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Parenteral formulation of larotaxel lipid microsphere tackling poor solubility and chemical instability

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ABSTRACT

The purpose of this study was to develop a parenteral larotaxel lipid microsphere (LTX-LM) and evaluate its stability. The preformulation study showed that LTX possessed poor solubility (0.057 μg/mL in aqueous phase) and chemical instability. LM was selected as the drug carrier due to its higher drug-loading capacities, higher physicochemical stability and reduced irritation and toxicity. High speed shear mixing and high-pressure homogenization were employed to prepare the LTX-LM. Particle size distribution (PSD), zeta-potential, drug content and entrapment efficiency (EE) were taken as indexes to optimize formulations. The dissolution studies were performed using a ZRS-8G dissolution apparatus according to the paddle method. Degradation kinetics test, freezing and thawing test and long term stability test were combined to evaluate the physicochemical stability of LTX-LM. From the degradation kinetics results, the shelf lives ($T_{90\%}$) of LTX in LM at 25 and 4 °C (165, 555 days) were about 20 times as long as those in aqueous phase (200, 676 h), which were dramatically prolonged. The activation energies in aqueous solution and in LM calculated from the slopes were 41.93 and 42.25 kJ/mol. And its frequency factors (A) were 4.9×10^3/s and 2.3×10^2/s, respectively. Freezing and thawing test showed the PSD of LTX-LM became larger and wider increasing from 166.9 ± 53.2 nm to 257.4 ± 85.5 nm with more freeze–thaw cycles. From the long term stability test results, all the parameters changes were in qualified range.

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1. Introduction

Larotaxel is a novel semi-synthetic taxane derivative (Fig. 1), prepared as a single diastereoisomer by partial synthesis from 10-deacetyl baccatin III, the major natural taxane extracted from the needles of the European yew trees, *Taxus baccata* (Bissery, 2001). Similar to the two approved taxanes docetaxel and paclitaxel, larotaxel exerts its cytotoxic effect by promoting microtubule assembly and stabilizing microtubule against depolymerisation, ultimately leading to apoptotic cell death by arresting cell cycle in the G2/M phase (Woods et al., 1995; Bissery et al., 2004; Fabbri et al., 2006).

Docetaxel and paclitaxel are substrates for the P-glycoprotein 170 (Pgp) encoded by the multidrug resistance-1 gene. The Pgp that functions as a drug efflux pump is one of the mechanisms conferring resistance. In contrast, LTX has substantially lower affinity for Pgp. Its activity against taxoid-sensitive/resistant and multidrug-resistant tumors has been demonstrated in preclinical studies (Bissery et al., 2004). The compound also can cross the blood–brain barrier with marked antitumor activity proved in nude mice bearing early stage intracranial glioblastomas, which may also be a consequence of its decreased recognition by P-glycoprotein (Kurata et al., 2000; Bissery et al., 2004).

It has been reported that LTX is insoluble in water but lipophilic (Liu et al., 2013), sharing common features with paclitaxel and docetaxel which necessitate the inclusion of surfactant vehicles in commercial formulations. Cremophor EL and polysorbate 80 (Tween 80) have long composed the standard solvent system for paclitaxel and docetaxel, respectively. Larotaxel injection being tested in phase III clinical trials in France also use polysorbate 80 to increase its solubility. However, numbers of pharmacologic and biologic effects related to both of these drug formulation vehicles have been described, including clinically relevant acute hypersensitivity reactions and peripheral neuropathy. And it is hard to avoid the precipitation of the drug during injection and a series of security issues have followed. Additionally, several reports have linked these solvents to alterations in the disposition of intravenously administered solubilized drugs (Albert et al., 2003). The clinical application of LTX was restricted at a large scale by its drawbacks in the physicochemical properties. So far no preparation researches of LTX have been reported in literature and no preparation products have been being commercially available.

Lipid emulsions (LEs) were well known as a source of calories and essential fatty acids for patients and the first prototype formulation was described as Intralipid™ (Weng et al., 2012).

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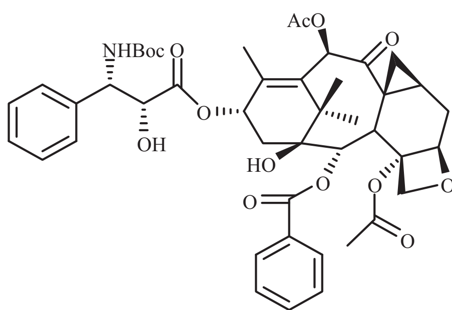

Fig. 1. Structure of larotaxel.

Over the last few decades, great efforts have been devoted to the development of drug-loaded emulsions. LM, firstly put forward by Japanese scholar in the early 1990s, is referred to as lipid emulsions or submicron emulsions with an average diameter of about 200 nm (Manfredi and Chiodo, 1998). LM embraces several potential advantages over other drug carriers such as higher drug-loading capacities, higher physicochemical stability, reduced irritation and toxicity and the possibility of large-scale production (Prankerd and Stella, 1990; Floyd, 1999; Tamilvanan, 2004; Date and Nagarsenker, 2008). The drugs incorporated in LM also showed an increased solubility and improved stability (Smith and Strozyk, 1994; Nasirideen et al., 1998; Strickley, 2004; Date and Nagarsenker, 2008). All these excellent characteristics make LM be an attractive carrier for i.v. administration of LTX.

In our study, a novel larotaxel lipid microsphere was designed and investigated by optimizing the formulations with regard to the drug content, PSD, EE and zeta-potential. Then degradation kinetics test, freezing and thawing test and long term stability test were combined to evaluate the physicochemical stability of LTX-LM.

2. Materials and methods

2.1. Materials

Larotaxel (LTX, purity >99%) was obtained from Shandong Target Drug Research Co. Ltd., Yantai, China). Long chain triglyceride (LCT) was purchased from TieLing BeiYa Pharmaceutical (Co., Tieling, China). Poloxamer188 (Pluronic F68) was purchased from BASFAG (Ludwigshafen, Germany). Lipoid E80, oleic acid, Lipoid S75 and medium chain triglyceride (MCT) were all purchased from Lipoid KG (Ludwigshafen, Germany). Glycerol was purchased from Zhejiang Suichang Glycerol Plant (Zhejiang, China). All other chemicals and reagents were of analytical or chromatographic grade.

2.2. Determination of physicochemical properties

2.2.1. Water and oil solubility

The solubility of LTX in aqueous or nonaqueous solutions was determined by the Higuchi and Connor method (Higuchi and Connors, 1965). In brief, excess amount of LTX was added to the phosphate buffer solution (PBS) with different pH values, distilled water, MCT and LCT in a capped vial. The oversaturated solutions were placed in a shaking air bath (HZQ-C, Dongming Medical Instrument Co., Harbin, China) functioning at 100 rpm and at 25 °C for 72 h to obtain solubility equilibrium. The resultant suspension was filtered through 0.22 μm microporous filter. The filtrate was appropriately diluted for HPLC analysis. All solubility samples were run in duplicate.

2.2.2. Determination of octanol/water partition coefficient

Dissolve moderate larotaxel in high purity analytical grade n-octanol pre-saturated with distilled water and PBS with a pH of 4.80, 6.30, 7.07, 8.07, and 9.78. Then 2 mL of octanol phase was mixed with 7 mL water, and the two phases were mutually saturated by shaking for 48 h in a shaking air bath at 25 °C. Then the solvent system was kept at room temperature for 24 h for phase separation. The LTX concentrations in the two phases were separately monitored by HPLC, and the partition coefficients ($\log P$) at different pH values were calculated from the equation below: where C_0 and C_w represent the concentrations of LTX in n-octanol and water, respectively.

$$\log P = \log \frac{C0}{Cw}$$

2.3. Preparation of LTX-LM

Firstly, LTX was added to the mixture of LCT and MCT in which Lipoid S75 and Lipoid E80 had already been dissolved at 75 °C. The aqueous phase consisting of F68, glycerin and sufficient double-distilled water was also heated to the same temperature. Then the oil phase was added slowly into the aqueous phase with continuous stirring using high speed shear mixing operating at 10,000 rpm for 5 min to get a coarse emulsion. The volume was adjusted to 100 mL with double-distilled water and the pH was adjusted to 5.5 with 0.1 mol/L NaOH or 0.1 mol/L HCL. The coarse emulsion was subjected to high-pressure homogenization at 800 bar for 8 cycles to gain final emulsion. Finally, the emulsion was transferred to vials under nitrogen gas and sterilized by autoclaving at 121 °C for 10 min.

2.4. Characterization of LTX-LM

The particle size distribution was measured by photo correlation spectroscopy (PSC, dynamic light scattering, DLS) with a Nicomp™ 380 particle sizing system (Weng et al., 2012). The Nicomp™ 380 particle sizing system was also utilized to determine the zeta potential by the ELS technique (Liu et al., 2009). Ultracentrifugation method was used to determine the EE of LTX-LM by measuring the concentration of LTX in the dispersion phase (Liu et al., 2007). Drug content was determined with the HPLC method (detailed later in this section). One mL of LTX-LM (1 mg/mL) was collected and transferred into a 50 mL volumetric flask followed by dilution to 50 mL with methanol. The volumetric flask was shaken to obtain the test sample with a concentration of 20 μg/mL. The resultant solution was filtered through 0.22 μm microporous membranes for HPLC analysis.

2.5. HPLC method

LTX concentrations were determined using a RP-HPLC system (Hitachi). The RP-HPLC system was composed of an autosampler (L-7200), four pumps (L-7100), an UV–VIS detector (L-7420), all interfaced with D-7000 HSM software along with an HiQ sil C18 column (250 × 4.5 mm, 5 μm; KYA TECH Corporation, Tokyo, Japan). The mobile phase consisted of water–acetonitrile (65:35, v/v) with the flow rate of 1 mL/min, and the detection wavelength was 230 nm. Prior to injection into the HPLC system, the lipid microsphere or buffer solution was diluted with methanol to the fixed concentration and passed through 0.22 μm microporous membranes.

2.6. Drug release in vitro

The in vitro release behavior of LTX was investigated using a ZRS-8G dissolution apparatus according to the paddle method of Invega Sustenna. Samples equivalent to about 9 mg LTX were directly

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