Chapter-2

Aims & Objectives
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2.1. Aim of the present investigation

Lercanidipine HCl is not only poorly water soluble (0.000156 mg/ml) but highly lipophilic (LogP 6.4). It is easily absorbed through intestine if in dissolved form. Moreover it is a weakly basic drug which shows pH dependent solubility and is better absorbed in presence of food. Oral bioavailability is reported to be only 10%, for which there are two main reasons: (1) Lipophilicity and poor water solubility and (2) First pass effect (Barchielli et al. S1-S15). The present research is done to overcome the first short coming i.e. poor solubility in an effective way.

Numerous dissolution enhancement techniques are reported in past decade i.e. salt formation, micronization, solid dispersions, complexation and lipid based drug delivery systems to address this problem. The lipid based drug delivery system is proved to be a standalone technique for improving the dissolution, more specifically saturation solubility of the drug in an aqueous environment with excellent dissolution stability. Lipid based formulations improve bioavailability of lipophilic drugs by a variety of mechanisms such as keeping the drug in dissolved state throughout gastrointestinal tract, inhibition of P-glycoprotein-mediated drug efflux, promotion of lymphatic transport, which delivers drug directly to the systemic circulation while avoiding hepatic first-pass metabolism and increasing GI membrane permeability. This is besides the availability of prodigious surface area of the oil globules. It includes traditional dosage forms like oily solutions, emulsion, microemulsion, nanoemulsion to more recent surfactant mixtures, micellar solutions and the most promising of them all, self -emulsifying drug delivery systems. Self-emulsifying drug delivery systems (SEDDS) are an isotropic mixtures of oil(s), surfactant(s), co-surfactant(s) and/or co-solvent(s), which result into fine sized emulsion, microemulsion or nanoemulsion when introduced into stomach using the peristaltic movement as kinetic energy.

Thus the thesis primarily aimed to prepare and characterize self-emulsifying drug delivery systems for LCH and to derive the optimized formulation capable of enhancing the dissolution of LCH. A systematic approach was used in selection of lipidic excipients with varying fatty acid chain lengths (i.e. long, medium and short) and preparing the formulation which was not affected by dilution and can reproduce the in-vitro release profile in different media tested without significant difference. One of the great challenge was to adopt the suitable in-vitro dissolution test capable of discriminating amongst the prepared formulation and assisting in selection of the optimized
formulation. According to Noyes-Whitney equation, the factors affecting dissolution kinetic include the surface area of the drug; the diffusion coefficient of the drug; the effective boundary layer thickness; saturation concentration of the drug under the local gastrointestinal intestinal conditions and the volume of the fluid available to dissolve the drug. Besides this one important parameter to be considered is dose/solubility ratio. The dose: solubility ratio indicates whether the capacity of the GI fluids is sufficient to dissolve the entire dose administered (Dressman and Reppas). The ratio > 250 indicates that the conditions in GI tract are less than optimal for dissolution, since the sink conditions will not prevail. LCH has dose/solubility ratio of 2439 ml (experimental solubility data) which clearly indicates that compendial dissolution media would not give any idea about the actual ability of the formulation to dissolve LCH. Therefore an attempt was made in the present study to simulate the gastric conditions and to check the behaviour of SEDDS in presence of physiologically relevant conditions. This study also discriminated between different lipid formulations which is not possible with conventional dissolution technique.

Hence the primary objective of the present investigation was to formulate an efficient self-emulsifying drug delivery system for Lercanidipine HCl and the secondary aim was to forecast the in-vivo behaviour with the help of \textit{in-vitro} release study in biorelevant media, \textit{in-vitro} lipid digestion and \textit{in-silico} methods

\textbf{2.2. The specific objectives of the thesis}

1. Determination of the quantitative solubility of Lercanidipine HCl in various lipid excipients, non-ionic surfactants and co-solvents and constructing a series of pseudo-ternary phase diagrams for identifying composition capable of self-emulsifying.


3. In-vitro release study and in-vitro lipid digestion study of selected formulations in biorelevant media.

4. Prediction of in-vivo absorption from optimized LC-SNEDDS using three in-silico methods (1) calculation of fraction of dose absorbed using a mathematical model (2) convolution method for predicting plasma concentration-time profile and (3) computer simulation software Gastroplus®.
2.3. References
