withdrawn samples were taken at 5, 10, 20, 30, 45, 60 min, then filtered, diluted appropriately and determined by UV spectrophotometrically at 284 nm.

3.4. In vivo pharmacokinetic study

The *in vivo* pharmacokinetic study was conducted with ethical permission which was permitted by Ethical Committee in China and was processed in accordance with the guides for human bioavailability and bioequivalence test. The pharmacokinetic study of lansoprazole enteric coated tablets was performed on 18 healthy male volunteers (age range 20–25 years old; height mean 172 cm; Body Mass Index 19–24). Every volunteer administrated 30 mg lansoprazole (two tablets) with a two-week washout period. Blood samples were taken at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7, 9, 12 h after dosing. The plasma was obtained by centrifuging the blood samples at 3500 r min^{-1} for 10 min, and stored at −20 °C.

The lansoprazole plasma concentrations were determined by a validated ultra performance liquid chromatography–dual mass spectrometry (UPLC–MS/MS) method after liquid–liquid extraction by anhydrous ether and dichloromethane (7:3, v/v) with glipizide as internal standard. The chromatographic separations were