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Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability

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Abstract

An ultrasonic-solvent emulsification technique was adopted to prepare vinpocetine loaded Glyceryl monostearate (GMS) nanodispersions with narrow size distribution. To increase the lipid load the process was conducted at 50 °C, and in order to prepare nanoparticle using an ultrasonic-solvent emulsification technique. The mean particle size and droplet size distribution, drug loading capacity, drug entrapment efficiency (EE%), zeta potential, and long-term physical stability of the SLNs were investigated in detail respectively. Drug release from two sorts of VIN-SLN was studied using a dialysis bag method. A pharmacokinetic study was conducted in male rats after oral administration of 10 mg kg^{-1} VIN in different formulations, it was found that the relative bioavailability of VIN in SLNs was significantly increased compared with that of the VIN solution. The amount of surfactant also had a marked effect on the oral absorption of VIN with SLN formulations. The absorption mechanism of the SLN formulations was also discussed. These results indicated that VIN absorption is enhanced significantly by employing SLN formulations. SLNs offer a new approach to improve the oral bioavailability of poorly soluble drugs.

Keywords: Solid lipid nanoparticles; Glyceryl monostearate; Ultrasonic-solvent emulsification technique; In-vitro; In-vivo

1. Introduction

SLNs have been reported as an alternative drug delivery system to traditional polymeric nanoparticles [1]. A clear advantage of solid lipid nanoparticles (SLNs) over polymeric nanoparticles is the fact that the lipid matrix is made from physiologically tolerated lipid components, which decreases the potential for acute and chronic toxicity [2]. At room temperature the particles are in the solid state [3,4]. SLNs combine the advantages of polymeric nanoparticles, fat emulsions and liposomes [5]. They can be produced on a large industrial scale by high-pressure homogenization [6], with low toxicity potential like emulsions and liposomes, produce sustained release due to their solid matrix, similar to polymeric nanoparticles, and can effectively target specific tissues after parenteral administration [7,8].

The process of solvent-evaporation method is based on the water immiscible solvents [9,10]. Upon transferring a transient oil-in-water emulsion into water, the drug dissolved in the organic solvent solidifies instantly due to diffusion of the organic solvent from the droplets to the continuous phase. But the SLNs prepared by this method always have large particle diameter and wide size distribution. The aim of this study was to investigate the feasibility of preparing glyceryl monostearate nanoparticles with different emulsifiers using ultrasonic-solvent emulsification technique to prepare drug loaded SLNs with particle diameter below 100 nm and low polydispersity.

Vinpocetine (VIN), the chemical structure of which is shown in Fig. 1, has been shown to improve cerebral circulation and metabolism in the treatment of various types of cerebrovascular circulatory disorder, e.g. cerebral infarction (CI), cerebral hemorrhage residual and cerebral arteries cirrhosis, etc. Due to its poor aqueous solubility and extensively metabolized during first pass, its clinical use is greatly restricted by the low bioavailability after oral administration [11] and so there is a need to improve its poor aqueous solubility to increase its oral bioavailability. An oral formulation with a high degree of oral absorption would, therefore, be highly desirable.

In this study, VIN-loaded SLNs were successfully prepared by an ultrasonic-solvent emulsification technique and the physicochemical characteristics of the SLNs were investigated.

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Drug release from the SLNs was studied and compared with the diffusion from a VIN solution using a dialysis bag method. The oral bioavailability of VIN in SLNs investigates the absorption enhancement of SLNs for poorly soluble drugs. In addition, the effect of surfactant on the oral absorption of VIN was also studied. The behaviour and absorption mechanism of the SLN formulations were discussed.

2. Materials and methods

2.1. Materials

VIN was supplied by DongBei Pharmaceutical Co. (Shenyang, China). Glyceryl monostearate (GMS) was purchased from ChangSha Chemical Co. (Hunan, China). Soya lecithin was provided by Shanghai TaiWei Pharmaceutical Co. (Shanghai, China). Polyoxyethylene hydrogenated castor oil was kindly donated by BASF (Luwigshafen, Germany). Tween 80 and dichloromethane were obtained from Shenyang Chemical Reagent Factory (Shenyang, China). All other chemicals were analytical reagent grade and used without further purification.

2.2. Preparation of VIN-SLNs

SLNs were prepared by an ultrasonic-solvent emulsification technique. The desired amounts of GMS and VIN were mixed with a sprinkle of dichloromethane and heated to 50 °C, emulsifiers (soya lecithin/Tween 80 or soya lecithin/Polyoxyethylene hydrogenated castor oil) were dispersed in 10 mL distilled water with magnetic stirring at the same temperature. After evaporating most of the dichloromethane, the water phase was added to the oil phase by drop-by-drop at 50 °C followed by magnetic stirring for 10 min, then the coarse emulsion was subjected to 600 W of ultrasonic treatment for 5 min using a high-intensity probe ultrasonicator (JY92-2D; Xinzhi Equ.Inst., China) with water bath (0 °C). The dispersions were immediately dispersed in bulks of distilled water (0 °C) followed by magnetic stirring to remove traces of organic solvents if any. After the dichloromethane had completely evaporated (data was not shown), the VIN-SLN suspensions were filtered through a 0.45 μm membrane in order to remove the impurity materials (e.g. metal) carried in when ultrasonication and then storage at 4 °C.

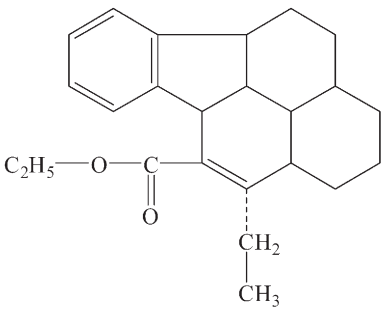

Fig. 1. The structure of vinpocetine.

Table 1
Composition of formulations for the oral administration study (wt.%)

Ingredient	SLN A	SLN B	SLN C	SLN D	SLN E	SLN F
VIN	0.1	0.1	0.1	0.1	0.1	0.1
GMS	3.0	3.0	3.0	3.0	3.0	3.0
Tween 80	2.0	1.5	1.0			
Polyoxyethylene hydrogenated castor oil				2.0	1.5	1.0
Soya lecithin	2.0	2.0	2.0	2.0	2.0	2.0
Dichloromethane	Trace	Trace	Trace	Trace	Trace	Trace
Water	92.9	93.4	93.9	92.9	93.4	93.9

All the formulations used were shown in Table 1.

2.3. Drug content and entrapment efficiency

One milliliter SLN dispersion was separated by Sephadex G-50 column (SINO-AMERICAN BIOTECHNOLOGY Co.; America). The parts of the outflow with opalescence and metered volume to 25 mL were collected, then 2 mL of which was dissolved in 3 mL tetrahydrofuran and added eluant to 10 mL, the lipid was preferentially precipitated by vortexing. After centrifugation (4000 rpm^{-1} for 15 min), the drug content in the supernatant was measured by HPLC. The HPLC system consisted of a mobile phase delivery pump (LC-10AD; SHIMADZU, Japan), a UV–VIS detector (SPD-10A; SHIMADZU, Japan) and a 20 μL loop (Rhenodyne model 7725i). A C_{18} reverse-phase column (Hypersil ODS C_{18}, 200×4.6 mm; Dalian, China) and a Phenomenex C_{18} security guard (4 mm×3.0 mm, 5 μm, Torrance) were utilized for drug separation, using methanol–0.01 M aqueous $(NH_4)_2CO_3$ (83:17, v/v) as mobile phase. The flow rate and UV wavelength were 1.0 mL min^{-1} and 273 nm, respectively.

Another 1 mL SLN dispersion was metered volume to 25 mL directly and then 2 mL of which was treated and analyzed as described above.

The equations for the drug content and loading efficiency are as follows:

$$\text{Entrapment efficiency } (\%) = \frac{W_S}{W_{total}} \times 100\%$$

$$\text{Load content } (\%) = \frac{W_S}{W_{lipid}} \times 100\%$$

W_s: amount of VIN in the SLNs; W_{total}: amount of VIN used in formulation: W_{lipid}: weight of the vehicle.

2.4. Characterization of VIN-SLNs

2.4.1. Particle size and zeta potential

The mean diameter of SLNs in the dispersion was determined by photon correlation spectroscopy (PCS) using a laser light scattering instrument (LS230; COULTER) at a fixed angle of 90° at 25 °C [12]. The particle size analysis data was evaluated using the volume distribution. Zeta potential