-Development and in vitro/in vivo performance of self nanoemulsifying drug delivery systems loaded with candesartan cilexetil


Abstract:

Candesartan cilexetil is widely used in the management of hypertension and heart failure. The drug delivery encounters obstacles of poor aqueous solubility, efflux by intestinal P-glycoprotein and vulnerability to enzymatic degradation in small intestine. Self-nanoemulsifying drug delivery systems (SNEDDS) loaded with candesartan cilexetil were successfully developed to overcome such obstacles. Preliminary screening was carried out to select proper surfactant, co-surfactant and oil combination for successful SNEDDS formulation. All screened excipients were reported for their P-glycoprotein and cytochrome P450 3A4 (CYP3A4) modulation activity. Ternary and pseudo ternary diagrams were constructed to optimize the system. Peppermint oil and clove oil showed a high emulsification ability. The nature of obtained dispersions was identified to be nanoemulsions. Twenty-four formulations were evaluated for stability, robustness to dilution and self-emulsification efficiency. All formulations showed a very short emulsification time of less than 2 min. The emulsification efficiency was significantly superior at pH 6.8, at which the largest self-emulsifying region was also observed. Eight formulations were selected for further characterization according to cloud point measurement; mean droplet size, poly dispersity index (PDI) and zeta potential determination in addition to in vitro drug release study. All selected formulations showed very high cloud points (70-90°C), ultrafine mean droplet size (12 ± 1.4 to 24.5 ± 2.13 nm), very low PDI values (0.015-0.1305) and almost a complete drug release after 12 h. Formulation F15 (Peppermint oil 55% w/w: Cremophor RH40 25% w/w: Labrasol 20% w/w) was selected for further characterization. Its droplet size showed robustness to different dilution folds with different media and its TEM photograph showed spherical particles without any apparent aggregation even after 24 h. Formulation F15 successfully controlled the systolic blood pressure of hypertensive rats for 24 h with the maximum effect was observed after 2 h. These results indicate that, SNEDDS could be promising delivery systems with a rapid onset of action and prolonged therapeutic effect of candesartan cilexetil.

Keywords:

Candesartan cilexetil; SNEDDS; Essential oil; nanoemulsion; P-glycoprotein; Pharmacodynamic study

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