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Preparation of lapatinib ditosylate solid dispersions using solvent rotary evaporation and hot melt extrusion for solubility and dissolution enhancement

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ABSTRACT

The objective of this study was to enhance solubility and dissolution of lapatinib (LB) ditosylate (DT) using solid dispersions (SD) prepared by solvent rotary evaporation (SRE) and hot melt extrusion (HME). A series of models based on solubility parameter, the solid-liquid equilibrium equation, and the Flory-Huggins equation were employed to provide insight to data and evaluate drug/polymer interactions. Experimentally, nine SD formulas were prepared and characterized by various analytical techniques including differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), scanning electron microscope (SEM), solubility, and dissolution. It was found that both material attributes (e.g., drug loading and solid state) and process parameters (e.g., extrusion temperature) significantly affected manufacturability and solubility/dissolution behaviors. Among the formulas investigated, Formula #9 containing LB-DT, Soluplus®, and poloxamer 188 at a weight ratio of 1:3:1 was screened as the first ranked one. While comparing production routes, the SDs prepared by SRE showed more amorphicity as well as higher solubility/dissolution. This study provided the insight of introducing theoretical models to guide SD formulation/process development and illustrating the potential of bioavailability enhancement for LB-DT.

1. Introduction

Lapatinib (LB) ditosylate (DT), a potent inhibitor of both ErbB-1 (EGFR) and HER2 (ErbB-2) tyrosine kinases, inhibited the proliferation of cancer cells that exhibited the overexpression of these two growth promoting factors (Nelson and Dolder, 2007; Burris, 2004). The commercial product TYKERB® (API: LB-DT) was developed into a tablet dosage form and approved in the therapy of advanced or metastatic breast cancer. Unfortunately, in spite of its high tumor-specific selectivity, the demonstration of clinical benefits of LB-DT with regards to efficiency and safety was challenging due to poor water solubility and permeability (categorized as a BCS Class IV drug Budha et al., 2012), which further lead to issues such as low bioavailability, large daily dose strength, and unacceptable side effects. Herein, there was interest in improving oral delivery of LB-DT, which might be accomplished via enhancing solubility/dissolution.

In an attempt to improve solubility/dissolution, a wide variety of formulation and chemical approaches were explored, including surfactant/micelle, co-solvency, self-emulsification, complexation, prodrug, salt/ionization/pH control, nanosuspension/nanocrystal, polymorphism, solid dispersion (SD), etc (Yalkowsky, 1999). Moreover, the combination of these approaches even engendered synergistic effects. One representative example was a third generation SD, which utilized surfactant or self-emulsifier as carriers/additives (Vo et al., 2013). In general, the surfactants chosen in this type of SD would influence on maintaining supersaturation, aiding manufacture process, enhancing product stability, etc. Hypothetically, for surfactant/micelle system, non-polar drug molecules were incorporated into the hydrophobic region (core). According to the two-phase (phase separation) model, drug solubility had a linear relationship with surfactant concentration above critical micelle concentration (CMC) (Yalkowsky, 1999). Comparatively, for SD system, dissolution rate enhancement was attributed to several factors such as transforming crystalline state to amorphous, reducing particle size, improving wettability and porosity, preventing particle agglomeration, etc (Vasconcelos et al., 2007). Based on the solid state of drug molecules, SD could be categorized into the

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following subgroups: crystalline SD, micro/nano crystalline SD, amorphous SD, and amorphous solid solution (Shah et al., 2013). The SD may also happen to form mixed systems e.g., coexistence of microcrystalline and amorphous SDs (Okonogi and Puttipipatkhachorn, 2006). In recent years, a synthetic polymer Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) have gained attention on its applicability in third generation SD. Soluplus® contained unique bifunctional features: an appropriate SD carrier and an amphiphilic surfactant for micellization in aqueous solution at all Gastrointestinal (GI) pH ranges (Shamma and Basha, 2013). Previous literature reported that Soluplus® was thermoplastic, amorphous (low glass transition temperature T_g), and inherently suitable for hot melt extrusion (HME) (Yun et al., 2014; Djuris et al., 2013). In addition, Soluplus® is applicable for other industrially scalable operations such as solvent rotary evaporation (SRE), spray drying, and freeze drying (Shamma and Basha, 2013). Furthermore, Linn et al. demonstrated that Soluplus® was an effective intestinal absorption enhancer which facilitated drug permeation in in-vitro (Caco-2 cell monolayers) and in-vivo (beagle dogs) studies (Linn et al., 2012). Zhong et al. also presented the similar finding that higher GI absorption was hypothetically induced by the uptake of intact Soluplus® micelle via pinocytosis and/or the inhibition of P-gp efflux transporter (Zhong et al., 2016). Hence, Soluplus® may simultaneously enhance both solubility/dissolution and permeability. Undoubtedly, these capabilities would be extremely valuable for BCS Class IV drug delivery.

To our knowledge, only a few research studies have been carried out to improve solubility/dissolution of LB free base or LB-DT. Gao et al. prepared core-shell LB-DT nanoparticles to improve the treatment of glioma (Gao et al., 2014). Wang et al. developed a methodology of loading LB together with doxorubicin in block co-polymer micelle for a new combinational therapy (Wang et al., 2014). Song et al. produced LB SD using spray drying and investigated different drug-polymer interactions (i.e., hydrogen bonding, ionic interaction) inside SD (Song et al., 2015). Moreover, Huang et al. developed a process to prepare pure amorphous LB-DT via freeze drying and LB-DT SD via spray drying (Huang and Yang, 2009). Even though, there was still a lack of exploration on its solubility/dissolution enhancement following these strategies. Indeed, further studies would be needed in the field of new formulation and process development. In this study, we introduced theoretical models to evaluate the feasibility of Soluplus® in LB-DT SD from thermodynamic point of view and provide insight to our experimental data. On the other hand, experimentally, we developed SD formulations which were manufacturable using both HME and SRE processes, characterized SDs' physicochemical properties, and examined their solubility/dissolution behaviors. Moreover, using this as a case study, we provided a new and practical strategy of utilizing theoretical models to guide and optimize formulation screening, process selection/development, and data analysis for solid dispersions.

2. Materials and methods

2.1. Materials

LB-DT was purchased from Yangzhou Qinyuan Medical Technology Co (Yangzhou, China). Soluplus® was kindly donated by Shanghai Yunhong Pharmaceutical Excipient Co (Shanghai, China). Poloxamer 188 was purchased from Guangzhou Kafen Biotech Co (Guangzhou, China). All reagents and solvents in this study were of analytical grade and used as is.

2.2. Calculation of the Hansen solubility parameter (SP)

The Hansen SP δ_t is determined by a total of the dispersion parameter δ_d, the polarity parameter δ_p, and the partial parameter associated with hydrogen bonds δ_h, according to the following equations (Eqs. (1)–(4)) (Hansen, 1969)

$$\delta_t = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \tag{1}$$

$$\delta_d = \frac{\sum F_d}{V} \tag{2}$$

$$\delta_p = \frac{\sqrt{\sum F_p^2}}{V} \tag{3}$$

$$\delta_h = \sqrt{\frac{\sum E_h}{V}} \tag{4}$$

where F_d is the dispersion component, F_p is the polar component, E_h is the hydrogen bonding components, and V is the calculated molar volume, all of which can be calculated from a group contribution (GC) method via adding values of different structural groups. In this study, a GC method developed by Just et al. was selected to calculate F_d, F_p, E_h, and V (Just et al., 2013).

2.3. Solubility estimation

Considering Soluplus® as a solvent and approximating drug-polymer system as a solid-liquid solution, the solubility of crystalline LB-DT can be estimated using the solid-liquid equilibrium (SLE) equation (Eq. (5)):

$$\ln x_{drug} = \frac{\Delta H_{fus}}{RT_m}\left(1-\frac{T_m}{T}\right) - \ln \gamma_{drug} \tag{5}$$

where x_{drug} is the mole fraction of solubilized drug, ΔH_{fus} is the heat of melting, γ_{drug} is the activity coefficient, T_m is the melting temperature of drug, T is the temperature at the solid-liquid equilibrium. Both ΔH_{fus} and T_m can be obtained from thermal experiments such as DSC. nseIn addition, γ_{drug} can be estimated using Eq. (6):

$$\ln \gamma_{drug} = \frac{V_{drug}}{RT}\{(\delta_d^{drug}-\bar{\delta}_d)^2 + 0.25[(\delta_p^{drug}-\bar{\delta}_p)^2 + (\delta_h^{drug}-\bar{\delta}_h)^2]\} + \ln\frac{V_{drug}}{\bar{V}} + 1-\frac{V_{drug}}{\bar{V}} \tag{6}$$

In which the mixture molar volume $\bar{V}$ and the mixture solubility parameter $\bar{\delta}$ can be calculated according to the following equations (Eqs. (7)–(9)):

$$\bar{\delta} = \sum_{k=1}^{n} \varphi_k \delta_k \tag{7}$$

$$\varphi_k = \frac{x_k V_k}{\bar{V}} \tag{8}$$

$$\bar{V} = \sum_{k=1}^{n} x_k V_k \tag{9}$$

In which the subscript k stands for the different components in the mixture, ϕ is the volume fraction, x is the mole fraction. In addition, all other parameters required for solubility estimation can be found in Table 1.

2.4. Drug-polymer miscibility estimation

The term "miscibility" refers to the tendency of homogeneous mixing of amorphous drug and amorphous polymer. Based on the Flory-Huggins theory, the free energy of mixing can be described by Eq. (10):

$$\Delta G_{mix} = RT[\varphi \ln \varphi + \frac{1-\varphi}{m}\ln(1-\varphi) + \chi\varphi(1-\varphi)] \tag{10}$$

where ϕ is the volume fraction, m is the ratio of polymer volume to drug volume, and χ is the drug-polymer interaction parameter. Moreover, m and χ can be calculated from Eqs. (11) and (12), respectively:

$$m = \frac{MW_{polymer}/\rho_{polymer}}{MW_{drug}/\rho_{drug}} \tag{11}$$