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Studies on oral absorption of stearic acid SLN by a novel fluorometric method

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Abstract

In this study, the fluorescein isothiocyanate (FITC) labeled otcadecylamine (ODA), otcadecylamine-fluorescein isothiocyanate (ODA-FITC), was synthesized and used as a fluorescence marker to be incorporated into stearic acid solid lipid nanoparticles (SLN) by solvent diffusion method. Approximately 97.9% of added ODA-FITC was incorporated into SLN. Under sink condition, approximately 7% and less than 3% of ODA-FITC leaked from SLN in 24 h, when the ODA-FITC loaded SLNs were dispersed in plasma or phosphate buffered saline (PBS, pH 6.8) containing 0.3 wt% sodium dodecyl sulfate (SDS), respectively. The ODA-FITC loaded SLNs were then subjected to the in vivo transport experiments. The results showed that the transport efficiency of SLN by oral administration was 30%. The SLN could be extensively absorbed, and indicated a linear absorption mechanism in gastrointestinal tract within certain range of concentrations. By the external diversion experiments on lymph, it showed that approximately 77.9% of absorbed SLN was transported into systematic circulation via lymph, which is a major SLN transport pathway in gastrointestinal tract. The rest of absorbed SLN was transported directly into blood, which might be through capillary vessel or intestinal epithelial cell by paracellular pathway. The further experiment demonstrated that the polyethylene glycol monostearate (PEG2000-SA)-modified SLN could also be absorbed in gastrointestinal tract and achieved a prolonged effect in vivo.
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Keywords: Otcadecylamine-fluorescein isothiocyanate; Solid lipid nanoparticles; Oral administration; In vivo research; Lymphatic transportation

1. Introduction

Solid lipid nanoparticles (SLN) are colloidal carriers for controlled drug delivery system followed by the development of emulsions, liposomes, microparticles and nanoparticles based on synthetic polymers [1]. Compared to traditional carriers, the SLN combine the advantages of polymeric nanoparticles and oil/water fat emulsions for drug delivery administration, such as good tolerability [2,3], high oral bioavailability [4] and large-scale production by high pressure homogenization [5].

Solid lipid matrices used as sustained drug delivery have well established for many years. Solid lipid nanoparticles possess a solid lipid matrix for controlled release of drugs. Lots of data showed that, solid lipid nanoparticles might prolong the release of drug in vitro (e.g., prednisolone-loaded) SLN showed a prolonged in vitro release for up to 5 weeks [6], which made it potential to achieve long-term treatment by using solid lipid nanoparticles as drug carrier.

Currently, solid lipid nanoparticles have been used through oral administration, which is aiming at target delivery and enhancing oral bioavailability. Sufficient data implicates that, the bioavailability of poorly water soluble drugs can be improved when these drugs encapsulated in lipid-base vehicles via the peroral route [7].

Nevertheless, as a probably route of administration, the mechanism of oral absorption for SLN still needs to be revealed. The uptake of particles from the gut is governed by many factors, including particle size, concentration, hydrophobicity and surface charge [8]. The main mechanisms of particle material across the intestine are the uptake via Peyer's patches, paracellular pathway or the mix of both pathways [9]. It appears that the major pathway of lipid absorption after oral administration is via Peyer's patches [10].

The main reason for many drugs which exhibit poor oral bioavailability is due to their extensive first-pass metabolism. In order to overcome this problem, intestinal lymphatic transport

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of drugs can be exploited. Transport of such drugs or carriers through the intestinal lymphatics via thoracic lymph duct to systemic circulation joining at the junction of the jugular and left subclavian vein avoids presystemic hepatic metabolism, and as a result, enhances the amount of orally administered drugs reaching into systemic circulation and viscera. In recent years, several immonosuppressant, such as cyclosporine, are selectively absorbed via pathway of lymph and subsequently exert their activities [11]. Therefore, it is important to clarify the mechanisms of uptake of solid lipid nanoparticles via lymph.

In the present study, a new compound named otcadecylamine-fluorescein isothiocyanate (ODA-FITC) was synthesized. The ODA-FITC was then used as a fluorescence marker to incorporate into stearic acid solid lipid nanoparticles (SLN) by solvent diffusion method. The in vitro properties of fluorescence labeled SLN were assessed. By using fluorescence labeled SLN, the transport and elimination of SLN and PEG2000-modified SLN after oral administration in male Sprague–Dawley (SD) rats were investigated against the intravenous administration. Furthermore, the thoracic lymph duct cannulation was used to the study of transport route for SLN via lymph.

2. Materials and methods

2.1. Materials

Stearic acid (SA) was supplied by Shanghai chemical reagent Co. Ltd. (Shanghai, China). Otcadecylamine (ODA, 95%) was purchased from Fluka. Fluorescein isothiocyanate (FITC) was purchased from Zhancheng bioscientific Co. Ltd. (Guangzhou, China). Polyethylene glycol monostearate (PEG2000-SA) was purchased from Tokyo Kasei Kogyo Co. Ltd. (Tokyo, Japan). All other solvents were analytical or chromatographic grade.

2.2. Animals

Male SD rats were obtained from Zhejiang University and housed according to institutional guidelines. The rats were kept in a temperature-controlled environment with a 12-h light/dark cycle and given a standard diet with water ad libitum. Rats were fasted overnight before oral administration. The animal protocol was approved by the Institutional Animal Use and Care Committee at Zhejiang University.

2.3. Synthesis of ODA-FITC

The ODA-FITC was synthesized by the reaction between amino group of ODA and isothiocyanate group of FITC. Seven milligrams of ODA was completely dissolved in 60 ml *N*,*N*-dimethylformamide (DMF) by sonicate treatment (Sonic Purger CQ250, Academy of Shanghai Shipping Electric Instrument). Twenty milligrams of FITC was dissolved in 5 ml DMF. The FITC and ODA solution was then mixed and shaked (HZ-8812S, Hualida Co. Ltd.) in water bath at 50 °C for 48 h. After reaction, the reaction mixture was cooled to room temperature, and 20 ml of distilled water was then added to the mixture to precipitate the ODA-FITC. The precipitate was collected by filtration with 0.45 μm millipore filter and washed twice by 20 ml distilled water. The final product (ODA-FITC) was lyophilized and stored in dark for further use.

^{1}H NMR spectrum was used to analyze synthesized ODA-FITC. The sample was measured at 298 K with 5 wt% $CDCl_3$ solution using a NMR Spectrometer (AC-80, Bruker Biospin, Germany).

2.4. Preparation of ODA-FITC loaded stearic acid SLN by solvent diffusion method in aqueous system

Sixty milligrams of stearic acid and 4.8 mg of ODA-FITC were dissolved in ethanol (6 ml) by sonicating (Sonic Purger CQ250, Academy of Shanghai Shipping Electric Instrument) in water bath. The resultant organic solution was injected into 60 ml of 70 °C distilled water under mechanical agitation (DC-40, Hangzhou Electrical Engineering Instruments, China) with 400 rpm for 5 min. The mixture was then cooled to room temperature to obtain FITC labeled SLN dispersion. The pH of the cooled dispersion was adjusted to 1.2 by adding 0.1 M hydrochloric acid solution to precipitate SLN, and the precipitated SLN was then collected by centrifugation (10,000 rpm, for 10 min, 3k30, SIGMA Labrorzentrifugen GmbH, Germany). The SLN was re-suspended in 3 ml distilled water containing 0.1% poloxamer 188 by probe-type ultrasonic treatment with 20 times (200 W, active every 2 s for a 3 s duration) (JY92-II, Scientz Biotechnology Co. Ltd., China), and used for further in vivo studies.

For preparation of PEG modified ODA-FITC loaded stearic acid SLN, 3.6 mg PEG2000-SA was dissolved in 6 ml ethanol along with 60 mg stearic acid and 4.8 mg ODA-FITC. The other procedures were the same.

2.5. Characterization of ODA-FITC loaded stearic acid SLN

The particle size and zeta potential of ODA-FITC loaded stearic acid SLN were determined by Zetasizer (3000HS, Malvern Instruments Ltd., UK) after the final re-suspensions were diluted 400 times with re-suspension medium. The pH value of the aqueous system with 0.1% Poloxamer 188 was 5.5, and the pH environment of the system remained unchanged after the dilution.

To determine the entrapment efficiency of ODA-FITC in the SLN and PEG modified SLN, the prepared SLN dispersion was centrifuged (25,000 rpm, for 10 min, 3k30, SIGMA Labrorzentrifugen GmbH, Germany), and the fluorescence intensity of supernate was determined by a fluorescence spectrophotometer (F-2500, Hitachi Co., Japan) with an excitation wavelength of 498 nm and an emission wavelength of 514 nm after the supernate filtered by 0.1 μm millipore filter. As a control, 4.8 mg of ODA-FITC was dissolved in the mixture of 6 ml ethanol and 60 ml distilled water. The fluorescence intensity of mixture was determined by a fluorescence spectrophotometer at the same

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