1. Aims and Objectives
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Solubilization of hydrophobic drugs with low aqueous solubility has been a major area of interest. Lipids and lipophilic excipients have shown beneficial effects on the absorption and plasma exposure for those lipophilic or poorly water soluble compounds. As a lipid based drug delivery system, microemulsion has generated considerable interest over the years. In 1981, Danielsson and Lindman defined microemulsion as "a system of water, oil and amphiphile which is an optically isotropic and thermodynamically stable liquid solution." Because of their unique properties, microemulsions have attracted increasing attention as potential drug delivery systems and have been investigated as oral, topical, transdermal, parenteral and vaginal drug delivery systems. The advantages offered by orally delivered microemulsions include improved drug solubilization, protection against enzymatic degradation, potential of enhanced permeability change, improved bioavailability, and reduced toxicity by changing bio-distribution (Constantinides, et al., 1994; Gao, et al., 1998).

The most popular alternative and commercially viable form of microemulsion is selfmicroemulsifying drug delivery system (SMEDDS). Compared to ready-to-use microemulsions, it has improved physical stability profile upon long-term storage, and can be filled directly into soft or hard gelatin capsules for convenient oral delivery. This system is able to rapidly selfmicroemulsify in GI fluids and forms fine O/W microemulsions under the gentle agitation by GI tract movements.

Oral delivery is currently the gold standard in the pharmaceutical industry because it is considered to be the safest, most convenient, the highest patient compliant and the most economical way to deliver the medicine. The oral delivery of hydrophobic drugs presents a major challenge because of the low aqueous solubility of such compounds. Self-microemulsifying drug delivery systems (SMEDDS) have attracted considerable attention from pharmaceutical scientists, who want to increase the oral bioavailability of such drugs with poor water solubility. Although many studies have been carried out, few drug products have actually been brought to market formulated as SMEDDS filled in capsules, which confirms the difficulty and challenge of the formulation, including the following:
1. Aims and Objectives

- Manufacturing process needs special equipments for filling, weight sorting and banding operations which increase the cost.
- Capsules are sensitive to moisture and gelatin has a tendency to cross-link with capsule contents.
- Hygroscopic fills may cause rapid capsule softening and leaking.
- The interactions between lipid components and capsule shells are often observed.
- Drug migration into the capsule shell can affect its release mechanism.

To address these problems, solid-SMEDDS have been extensively explored in recent years because they are more physically stable, more effective and better patient compliant alternatives to the conventional liquid SEDDS. In this research work, adsorption on solid carrier technique was studied and employed as a tool to solidify the liquid self microemulsion.

Felodipine is a dihydropyridine calcium-channel blocker used alone or with an angiotensin-converting enzyme inhibitor to treat hypertension and chronic stable angina pectoris. The drug belongs to BCS class II (low solubility and high permeability). Felodipine is rapidly absorbed from the gastrointestinal tract and approximately 80% of an oral dose is absorbed. However, because of low solubility and extensive first pass metabolism, absolute bioavailability is only 15% and the metabolite is excreted primarily in the feces. Microemulsion of Felodipine is expected to enhance the aqueous solubility and dissolution rate, minimize the variability in absorption and minimize the first pass hepatic metabolism. Enhancement of bioavailability of Felodipine can reduce the dose required to elicit the same pharmacological action and hence reduce the side effects associated with the drug.

Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype. It is categorized in angiotensin receptor blocker. Valsartan is poorly soluble and belongs to BCS class II. The drug is rapidly absorbed following oral administration, with a bioavailability of about 23%. Peak plasma concentrations of Valsartan occur 2 to 4 h after an oral dose and 94% to 97% of the drug is bound to plasma proteins. Rapid onset of action is desirable to provide fast relief in the treatment
1. Aims and Objectives

of heart failure. Therefore, it is necessary to enhance the aqueous solubility and dissolution rate of Valsartan to obtain faster onset of action, minimize the variability in absorption, minimize first pass hepatic metabolism and to improve its overall oral bioavailability.

From above discussions, the hypotheses of the work are as given below:

1. Lipid based formulation of Felodipine such as microemulsion is expected to be absorbed through the lymphatic route and hence the first pass hepatic metabolism can be decreased. Moreover, because the drug would be in solubilized form and in a fine state of sub-division, the absorption and bioavailability can be increased significantly.

2. Lipid delivery system in the form of SMEDDS could potentially increase the dissolution of Valsartan which in turn would enhance its absorption and bioavailability when administered orally.

3. Solid SMEDDS formulation of Valsartan would show higher kinetic and thermodynamic stability profile, better patient compliant, transport and storage as compared to liquid SMEDDS formulation.

Microemulsion based drug delivery system carries the significant advantages which assure the significance of this study.

Clinical: Improved drug solubilization and absorption; faster onset of action and minimized first-pass effect due to pre-gastric absorption; improved bioavailability for drugs with poor water solubility.

Technical: SMEDDS facilitates the transport, storage and stability of conventional microemulsions; avoids the potential challenges in the manufacture of liquid SMEDDS such as sensitivity of capsules to the moisture, capsule softening and leaking, interactions between drugs, lipids and capsules; improved stability because of unit solid dose packaging; can be manufactured with common process and conventional equipment.

With in-vitro intestinal permeability (ex-vivo drug release) study, it is possible to accurately determine the drug release rate and total drug release amount from the microemulsions which are crucial for studying the drug release mechanism, predicting the in- vivo performance, and optimizing the formulation.
1. Aims and Objectives

Objectives of present work

The objective of the present research study was to formulate, develop and optimize microemulsion systems for oral delivery of poorly water soluble active pharmaceutical ingredients. At present, development of a microemulsion drug delivery system is mainly performed via pseudoternary phase diagram. Lipids and surfactants are combined randomly and selection of a suitable mixture is often solely based upon droplet size measurements of formulation. Within the framework of these aforementioned hypotheses, following specific objectives are set;

1. To formulate, develop and optimize oil in water microemulsion system containing Felodipine using suitable oil, surfactant and co-surfactant.
2. To formulate, develop and optimize self-microemulsifying drug delivery system containing Valsartan using suitable oil, surfactant and co-surfactant.
3. To select formulation components like oils, surfactants and co-surfactants based on the drug solubility studies.
4. To optimize the ratio of surfactant and co-surfactant to formulate stable microemulsion system using Pseudo ternary phase diagram.
5. To characterize the microemulsion and SMEDDS with respect to their physical properties.
6. To perform and compare In-vitro intestinal permeability study (ex-vivo drug release study) for optimized microemulsion, SMEDDS systems and plain drug suspension.
7. To develop and optimize Solid SMEDDS formulation of Valsartan using the optimized liquid SMEDDS formulation of Valsartan by adsorbing on solid carriers and to investigate the effect of hydrophilic and hydrophobic solid carriers on drug release.
8. To compare the in-vitro drug release study of optimized Liquid SMEDDS, Solid SMEDDS with marketed conventional tablet formulation of Valsartan
9. To perform pharmacokinetic study using suitable animal model to evaluate oral bioavailability of Felodipine when delivered as microemulsion and plain drug suspension.
10. To perform the stability study of optimized microemulsion, SMEDDS and Solid SMEDDS system.