Colloids and Surfaces B: Biointerfaces 112 (2013) 337–343

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

Self nanoemulsifying drug delivery system (SNEDDS) of Rosuvastatin calcium: Design, formulation, bioavailability and pharmacokinetic evaluation

Krishnamoorthy Balakumar[a,*], Chellan Vijaya Raghavan[a,1], Natarajan Tamil selvan[a,2], Ranganathan Hari prasad[b,3], Siyad Abdu[a]

[a] Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore 641044, Tamil Nadu, India
[b] Department of Pharmaceutical Analysis, PSG College of Pharmacy, Coimbatore 641044, Tamil Nadu, India

ARTICLE INFO

Article history:
Received 28 November 2012
Received in revised form 9 August 2013
Accepted 16 August 2013
Available online 28 August 2013

Keywords:
Self nanoemulsifying drug delivery system
SNEDDS
Rosuvastatin calcium
Bioavailability
Pharmacokinetic study
Poorly water soluble drug

ABSTRACT

The aim of the present study is to improve solubility and bioavailability of Rosuvastatin calcium using self nanoemulsifying drug delivery system (SNEDDS). Self emulsifying property of various oils including essential oils was evaluated with suitable surfactants and co-surfactants. Ternary phase diagrams were constructed based on Rosuvastatin calcium solubility analysis for optimizing the system. The prepared formulations were evaluated for self emulsifying time, robustness to dilution, droplet size determination and zeta potential analysis. The system was found to be robust in different pH media and dilution volume. The globule size of the optimized system was less than 200 nm which could be an acceptable nanoemulsion size range. The zeta potential of the selected CN 7 SNEDDS formulation (cinnamon oil 30%; labrasol 60%; Capmul MCM C8 10%) was -29.5 ± 0.63 with an average particle size distribution of 122 nm. *In vitro* drug release studies showed remarkable increase in dissolution of CN7 SNEDDS compared to marketed formulation. In house developed HPLC method for determination of Rosuvastatin calcium in rat plasma was used in the bioavailability and pharmacokinetic evaluation. The relative bioavailability of self nanoemulsified formulation showed an enhanced bioavailability of 2.45 times greater than that of drug in suspension. The obtained plasma drug concentration data was processed with PKSolver 2.0 and it was best fit into the one compartment model.

1. Introduction

Lipid based drug delivery system has attained increasing interest in oral route of administration of poorly bioavailable drug as a means to bypass the drug passage in the hepatic portal vein and consequently its hepatic degradation. This hypothesis was believed to be attained chiefly, by lymphatic transport *via* Peyer's patches along the GI tract [1]. Self emulsifying drug delivery system is one among the lipid based drug delivery systems that has been currently investigated for its advantages, providing a large interfacial area for partitioning the drug between oil and GI fluid [2]. This technique improves the oral bioavailability of poorly soluble drugs by enhancing the solubility and maintaining the drug in a dissolved state, in small droplets of oil, all over its transit through the gastrointestinal tract [3,4].

Self nanoemulsifying drug delivery system (SNEDDS) is an isotropic mixture of oil, surfactants and co-surfactants that form fine oil-in-water nanoemulsion, upon mild agitation, followed by administration into aqueous media, such as GI fluids [5]. Upon dilution, SNEDDS typically produces droplet sizes between 20 and 200 nm. These nano-sized droplets may offer an improvement in dissolution rates as well as bioavailability which results in more reproducible blood–time profiles. SNEDDS is a physically more stable formulation when compared to emulsions, and easier to manufacture in a large scale. The rationale to use SNEDDS for the delivery of poorly soluble drugs is that, they are presented in the form of preconcentrated solution. Hence, the dissolution step required for solid crystalline compounds shall be avoided. In addition, the formation of a variety of colloidal species on dispersion and subsequent digestion of SNEDDS facilitates drug absorption [6,7]. Rosuvastatin calcium (ROS) is a synthetic lipid-lowering agent, chemically known as (3*R*,5S,6E)-7-{4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]

* Corresponding author. Tel.: +91 422 2210075x164.
E-mail addresses: balakumar_27@yahoo.co.uk, bala.k.2006@gmail.com (K. Balakumar), c_vijayan_2k@yahoo.com, drvijayaragha@gmail.com (C.V. Raghavan), tselvan24@gmail.com (N.T. selvan), hari2gallen@gmail.com (R.H. prasad), siyadabdu2001@gmail.com (S. Abdu).
[1] Tel.: +91 422 2210075x164.
[2] Mobile: +91 9894234528.
[3] Mobile: +91 9787308817.

0927-7765/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.colsurfb.2013.08.025

pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid calcium salt (2:1) [8]. It is also used in the treatment of osteoporosis, benign prostatic hyperplasia, and Alzheimer's disease [9]. The oral bioavailability of ROS is 20% because of low aqueous solubility due to its crystalline nature and is extensively metabolized by liver *via* oxidation, lactonisation, and glucuronidation. The metabolites are eliminated by biliary secretion and direct secretion from the blood to the intestine [10–12]. For these reasons, enhancing the solubility and by passing hepatic metabolism of Rosuvastatin calcium is a desirable approach to improve its therapeutic performance. After oral administration of ROS, the peak plasma concentration was attained within 3–5 h, the volume of distribution was 1.1–1.4 liter/kg, and plasma protein binding was 90%.

The present study is aimed to design and develop Rosuvastatin calcium loaded SNEDDS with the objective of increasing its solubility and achieving higher bioavailability. To accomplish this, the formulation was studied for drug solubility in various oils, surfactants and co-surfactants. From this, essential oils showed higher solubility data when compared to others. Hence, the essential oils were evaluated for their self emulsifying properties with surfactants and co-surfactants. Generally essential oils are recognized as GRAS (generally recognized as safe) compositions by the Code of Federal Regulations [13]. Further, Benet et al. (1998) studies revealed that the oral bioavailability of cyclosporine was improved with essential oils by inhibiting cytochrome P450 in the gut wall and by inhibiting P-glycoprotein efflux transporter. The prepared ROS loaded SNEDDS was evaluated for self emulsification time, robustness to dilution, droplet size of the dispersion, *in vitro* drug release and bioavailability.

2. Materials and methods

2.1. Materials

Rosuvastatin calcium was gifted by Microlabs Pvt. Ltd., Bangalore; cinnamon oil, lavender oil, peppermint oils were purchased from S.D. Fine Chemicals, Mumbai, India. Labrasol was a gifted sample from Gattefosse limited, Mumbai, India. Capmul MCM, Capmul MCM C8 were obtained as gift samples from Abitech Corporation, USA. Brij, Ethyl oleate, Isopropyl myristate, Cremophore EL, Cremophore RH 40, Span 80, Tween 80, Acetonitrile and Methanol were purchased from Sigma Aldrich, USA. Formic acid was obtained from Qualigens, Mumbai. Dialysis Membrane-110 (Mol. weight 12,000–14,000) was obtained from HiMedia, Mumbai, India.

2.2. Methods

2.2.1. Solubility study

The solubility of ROS was determined in various essential oils, surfactants and co-surfactants by pouring an excess of drug into 1 ml of each vehicles. The obtained mixtures were mixed continuously for 2 min using cyclo mixer (Remi Mumbai, India). The mixtures were shaken (100 rpm) for 24 h at 25 °C in a thermostatically controlled shaking water bath followed by equilibrium for 12 h. The equilibrated samples were removed and centrifuged at 10,000 rpm (10,621 × *g*) for 5 min. The supernatant solution was taken and filtered through a Millipore membrane filter (0.45 μm) and then suitably diluted with methanol. The concentration of Rosuvastatin calcium was determined using UV Spectrophotometer (Shimadzu 1700, Japan) at 244 nm. The experiment was repeated in triplicates [14,15].

2.2.2. Construction of ternary phase diagrams

Ternary phase diagrams were constructed using essential oils, surfactants and co-surfactants; the selection of these excipients was based on the solubility study of ROS [16]. A series of self-emulsifying systems was prepared in the formula with varying concentrations of oil (25–70%w/w), surfactant (30–75%w/w), co-surfactant (0–25%w/w) (Table 1) at room temperature (25 °C) for 72 h. For any mixture, the total of surfactant, co-surfactant and oil concentration added was always 100% [3]. Sixty of such mixtures with varying concentrations were prepared in this investigation. Ternary phase diagrams were constructed in the absence of Rosuvastatin calcium to identify the self-emulsifying regions. The phase diagram was plotted using CHEMIX ternary plot software. All the studies were repeated thrice, with similar observations being made between repeats.

Table 1
Different compositions of essential oils, surfactants and co-surfactants.

Sl. no.	Group	Essential oils	Surfactants	Co-surfactants
1	Group I	Cinnamon oil	Labrasol	Capmul MCM C8
2	Group II	Lavender oil	Brij	Capmul MCM C8
3	Group III	Peppermint oil	Brij	Capmul MCM

2.2.3. Preparation of Rosuvastatin SNEDDS

Once the self emulsifying region was identified, the desired component ratios of SNEDDS were selected (Table 2) for drug incorporation and further optimization. Ten milligram of drug and mixed surfactant and co-surfactant were incorporated in their determined ratios into oil phase containing drug. Finally homogeneous mixture was obtained by vortex mixing. The prepared Rosuvastatin calcium SNEDDS was kept in a tightly closed bottle at 25 °C and from these the stable formulations were subjected to further studies *i.e.* dilution studies, droplet size analysis, self-emulsification time, particle size analysis and zeta potential analysis.

2.3. Characterization of formulations

2.3.1. Self emulsification time

Self emulsification time is the time required by the preconcentrate to form a homogeneous mixture upon dilution, when disappearance of SNEDDS is observed visually. The efficiency of self emulsification of SNEDDS was assessed by using a standard USP XXII dissolution apparatus. One ml of each formulation was added dropwise to the medium (900 ml of water with a paddle speed of 100 rpm at 37.0 ± 0.5 °C) by a dropping pipette and the time required for the disappearance of the SNEDDS was recorded [17]. The efficiency of self emulsification was visually assessed.

2.3.2. Robustness to dilution

Robustness of Rosuvastatin calcium SNEDDS to dilution was studied by diluting it 50, 100 and 1000 times with various dissolution media *i.e.* water, buffer pH 1.2, buffer pH 3.0 and buffer pH 6.8. The diluted samples were stored for 12 h and observed for any signs of phase separation or precipitation [18,19].

Table 2
Selected SNEDDS formulations containing drug.

Drug (mg)	Formulation code	Essential oils	Surfactants	Co-surfactants
10	CN7	30%	60%	10%
10	CN10	40%	40%	20%
10	CN12	40%	60%	–
10	CN13	50%	30%	20%
10	PEP 3	25%	55%	20%
10	PEP 7	30%	50%	20%
10	PEP 12	40%	60%	–
10	LAV16	50%	45%	5%
10	LAV17	60%	35%	5%
10	LAV18	60%	30%	10%