Chapter 1

Proposed plan of work

1.1. Introduction:

High-throughput screening technologies in drug discovery present an efficient way to find new powerful substances. But in recent years it has become evident that the development of new drugs alone is not sufficient to ensure progress in drug therapy. Poor water solubility of drug molecules, insufficient bioavailability, fluctuating plasma levels or high food dependency is the main and common problems. Major efforts have been spent for the development of customized drug carriers to overcome the disappointing in vivo fates of the drug. For carriers non-toxicity (acute and chronic), sufficient drug loading capacity, possibility of drug targeting, controlled release characteristics, chemical and physical storage stability (for both drug and carrier) and feasibility of scaling up production with reasonable overall costs are requested (W. Mehnert et al 2001) (G. M. Barratt et al., 2000) (P. Couvreur et al 1995).. Colloidal carriers have attracted the main interest because they are promising systems to fulfill the requirements mentioned above. But in the first place, nanosized carriers are treated as hopeful means to increase the solubility and therefore the bioavailability of poorly water-soluble active ingredientsbelonging to the classes II and IV in the biopharmaceutical classification system (BCS)

The common characteristic of all colloidal carriers is the submicron particle size. Nanometric carriers might differ in materials, composition, drug loading and application spectrum. Corresponding to the broad diversity of colloidal carriers, the possible administration routes vary. Dermal, peroral, parenteral, ocular and pulmonary applications are known for nanocarriers.

In recent years, considerable emphasis has been given to the development of microemulsion (o/w or w/o) as drug carrier system because of its improved drug solubilization, long shelf life, ease of preparation, modified drug release characteristic, improvement of bioavailability etc. Microemulsion allows the incorporation of hydrophilic as well as lipophillic compound depending on their internal structure. These aggregates have been described as reservoir systems, which allow slow release of drugs thus providing prolonged effects and avoiding high concentration in the blood. Microemulsion when formulated with balanced concentration of surfactant / alcohol and oils of pharmaceutical use may be used for topical application in therapeutic system.

Since microemulsion contains surfactant in its components, the application on the skin surface usually produces an increase in the membrane permeability and thus facilitating transdermic transport. Since o/w microemulsions are able to incorporate lipophillic substances, they can be used to facilitate the administration of water insoluble drugs.

The following are the possible mechanism of oral bioavailability enhancement

1. Enhanced wetting of hydrophobic solids with formulation components resulting in enhanced rate of dissolution.
2. Increased rate of dissolution into the aqueous environment from oil droplets of high surface area
3. Enhanced thermodynamic activity via super-saturation of the aqueous environment of the gastrointestinal tract
4. Promotion of absorption via intrinsic lipid pathways.
5. Targeting of small hydrophobic particles toward Peyer's patches.
6. Short circulating of the aqueous boundary layer
7. Inhibition of active drug efflux from enterocytes.

A marketed oral formulation of cyclosporine (Sandimune, Neural®), a microemulsion preconcentrate with self emulsifying properties, is reported to improve oral bioavailability and reduce inter and intra subject variability in cyclosporine pharmacokinetic. For selecting a suitable surfactant / cosurfactant blend, it is important to asses a) the drug solubility in various components b) the area of self emulsification region in the phase diagram c) droplet size distribution.

In the middle of the 1990s, the attention of different research groups has focused on alternative nanoparticles made from solid lipids, the so-called solid lipid nanoparticles (SLN or lipospheres or nanospheres). The main features of SLN are the excellent physical stability, protection of incorporated labile drugs from degradation, controlled drug release (fast or sustained) depending on the incorporation model, good tolerability and site specific targeting. Potential disadvantages such as insufficient loading capacity, drug expulsion after polymorphic transition during storage and relatively high water content of the dispersions (70–99.9%) have been observed. No matter what the mechanism by which lipid based systems operate in the gastrointestinal tract, physical

chemical possesses at work in the lipid aggregate play a decisive role in the successful application of formulations. A better mechanistic understanding of the physical/ chemical aspects of the aggregates will aid the rapid and rational application of lipid based formulations.

Acyclovir:

Acyclovir is a synthetic purine nucleoside analogue, which is the most widely used antiviral agent used in its original form or as the prodrug valacyclovir in the treatment of infection caused by herpes simplex virus (HSV) and verciella zoster virus (VZS). The oral bioavailability of acyclovir ranges form 10% to 20% only and decreases with increasing dose. The decrease in bioavailability is a function of the dose and not the dosage form. Microemulsion and solid lipid nanoparticles may be one of best possible answer to overcome the low bioavailability as well as poor aqueous solubility of acyclovir.

Efavirenz:

Efavirenz is a non-nucleoside reverse transcriptase inhibitor that has been approved by the U.S. Food and Drug Administration for the treatment of HIV, which causes the acquired immunodeficiency syndrome (AIDS). It is practically insoluble in water (<10 μg/mL). Peak efavirenz plasma concentrations of 1.6-9.1 μM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. A delivery system which can utilize the inherent good lipid solubility of drug as well increase the oral bioavailability would be the advantageous to minimize the overall dose of the drug and reduction of overall cost of treatment, such goals can be achieved by microemulsion as well as by solid lipid nanoparticle systems.

1.2. Proposed plan of work

The proposed plan of work as follows:

1.2.1. Microemulsion:

1. Solubility determination of acyclovir and efavirenz in different oil, surfactant and cosurfactant.
2. Find out the optimum surfactant and cosurfactant mixture for particular oil by checking the interracial tension.
3. Preparation of microemulsion containing different surfactants, cosurfactant and oil.
4. Optimization of the microemulsion formulation by pseudoternary phase diagram study.
5. Characterizations of the developed microemulsion of acyclovir and efavirenz by methods useful for ascertaining the well documented microemulsions parameters (size, viscosity, electro-conductivity, percolation behavior, refractive index, % transmittance, Transmission electron microscopy etc)
6. In vitro drug diffusion study, using an appropriate method for evaluation of the release of acyclovir and efavirenz from microemulsion.
7. Stability study of the developed formulations at different storage condition.
8. In-vivo pharmacokinetic studies of the developed acyclovir and efavirenz microemulsion using suitable animal model
9. Comparative in-vivo studies of the developed formulation with commercially available dosage form.
10. Toxicity evaluation of the developed formulation using suitable animal model

1.2.2. Solid Lipid Nanoparticles (SLN)

1. Preparation of SLN by high pressure homogenization technique using different lipid, surfactant.
2. Optimizations of different process parameters of homogenization for the preparation of SLN.
3. Optimization of SLN formulation using suitable statistical model
4. Characterization of the developed SLN by methods useful for ascertain the well documented SLN parameters (size, shape, drug entrapment, surface charge, DSC etc)

5. In vitro drug diffusion study, using an appropriate method for evaluation of the release of acyclovir and efavirenz from SLN.
6. In-vivo pharmacokinetic studies of the developed acyclovir and efavirenz SLN using suitable animal model
7. Toxicity evaluation of the developed formulation using suitable animal model