1. INTRODUCTION

1.1 BACKGROUND OF RESEARCH

Recently, obesity is increasing at an alarming rate, which is becoming a major public health issue with unaccountable health cost to an individual. In fact, it opens the door to develop various types of the metabolic disorders such as diabetes, hypertension and cardiovascular diseases, in addition to chronic diseases such as stroke, osteoarthritis, sleep apnea, some cancers and inflammatory consequences. Obesity is a disorder, characterized by the increase in body weight due to the excess amount of fat in the body. It is developed when energy intake is more than the energy expenditure. The body mass index (BMI) is considered as an indicator of obesity. It is defined as “the weight in kilogram divided by the square of the height in meters (kg/m$^2$)”. BMI above 25 kg/m$^2$ is defined as an overweight whereas, BMI above 30 kg/m$^2$ is referred as an obese. Obesity is classified into the various types based on body mass index. BMI in range of 30-34.9 is classified as class-I, BMI 35.0-39.9 is class-II and BMI > 40 is class –III (Table1). Here, class-I and class–II obesity shows moderate to high risk whereas class-III shows very high-risk factor.$^{1,2}$

<table>
<thead>
<tr>
<th>Type</th>
<th>BMI (kg/m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 - 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25 - 29.9</td>
</tr>
<tr>
<td>Obesity(Class –I)</td>
<td>30 - 34.9</td>
</tr>
<tr>
<td>Class-II</td>
<td>35.0 - 39.9</td>
</tr>
<tr>
<td>Class-III</td>
<td>&gt; 40</td>
</tr>
</tbody>
</table>

Table 1: Classification of obesity
There are various therapies available to treat obesity such as antiobese drugs may be taken to inhibit fat absorption in a body such as Orlistat. Some life style modifications like diet, exercise are helpful during therapy. If diet, exercise, medications becomes ineffective, surgery is preferred. Ayurvedic extracts such as Green tea extract, Guggul extract etc. found to be effective in management of the obesity. A traditional therapy like Panchkarma is practiced.  

Prevalence\(^2,4\)

The prevalence of obesity varies among countries based on races, heredity, age, sex, diet, eating pattern, life style and behavior. The extent of obesity is more in areas where modernization, economic development and urbanization has taken place. The WHO estimates that at least 500 million adults (greater than 10%) are obese worldwide till date i.e. 1 in 10 peoples, with higher rates among women than men. As per the data released by Mexico bariatric centre (2013), in India 84.3million people were found obese (Figure 1).

![Fig. 1: Prevalence of obesity world wide in 2013 (In Millions)](image)
Causes of obesity

An energy imbalance is the basic cause of the obesity as well as overweight. This imbalance is aroused due to difference in calories consumed and calories utilized by an individual.

It is caused due to,

- Increased consumption of high fat diet and energy dense food.
- An increase in physical inactivity due to the increasingly sedentary nature of various type of work, changing modes of transportation and increasing urbanization.
- The environmental and societal things change the dietary habits and physical activity patterns.
- Lack of development and supportive policy in sectors like environment, health, agriculture, urban planning, food processing, marketing and education.

Drugs used to treat obesity

Commonly prescribed weight-loss medications listed in Table 2

Table 2: Drugs used to treat obesity

<table>
<thead>
<tr>
<th>Name of the drugs</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>120 mg capsule three times a day with each main meal containing fat</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>10 mg or 20 mg tablet per day</td>
</tr>
<tr>
<td>Phentermine</td>
<td>15 mg /30 mg tablet per day</td>
</tr>
<tr>
<td>Topiramate</td>
<td>A combination product containing phentermine and topiramate extended-release called QSYMIA® is indicated for the management of obesity.</td>
</tr>
<tr>
<td>Bupropron</td>
<td>150 mg extended Release tablet</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>50 mg tablet</td>
</tr>
<tr>
<td>Diethylpropion Hydrochloride</td>
<td>25 mg / 75 mg tablet</td>
</tr>
</tbody>
</table>
Currently, orlistat is widely used anti-obesity agent. It acts in stomach and small intestine. It is obtained from *streptomyces toxytricini*. It inhibits pancreatic lipase and gastric lipase. It plays a crucial role in digestion of long chain triglycerides. It blocks lipase activity, hence triglycerides from the diet are not hydrolyzed into absorbable free fatty acids and thus excreted undigested, thereby reducing caloric intake.

The single dose administration of orlistat prevents approximately 30% of dietary fat from being absorbed, which indicates its effectiveness in controlling body weight. Orlistat was found to be playing important role in management of obesity associated with type-2 diabetes. In obese patients, the incidence of type-2 diabetes was reduced with Orlistat by 6.2% when compared with placebo. There are different brands of Orlistat available in the market such as, Cobese, Obelit, Xenical etc. In spite of such numerous advantages, Orlistat capsule which is available in the market has major limitations such as insolubility, poor bioavailability, short half life (<2h) which results in multiple dosing frequency (Three times in a day). Orlistat is waxy in nature having low melting point (44 °C), so requires specific storage condition (2–8 °C), and is poorly water soluble which limits its performance. It is a white to off–white crystalline powder with lipophilic properties and very low aqueous solubility within gastrointestinal tract.

### 1.2 LITERATURE REVIEW

#### 1.2.1 Liquisolid technique

This technique includes preparation of acceptably free flowing and compressible form of liquid medication. Here, term liquid medication entails to oily solution of drug or solution of water insoluble drug into the non-volatile solvent.
systems. As per technique, the liquid solution of the drug is transferred on solid carrier system. It involves routine production process as that of the conventional tablets so this simple technique will be cost effective to achieve maximum dissolution rate. The various excipients required for this technique are conventional and commonly available. The liquisolid technique has been proved to be one of the promising strategy for the solubility enhancement.

**Fig 2: Schematic presentation of preparation of liquisolid system**

1.2.2 Components of LSDDS

**Liquid /solid drug**

It is one of the important part of formulation; the drug may be available in liquid or solid form. If drug is solid in nature then it solubilized into the suitable non-volatile solvent.
Carrier material

It is porous material possessing sufficient absorption properties such as microcrystalline cellulose and amorphous cellulose, which contributes in liquid absorption.

Coating material

It is very fine material with high adsorptive surface, such as various type of amorphous silicon dioxide (silica), which contributes in layering the wet carrier particles. These adsorptive particles have particle size range of about 10 nm to 5000 nm diameter.

Disintegrants

The disintegrants are used to break the compacts into smaller fragments or pieces. Examples:- Sodium starch glycolate (SSG), Explotab, Pre-gelatinized starch, Crospovidone and Sodium Croscarmellose.

Lubricants

These are used to minimize interparticular friction in material.

Examples: - Stearic acid, Stearic acid salts and Talc etc.

Glidants

These are used to reduce friction between particles to enhance flow properties.

Examples: - Silica derivatives, Talc and Corn starch etc.

1.2.3 Theoretical aspects

Determination of Flowable Liquid retention potential (Φ- value)

It is defined as the maximum weight of liquid that can be retained by unit weight of powder material in order to get acceptably flowable powder admixture. The flowable liquid-retention potential (Φ-value) of powder is calculated by following equation,
\[ L_f = \Phi + \Phi (1/R) \]  

\( \Phi = \) Flowable liquid retention potential of carrier material

\( \Phi = \) Flowable liquid retention potential of coating material

Liquid load factor \( (L_f) \) is calculated by following equation,

\[ L_f = \frac{W}{Q} \]  

\( W = \) Weight of liquid medication

\( Q = \) Amount of carrier material

Optimum amount of the carrier powder is calculated by using following equation,

\[ R = \frac{Q}{q} \]  

\( q = \) Amount of coating material

1.2.4 Advantages of liquisolid drug delivery system

- It is established that, improved bioavailability can be achieved by formulating the water insoluble drug in liquisolid system.

- The production cost is very low; it is as similar as that of the conventional tablet.

- More drug surface area is exposed to the dissolution medium hence, liquisolid system exhibit improved drug release.

- The drugs, which are practically water-insoluble, slightly soluble and very slightly soluble solid or liquid can be formulated into the liquisolid system.

Prajapati et al (2013) developed liquisolid compacts of the Olmesartanmedoxomil, which is highly lipophilic and a poorly water-soluble drug with absolute bioavailability of 26 %. From the dissolution studies for liquisolid compacts and conventional formulations it was found that liquisolid compacts with 80 %w/w of Acrysol EL 135 showed significant higher drug release rates than conventional tablets.
1.2.5 Self-emulsifying drug delivery system (SEDDS) \(^{16-21}\)

SEDDS is defined as an isotropic mixture of the oil, surfactant and cosurfactant/solvent of natural or synthetic origin, which may be in solid or liquid form. These are anhydrous liquid mixtures called as pre-concentrates. SEDDS constitutes of oil, surfactant and co-surfactant/solvent of natural or synthetic origin as an isotropic mixture. These are anhydrous liquid mixtures called as pre-concentrates. It is distributed very easily in the gastrointestinal tract because of intestinal motility, which forms emulsion. SEDDS have potential to increase the \textit{in vivo} performance of the drug by availing the drug in solubilized form at the site of the action by working with multiple mechanisms.

1.2.6 Formulation components of SEDDS

\textbf{Active pharmaceutical ingredient (API) or drug}

Lipophilicity and unit dose of the drugs are the important selection criteria for the SEDDS. As, it is required that drug must show its solubility into the oil components or vehicles which are lipoidal in nature and this must involves unit dose of drug in the minimum volume. These are the basic requirement which need to be taken into consideration while development of the SEDDS. The dissolved amount of the drug can be easily emulsified on dilution with gastric fluid on administration.

\textbf{Oils}

Modified long chain and medium chain triglyceride oils with different degree of hydrolysis are used to develop SEDDS. Natural oils can be effectively used in design and development of SEDDS but it has propensity to solubilize little amount of lipophilic drugs so it is not possible to incorporate large amount of drug in it.
**Surfactants**

Surfactants play a very crucial role in the success of SEDDS; it contributes to the emulsifying property of the system. The concentration of surfactants in formulation has a huge impact on the final droplet size as well as gastric mucosal irritation so concentration of surfactants should be kept constant. Sometimes, a mixture of surfactants is preferred to avoid previously mentioned problems.

**Co-solvents**

Co-solvents are the essential components for the preparation of the SEDDS. These are used to aid solubilization of active component into the surfactant. These are being used to increase the drug loading capacity of the isotropic system. Alcohol and other volatile co-solvents are not suitable because they have a tendency of evaporating from the system as time passes which leads to precipitation of the system. Examples are ethanol, propylene glycol and polyethylene glycol etc.

**1.2.7 Mechanism of self-emulsification**

There are different mechanisms of spontaneous emulsion formation. The process of spontaneous emulsion formation is influenced by various factors like composition of the system and physicochemical properties. It is based on the fact that how the entropy of the system changes. The free energy of the emulsion formation is based on energy required to form new interfaces formed between two phases. It is given by the following formula,

\[
\Delta G = \sum_i (N_i \delta \Pi r_i^2 \sigma)
\]  

(4)

Where,

\(\Delta G\) - Free energy of the process,

\(N\) - Number of droplets of radius \(r\),

\(\sigma\) - Interfacial energy.
In the process of spontaneous emulsion formation, the energy required is low or negative.

1.2.8 Advantages of SEDDS

**Stability**

The SEDDS constitutes of the isotropic admixture of non-aqueous solvents, which improves the stability on long-time storage.

**Patient compliance**

SEDDS can be effectively delivered *via* capsule /tablet as dosage form as these dosage forms have better patient compliance.

**Palatability**

As these formulations can be filled into capsules, no palatability issues are observed as compared with other liquid formulations.

**Drug loading**

These systems have advantage of the maximum drug loading efficiency because isotropic mixture contains more concentration of the surfactants / co-surfactants than oils. This is one of the important factor in the commercialization of the technique.

**Early onset of action**

It has inbuilt ability to carry drug candidate in dissolved or solubilized state. This is one the advantage of SEDDS, which can be utilized effectively in many physiological disorders to produce quick onset of action.

**Scale up potential**

This technique is having scale up potential because it requires simple manufacturing utility to manufacture on large scale, which results in financially viable settlement of products at commercial level.
Patel et al (2013) designed and evaluated self-micro emulsifying drug delivery system to improve the oral bioavailability of poorly soluble drug Tacrolimus. The optimized liquid and solid SMEDDS showed higher drug release than the marketed formulation and pure drug. The globule size of the optimized liquid SMEDDS and solid SMEDDS was found to be 113 nm and 209 nm respectively. From this study, it has been concluded that SMEDDS and solid SMEDDS of Tacrolimus, have potential to enhance the solubility of the drug.22

1.2.9 Literature review related to orlistat

Jain et al (2006) prepared porous carriers based floating microspheres of orlistat for gastric delivery. From the study it has been observed that, the extent of drug loading influenced by particle size distribution of microspheres. Drug entrapment efficiency was observed in range of 70 - 82 %.23 Dolenc et al (2010) developed nanosized particles of orlistat by using melt emulsification method followed by the high-pressure homogenization of suspension. As these process involved continuous exposure of drug for hot environment.24 Sateesha et al (2011) formulated gastro retentive Orlistat microsphere to control and prolong the drug release at site of action. These microspheres showed encapsulation efficiency in range of 32.48% to 59.95%.24 Anne et al (2011) prepared solid dispersion of Orlistat by using the solvent evaporation technique to enhance solubility. Study concluded that the dissolution of the orlistat increased than the pure drug.25 Samyukta et al(2011) developed niosomal formulation of the orlistat from proniosomes which requires sonication for 30 min. Cholesterol and Span 60 and β-cyclodextrin were used in different concentration for the preparation.26 Singh et al (2011) prepared solid dispersion of orlistat with Poloxomer -188 as a hydrophilic carrier. From the results obtained, it was concluded that the dissolution rate of Orlistat could be enhanced by
the use of solid dispersion technique. Molavi et al (2012) developed Nano suspension of orlistat to increase dissolution rate. This Nano suspension was spray dried, optimized formulation showed particle size range 200 nm ± 10 nm and acceptable dissolution rate when compared with the pure drug. Vavia et al (2012) prepared multiple unit particulate system (SEDDS) of Orlistat by formulating its Nano suspension followed by lipase inhibition study. Luhadiya et al (2012) prepared solid dispersion of orlistat in PEG-6000 containing five different ratios 1:1 1:2 1:3 1:4 and 1:5. They concluded that, inclusion complexes prepared with β-cyclodextrin showed higher dissolution rate. Gaikwad et al (2012) prepared and evaluated self-micro emulsifying drug delivery system of orlistat wherein Oleic acid, Cremophor EL and Tween 80 were used as formulation components. The formulation composition was fixed after determination of micro emulsifying region in ternary phase diagram. From the in vitro drug release study, it was observed that only 51.82% drug was released from the developed formulation within 60mins whereas, marketed formulation showed only 37% drug release. However, the dissolution media containing 3% of sodium lauryl sulphate and 0.5 % sodium chloride was used. Shaikh et al (2013) formulated repeat action tablet of Orlistat in combination with Drotaverine hydrochloride to obtain a better drug release profile of orlistat and to minimize the adverse effect associated with the Orlistat. Different synthetic polymers such as HPMC E15 and CMC at different proportions were used.

1.2.10 Literature review related to the analytical methods

Mohammadi et al (2006) developed and validated a stability-indicating HPLC method for the quantitative determination of orlistat in capsule dosage forms. The method was linear over the concentration range of 0.02–0.75 mg/ml (r = 0.9998) with a limit of detection and quantitation 0.006 and 0.02 mg/ml, respectively. Souri et al
Kumar et al (2011) developed simple, reproducible spectroscopic method for determination of Orlistat in pure and dosage form. The percentage recovery observed in range of 99.53 - 100.17% indicating no interferences of the capsule excipients. Linearity was found in the concentration range of 10-100μg/ml with correlation coefficient of 0.9982. The analytical results validated statistically and recovery studies confirmed the accuracy and precision of the proposed method. Kumar et al (2012) developed simple and efficient RP-HPLC method and validated for the quantitative determination of Orlistat SSRR Impurity in Orlistat dosage forms. Bindaiya et al (2013) developed stability indicating HPLC method to determine orlistat content in bulk and its degradation products. Degradation impurities were not interfered during analysis. Gaddam et al (2013) developed differential derivative UV spectroscopic method of orlistat. It was observed that, spectrum differentiation corrects errors resulting from overlapping background. Beer's-Lambert’s law obeyed in the concentration range 10-30 μg/ml for zero, first and second orders. Dongzhou et al (2012) developed an analytical method to test lipase activity and inhibition. Porcine pancreatic lipase and para-Nitrophenyl Palmitate (p-NPP) were used for enzyme assay.
in pH 8.0 reaction buffer at 37°C. Samples were checked for absorbance changes at 410 nm. The dissolution of two Orlistat formulations was tested with a USP Type II apparatus. Samples were analysed by HPLC to determine release profile, which was evaluated for inhibitory effect. In this study, Orlistat showed highly potent and time dependent inhibition with 5 ng / ml effecting 50 % activity after 5 min in the Lipase-P-NPP system. Mohamed et al (2013) developed a simple, rapid and precise method for determination of lipase activity in microbial media. The method was based on the use of phenyl acetate as substrate for lipase and determination of liberated phenol by Folin Ciocalteu reagent. Linearity for the measurement was observed in the concentration range 0 - 0.8 g / L lipase.
1.3 JUSTIFICATION FOR THE STUDY

From the literature review, it has been revealed that, different approaches were used to enhance the solubility of water insoluble orlistat for improved lipase inhibition. It has been noticed that, orlistat is waxy in nature with low melting point (44 °C), requires specific storage condition (2 –8°C), and poor water solubility. Its poor water solubility and dissolution rate limited its performance. Hence, it required to be administered on larger quantity to achieve therapeutic benefits. In addition, it is not technologically manageable substance reported by (Dolenceetal2010). From the earlier studies reported by different researchers, various attempts have been made to increase its solubility and dissolution rate. Majority of the studies were time consuming, generates heat and demanding procedures. The techniques such as melt extrusion, high-pressure homogenization, spray drying and solid dispersions were used to prepare different type of formulations. Hence, by taking into consideration problems associated with orlistat, it was necessary to select the process, which must be devoid of heat or must be suitable for the drug, which assures maximum stability of drug.

In the studies reported by Nokhodchi et al (2005), Tiong et al (2009), Yousef et al (2007) and Chella et al (2012) prepared liquisolid compacts of Indomethacin, Naproxen, Carbamazepine and Valsartan respectively, to enhance dissolution characteristics of poorly soluble drugs.\textsuperscript{40-43} From the literature survey, it has been observed that, the liquisolid technique is most promising approach for improving dissolution of poorly soluble drugs. The present study deals with LSDDS, as it involves routine production process as that of the conventional tablets, which will be cost effective to achieve maximum dissolution rate. The various excipients required
for this technique are conventional and commonly available. The LSDDS proved to be one of the promising strategy for the solubility enhancement.\textsuperscript{44}

Nowdays, self-emulsifying drug delivery system (SEDDS) attracted substantial attention of the researchers due to its inbuilt ability to carry drug candidate in dissolved form / state at the site of absorption or action, which is pre-requisite for the drug candidate to be absorbed by biological membrane. It is an isotropic mixture of the oil, surfactant, and cosurfactant/solvent of natural or synthetic origin, which may be in solid or liquid form. These are anhydrous liquid mixtures called as pre-concentrates. SEDDS spreads easily in the gastrointestinal tract whereas intestinal motility provides agitation, which results into the self-emulsification. SEDDS is thermodynamically highly stable system, which is able to form a spontaneous emulsion. SEDDS reported to have less inter and intra-subject variability in plasma drug level on administration.\textsuperscript{45} Self-emulsifying drug delivery system is one of the popular formulation strategy. Due to the usage of lipids or lipoidal vehicles, it helped in enhancing solubility, dissolution by providing the high interfacial area to the drug in between the oil and aqueous phase, i.e., gastrointestinal fluids. From a formulation point of view, SEDDS involves very simple step of preparation; a major part of development is to determine best composition of surfactant co-surfactant and oil components, which gives minimum globule size with good dispersion ability for unit dose of drug substances.\textsuperscript{46} Atef et al (2008) and Maria et al (2013) prepared SEDDS of Phenytoin and Gliblenclamide in which \textit{In vitro} drug release of S-SEDDS was much higher than that of plain drug and marketed formulation\textsuperscript{47,48} Therefore, SEDDS can be used effectively to increase the solubility and \textit{in vivo} performance of poorly soluble drugs. SEDDS has good dosing and metering property so it reduces variation in individuals on administration. Solubility and dissolution can be enhanced by using
lipids or lipoidal vehicles, which provides the high interfacial area to the drug in between the oil and aqueous phase, i.e., gastrointestinal fluids. SEDDS requires simple production utility such as stirrer and tanks, which is financially viable. As part of advancement into the SEDDS, solid emulsions or dry emulsions are prepared from liquid emulsions. Solid SEDDS is having stability, excellent transportability and lesser manufacturing cost. Here, the main intention behind the conversion of liquid SEDDS to the solid self-emulsifying tablet was for better stability and patient compliance. In the present study, it was decided to formulate and characterize liquisolid drug delivery system and self-emulsifying drug delivery system of orlistat. A $3^2$ full factorial design was used to prepare LSDDS and liquid SEDDS. The independent variables were investigated for their effects on dependent variables. An optimized SEDDS formulation was freeze-dried, which converted into the tablet. A factorial design was implemented in the present study as a part of quality by design (QbD) and FDA’s quality initiatives on GMP compliance. It involves systematic, scientific, risk-based, holistic approach to achieve the product with predefined quality attributes. \textsuperscript{49,50}
1.4 AIM, OBJECTIVES AND PLAN OF WORK

1.4.1 Aim of the study:-

To prepare and evaluate Liquisolid drug delivery system (LSDDS) and Self-emulsifying drug delivery system (SEDDS) of orlistat to enhance the solubility.

1.4.2 Objectives of the study:-

1. Development and evaluation of formulation like Liquisolid drug delivery system (LSDDS) and Self-emulsifying drug delivery system (SEDDS).
2. \textit{In vivo} pharmacodynamic study of formulations.
3. Stability studies of the formulations.

1.4.3 Plan of work:-

1) Preformulation studies.

A) Identification Tests.
   - Solubility studies.
   - Melting point determination.
   - FTIR analysis.
   - Analytical method.

B) Compatibility studies by FTIR Spectroscopy

2) Optimization studies for formulation (like Liquisolid drug delivery system and Self emulsifying drug delivery system)\textsuperscript{44}

3) Characterization of formulations\textsuperscript{47}
   - Droplet size determination
   - Determination of drug content
   - Determination of Zeta Potential
   - Surface Morphology Study/TEM
   - Differential scanning calorimetry
   - X- ray diffraction
4) *In vitro* drug release study.

5) *In vivo* evaluation of formulations.

6) Stability studies.