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Bioavailability and pharmacokinetics of sorafenib suspension, nanoparticles and nanomatrix for oral administration to rat

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ABSTRACT

Sorafenib is slightly absorbed in the gastrointestinal tract due to its poor solubility in water. To improve its absorption, a novel nanoparticulate formulation-nanomatrix was used in the study. The nanomatrix was a system prepared from a porous material Sylysia® 350 and a pH sensitive polymer Eudragit®. The formulations were optimized by orthogonal design ($L_9(3^4)$) and their bioavailability were evaluated in rat, comparing to pH-sensitive Eudragit nanoparticles and suspension of sorafenib. In the formulations, the ratio of sorafenib to Eudragit® S100 was found to be more important determinant of the sorafenib bioavailability than the ratio of sorafenib to Sylysia® 350. As for the bioavailability, the $AUC_{0-36\,h}$ of sorafenib nanomatrix was 13–33 times to that of sorafenib suspension, but only 16.8% to 40.8% that of Eudragit® S100 nanoparticles. This may be resulted from the different drug dispersion degree, release character and bioadhension activity. However, because all the materials used in the nanomatrix formulation are commonly adjuvant, safe, easy to get and cheap, above all, the nanomatrix formulation can solve the stability and scaling up problems in the nanoparticles, it had potential to develop into a product in the future.

1. Introduction

With the development of combinatorial chemistry, high throughput screening and cell based activity assays (Stegemann et al., 2007), more and more new chemical entities (NCE) are developed. However, up to 40% of the NCE in development have been suggested to be 'poorly water-soluble' (Porter et al., 2008). To improve the oral bioavailability of these poorly water-soluble NCE, many strategies have been applied, such as using water soluble polymer (Savolainen et al., 1998), surfactant (Ruddy et al., 1999), micronization (Rasenack et al., 2003), solid dispersion technology (Vasconcelos et al., 2007), lipid-based formulations (Douroumis and Fahr, 2006), nanocrystal technology (Junghanns et al., 2008), self-microemulsifying drug delivery system (SMEDDS) (Lee et al., 2009) and nanoparticulate technology (Merisko-Liversidge and Liversidge, 2008).

Nanoparticles are carriers ranging in size from 10 to 1000 nm, generally smaller than 200 nm. It has been widely used to improve the bioavailability of poorly water-soluble drugs (Merisko-Liversidge and Liversidge, 2008; Jaeghere et al., 2000; El-Shabouri, 2002; Wang et al., 2008). The previous study in our lab embedded cyclosporine A into a serious of pH sensitive nanoparticles, and demonstrated the effectiveness of such approach in terms of oral absorption enhancement (Wang et al., 2004, 2008; Dai et al., 2004).

Although nanoparticles are used to improve the absorption successfully, there are also some obstacles for such formulation to be commercialized. First, the stability of such a system is a challenge. Nanoparticle dispersion is a typical thermodynamically unstable system due to its large specific interfacial area. After a period of storage, particle aggregation often occurs. Mainly two important efforts have been adopted to increase the stability. One technique is lyophilization and the other is adding suspending agents. As for lyophilization, the particle size could increase during the procedure of freeze drying, which may affect the drug pharmacokinetic characteristics (Saez et al., 2000) or the lyophilized nanoparticles may aggregate after some time of storage (Chacón et al., 1999, Dai et al., 2005). In the second method, we had demonstrated the improvement in stability of nanoparticle colloid by adding some suspending agents. Although the relative bioavailability was also bioequivalent to the initial after 18 months storage at 25 °C, it was indeed decreased (nearly 20%) (Wang et al., 2006b). Furthermore, the dosage form was oral solution, which was not so convenient as tablets or capsules.

Another challenge of the nanoparticle colloid system is the possibility in scaling-up, which is an essential process for a marketed product.

Here, we introduce a novel technology, nanomatrix technology to solve these difficulties. We define the nanomatrix as a

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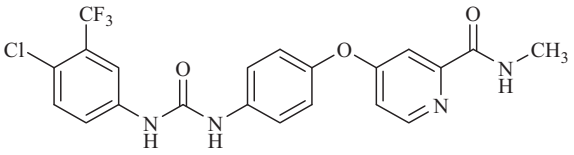

Fig. 1. Chemical structures of sorafenib.

system composed of a matrix material with nano-structure, drug and other excipient. The mesoporous silica particles of Sylysia 350 in this study, with a mean particle size of 3.9 μm and a large number of internal pores about 21 nm, are the typical matrix material with nano-structure. And they provide large specific surface area (300 m^2/g) (Wang et al., 2006a) to support and disperse drug molecules as well as excipient, such as the pH sensitive polymer tested here. Eudragit S100 may disperse drug molecules, prohibit drug crystallization and enhance the bio-adhesion of the system in GI tract. Anyhow, a nanomatrix system seems favorable in terms of drug absorption enhancement.

The drug used in the study was sorafenib. Sorafenib (Fig. 1) is a small molecule that inhibits tumor-cell proliferation and tumor angiogenesis and increases the rate of apoptosis in a wide range of tumor models (Wilhelm et al., 2004; Chang et al., 2007). It has been approved by the FDA for the treatment of patients with advanced renal cell carcinoma in 2005 and unsecretable hepato-carcinoma in 2006. However, sorafenib is poorly soluble in water and its solubility was smaller than the quantitative limit (25 ng/ml in HPLC method) in our previous test in deionized water. To improve its solubility, sorafenib tosylate is used and prepared into tablets (Nexavar, Bayer HealthCare Pharmaceuticals-Onyx Pharmaceuticals). Practically, sorafenib tosylate is also insoluble in aqueous media (PCT, 2008), and its solubility is only 60 μg/ml in water at pH 6. Because of its poor water solubility, sorafenib tosylate is slightly absorbed in the gastrointestinal tract and exhibits a large interindividual variability in pharmacokinetics (Blanchet et al., 2009). Up to now, there are only a few studies on the absorption improvement of sorafenib (PCT, 2008; Liu et al., 2011).

In the present study, sorafenib suspension, nanoparticle colloids and nanomatrix were prepared and their oral absorption was evaluated.

2. Materials and methods

2.1. Materials

Sorafenib was purchased from Wish pharmaceutical Co., Ltd (China). Internal standard megestrol acetate was from Qingdao Ruige Co., Ltd (China). Methanol and acetonitrile were the products of Merck (Germany). Eudragit L100-55, Eudragit L100 and Eudragit S100 were from Evonik (Germany). Sylysia 350 was the gift from Fuji Chem. (Japan). All other chemicals were of analytical grade. Sprague-Dawley (SD) rats were obtained from Animals Center of Peking University Health Science Center. The animal experiment was adhered to the principles of care and use of laboratory animals and was approved by the Institutional Animal Care and Use Committee of Peking University Health Science Center.

2.2. Preparation of sorafenib and sorafenib tosylate suspension

Sorafenib suspension and sorafenib tosylate suspension were prepared by dispersing sorafenib or sorafenib tosylate in 0.9% saline containing 4 mg/ml starch (final concentration of sorafenib was 10 mg/ml) through ultrasonication for 3 min.

2.3. Preparation of sorafenib nanoparticle colloids

Three types of Eudragit (Eudragit L100-55, Eudragit L100 and Eudragit S100) nanoparticles used in this study were prepared by solvent displacement method. Briefly, 37.5 ml ethanol containing 9 mg sorafenib and 187.5 mg Eudragit was injected as soon as possible into 93.8 ml stirring water containing 2 mg/ml Pluornic F_{68} with a 7# needle for bone marrow puncture. Afterward, the mixture was stirred for another 15 min and evaporated to about 30 ml in a 60 °C water bath. The particle size was determined by dynamic light scattering (Malvern Zetasizer Nano-ZS, Malven Instruments, Malven, UK).

2.4. Preparation of sorafenib nanomatrix

The sorafenib nanomatrix was prepared as follows: first, 100 mg sorafenib and prescribed Eudragit S100 were dissolved in 40 ml ethanol. Then prescribed Sylysia 350 was dispersed into the solution under stirring. After ultrasonication for 20 min, the dispersed system was transferred to rotary evaporation to remove the ethanol. The solid product was collected, milled and sieved through 100 mesh. The sieved powder was used for the bioavailability studies.

Totally nine sorafenib nanomatrix formulations were prepared for optimization, which was conducted by an orthogonal design ($L_9(3^4)$, Table 1). The factors include the ratio of sorafenib to Eudragit S100 and the ratio of sorafenib to Sylysia 350. The evaluation index is the area under the concentration–time curve ($AUC_{0-36\,h}$) of different formulations in bioavailability studies.

2.5. Bioavailability studies

The formulations used in this study include: (1) sorafenib suspension and sorafenib tosylate suspension; (2) sorafenib Eudragit nanoparticle colloids; (3) sorafenib nanomatrix formulations. Healthy male Sprague-Dawley rats (weighing 160–190 g) were used and they were fasted overnight with free access to water.

The experiments were done by three times. First, 10 rats were divided into two groups at random (5 each group). One group was administered with a single dose of sorafenib suspension at 100 mg/kg. The other group was given sorafenib tosylate suspension at a single dose 137 mg/kg (including sorafenib 100 mg/kg). Second, 18 rats were divided into three groups at random (6 each group). Each group was administered with a single dose of sorafenib Eudragit nanoparticle colloids at 3 mg/kg, respectively. Third, 45 rats were divided into nine groups at random (5 each group). Each group was administered with a single dose of sorafenib nanomatrix at 15 mg/kg, respectively.

After administration of different formulations to rats by gavage, blood samples were collected from orbital venous into the heparinized tubes at preset time points of 0.5, 1, 2, 4, 8, 12, 24 and 36 h. Blood samples were centrifuged at 3000 rpm for 10 min and the resultant plasma were transferred into capped tubes and stored at −20 °C until analysis.

2.6. HPLC assay of sorafenib in plasma

The concentration of sorafenib in the plasma was determined by HPLC. The Shimadzu LC-10A HPLC analysis system equipped with an ultraviolet detector (SPD-10A) was used. Chromatographic separation was achieved on a reversed phase C18 column (250 mm × 4.6 mm, 5 μm, Phenomenex, USA) maintained at 40 °C with a mobile phase consisted of acetonitrile and water phase (70:30, v/v) at a flow rate of 1.0 ml/min. The water phase contained triethylamine (20 ml/1000 ml) besides distilled water, and