



IN-VIVO STUDY OF SELF-EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS) OF EPROSARTAN

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Abstract This study has explored the use of self-emulsifying drug delivery system (SEDDS) to enhance the oral bioavailability of the poorly water soluble drug eprosartan. On the basis of solubility studies Labrafac Lipophile WL 1349 was selected as oil phase, Tween 80 as surfactant and capryol 90 as cosurfactant. Pseudo-ternary phase diagrams were plotted to check for the micro-emulsification range. Percentage transmittance, spontaneous emulsification test, robustness to dilution, emulsification time, thermodynamic stability studies and globule size analysis were carried out to characterize optimized formulations. The influence of surfactant and cosurfactant concentration on droplet size of selected system was assessed. The optimized formulation was found to show a significant *in vitro* drug release i.e. 98.3% (data is under process to publish). The bioavailability of the drug from SEDDS formulation and aqueous suspension was investigated in rats and it was found that the SEDDS formulation enhanced drug absorption and oral bioavailability compared to the aqueous suspension.

Keywords Eprosartan, Self-emulsifying drug delivery system (SEDDS), Bioavailability, Labrafac lipophile WL 1349, Capryol 90, Tween 80

Introduction

A large majority of the newly discovered chemical entities and many existing drug molecules are poorly water soluble presents a serious challenge to the successful formulation and marketing of new drugs in the pharmaceutical industry. Since in many cases the dissolution step is the rate limiting step, formulation design can be a useful approach to improve the absorption and thus the oral bioavailability of such drug candidates [1]. Thus for such compounds, the absorption rate from gastrointestinal lumen is controlled by dissolution, modification of physiochemical properties, such as salt formation and particle size reduction of compound may be one approach to improve the dissolution rate of the drug. However these methods have their own limitations. For instance, salt formation of neutral compounds is not feasible and the synthesis of weak acid and base salts may not always be practical. Various other formulations strategies are also reported in literature including the use of surfactant, cyclodextrine, solid dispersion, nanoparticles, micronization, lipid and permeation enhancers [2]. Oral route has been the major route of drug delivery for the chronic treatment of many diseases. However, oral delivery of 50% of drug compounds is hampered because of the high lipophilicity of drug itself [3]. Lipid based formulations represents a unique solution to delivery of poorly soluble compounds. Among the lipid-based systems, the self-emulsifying drug delivery system (SEDDS) is a promising technology to improve the rate and extent of absorption of poorly water-soluble drugs [4]. Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants



ideally isotropic, sometimes including cosolvents which emulsify under condition of gentle agitation, similar to those which would be encountered in the gastrointestinal tract [5, 6].

Eprosartan is an angiotensin II receptor antagonists used for the treatment of high blood pressure. Eprosartan is a BCS Class II compound i.e. drugs with low solubility and high permeability. Such compounds have poor bioavailability due to low drug solubility and any metabolism or degradation of the drug before it reaches the circulation. The oral bioavailability of eprosartan is about 13 % with 300 mg dose [7, 8]. The objective of the present study was to enhance the oral bioavailability of eprosartan by self-emulsifying drug delivery system.

Material and Methods

Materials

Eprosartan was obtained from Hetero Drugs Ltd. (Andhra Pradesh), Labrafac lipophile WL 1349, Capryol 90, Labrasol and Peceol were provided by Gattefosse (Mumbai), Tween 80, PEG 600, Tween 60, Tween 20, SPAN 80 Sodium chloride, Potassium dihydrogen orthphosphate, Ethanol, Methanol and Acetonitrile were obtained from CDH (Mumbai). All other chemicals were of analytical grade.

In vivo pharmacokinetic evaluation in rats

Approval to carry out *in vivo* study was obtained from Rajasthan Pharmacy College, Institutional Animal Ethics Committee and their guidelines were followed for the studies ((CPCSEA NO: RPC/CPCSEA/CER/2013/211). The *in vivo* bioavailability studies both for eprosartan drug and optimized SEDDS formulation was carried out in albino wistar rats (n=6). Food was stopped to all animals 8–10 h prior to experimentation. Food and water was not given to animals till 2 h after the start of the study. Each of the animals received a single dose of eprosartan (1mg/kg) as pure drug and the SEDDS formulation orally. Blood samples (1 ml) were collected predose (0 hr) and 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hr post dose after the oral administration. The samples were centrifuged at 2000 rpm for 20 min at 25°C and plasma was separated. The centrifuged plasma samples were stored at -20°C until analyzed.

Preparation of standard solutions

Accurately weighed quantity of eprosartan (10mg) was dissolved in HPLC grade acetonitrile and volume was made up to 10ml in volumetric flask (Stock A). From this stock solution 1 ml of solution was taken in 10 ml volumetric flask and the volume was made up with acetonitrile (Stock B). Different dilutions were prepared in the concentration range of 125, 250, 500, 1000 and 2000 ng/ml. Calibration standards were prepared by spiking the drug from the serially diluted solutions into the blank serum and absorbance was measured at 232.0 nm.

Extraction procedure

The collected blood samples were centrifuged at 2000 rpm for 20 min at 25°C and plasma was separated. The centrifuged plasma samples were stored at -20°C until analyzed. To aliquot of 500 µl of plasma samples, 1.5 ml of acetonitrile was added and vortex mixed for 1 min to ensure complete precipitation and centrifuged at 10,000 rpm at 4 °C for 20 min. Supernatant of the centrifuged samples was collected and analyzed using HPLC.

HPLC assay

The quantitative determination of drug in plasma was performed by HPLC assay using acetonitrile: buffer pH 4 (60:40 V/V) mixture as mobile phase delivered at 1.0 ml/min. Twenty microliters of injection volume was eluted in C-18 column (Phenomenex) at room temperature. The column was monitored at 232 nm using diode array UV detector.

Results and Discussion

The mean plasma eprosartan concentration versus time profiles obtained with the SEDDS formulation and eprosartan aqueous suspension are shown in Figure 1. The two profiles showed a rapid increase in plasma eprosartan



concentration after dosing. It is also apparent from the plots that the complex achieved much higher plasma drug levels, with peak plasma concentrations approximately twice that of the reference preparation, thus indicating a higher rate and extent of eprosartan absorption. The individual numerical values of AUC_{0-t} , C_{max} and T_{max} obtained with the two preparations are given in Table 1. The parameters T_{max} and AUC_{0-t} are indicative of the respective rate and extent of drug absorption, whereas C_{max} is related to both processes. The relative bioavailability of SEDDS formulation when compared with the aqueous suspension of eprosartan was found to be 198.74% which suggest the significant improvement in the rate and extent of drug absorption.

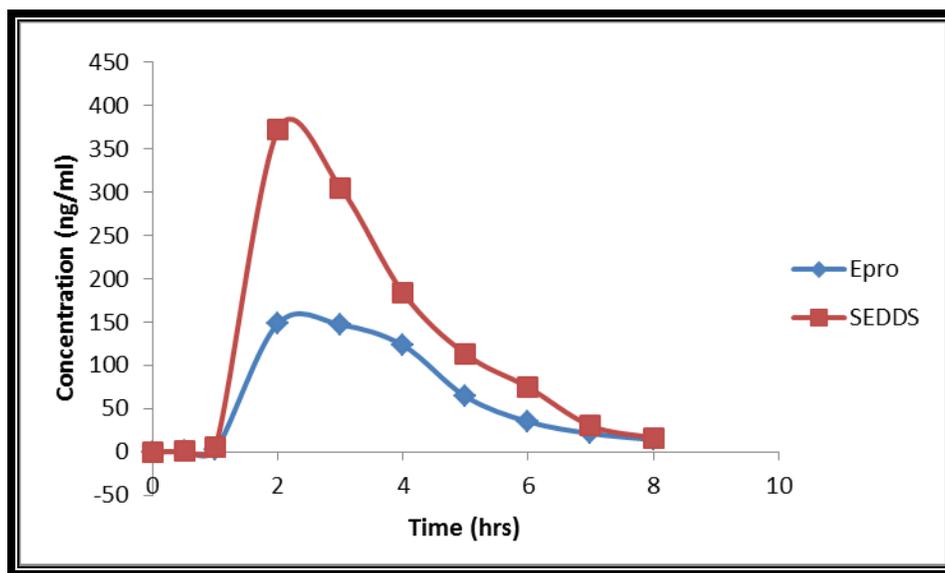


Figure 1: Plasma concentration–time profile of Eprosartan (EPR) and SEDDS formulation

Table 1: Pharmacokinetic response of eprosartan and SEDDS in rat

S. No.	Pharmacokinetic response	Eprosartan	SEDDS
1.	C_{max} (ng/ml)	148.31±21.64	371.83±5.36
2.	T_{max} (hr)	2	2
3.	AUC_{0-t} (ng.hr/ml)	548.99±52.30	1090.20±110.93
4.	Fr %	100	198.74

Conclusion

Self-emulsifying drug delivery system (SEDDS) represent an interesting prospect for the development of formulation for use as vehicle to deliver drug to the body. Hydrophobic drug can often be dissolved in SEDDS allowing them to be encapsulating as unit dosage forms for oral administration. It can be concluded that the self-emulsifying drug delivery system (SEDDS) of eprosartan can overcome the disadvantage of poor and erratic oral



bioavailability of eprosartan associated with currently marketed formulations. This increased and predictable availability of eprosartan from designed formulation may result in substantial dose reduction.

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