1. INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Oral drug delivery is used from many years through different dosage forms because of its easiness in administration, good patient compliance and agility in intend of dosage form. (Jain K. K., 2008). It has been projected that between 40 - 70 %t of new chemical entities (NCE) inflowing drug development programs have poor water solubility. (Hauss D. J., 2007) So poor bioavailability is a problem often faced in the process of drug development. Improved bioavailability of poor water soluble drugs becomes far more challenging pharmaceutical scientist.

1.1.1 Solubility and Process of Solubilization

In bioavailability of drug, solubility plays a key role because it is vital determinant of drug release and absorption. Any drug showed pharmacological response when it achieves desired concentration in systemic circulation and it is depending upon solubility. Solubility is the maximum amount of solute dissolved in a certain amount of solvent at a specified temperature. (Shinde A. J., 2007)

1.1.1.1 Process of solubilization

The process of solubilization is shown in Figure 1.1.

Factors affecting solubility (James K., 1986)

- Particle size
- Temperature
- Pressure
- Other: Nature of the solute solvent, Molecular size, Polarity, Polymorphs
1.1.2 Bioavailability

1.1.2.1 Absolute bioavailability and Relative bioavailability

**Absolute bioavailability**

Intravenous dose is selected as a standard because the drug is administered directly into the systemic circulation (100% bioavailability) and avoids absorption step. Intramuscular dose can also be taken as a standard if the drug is poorly water soluble. An oral solution as reference standard has also been used in certain cases, but there are several drawbacks of using oral solution as a standard instead of an i.v. dose. (Brahmankar D. M., et al., 2009)

**Relative or comparative bioavailability**

It is also termed as comparative bioavailability. It is denoted by $F_r$. In contrast to absolute bioavailability; it is used to characterize absorption of a drug from its...
formulation. F and Fᵣ are generally expressed in percentage. (Brahmankar D. M., et al., 2009)

1.1.2.2 Methods for enhancement of bioavailability

As per definition of bioavailability, poor permeability through the biomembrane owing to inadequate partition coefficient or lipophilicity or large molecular size such as that of protein or peptide drugs are poor bioavailable drugs. Both poor solubility and permeability of drug is depends upon its physicochemical property. (Brahmankar D. M., et al., 2009)

**Biopharmaceutical Classification System (BCS)**

Based on intestinal permeability and solubility of drugs, Amidon et al., developed Biopharmaceutical Classification System (BCS) which classify drugs into one of the four groups.

**Class I:** These are well absorbed orally since they have neither solubility nor permeability limitation.

**Class II:** Shows variable absorption owing to solubility limitation.

**Class III:** also shows variable absorption owing to permeability limitation.

**Class IV:** are poorly absorbed orally owing to both solubility and permeability limitation.

There are three approaches in overcoming bioavailability problems are:

- **Pharmaceutical approach:**
  It includes alteration of formulation, manufacturing process or physicochemical properties of drug devoid of changing chemical structure.

- **Pharmacokinetic approach:**
  It includes modification of pharmacokinetic of drug by changing its chemical structure by developing new chemical entity with desirable feature or prodrug design.

- **Biological approach:**
In include alteration of route of drug administration such as altering from oral to parenteral route.

Pharmacokinetic approach has many drawbacks such as expensive, time consuming, repetition of clinical studies and long time of regulatory approval. Hence pharmaceutical approach is mainly aimed at altering the biopharmaceutical properties of drug by using one of the following ways:

- **By enhancing drug solubility or dissolution rate:**
  - Micronization
  - Nanonization
  - Supercritical fluid recrystallization
  - Spray freezing into liquid
  - Evaporative precipitation into aqueous solution
  - Use of surfactants
  - Use of salt forms
  - Use of precipitation inhibitors
  - Alteration of pH of drug microenvironment
  - Use of amorphous, anhydrates, solvates and metastable polymorphs
  - Solvent deposition
  - Precipitation
  - Selective adsorption on insoluble carriers
  - Solid solution
  - Eutectic mixture
  - Solid dispersion
  - Molecular encapsulation with cyclodextrin

- **By enhancing drug permeability across biomembrane**
  - Lipid technology
  - Ion pairing
  - Penetration enhancers

- **By enhancing drug stability**
  - Enteric coating
  - Complexation
- Use of metabolism inhibitors

By Gastrointestinal retention

1.1.2.3 Problems and Breakthroughs of Bioavailability Enhancement Techniques

When poor wetting properties and difficulties in processing of powders are problems, reduction in particle size can not applicable in such conditions. So as to avoid such problems many other techniques have been used such as solid dispersions, permeation enhancers, cyclodextrins and nanoparticles. In fact, in some special cases, such approaches have been doing well. (Gursoy R. N., et al., 2004)

In the technique of reducing the size of particles, there is affinity for agglomeration of particles due to high surface charges on small discrete particles. (Vemula V. R., et al., 2010)

1.1.3 Lipid based drug delivery

Ideal properties of Lipid based formulations: (Cannon J. B., 2011)

1. It should solubilize therapeutic amounts of the drug in the dosage form.
2. It should maintain adequate drug solubility over the entire shelf-life of the drug product (generally 2 years) under all anticipated storage conditions.
3. It should provide adequate chemical and physical stability for the drug and formulation components.
4. It must be composed of approved excipients in safe amounts.
5. It should adapt to the digestive processes of the GI tract such that digestion either enhances or maintains drug solubilization.
6. It should present the drug to the intestinal mucosal cells such that absorption into the cells and into the systemic circulation is optimized.

Lipid formulation classification system

In 2000 Pouton C. W. was introduced the Lipid Formulation Classification System (LFCS) as a working model (Pouton C. W. 2000) and an extra ‘type’ of formulation (Type IV) was added in 2006 (Pouton C. W. 2006). Now days the LFCS is concentrated broadly in the pharmaceutical industry to find a harmony that can be
utilized as a support for comparing the performance of lipid-based formulations. (Pouton C. W., et al., 2008).

1.1.4 Self Micro Emulsifying Drug Delivery System

Self-emulsifying drug delivery systems (SEDDS) or self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants.

Gentle agitation and then by dilution in aqueous media, such as gastrointestinal fluids, these systems can form fine O/W emulsions or microemulsions (SMEDDS). Hence so as to enhance rate and extent of absorption of poorly water soluble drugs which shows dissolution rate limited absorption such a system is better. (Gursoy R. N., et al., 2004 and Kohli K., et al., 2010)

1.1.4.1 Formulation approach of SMEDDS

Components of SMEDDS

- Active Pharmaceutical Ingredient (API)
- Oils
- Surfactant
- Co-surfactant
- Co-solvent
- Consistency Builder
- Enzyme Inhibitor
- Polymers

Active Pharmaceutical Ingredient

Lipid based compound forms a possible platform for improving oral bioavailability of drug belonging to BCS class II and IV. For formulation of SMEDDS Log P value should be 2-4. Dose of API and melting point should be high. (Pouton C. W., et al., 2008, Kohli K., et al., 2010 and Patel M. J., et al., 2010)
**Oils:**

Major role of this component is to solubilize API, enhance self emulsification and intestinal lymphatic transport of API so that it can enhance drug absorption from GI tract. Hence its molecular structure is most important consideration. (Kimura M., et al., 1994) Edible oils are logically chosen component for SMEDDS but are not regularly selected because of its poor capacity to solubilize large amount of API. Hydrolyzed and modified vegetable oils shows good emulsification property with many surfactants and it also have good solubilizing property for API. Also their degradation products are like natural end product of digestion, hence extensively used in formulation of SMEDDS. (Gursoy R. N., et al., 2004, Patel M. J., et al., 2010)

**Examples:** Acconon CC 400, Acconon E, Acconon Sorb-20, Acrysol K 140, Brij 30, Brij 90 Campul GMO, Campul MCM, Caprol ET, Capryol 90, Captex 355, Carprofen, Imwitor 742, Labrafac CC, Labrafac Lipophile, Labrafac PG, Labrafil, Labrasol, Labrafac CM-1O, LabrafacLipophil WL 1344, Lauroglycol 90, Lauroglycol FCC, Miglylol 812, Olive oil, Peanut oil, Peceol, Plurol oleique, Sefsol ET, Sesame oil, Solutol, Solutol HS, Soybean oil, Sunflower oil, Triacetin, Paraffin oil, Neobee M5, etc.

**Surfactant**

Non-ionic surfactants such as solid and liquid Tween 80 having high HLB are generally used in SMEDDS. While selecting surfactant for SMEDDS safety is major consideration. Natural emulsifiers are safer than synthetic but have less self emulsification power. Drawback of non-ionic surfactant is that, it may reversibly change permeability of the intestinal lumen. Generally 30 and 60 % w/w concentration of surfactant is used to get stable SMEDDS. Larger concentration may cause GI irritations. (Gursoy R. N., et al., 2004 and Gupta R. N., et al., 2009)

**Co-surfactant**

In some combination of oil, surfactant and water there is formation of lamellar phase. Hence it is necessary to add co-surfactant so as to lower interfacial tension. (Patel M. J., et al., 2010) Co-surfactants having HLB value 10-14 are generally used in formulation of SMEDDS. (Gupta R. N., et al., 2009)
Examples of Surfactants and co-surfactants: Campul MCM C8, Capryol 90, Carbitol, Cremophor EL, Cremophor RH 40, Crodamol EO, Crodamol GTCC, Emulsifier OP, Ethoxylated polyglycolysed glycerides, Gelucire® 44/14, Glycerine, Glycerol, Hexanol, Labrafac PG, Labrafil 2609 WL, Lauroglycol FCC, Maisine 35-1 (glyceryl monolinoleate), Octanol, Oleic acid, PEG 200, PEG 400, Pentanol, Plurol Oleique, Plurol Oleique CC 497, Polaxamer 188, Polaxamer 407, Polysorbate 80, Propylene glycol, Solutol HS 15, Span 20, Span 80, Transcutol, Transcutol HP, etc.

Co-solvent

So as to facilitate dissolution of drug in oily base, polyethylene glycol are necessary to be used as co-solvent in microemulsion formulations. While using organic solvents and alcohols as a co-solvent in such a condition have disadvantage of precipitating drug after evaporation in the hard or soft gelatin shell in conventional SEDDS. (Gursoy R. N., et al., 2004)

Consistency Builder

Materials such as beeswax, stearic acids, cetyl alcohol and tragacanth are used to modify consistency of microemulsion. (Gupta R. N., et al., 2009)

Enzyme Inhibitor

If there is degradation of drug due to enzymatic action there is need of using enzyme inhibitors in SMEDDS formulations. (Shinde G., et al., 2011)

Polymers:

So as to get sustained release SMEDDS formulations, inert polymer having matrix forming capability and which are not ionizable at physiological pH can be used in the proportion of 5-40% of its weight of composition. Such polymers form gel when comes in contact with GI fluid and release the drug for extended period of time by diffusion mechanism. Examples are hydroxypropylmethyl cellulose and ethyl cellulose. (Shinde G., et al., 2011)

1.1.4.2 Construction of Pseudo Ternary Phase Diagram

Pseudo-ternary phase diagram is constructed by water titration method. For identification of micro emulsion region and its relation with other phases of system, it is necessary to construct pseudo-ternary phase diagram. It gives proper concentration of different components of micro emulsion. At particular
surfactant/cosurfactant weight ratio pseudo-ternary phase diagrams of oil, water and surfactants co-surfactant mixture is constructed by mixing all these ingredients in to glass vials and then titrated with water at room temperature. Then system is visually inspected so as to determine monophasic or biphasic system. System is monophasic when there is formation of clear and transparent mixture. This sample is marked as point in phase diagram and micro emulsion reagation is one which is formed by area covered by such points. (Jha S. K., et al., 2011)

![Figure 1.2: Hypothetical ternary phase diagram](Adopted from Reference Lawrence M. J, et al. 2000)

### 1.1.4.3 Evaluation of SMEDDS


- Visual assessment
- Droplet polarity and droplet size
- Zeta potential
- Transmission Electron Microscopy
- Turbidimetric Evaluation
• Refractive Index and Percent Transmittance
• Thermodynamic stability study
• In-vitro Intestinal Permeability Studies
• Absorption study

1.1.4.4 Solid Self Micro Emulsifying Drug Delivery System (S-SMEDDS)

Generally these SMEDDS are formulated in liquids or get encapsulated in soft gelatin capsules. In this case liquid SMEDDS showed incompatibility with shells of soft gelatin. Also this dosage form is not convenient to use and there are many disadvantages in manufacturing process which may increase cost of production. Hence it is necessary to convert liquid SMEDDS to solid. (Kumar A., et al., 2010)

1.1.4.5 Self-emulsifying sustained/controlled-release system

Sustained release dosage form of SMEDDS can be formulated by using inert polymer having matrix forming capability and which are not ionizable at physiological pH. Such polymers form gel when comes in contact with GI fluid and release the drug for extended period of time by diffusion mechanism. (Gupta R. N., et al., 2009, Tahara K., et al., 1995, Vyas S. P., et al., 2002 and Yi T., et al., 2008)

Yi T., et al. developed CR SMEDDS for oral delivery of Nimodipine using HPMC by spray drying technique. In this formulation hydration of HPMC occurs when it comes in contact with aqueous media which form gel layer and gives controlled release of drug. (Yi T., et al., 2008)
1.1.4.6 **Biopharmaceutical aspects of SMEDDS** (Shah I., 2001 and Kumar A., et al., 2010)

- Alterations or reduction in gastric transit
- Increase in effective luminal drug solubility
- Stimulation of intestinal lymphatic transport
- Changes in the biochemical barrier function of the GI tract
- Changes in the physical barrier function of the GI tract
- Effect of oils on the absorption
1.1.4.7 Pharmaceutical products formulated as self-emulsifying systems


<table>
<thead>
<tr>
<th>Drug name</th>
<th>Trade name</th>
<th>Company</th>
<th>Dosage form</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>Agenerase®</td>
<td>GSK</td>
<td>SGC</td>
<td>HIV antiviral</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>Targretin®</td>
<td>Ligand</td>
<td>SGC</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Rocaltrol®</td>
<td>Roche</td>
<td>SGC</td>
<td>Calcium regulator</td>
</tr>
<tr>
<td>Cyclosporine A/I</td>
<td>Neoral®</td>
<td>Novartis</td>
<td>SGC</td>
<td>Immune suppressant</td>
</tr>
<tr>
<td>Cyclosporine A/II</td>
<td>Sandimmune®</td>
<td>Novartis</td>
<td>SGC</td>
<td>Immune</td>
</tr>
</tbody>
</table>

Figure 1.4: Pathways for drug absorption from lipid based formulations (Adopted from Reference Porter C. J. H., et al., 2007 and Shah I. 2011)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine A/III</td>
<td>Gengraf®</td>
<td>Abbott Laboratories</td>
<td>Immune suppressant</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Lipirex®</td>
<td>Sanofi-Aventis</td>
<td>Antihyperlipoproteinemic</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Solufen®</td>
<td>Sanofi-Aventis</td>
<td>NSAID</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir®</td>
<td>Abbott Laboratories</td>
<td>HIV antiviral</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Fortovase®</td>
<td>Hoffmann-La Roche Inc.</td>
<td>HIV antiviral</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Vesanoid®</td>
<td>Roche</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Convulex®</td>
<td>Pharmacia</td>
<td>Anti-epileptics</td>
</tr>
</tbody>
</table>
1.2 REVIEW OF LITERATURE

Shah N. H., et al., (1994) investigated emulsification efficiency of polyglycolyzed glycerides (PGG) and polyethylene glycol (PEG). They prepared SEDDS using different concentrations of PGG as emulsifiers. Neobee M5 and Peanut Oil were selected as oil. Drug having good solubility in oil was selected for this study. Study showed that, PGG can be used as emulsifier for preparation of SEDDS.


Khoo S. M., et al., (1998) formulated self-emulsifying formulation of halofantrine. These formulations were evaluated for self emulsification efficiency and droplet size determination and optimized formulation. Optimized formulations were evaluated for absolute bioavailability study. Results showed that, formulations prepared by long-chain glyceride have good emulsification capacity in water than that of prepared by medium-chain glyceride. Study concluded that, bioavailability of halofantrine can be enhanced by lipid based formulation.

Kim H. J., et al., (2000) developed SMEDDS of idebenone using Labrafil 2609, Labrasol. Transcutol and Plurrol oleique WL1173 so as to enhance bioavailability. Results showed that, in-vitro dissolution rate of drug were increased 2 folds than that of tablet. Study concluded that, SMEDDS can be used as substitute for traditional oral formulations to enhance bioavailability of idebenone.


Holm R., et al., (2003) examined oral absorption and lymphatic transport of halofantrine in SMEDDS containing triglycerides, Maisine-35-1 and Cremophor EL. Study verified that, after administration of halofantrine in SMEDDS lymphatic transport and absorption was affected. Study concluded that, by using different
structure of triglycerides it is achievable to enhance lymphatic transport of compound without affecting its availability.

Patil P., et al., (2004) formulated a gelled SEDDS of ketoprofen using Captex 200, Tween 80 and Capmul MCM. Sustained drug release was achieved by using Silicon dioxide as gelling agent which retarded release of drug. Study concluded that, as concentration of gelling agent increases it increase droplet size of emulsion formed which helps in slowing drug diffusion. It was also found that, as concentration of co-surfactant increase drug release from dosage form also increases.

Kang B. K., et al., (2004) prepared SMEDDS of simvastatin using Carpyrol 90, Cremophor EL and Carbitol. Prepared formulations were evaluated for droplet size determination, in-vitro dissolution study and bioavailability study. Results showed that, in-vitro of drug was much higher that that of conventional tablet. It was also found that, there was 1.5 fold increases in bioavailability than tablet. Study concluded that, SMEDDS can be beneficial for oral delivery of poorly water soluble drug such as simvastatin.

Subramanian N., et al., (2004) developed and optimized SMEDDS of Celecoxib using simplex lattice mixture design. Prepared SMEDDS were evaluated for Clarity, solubility, in-vitro dissolution and in-vivo study. Results showed that, there was significant increase in rate and extent of absorption of drug as compared to capsule. Relative bioavailability with capsule was found to be 132 %. Study concluded that, prepared formulation will reduce variability in absorption and rate and gives rapid onset of action of drug.

Sha X., et al., (2005) studied effect of charge and dilution on TEER and permeability of mannitol by formulating SMEDDS using Labrasol and also studied effect of dilution of surfactant on ZO-1 and F-actin. Study concluded that, SMEDDS of both positive and negative charge containing Labrasol are capable of enhancing the paracellular transport of mannitol across Caco-2 cell at different dilutions.

Ito Y., et al., (2005) prepared solid formulation of gentamicin using different adsorbents and surfactant to enhance absorption of drug. Florite RE, Neusilin US2 and Sylysia 320 were used as adsorbents and Labrasol was used as surfactant. Solid preparation was prepared to study absorption of drug in rat and dog. Results showed
that Florite RE gives more absorption of drug both in rat and dog. Study concluded that by using adsorbent and surfactant system oral solid formulations can be prepared so as to increase absorption of poorly absorbable drug.

**Wu W., et al., (2006)** prepared SMEDDS of silymarin. From solubility study of drug Tween 80, ethyl alcohol and ethyl linoleate were selected as formulation components. Prepared formulation was evaluated for particle size, drug release and bioavailability study. Results showed that, there is increase in particle size as increase in drug loading in formulation. Drug release was much higher than that of crude drug powder. Study concluded that by using SMEDDS bioavailability of silymarin can be enhanced.

**Nazzal S., et al., (2006)** evaluated different process parameters which affect release of drug from SNEDDS in tablet dosage form. SNEDDS of CoQ10 was prepared and granulated and evaluated for different micromeritic properties then converted into tablet. Prepared tablets were evaluated for dissolution and stability studies. Results showed that, different process parameters affect dissolution rate of drug from tablet. Study concluded that, controlled release of drug can be obtained from lipid formulations in tablet dosage form.

**Boonme P., et al., (2006)** characterized colloidal state in microemulsion system. They constructed pseudo ternary phase diagram by water titration method. Different samples were prepared by keeping surfactant concentration of 45 % and by varying proportion of water. Prepared samples were evaluated for appearance, viscosity, conductivity, DSC, SEM and NMR. Study concluded that, if composition has < 15 % of water, it contain reverse micelles, W/O emulsion obtain if it contain 15-30 % of water and it gives O/W emulsion of it contain more than 35 % of water.

**Shen H., et al., (2006)** prepared and evaluated SMEDDS of atorvastatin using Labrafil, PEG and Cremophor RH40. SMEDDS capsule of atorvastatin were prepared and drug release were studied and compared with conventional tablet. Results showed that release of drug was much higher from SMEDDS capsule than that of tablet. Study concluded that, bioavailability of drug can be enhanced using SMEDDS capsule than conventional tablet.
Patel A. R., et al., (2007) formulated and evaluated SMEDDS of fenofibrate. From solubility study of drug in different components oil, surfactant and co-surfactant were selected and pseudo ternary phase diagram were constructed. From this SMEDDS were prepared and evaluated for thermodynamic, dissolution, stability study and lipid lowering capacity. Study concluded that, SMEDDS can improve dissolution rate and hence bioavailability of drug which become substitute for oral drug delivery system.

Patil P., et al., (2007) formulated a SEDDS for simvastatin. Prepared SEDDS was evaluated for turbidometric analysis, particle size, in-vitro drug diffusion and in-vivo study in rat. Results showed that there were 5 fold reductions in plasma cholesterol and 4 fold reductions in plasma triglycerides when compared with reference formulation of drug suspension. Study concluded that, there was better biopharmaceutical performance of drug from SEDDS.

Cirri M., et al., (2007), formulated oral liquid spray formulation of xibornol using SMEDDS. Prepared formulations were evaluated for rheological, stability, SAXS and in-vivo study. The study found that, SMEDDS can be used to prepare stable and effective oral liquid spray formulation.

Patel D., et al., (2007) developed SMEDDS of Acyclovir. Prepared formulations were evaluated for different parameters. Absorption of drug from SMEDDS was compared with plain drug solution. Results showed that, there was 3.5 fold increases in bioavailability by SMEDDS. Study concluded that, bioavailability of drug can be enhanced using SMEDDS approach.

Lu J. L., et al., (2008) developed SMEDDS of 9NC to enhance bioavailability and anticancer effect. They prepared microemulsion of 9NC and characterized for citotoxicity and bioavailability study. Bioavailability and anticancer effect have been compared with suspension of 9NC. Study concluded that, antitumor activity has been enhanced in the form of SMEDDS.

Abdalla A., et al., (2008) developed self emulsifying formulation in the form of pellets by extrusion and spheronization technique. They have studied effect of dilution media and enzymatic digestion on solubilization of drug. In this study they found that, droplet size decreases after dilution. Study concluded that, solubilization depend on concentration of secretions like bile salts and phospholipid. SMEDDS can be
successfully transformed into pellets form and can become another method to encapsulate material into hard gelatin capsule.

**Yi T., et al., (2008)** developed a S-SMEDDS of nimodipine. Prepared S-SMEDDS was evaluated for *in-vitro* and *in-vivo* absorption study. Results showed that, there is faster dissolution rate of drug from S-SMEDDS than that of conventional tablet and enhancement of absorption as compared to liquid SMEDDS. Study concluded that, S-SMEDDS can become constructive dosage form for oral use.

**Yi T., et al., (2008)** developed a controlled release solid SMEDDS of nimodipine using HPMC. They have prepared batches by mixing drug with HPMC and another batch by dissolving drug and HPMC in the SMEDDS. Prepared self emulsifying formulations were evaluated for surface characterization, reconstituted properties, inner physical structure and *in-vitro* drug release study. Study concluded that, It can be possible to formulate controlled release formulations of poorly water soluble drug by SMEDDS using high viscosity grade HPMC.

**Mandawgade S. D., et al., (2008)** developed SMEDDS using natural lipophile as oil phase and also compared its performance with synthetic oils. For this study beta-Artemether was used as drug. Oil was previously evaluated for toxicity studies. Prepared SMEDDS was evaluated for globule size, *in-vitro* and *in-vivo* study. Study concluded that, performance of natural lipophiles is better than that of commercially available synthetic oils hence can be used in SMEDDS as it is safe.

**Woo J. S., et al., (2008)** developed SMEDDS of Itraconazole and studied and compared *in-vivo* study in human volunteers with marketed formulation having double dose. Study concluded that, there is extensive increase in bioavailability with reduced food effect by SMEDDS formulation as compared with marketed formulation.

**Shikov A., et al., (2008)** Prepared and characterized SMEDDS of flavonoids. Prepared SMEDDS formulation was evaluated for self emulsification capacity, droplet size and for bioavailability. Results showed that, there was 2-5 fold increase in bioavailability as compared to flavonoid in powder form.

Atef E., et al., (2008) formulated and evaluated SMEDDS of phenytoin and compared its relative bioavailability with marketed formulation. Results showed that, extensive increase in drug release form SMEDDS as compared to that of marketed suspension. Also in-vivo study showed improvement in bioavailability. Study concluded that, SMEDDS is promising formulation to increase drug release as well as bioavailability of poorly water soluble compounds.

Shaji J., et al., (2008) formulated and evaluated SMEDDS of Celecoxib. They optimized formulation using $3^3$ factorial design. Particle size was taken as response variable. Study showed that, concentration of different components showed prominent effect on particle size and appearance of dispersion.

Singh A. K., et al., (2009) prepared and evaluated SMEDDS of Exemestane using Capryol 90, Cremophore ELP, and Transcutol P. They compared drug release with marketed formulation in different pH. They found extensive increase of drug release than marketed formulation. They also compared absorption of drug with that of drug suspension. They found enhanced drug absorption from SMEDDS. Study concluded that, SMEDDS have potential of enhancing solubility, absorption and hence bioavailability of poorly water soluble drug.

Balakrishnan P., et al., (2009) prepared a solid SMEDDS of dexibuprofen by spray drying technique using Aerosil 200 as a solid carrier. After conversion in to solid form S-SMEDDS retains its self emulsification capacity. In-vitro drug release showed that, there was increase in drug release as compared to powder formulation. In-vivo study showed that increase in bioavailability. Study concluded that, in the form of Solid SMEDDS it retains all characteristics of liquid and it can become helpful solid dosage form.

Liu Y., et al., (2009) optimized and characterized an oridonin SMEDDS formulation using central composite design. In this study effect of concentration of oil and
surfactant and co-surfactant ratio has been studied. Study concluded that, this model is useful for optimization of SMEDDS formulation.

Agarwal V., et al., (2009) investigated effect griseofulvin SMEDDS addition to silica and silicate on flow properties and in-vitro drug release. Results showed that, increase in surface area increases dissolution of drug. Study concluded that, nature and amount of adsorbent affect flow properties and dissolution of drug in SMEDDS.

Setthacheewakul S., et al., (2010) developed and characterized of SMEDDS of curcumin in liquid and pellet. They studied in-vitro dissolution and in-vivo absorption of drug from liquid, pellets and plain (suspension of drug) curcumin. Results showed that there is enhancement of in-vitro dissolution and in-vivo absorption of drug from both the form of SMEDDS. Study concluded that, SMEDDS is promising way to enhance bioavailability of drug having poor oral bioavailability.

Nekkanti V., et al., (2010) developed and characterized S-SMEDDS of candesartan cilexetil. They first prepared liquid SMEDDS and then converted in to solid powder using adsorbent as solid carrier. In-vitro dissolution study performed on S-SMEDDS and marketed formulation. Results showed that, there is enhancement of dissolution of drug. Study concluded that, conversion in to solid form there is no any effect on self emulsification property of SMEDDS. Also there is enhancement of dissolution rate as compare to marketed formulations.


Deshmukh A., et al., (2010) formulated and evaluated SMEDDS of Furosemide to increase the dissolution rate of Furosemide. They studied in-vitro dissolution in acidic and basic pH. Results showed that, there is enhancement in dissolution rate as compared with marketed formulation. They also found that, drug release is not depend on pH. Study concluded that, this system increases pH independent dissolution rate and may enhance bioavailability.
Shukla J. B., et al., (2010) formulated SMEDDS of candesartan cilexetil and evaluated its *in-vitro* dissolution study. Results showed that, there is enhancement of solubility and dissolution rate. Study concluded that, by using SMEDDS approach solubility, dissolution and hence bioavailability of poorly soluble drug can be increased.

Patro M. N., et al., (2010) developed a stable SMEDDS of valproic acid (VPA) and evaluated its *in-vitro* potential. Results showed that, *in-vitro* drug release get enhanced as compared to pure drug and marketed formulation. Study concluded that, SMEDDS can become alternative approach for marketed formulation which can enhance dissolution rate.

Buyukozturk F., et al., (2010) studied how formulation design of SMEDDS affects physicochemical properties of micro emulsion which may affect gastrointestinal absorption of drug. They developed different formulations of SMEDDS and studied intestinal permeability and drug release. Study concluded that, formulation parameters affect different emulsion properties and hence formulation performance.

Zvonar A., et al., (2010) developed microencapsulation of furosemide SMEDDS so as to increase solubility and permeability of drug. Prepared SMEDDS encapsulated in Ca-pectin microspheres and evaluated for solubility, dissolution and permeability study. Results showed that there is enhancement in solubility dissolution and permeability as compared to microspheres of drug without SMEDDS. Study concluded that, encapsulation of SMEDDS can become useful formulation for oral drug delivery for drugs having poor oral bioavailability.

Krupa A., et al., (2010) evaluated interactions between Neusilin US2 and ibuprofen at higher temperatures. Different binary mixtures of drug and Neusilin US2 were prepared and studied using TGA, QMS and DSC. Study concluded that Neusilin US2 shows significant effect on stability of ibuprofen at higher temperature.

Bandhivadekar M. M., et al. (2011) prepared S-SMEDDS of Ramipril by adsorbent technique so as to enhance dissolution rate. Liquid SMEDDS adsorbed on Aerosil 200. Results showed that, dissolution rate have been enhanced as compared to marketed capsule. Study concluded that, S-SMEDDS is promising approach for enhancement of dissolution rate and hence bioavailability of poorly soluble drug.
1.3 NEED OF WORK

It is needed to develop S-SMEDDS of cardiovascular drugs such as Telmisartan and Verapamil Hydrochloride to enhance solubility, dissolution rate which may improve therapeutic performance and drug loading capacity so as to develop alternative to traditional oral formulations to improve bioavailability.

1.4 OBJECTIVES OF WORK

By considering above need the objectives of present work are as follows:

➢ To develop liquid SMEDDS of Telmisartan and Verapamil Hydrochloride

➢ To develop S-SMEDDS of Telmisartan by spray drying technique using maltodextrin.

➢ To develop S-SMEDDS of Verapamil Hydrochloride by spray drying technique using HPMC K15M as water soluble solid carrier to modify the release pattern

➢ To develop S-SMEDDS of Telmisartan by adsorption technique

➢ To characterize liquid SMEDDS and S-SMEDDS for its globule size, PDI, zeta potential, viscosity, thermodynamic stability, reconstitution properties and micromeritic properties

➢ To carry out solid state characterization of S-SMEDDS

➢ To perform comparative determination of in-vitro release profile of S-SMEDDS and plain drug

➢ To perform ex-vivo intestinal permeability studies and bioavailability study for optimized S-SMEDDS