LITERATURE REVIEW
2. LITERATURE REVIEW

2.1 Methods for enhancement of bioavailability:

Pouton et al., 2000 in his article explained clearly about how the lipid formulations increase bioavailability of hydrophobic drug and he also provided with simple classification system for lipid formulations based on polarity of blend and their mechanisms in improving the bioavailability.

2.2 Lipid based drug delivery systems (LBDDS)

Hoffman et al., 1963 studied the impact of lipid based formulations of lipophilic drugs on in vitro solubilization and intestinal ex vivo permeability studies indicated the dynamic in vitro lipolysis and equivalent performance of different formulations for dexamethasone and increase order of MCT>LCT>SCT>H2O for gresiofulvin. The *ex vivo* permeability studies of SCT formulations resulted in enhanced permeation with doubled permeability coefficient for both drugs. The *in vivo* bioavailability of both drugs co related well with *in vitro* data i.e LCT=MCT=SCT for dexamethasone and MCT>LCT>SCT>H2O for gresiofulvin. The total work reveals that the *in vitro* lipolysis model would be a useful for oral lipid formulation for lipophilic drugs

Puton et al., 2000 showed that digestion of lipid based formulation can generate supersaturation which depends on the hydrophilicity of the formulation components. The report also investigated that high supersaturation ratios are strongly promoters of precipitation and crystallization from lipid rich formulations that did not contain any co-solvents. Hence proper selection and type of lipid and surfactant is necessary to ensure that the positive effect of supersaturation to drug absorption should be exploited before formulating lipid based system

Gao et al., 2007 in his study explained about the impact of formulation ingredients on the biopharmaceutical properties of drugs and their inclusion in formulation to increase bioavailability of drugs
**Shafiq et al., 2007** studied the development and bioavailability assessment of ramipril nanoemulsion formulation. Ramipril solubility was checked in various oils, Sefsol 218 was selected as an oil phase. Tween 80 and Labrasol were used as surfactants and carbitol and plurol olequie used as cosurfactants. Formulations were subjected to various evaluation tests globule size analysis, viscosity determination and TEM studies. The *in vivo* studies revealed significantly greater extent of absorption than the conventional capsule formulation.

**Richardson et al., 2007** in his article capsule filling gave information about various lipid excipients that can be filled in gelatin capsule and assessment of compatibility of fill materials with gelatin capsule.

**Kazi Mohsin et al., 2009** studied the precipitation of lipophilic drug after dispersion of the formulation into the water was observed. They also investigated the precipitation of lipophilic drugs from an dispersion of lipid formulations in water. The model drug fenofibrate with different lipid delivery system using medium chain glycerides polysorbates and propylene glycol resulted in turbid emulsions with water in-soluble lipid formulations and very low precipitation of maximum of 7% of dose of the drug was observed whereas with water soluble materials resulted in more rapid precipitation moreover extensive precipitation with micellar solution comprising only surfactants and co surfactants. The study also supports the supersaturation with respect to the drug on dilution but the extend of precipitation varied significantly between formulations and was influenced by the extent of supersaturation after dilution.

**Mohsin et al., 2013** shows the effects of different components of lipids and different ratios on the particle size. They studied the effect of lipid surfactant ratio and the presence of cosolvents on the performance of formulations. The report from Mohsin and Puton shows that mono and di glycerides in the formulation systems lead to increase efficiency of emulsification system.
2.3 Self emulsifying drug delivery systems

Simon Benita et al., 2004 stated the importance of SEDDS in market and gave a detailed description regarding the components used in SEDDS their role and the selection criteria. He also stated that Novel semisynthetic Amphiphilic compounds are preferred as oils and Nonionic surfactants with high HLB value are most widely recommended as they are less toxic.

Nagarsenker et al., 2007 clearly explained about screening of surfactants and cosurfactants for peroral delivery to achieve optimum emulsification for selected oil. The prepared SNEDDS were tested for Robustness to dilution with various media. In vitro release of SNEDDS was assessed by filling it into Size 4 Hard gelatin capsules using Type I dissolution apparatus. The prepared SNEDDS were robust to all dilutions and can accommodate high dose of Cefpodoxime proxetil and exhibited rapid release independent of pH of dissolution media.

Dimitrios G. Fatouros et al., 2008 gives a detail description about the different morphological changes which takes place through the lipolysis process. He observed these changes with the help of crto TEM apparatus. He observed that within 5 mins unilamellar vesicles were formed but as the lipolysis process progressed bilamellar vesicles were also formed. Few products were also seen which was from pancreatin. At the end of the lipolysis process only unilamellar vesicles were present. The zeta potential of the formulation was measured. This was done in order to find out the electrostatic interaction occurring during the lipid digestion. An increased to the zeta potential to the hydrolyzing SNEEDS observed v/s time. This preannounced changes occurred at different time is an qualitative indication of the interactions occurring on the droplet surface expressing the degree of partition of bile salts on the surface which is a reflection of changes in the zeta potential values.

Shakeel et al., 2008 studied the stability and evaluation of celecoxib nanoemulsion prepared by low energy emulsification method. Stability studies were performed for the period of 3 months. The results indicated that stability of celecoxib can be enhanced in nanoemulsion formulation prepared using tween 80.
**Basalious et al., 2009** prepared SNEDDS containing bioenhancers cremophor/tween 80 for improvement of dissolution and oral absorption of lacidipine. In his study he found that there is a good correlation between rapid emulsification and lower content of oil and higher content of co surfactant which result in lower viscosity of the system. The optimized formulation having lower particle size, lower viscosity showed good increase in drug dissolution rate compared to aqueous drug suspension.

**Elnaggar et al., 2009** prepared a self- nano emulsifying drug delivery system using capryol 90 and maisine 35-1 as oils, cremophor RH 40 and propylene glycol as surfactant and cosurfactant. Tamoxifen citrate is a highly lipophilic drug, and having first-pass metabolism and P-gp pump efflux in intestine. The prepared SNEDDS showed a significant increase in release rate compared to drug suspension and anticipated to solve oral problems of tamoxifen citrate.

**Ghosh et al., 2009** in his study demonstrates that the microemulsion formulation can be employed to improve the bioavailability of a poorly absorbed drug Acyclovir. The ratio of Labrasol:Plurololeique:Labrafac played a major role in formulating the microemulsion. The optimum microemulsion formulation contained labrafac 10%), labrasol (32%), plurol oleique (8%), and water (50%), which was a transparent and less viscous system. After oral administration in rats, the microemulsion showed an absolute bioavailability of 27.83%, which is 12.78 times higher than that of commercially available tablets (Aquivir).

### 2.4 Lipolysis

**Zangenberg et al., 2001** the lipolysis model was characterized and evaluated for probucol and danazol in aqueous phase. The effect of different levels of bile salts from 5 to 30 mM resulted in increased solubility of the drugs ie the increased concentration of bile salts resulted in increased aqueous solubility of the drugs. Investigation also revealed probucol dissolution depends on the partition between lipophilic and aqueous phase on the other hand dissolution of danazol is dependent on solubilization capacity of aqueous medium. The investigation was based on the oils soybean which is LCT and oleic acid MCT.
Zangenberg et al., 2001 the effect of continuous addition of calcium on the rate of lipolysis was reported. It was shown that the rate of lipolysis can be controlled by rate of addition of calcium. The initial hydrolysis rate was influenced by bile salt concentration and after the initial stage hydrolysis become dependent on the rate of calcium addition. The article also reveals the lipase activity had only a minor effect on the lipolysis. The oil used in this case was soybean oil.

Yvonne Elisabeth Arnold et al., 2011 suggests that the drug has got an effect on the oil, HLB value, viscosity and the critical packaging parameters. The drug effect on oil viscosity and the surface tension appear to play a minor role in reducing the lipolysis rate and the lipolysis kinetics was not effective by the drug load. They studied the effect of concentration of various poorly water soluble drugs on in vitro lipolysis rate of MCT. Different drugs exhibited varying effects on the oil, viscosity and the surface tension. However all drugs significantly lowered the apparent lipolysis rate of the oil. It also reports that the drug orlistat practically blocked lipolysis because of a potent direct inhibition.

Mohsin et al., 2012 investigated the lipid formulation digestibility in the simulated GI media. Oils pertaining to LCT and MCT with non ionic surfactants were studied. The formulations were subjected to in vitro digestion to predict the fate of the drug in GI tract after exposure of the formulation to pancreatic enzymes and bile. The digestion of MCT was faster than the LCT. But solubilising capacity in the post digestion was less. MCT are good solvents for model drug fenofibrate since it is rapidly digested but to improve the drug concentration in post digestion long chain mixed glycerides is suggested.

2.5 Lymphatic absorption

Christopher J.H. Porter et al., 2001 described highly lipophilic candidate drug molecules has led to an increase in interest in intestinal lymphatic drug transport and they provide a brief background to the mechanism of access of drugs to the intestinal lymph and the role of lipid digestion and absorption in the stimulation of lymphatic transport. Recent studies are described in which the extent of lymphatic transport of a highly lipophilic antimalarial, halofantrine, was investigated after post-prandial administration to
greyhound dogs. Finally the possible future directions for studies of intestinal lymphatic transport are discussed, including the use of cell culture models.

**Glenn A. Edwards et al., 2001** in this study says about the drug transport via the intestinal lymphatic system has been shown to contribute to the absorption of a number of orally administered highly lipophilic drugs. The developed of improved oral formulations, the use of appropriate animal models is required for to assessment the absorption. This describes in detail the conscious rat model in laboratory purpose to study the influence the outcome of intestinal lymphatic drug transport studies with these models.

**Michael Boyd et al., 2004** studied the stepwise surgical procedure to investigate the lymphatic transport of lipid-based oral drug formulations: Cannulation of the mesenteric and thoracic lymph ducts within the rat. They were concluded that the animal model can be utilized for the assessment of drug transport by the lymphatic and for determining what percentage of lymphatic transport is observed from the results of only intestinal lymphatic study.
AIM AND OBJECTIVE
3. AIM AND OBJECTIVES OF THE STUDY

Aim of the present work was to develop a novel o/w self nanoemulsifying drug delivery system for poorly soluble BCS class II drugs Atorvastatin, Fenofibrate and Olanzapine using low energy spontaneous emulsification method.

The major objectives of the present investigation include

- Selection of oil through lipolysis (lipid digestion) and characterization for the development of o/w self nanoemulsifying drug delivery system
- Nanoemulsion formulation development and optimisation by spontaneous emulsification technique
- Evaluation of nanoemulsions for self-emulsification, particle size, thermodynamic stability studies and in vitro release behaviour studies
- In vivo bioavailability study and assessment of pharmacokinetic data
- Intestinal lymphatic absorption study