International Journal of Pharmaceutics 495 (2015) 374–384

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Role of solid carriers in pharmaceutical performance of solid supersaturable SEDDS of celecoxib

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ARTICLE INFO

Article history:
Received 1 July 2015
Received in revised form 1 September 2015
Accepted 8 September 2015
Available online 10 September 2015

Keywords:
SEDDS
Solid carrier
Silicon dioxide
Porosity
Surface area
Hydrophobicity-hydrophilicity
In vitro drug release

ABSTRACT

Self emulsifying drug delivery system (SEDDS) has been increasingly used for improving the oral bioavailability of poorly water soluble drugs. SEDDS can be solidified by adsorbing them on different solid carriers. In the present study, the impact of properties of solid carrier on drug release profile from solid SEDDS was investigated. Celecoxib (CEL) loaded supersaturable SEDDS (S-SEDDS) was prepared and optimized by using optimal response surface design. Optimum composition of S-SEDDS corresponded to 10:45:45% v/v ratio of oil (Capryol 90), surfactant (Tween 20) and cosurfactant (Transcutol HP) with Soluplus (40 mg) as precipitation inhibitor. Different grades of silicon dioxide were selected based on their properties like surface area, porosity and hydrophobicity–hydrophilicity, and used for preparation of solid S-SEDDS (SS-SEDDS) by adsorption method. All SS-SEDDS formulations in release studies, gave droplet size, PDI and zeta potential similar to S-SEDDS. The percent drug release after 120 min from CEL powder, S-SEDDS and SS-SEDDS with Sylysia 350 fcp, Aerosil 300 Pharma, Aerosil 200 Pharma and Aerosil R 972 Pharma was found to be 0.58%, 100%, 38.44%, 9.63%, 2.53% and 5.99%, respectively. Drug release profiles were compared by using model independent methods. The differential drug release behavior of SS-SEDDS was attributed to the different physico–chemical properties of solid carriers. SS-SEDDS with Sylysia 350 fcp showed higher drug release and greater dissolution efficiency. Oral bioavailability study also demonstrated 2.34 fold increase in C_{max} and 4.82 fold increase in AUC (0–24 h) when compared with CEL powder. This study highlights the rational for selection of solid carriers in the formulation development of solid SEDDS.

1. Introduction

Several successful oral pharmaceutical products have been marketed as lipidic systems, notably cyclosporin A (Sandimmune® and Nerol®), ritonavir (Kaletra®), sanquinavir (Fortovase®) and tipranavir (Aptivus®) (Grove et al., 2006; Pouton, 1997, 2000). Consequently, there is now considerable interest in the potential of lipid formulation for oral administration, with particular emphasis on liquid self emulsifying drug delivery systems (SEDDS) (Neslihan Gursoy and Benita, 2004; Pawar et al., 2012; Pouton and Porter, 2008). However, the commercial application of this technology is still limited. One of the primary reason for lack of widespread use of lipid based system is that these formulations are typically consist of liquid filled in soft or hard gelatine capsules. Sandimmune® (Novartis) and Gengraf® (Abbott) are marketed as soft gelatin capsules and hard gelatin capsules, respectively (Kohli et al., 2010). These formulations pose challenges like potential risk of drug precipitation and chemical degradation (Cole et al., 2008; Dixit and Nagarsenker, 2008; Grove et al., 2006; Gumaste et al., 2013; Piao et al., 2014; Yi et al., 2008a).

Solidification of liquid SEDDS has already been investigated to address the drawbacks associated with conventional liquid SEDDS (Agarwal et al., 2009; Beg et al., 2012; Cho et al., 2013; Deshmukh and Kulkarni, 2014; Ito et al., 2005; Tarate et al., 2014; Yi et al., 2008b). Solid SEDDS combine the advantages of conventional liquid SEDDS like enhanced solubility and bioavailability with those of solid dosage forms like relatively lower production costs, convenience of process control, better stability, reproducibility, better patient compliance, precise dosing and ease in handling and storage (Agarwal et al., 2009; Deshmukh and Kulkarni, 2014; Kang et al., 2012; Kumar et al., 2010; Müllertz et al., 2010; Tan et al., 2013). Many recent studies on development of solid SEDDS, in which lipids and surfactants were adsorbed on to the solid carrier, were reported in literature (Balakrishnan et al., 2009; Beg et al., 2012; Cho et al., 2013; Deshmukh and Kulkarni, 2014; Ito et al.,

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http://dx.doi.org/10.1016/j.ijpharm.2015.09.011
0378-5173/

2005; Jain et al., 2013; Kang et al., 2012; Wang et al., 2010; Yi et al., 2008b). However, till date, no attempt has been made to systematically investigate the role of properties of solid carrier on drug release profile from solid SEDDS. In the present study, the impact of physico–chemical properties of solid carriers on drug release profile from solid SEDDS was evaluated.

Celecoxib (CEL) is a selective Cox-2 inhibitor. It has challenging biopharmaceutical properties in terms of poor solubility and dissolution rate (Bansal et al., 2007; Gupta et al., 2004; Modi et al., 2014a; Modi et al., 2013). These properties laid ground for development and optimization of lipid based formulation of CEL. In the present study, we have developed supersaturable SEDDS (S-SEDDS) of CEL and statistically optimized it by an optimal response surface design. This optimized composition of S-SEDDS has higher solubility and better physical stability than previously reported S-SEDDS (Song et al., 2013). Solid S-SEDDS (SS-SEDDS) were prepared by adsorbing S-SEDDS on different solid carriers and evaluated for drug release. We selected different grades of silicon dioxide as solid carrier based on their physico–chemical properties like surface area, porosity and hydrophobicity–hydrophilicity. Further, oral bioavailability study in Sprague Dawley (SD) rats was carried out to assess improvement in oral bioavailability.

2. Material and methods

2.1. Material

CEL was received as a generous gift from Glenmark Generics Ltd., New Delhi, India. Capryol 90 was obtained as a gift sample from Abitec Corporation (Janesville, USA). Labrasol (Caprylocaproylmacrogol glycerides) and Transcutol HP (Diethylene glycol monoethyl ether) were gifted by Gattefosse (Saint-Priest Cedex, France). Soluplus was obtained as a gift sample from BASF SE, Germany. Tween 20 (Polyoxyethylene glycol 20 sorbitan monolaurate) was purchased from HiMedia (Mumbai, India). Aerosil 200 Pharma, Aerosil 300 Pharma and Aerosil R 972 Pharma were received as a gift sample from Evonik Degussa India Private Limited. Sylysia 350 fcp was obtained as gift sample from Fuji Sylysia, Japan. Acetonitrile and methanol were of high performance liquid chromatography (HPLC) grade. All the other chemicals and solvents were of analytical grade. Double distilled water was generated in house, using glass distillation assembly.

2.2. Solubility of CEL in various excipients

It was reported that CEL has highest solubility in Capryol 90 for oil component, and Tween 20, Transcutol HP, Tetraglycol, Labrasol and PEG 400 for surfactant/ cosurfactant component (Song et al., 2013). Initially it was planned to use a reported S-SEDDS composition and convert it to SS-SEDDS. However, preliminary experiments on the reported S-SEDDS consisting of Capryol 90, Tween 20, Tetraglycol and Soluplus revealed a problem of precipitation after 2 h of reconstitution. Hence, we designed a new composition using the reported solubility data. The compositions are detailed in Table 1.

The equilibrium solubility of CEL in different compositions mentioned in Table 1 was determined by adding an excess amount of the CEL in 5 mL of SEDDS composition in 5 mL screw capped glass vials (Shen and Zhong, 2006). These vials were then shaken mechanically in a shaker water bath (Julabo Labortechnik GmbH, Seelbach, Germany) at 100 rpm maintained at 37 °C. These mixtures were centrifuged at 13,000 rpm for 10 min to separate the excess CEL. The concentration of CEL in supernatant was measured by previously reported HPLC method (Dhabu and Akamanchi, 2002; Modi et al., 2014a; Modi et al., 2013; Saha et al., 2002) after appropriate dilution with methanol. Based on solubility, droplet size and polydispersity index (PDI), T_2 composition of S-SEDDS was selected for further optimization.

2.3. Formulation development of S-SEDDS

An optimal response surface design of constrained region was employed to optimize the S-SEDDS composition, which was selected based on maximum loading of CEL, droplet size and PDI of submicron emulsion resulted after dilution. A methodical optimization of various dependent variables (CEL loading, droplet size and PDI of diluted emulsion) was performed by varying the percentage of (i) oil and (ii) blend of surfactant and cosurfactant (S/CoS) in liquid SEDDS, which were considered as the independent variables. The response surface methodology of two component system was performed, using a blend ratio of S/CoS as 1:1 (v/v). The proportion of oil in the mixture with S/CoS blend was varied from 9:1 to 1:9. Design Expert software (Version 7.1, 2007, Stat-Ease Inc., Minneapolis, MN, USA) was employed for the optimization study and plots of all the three responses (droplet size, PDI and CEL content) were constructed. The responses of all the eleven runs were fitted in the quadratic polynomial model. The polynomial equations were generated for each response using the Design Expert software. The appropriate fitting model for each response was selected based on the comparison of various statistical parameters such as R^2, sequential model sum of squares, lack of fit and partial sum of square was provided by the analysis of variance (ANOVA).

2.3.1. Preparation of S-SEDDS

CEL (180 mg) was dissolved in 1 mL of the optimized composition of Capryol 90, Tween 20 and Transcutol HP. The mixture was vortexed until a clear solution was obtained. Finally Soluplus, the precipitation inhibitor, was added to the formulation. Song et al. have already screened various polymeric excipients for efficient precipitation inhibition of CEL from S-SEDDS by the dissolution test. Moreover, they have systematically finalized the quantity (40 mg/mL) of Soluplus by evaluating the concentration-dependent stabilizing effect of Soluplus on supersaturation (revealing the greatest dissolution with delayed drug crystallization by the addition of Soluplus at 40 mg/mL concentration) (Song et al., 2013). The final drug loading in the S-SEDDS was 18% w/v. The formulation was examined for signs of turbidity or phase separation prior to self-emulsification. The droplet size and PDI of the emulsion was then measured using Zetasizer® Nano ZS.

Table 1
Characteristics of CEL loaded SEDDS formulations.

Formulation	Component (% v/v)			Solubility (mg/mL)	Globule size (nm)	PDI
	Capryol 90	Tween 20	Transcutol HP			
T_1	10	30	60	874.39 ± 10.30	119.24 ± 5.80	0.476 ± 0.011
T_2	10	45	45	874.66 ± 20.68	125.38 ± 2.75	0.217 ± 0.073
T_3	10	60	30	819.57 ± 8.96	146.46 ± 5.00	0.470 ± 0.013