Introduction

Chapter 1

1.1. Oral drug delivery

Drugs can be administered by oral, nasal, parenteral and topical routes. Unarguably, oral delivery is the most favorable route of drug administration in conscious and co-operating patients. This preference is due to convenience, possibility of self administration and improved compliance. Currently, more than 60% of drugs are marketed in the form of oral products [1].

However, more than 40% new chemical entities exhibit poor oral bioavailability due to undesired physicochemical and pharmacokinetic properties [2]. In some cases, over 90% of the administered drug is lost to presystemic metabolism [3]. This has, in some cases, led to the choice of other routes of administration, which may compromise the patient convenience and increase the risk of non-compliance.

Published results on structurally diverse drugs have shown that the inter-subject bio-variability is higher with poorly water soluble drugs [4]. This would be particularly of concern for drugs with a narrow therapeutic index or a steep dose versus effect profile. Poor oral bioavailability is increasingly an issue in the drug discovery process as well as dosage regimen design. Poor bio-availability has lead to administration of higher than normally required oral dose which often raises economic wastages, risk of toxicity, erratic and unpredictable responses. The challenge over the years has been to design techniques that will allow oral administration of most drugs, irrespective of their properties, to achieve a therapeutic systemic availability. This will be a worthy achievement since over 90% of therapeutic compounds are known to possess oral bioavailability limitations. Therefore, identification of some novel formulation approaches for drugs having poor water solubility is the basis of drug delivery research throughout the world.

There are several factors that influence oral bioavailability and these can be broadly divided into three categories:

(1) Drug properties and dosage form
(2) The physiology of the gastrointestinal tract (GIT)
(3) Patient factors

Drug properties include solubility, acid-base characteristics, partition coefficient and aqueous ionization potentials. The dosage form of an active ingredient can have a great effect on its solubility and permeability, thereby affecting bioavailability. The Biopharmaceutics Classification System classifies drugs into four groups:

Class 1: Highly soluble, highly permeable;

Class 2: Low soluble, highly permeable;

Class 3: Highly soluble, Low permeable; and

Class 4: Low soluble, low permeable.

Low bioavailability is often associated with oral dosage forms of Class 2 and Class 4 drugs. The poor solubility of these drugs make their oral delivery very challenging.

While the GIT forms a barrier to absorption, the presence of metabolizing enzymes and efflux proteins in the GI lumen, the physico chemical properties of the GI fluids and the irreversible removal by first-pass organs including the intestine, liver and lungs, are additional hurdles for drug absorption.

Patient related factors like age, sex, race, weight, presence of diseased condition etc. also affects the bioavailability of the drug [5].

Arising approaches, such as formulation modification techniques; novel drug delivery systems, which exploit the GI regionality of drugs, and include the pharmaceutical application of nanotechnology as an emerging area in drug delivery; inhibition of efflux pumps; and inhibition of presystemic metabolism have been more extensively addressed to overcome these barriers [4]. Some of the approaches to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs are:

1. The Pharmaceutical Approach
   - ✓ Lipid based system
   - ✓ Micronization
   - ✓ Use of salt form
   - ✓ Alteration of pH of the drug micro environment
   - ✓ Use of metastable polymorphs
   - ✓ Solute-solvent complex formation
   - ✓ Solvent deposition
   - ✓ Selective adsorption on insoluble carriers
   - ✓ Solid dispersion
   - ✓ Molecular encapsulation with cyclodextrins
2. The Pharmacokinetic Approach
3. The Biological Approach

One of the above promising techniques is **lipid based drug delivery system** which comprises Self Emulsifying Drug Delivery Systems (SEDDS), Nanoemulsion, Microemulsion, Solid lipid nanoparticles, mixed micelles, liposomes etc. The lipid

component enhances the extent of lymphatic transport and increases bioavailability directly or indirectly via a reduction of first pass metabolism [6]. Moreover, presence of lipid in the GIT stimulates an increase in Bile Salts (BS) and endogenous biliary lipids like Phospholipid (PL) and cholesterol (CL) leading to formation of BS/PL/CL intestinal mixed micelles and increases solubilization capacity of the GIT. Some surfactants, which are generally a part of these systems like Polysorbates, Cremophor etc., have the ability to minimize the activity of intestinal efflux transporters like p-glycoprotein (Pgp) efflux pump. Similarly, the enterocyte based metabolism is also reduced [7-9].

1.2. Lipid Based Systems

Formulation of lipid based system like SMEDDS and Nanoemulsion requires active drug, oil, surfactants/cosurfactants/ cosolvent; aqueous phase and additives.

1.2.1. Self Emulsifying Drug Delivery Systems (SEDDS)

SEDDS are mixtures of oils and surfactants, ideally isotropic, sometimes including co-solvents, which emulsify under conditions of gentle agitation, similar to those which would be encountered in the GIT. Typical size of a droplet lies in the range of 10-200 nm. Hydrophobic drugs can be dissolved in SEDDS allowing them to be encapsulated as unit dosage forms for peroral administration. When such a formulation is released into the GI lumen, it disperses there to form a fine emulsion containing solubilized drug thereby avoiding the dissolution step which frequently limits the rate of absorption of hydrophobic drugs from the crystalline state [10, 11]. Generally this can lead to improved bioavailability and a more consistent temporal profile of absorption from the gut thereby enabling reduction in dose, selective targeting of drug(s) toward specific absorption window in GIT and protection of drug(s) from the unreceptive environment in gut. SEDDS are easy and economical to manufacture and scale up. Simple mixer with an agitator and volumetric liquid filling equipment are in fact sufficient. Finally, SEDDS offer numerous delivery options like hard or soft gelatin capsules or tablets as final dosage form [12].

Table 1.1: Examples of marketed SEDDS formulations

Drug	Brand name	Company
Cyclosporine A	Neoral®	Novartis
Ritonavir	Norvir®	Abbott Laboratories
Saquinavir	Fortovase®	Hoffmann-LaRoche Inc.
Amprenavir	Agenerase®	Glaxo Smithkline
Bexarotene	Targretin®	Ligand
Calcitriol	Rocaltrol ®	Roche
Valproic acid	Convulex®	Pharmacia
Fenofibrate	Lipirex®	Genus

1.2.2. Nanoemulsion

Nanoemulsion is one of the promising technology, which is being applied to enhance the oral bioavailability of poorly soluble drugs. The term 'Nanoemulsion' (NE) refers to a kinetically stable dispersion of two immiscible liquids, such as oil and water stabilized by an interfacial film of surfactant molecules. Cosurfactant or cosolvent is used in many cases in addition to the surfactant, the oil phase and the water phase. The dispersed phase droplet size is about 5-200 nm [13]. Nanoemulsions are non-equilibrium systems with a spontaneous tendency to separate into the constituent phases. Nevertheless, nanoemulsions may possess a relatively high kinetic stability [14]. In addition, high kinetic stability, low viscosity and optical transparency make them very attractive systems for industrial applications in the pharmaceutical field as drug delivery systems [15]. The nanosized droplets leading to enormous interfacial areas associated with nanoemulsions would influence the transport properties of the drug, an important factor in targeted drug delivery [16]. The attraction of formulating o/w nanoemulsion systems lies in their ability to incorporate hydrophobic drugs into the oil phase thereby enhancing their solubility [17]. Nanoemulsions have been reported to make the plasma concentration profiles and bioavailability of drugs more reproducible. There are broadly two techniques (High and low energy methods) involved in the preparation of nanoemulsion. In high energy methods, large disruptive forces are provided by the use of mechanical devices such as ultrasonicators, microfuidisers and high pressure homogenizers which produce small sized droplets. In low energy methods, no external force is provided; instead it makes use of the intrinsic physiological properties of the system for production of nanoemulsions [18].

Table 1.2: Examples of marketed Nanoemulsion formulations

Drug	Brand name	Company
Propofol	Diprivcan®	Astra Zeneca
Dexamethasone	Limethason®	Mitsubishi Pharmaceutical
Palmitate Alprostadil	Liple®	Mitsubishi Pharmaceutical
Flurbiprofen axetil	Ropion®	Kaken Pharmaceutical
Vitamin A,D,E,K	Vitalipid®	Fresenius Kabi

General characterization and evaluation for lipid based systems

Lipid based drug delivery systems are generally characterized for- droplet size and distribution measurement, drug content, percent transmittance, emulsification time, thermodynamic stability studies, dispersibility, zeta potential, drug precipitation /stability on dilution and *in vitro*, *ex-vivo* drug release and *in vivo* studies [19].

1.3 INTRODUCTION TO THE DRUGS

1.3.1) Nisoldipine

Nisoldipine (NISO), a calcium channel blocker of the dihydropyridine class, is used in the treatment of hypertension. It acts primarily on vascular smooth muscle cells by stabilizing voltage gated L-type calcium channels in their inactive conformation. It is a BCS class II drug. The chemical name of NISO is 3, 5-pyridinedicarboxylic acid, 1, 4-dihydro-2, 6-dimethyl-4-(2-nitrophenyl)- methyl 2-methyl-propyl ester corresponding to molecular formula of $C_{20}H_{24}N_2O_6$.

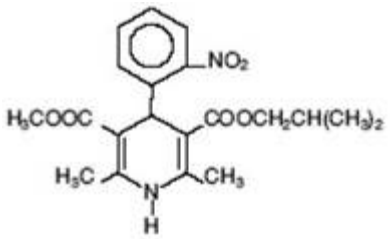

Figure 1.1. Structural formula of NISO

NISO is a yellow crystalline substance, practically insoluble in water and having molecular weight of 388.4. The absolute bioavailability of NISO is about 5% while the half life is 7-12 h. The low bioavailability is partly due to pre-systemic metabolism in the gut wall, which decreases from the proximal to the distal parts of the intestine [20]. A pronounced food-effect is observed when the product is administered with a high-fat

meal resulting in an increased peak concentration (C_{max}) of up to 245%. It has also been reported that incorporation of lipids can enhance the dissolution property of NISO [21].

1.3.2) Dabigatran etexilate

Dabigatran (DAB) is a potent, synthetic, non-peptide competitive, rapidly acting oral direct thrombin inhibitor belonging to BCS class II. It is poorly absorbed following oral dosing; hence needs to be administered in the form of pro-drug: Dabigatran Etexilate (DE) which does not possess anticoagulant activity. After oral administration, DE is rapidly absorbed and converted to DAB by esterase-catalysed hydrolysis in plasma. Furthermore, DE is also used in its salt form Dabigatran Etexilate Mesylate (DEM) which specifically and reversibly inhibits thrombin, the final enzyme in the coagulation cascade. Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. DAB also inhibits free thrombin, fibrin-bound thrombin and thrombin induced platelet aggregation. The granted indication is primary prevention of venous thrombo embolism in patients undergoing elective major orthopedic surgery (total knee replacement or total hip replacement surgery). It is also indicated for the treatment of deep venous thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5-10 days [22]. In 2010, it was approved in the US and Canada for prevention of stroke and systemic embolism in patients with atrial fibrillation [23].

The chemical name of dabigatran etexilate is ethyl 3-[[2-[[4-[(Z)-N'-hexoxycarbonylcarbamimidoyl]anilino]methyl]-1-methylbenzimidazole-5-carbonyl]-pyridin-2-ylamino]propanoate. The molecular formula is $C_{34}H_{41}N_7O_5$. The molecular weight is 627.746 [23]. DE is a white to off white crystalline powder.

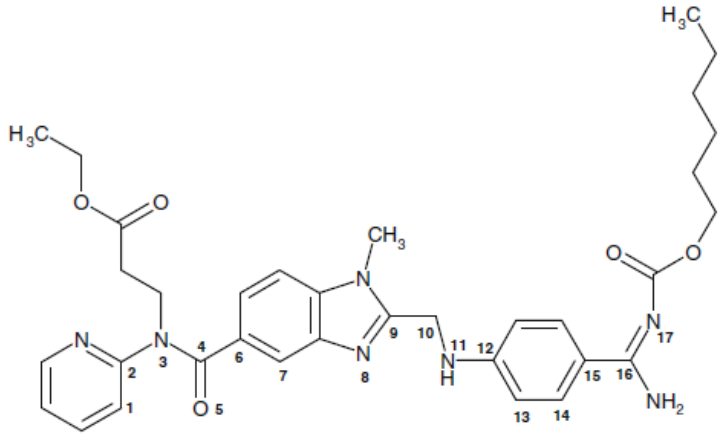

Figure 1.2. Structural formula of DE

The partition coefficient (log P) of the neutral form (free base) is 3.8. Solubility is strongly pH dependent with increased solubility at acidic pH and reduced solubility at alkaline pH. The absolute bioavailability of dabigatran following oral administration is approximately 6.5%. This low bioavailability is attributed to the low solubility, Pgp efflux and acid hydrolytic degradation. C_{max} is attained within 0.5 to 2.0 h post administration. Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 h. The biological half-life is 12-14 h in healthy volunteers and 14-17 h in patients treated for prevention of venous thromboembolism following hip or knee replacement surgery [24].

1.4 Aims and Objectives

The aim of the present study was to formulate SMEDDS and Nanoemulsion for poorly water soluble drugs- Dabigatran etexilate and Nisoldipine with the objective of enhancing their bioavailability and thereby reducing their therapeutic dose and associated side effects. It was envisaged that the present work would provide platform technology for developing lipid based formulations for drugs exhibiting poor water solubility.

1.5 Hypothesis

- Formulation of Nisoldipine into nano system could increase its solubility and avoid first pass metabolism by lymphatic uptake. Since it is reported that high fat meal increases the absorption of NISO, lipid based system could enhance the systemic bioavailability of NISO.
- Formulation of Dabigatran etexilate into nano system would increase its solubility. Also, incorporation of P-gp inhibitor (surfactant and co-surfactant) could reduce the drug efflux thereby increasing its bioavailability.

Hence, it was hypothesized that SMEDDS and Nanoemulsion formulations of NISO and DE might lead to improved oral bioavailability due to enhanced solubility, dissolution and absorption from GIT. Prepared formulations might also bypass the hepatic metabolism and increase plasma concentration of drug, through intestinal lymphatics.

1.6 Plan of work

- Literature search and assessment, procurement of active and inactive ingredients.
- Analytical method selection/ development (UV/HPLC).
- Preformulation studies : Screening of excipients and characterization of API, Drug-Excipient compatibility studies.
- Fabrication of SMEDDS and NE.
- Optimization of formulations using statistical design.
- Characterization and evaluation of droplet size/ distribution measurement, drug content, % Transmittance, zeta potential, *in vitro* and *ex-vivo* drug release study.
- Cell line studies: Viability, cell uptake and permeability studies.
- Stability studies : Short and long term studies of optimized formulations as per ICH guidelines.
- *In vivo* evaluation of the optimized formulations using suitable animal models: pharmacokinetic and pharmacodynamic study.

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