Abstract

Lercanidipine HCl (LCH) is poorly water soluble anti-hypertensive drug. It is highly lipophilic (LogP = 6.4) and exhibit variable bioavailability as low as 10% when given orally. To overcome the dissolution issue, Self-emulsifying drug delivery systems were prepared. The lipidic excipients were grouped according to the fatty acid chain length in their structures as long (LC), medium (MC) and short (SC) chain glycerides. An extensive quantitative solubility studies and pseudo-ternary phase diagrams were conducted. Three formulations i.e. LC-SNEDDS, MC-SMEDDS and SC-SMEDDS were developed and characterized for self-emulsification time, % transmittance, globule size, zeta potential and in-vitro drug release. To conclude the best formulation among the three, drug release in biorelevant media and in-vitro lipid digestion studies were employed. Two way ANOVA was conducted to see the effect of dissolution medium and type of formulation on drug release. Finally, the optimized formulation was used for prediction of in-vivo absorption from the in-vitro release data in biorelevant media. The LC-SNEDDS contained ricebran oil: GMO (1:9) as oil phase, tween 80 and propionic acid as surfactant and co-surfactant respectively. The MC-SMEDDS was made up of Capmul MCM as oil phase and Cremophor RH 40 with PEG 400 as surfactant and co-surfactant respectively. Whereas SC-SMEDDS composed of triacetin as oil and tween 80 as surfactant without co-surfactant. The LC-SNEDDS resulted in a transparent (with bluish tinge) nanoemulsion after spontaneous process with globule size of as low as 8 nm. Zeta potential was found to be a positive value i.e. 14.3 mV due to presence of propionic acid. LC-SNEDDS released more than 80% drug release in all the tested dissolution media. However, two way ANOVA suggested that type of lipid formulation and different dissolution medium i.e. whether fasted or fed, had significant influence (p < 0.05) on the % drug released. This finding proposed to be due to interplay of formulation derived lipid excipients and components of biorelevant dissolution medium. Though LC-SNEDDS was less affected by change in pH and food like condition as compared to other formulations. In-vitro lipid digestion study revealed that maximum amount of drug in the aqueous phase was released after lipolysis of LC-SNEDDS, which was due to digestion of both oil and surfactant. Three dimensionless parameters i.e. Absorption number (An), dose number (Do) and dissolution number (Dn) were calculated to find the fraction of dose absorbed (F) mathematically. F was found to be 0.9 (90% absorption) for LC-SNEDDS as compared to 0.1 (10% absorption) for untreated LCH. The convolution approach was used to predict plasma concentration-time profile. The C\text{max} and AUC were estimated to be 17 fold higher than those calculated for untreated LCH. Similarly, a simulation software Gastroplus® also showed
99.96% drug to be absorbed from LC-SNEDDS as compared to 7.69% which was absorbed in case of untreated LCH. Thus, LC-SNEDDS was proved to be the best formulation among the developed compositions using sound scientific principles and was concluded to be the viable prospect for improving dissolution of LCH in biorelevant conditions.