1. INTRODUCTION

1.1 Nanocarrier for Drug Delivery

Amongst various developing facets for drug delivery and its route of administrations, the fastest developing "nanotechnology" is expected to have an intense impact on medicine [1]. The application of nanotechnology for treatment is determined as nanomedicine. Amongst the approaches for utilizing nanotechnology developments in pharmaceuticals, various nanoparticulates offer distinctive advantages as drug delivery systems [2].

The practice of using nanoparticulate pharmaceutical carriers to enhance the *in vivo* efficiency of different drugs is well established over the past decades; both in pharmaceutical research and health care facilities; and does not need any further evidence [3]. Several nanoparticle-based oral drug delivery and drug targeting systems are currently developed or under development. Their use aims to diminish drug degradation upon administration, prevent undesirable side effects, and increase drug bioavailability. Pharmaceutical drug carriers are expected to be easy and reasonably cheap to prepare, have small particle size, possess high loading capacity, and, ideally, increase bioavailable fraction [4].

There are numerous engineered constructs or assembled nanoparticulate systems which are having shared feature of nanometer scaled size range from few to 250 nm. These include polymeric, lipid, metal, ceramic and silica nanoparticles, niosomes, liposomes, micelles, quantum dots, dendrimers, microcapsules, cells, lipoplexes and other different nanoassemblies [5]. Therapeutic moieties are either encapsulated, covalently attached, or adsorbed on such nanocarriers. These approaches can easily overcome drug solubility issues, particularly with the large proportions of newly emerging drug candidates formed using high-throughput drug screening as they are water insoluble. Overall, the development of nano-delivery systems for poorly soluble drugs represents a special task and it still faces some unresolved issues [1]. As low water-solubility results in dissolution rate limitation and low bioavailability, the therapeutic application of hydrophobic agents is associated with some serious problems. In addition, drug aggregation after oral ingestion might lead to other complications. Despite the fact that high Log P value and the resulting hydrophobicity and low water solubility are useful for a drug molecule to penetrate a cell membrane and reach important intracellular targets; the low water solubility hinders its absorption [6]. To overcome this, sometimes clinically acceptable organic solvents are used in formulations. Another alternative is to use various surfactants in

formulations of insoluble drugs. More often, lipid-based drug delivery systems (LBDDSs) for oral use are also designed. It presents a poorly soluble drug in a pre-solubilized form which eliminate dissolution of crystalline material as the rate-limiting step to absorption [7]. By introducing the drug in solubilized form, lipid-based formulations have the potential to increase bioavailability and eliminate the food effect. While considering LBDDS for oral delivery, it encompasses a broad array of formulations based on blends of acyl-glycerides, fatty acids, fatty acid derivatives, and emulsifiers. Here, in the present thesis, we have worked upon self-assembling system such as self-microemulsifying drug delivery system (SMEDDS) and Self assembled nano vesicles made of surfactants called "Niosomes".

1.2 Lipid Based Drug Delivery Systems (LBDDS)

Lipid-based delivery systems are becoming popular approach for the oral delivery of poorly water-soluble drugs, especially BCS class II drugs. Amidst possible mechanisms for increased oral bioavailability, improved solubilization in GIT is notable means of absorption enhancement [8].

The primary constituent in LBDDSs is the lipid part, which may be either used as single material or blend of several types of lipids. As per its definition, lipids are those components of biological material that are water insoluble but soluble in organic solvents. This definition includes materials such as cholesterol and other sterols in the category of lipids and aliphatic chain lipids such as fatty acids [7].

LBDDS range from liquid system, solid systems and vesicular to particulate drug delivery systems. The formulation approaches explored herein are:

A. Lipid based emulsion: Self Microemulsifying Drug Delivery System (SMEDDS)

The SMEDDS is an isotropic mixture of oil and surfactant which emulsifies in water with gentle agitation. SMEDDS spontaneously emulsifies if the entropy change favoring dispersion is larger than the energy required to increase the surface area of the dispersion.

SMEDDS produce emulsions with lipid droplet size of approximately <50 nm after its self-assembly in GIT. The small lipid droplet size and associated greater lipid surface area produced by SMEDDS formulations facilitates lipid digestion resulting in more rapid incorporation of drug into bile salt mixed micelles [9]. The SMEDDS components promote the intestinal

lymphatic transport of drugs. The main mechanisms include increased membrane fluidity to facilitate paracellular transport to increase absorption, stimulating lipoprotein/chylomicron production by lipid, inhibition of CYP450 enzymes, opening of tight junction, increased intracellular concentration and residence time by surfactants.

B. **Lipid as vesicular system: Niosomes**

Vesicular system is a unique strategy of drug delivery which enhances bioavailability and provides therapeutic activity in a controlled manner for a prolonged period of time for the encapsulated drug [10]. Niosomes are vesicular systems which arise when amphiphilic molecules self-assemble in aqueous media in an attempt to reduce the high energy barrier between the hydrophobic portion of the amphiphile and the aqueous disperse phase. Niosome, not only contains a non-ionic surfactant, but it also has cholesterol as a membrane stabilizer [1].

1.3 Drug candidate selection

A. Vardenafil HCl trihydrate

Vardenafil hydrochloride tri-hydrate (VDN) is a potent and highly selective inhibitor of cGMP specific Phosphodiesterase – 5 (PDE-5), which belongs to BCS class II. The chemical class of the drug is benzenesulfonamide. VAR has been proven to be safe and effective in treatment for Erectile Dysfunction (ED). It is the most potent and specific of the three commercially available PDE-5 inhibitors. The drug is generally well tolerated, with a favorable safety profile. However, it is poorly absorbed following oral administration and its absolute oral bioavailability is only 15% due to high first pass metabolism [11]. Hence it is necessary to develop a formulation that will help to overcome the above limitations and enhance its bioavailability.

B. Iloperidone

Iloperidone (ILO), a D2 and 5 HT2 receptor antagonist, is a drug of choice for treatment of schizophrenia because of reduced liability to extrapyramidal side effects. But its low solubility in water (0.012 mg/mL) restricts its effectiveness after oral administration. Significant first pass metabolism leads to poor absolute bioavailability. The absolute oral bioavailability of

Iloperidone is only 36% [12]. Hence it is necessary to develop a formulation which will help to overcome the above limitations.

1.4 Aims and Objectives

The current research was aimed at exploration of the potential of different Lipid based Drug Delivery Systems (LBDDS) for enhancement of oral bioavailability of the selected drugs, Vardenafil HCl trihydrate (VDN) and Iloperidone (ILO).

Objectives:

• To formulate nano sized lipid-based formulation development of selected molecules with improved dissolution rate and increased permeability which will ultimately increase absorption of the poorly bioavailable drugs

• To optimize formulations using Design of Experiment and Soft Computing Techniques

• To develop control space in the explorable space by specifying tolerance interval limits

• To characterize the fabricated systems

• To study *In vitro*, *Ex vivo* and *In vivo* performance of the developed formulations

1.5 Hypothesis

It is hypothesized that lipid based nano drug delivery system would lead to enhancement of bioavailability and thereby reduce dose by:

1. Dissolution of active substances in the dosage form.
2. Maintaining the drug in solution (supersaturation is possible) in the gastro-intestinal tract.
3. Stimulation of biliary secretion – presence of lipids in GI tract stimulates secretion of bile salts which forms mixed micellar solution with lipids of formulation and endogenous lipids such as phospholipid and cholesterol. The mixed micelles aids solubilization of drug.
4. Reducing first pass metabolism by targeting lymphatic route of absorption.
5. Facilitation of the drug permeability through the intestinal epithelium – Surfactants may increase the permeability of drug by disturbing the cell membrane as these amphiphilic

molecules are capable of partitioning into the cell membrane. Surfactant molecules embed themselves between the lipophilic tails of the bilayers, resulting in a disruption of the lipid-packing arrangement. Moreover, surfactants also have reversible effect on the opening of tight junction.

1.6 Plan of Work

1. Procurement of drugs, excipients and other chemicals and reagents
2. Analytical method development for drugs, residual solvents and biomarker detection
3. Formulation development of SMEDDS and Niosome formulations
4. Optimization of formulations using different statistical approaches
   Artificial Neural Network, Design of Experiment
5. Characterization of formulations
   Size, Zeta Potential, Rheology, DSC, FTIR, Cryo-TEM, XRD, Thermodynamic Stability Study, Dispersibility study, Cloud point determination, Drug Release
6. *In vitro* cell line studies
   Toxicity study, Cellular uptake, Confocal imaging, FACS study, Permeability
7. *Ex vivo* Permeation
8. *In vivo* animal studies
   Pharmacodynamics and Pharmacokinetics

References:

1. Torchilin, V. P. (2006). Introduction. Nanocarriers for Drug Delivery: Needs and Requirements. In V. P. Torchilin (Ed.), *Nanoparticulates as drug carriers* (pp. 1-8). London: Imperial college press.
2. Safari, J., & Zarnegar, Z. (2014). Advanced drug delivery systems: Nanotechnology of health design A review. *Journal of Saudi Chemical Society, 18*(2), 85-99, doi:https://doi.org/10.1016/j.jscs.2012.12.009.
3. Singh, R., & Lillard, J. W. (2009). Nanoparticle-based targeted drug delivery. *Experimental and molecular pathology, 86*(3), 215-223, doi:10.1016/j.yexmp.2008.12.004.

4. Souto, E. B., & Muller, R. H. (2010). Lipid Nanoparticles: Effect on Bioavailability and Pharmacokinetic Changes. In M. Schäfer-Korting (Ed.), *Drug delivery* (Vol. 197, pp. 115-142). Heidelberg: Springer Science & Business Media.

5. Ebbesen, M., & Jensen, T. G. (2006). Nanomedicine: Techniques, Potentials, and Ethical Implications. *Journal of Biomedicine and Biotechnology, 2006*, 1-11, doi:10.1155/JBB/2006/51516.

6. Barua, S., & Mitragotri, S. (2014). Challenges associated with Penetration of Nanoparticles across Cell and Tissue Barriers: A Review of Current Status and Future Prospects. *Nano today, 9*(2), 223-243, doi:10.1016/j.nantod.2014.04.008.

7. Liu, R. (2008). Introduction. In R. Liu (Ed.), *Water-insoluble drug formulation* (2nd ed., pp. 1-4). London: CRC press.

8. Porter, C. J. H., Pouton, C. W., Cuine, J. F., & Charman, W. N. (2008). Enhancing intestinal drug solubilisation using lipid-based delivery systems. *Advanced Drug Delivery Reviews, 60*(6), 673-691, doi:https://doi.org/10.1016/j.addr.2007.10.014.

9. Mundada, V., Patel, M., & Sawant, K. (2016). Submicron Emulsions and Their Applications in Oral Delivery. *Critical Reviews™ in Therapeutic Drug Carrier Systems, 33*(3), 265-308, doi:10.1615/CritRevTherDrugCarrierSyst.2016017218.

10. Kumar, G. P., & Rajeshwarrao, P. (2011). Nonionic surfactant vesicular systems for effective drug delivery—an overview. *Acta Pharmaceutica Sinica B, 1*(4), 208-219, doi:https://doi.org/10.1016/j.apsb.2011.09.002.

11. . Levitra (vardenafil HCl) (2008). USA: Bayer Pharmaceuticals Corporation.

12. Pharmacology Review of Iloperidone (2008). Department of Health and Human Services, Food and Drug administration, Center for Drug Evaluation and Research.