IJPSR (2012), Vol. 3, Issue 1 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 August, 2011; received in revised form 16 November, 2011; accepted 12 December, 2011

SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM: A METHOD FOR ENHANCEMENT OF BIOAVAILABILITY

Urvashi Goyal*, Ankit Gupta, Avtar Chand Rana and Geeta Aggarwal

Rayat Institute of Pharmacy, V.P.O. Railmajra, Tehsil. Balachaur, Distt. S.B.S. Nagar- 144533, Punjab, India

Keywords:

SMEDDS,
Oral Bioavailability,
Lipophilic Drug,
Solid SMEDDS

Correspondence to Author:

Urvashi Goyal

Research Scholar, Rayat Institute of Pharmacy, V.P.O. Railmajra, Tehsil. Balachaur, Distt. S.B.S. Nagar- 144533, Punjab, India

ABSTRACT

Oral route is the easiest and most convenient route of drug administration, being non invasive and cost effective, thereby leading worldwide drug delivery market. But major problem encountered in oral formulations (as estimated more than 50 % of oral formulations are found to be poorly aqueous soluble), is low bioavailability, giving rise to further problems like, high inter and intra subject variability, lack of dose uniformity and finally leading to therapeutic failure. The challenging task is to increase the bioavailability of drugs. Number of technological strategies are investigated and reported in literature for improving bioavailability like solid dispersions, cyclodextrins, micronization etc. But Self-microemulsifying Drug Delivery System (SMEDDS) have gained exposure for their ability to increase solubility and bioavailability of poorly aqueous soluble drugs with reduction in dose and also drugs are protected from hostile environment in gut. SMEDDS are isotropic mixture of oil, surfactant, drug and sometimes containing co-surfactant and administered orally which on mild agitation with GI fluids forms o/w microemulsion. This review gives complete overview of SMEDDS but special attention has been paid to formulation design, evaluation and little emphasis on application of SMEDDS.

INTRODUCTION: Poor aqueous solubility of lipophilic drugs creates problems in formulation as well as in oral administration. Various approaches have been developed to resolve poor aqueous solubility of lipophilic drugs. As oral route for drug administration is most commonly used among all the routes of administration due to its convenience, non-invasiveness and cost effectiveness it become necessary that drug should have some aqueous as well as some lipid solubility for their absorption.

Whenever a drug is administered by oral route it undergoes many steps like solubilisation followed by permeation to produce the desired effect. After oral administration drug solubilises first due to aqueous solubility then undergoes permeation through membrane due to lipid solubility. This solubilization is difficult for drugs which have poor aqueous solubility thus act as the rate limiting step for absorption from gastrointestinal tract. Due to poor aqueous solubility of drug their efficacy also hindered leading to low absorption after oral administration. A part of administered dose of such drug absorbed and reaches to therapeutic site and the remaining part produce toxicity or side effects due to imbalance in bio-distribution. For the therapeutic delivery of poorly aqueous soluble active moieties, lipid based formulations are introduced.

Various formulation approaches such as micronization, solid dispersions and complexation with cyclodextrin have been used but these approaches have some disadvantages [1, 2]. Advanced approaches include incorporation of active moiety into inert lipid vehicles [3] like oils [4], surfactant dispersions [5, 6] and self-microemulsifying delivery system [7, 8] emulsions [9, 10] and

liposomes [11]. By loading the drug in lipid based delivery system enhancement in efficacy and reduction in side effects will be achieved [12].

Self-microemulsifying drug delivery system (SMEDDS) is one of the most widely used approaches for enhancing the bioavailability of poorly aqueous soluble drugs. Improvement in bioavailability through this system is due to increased solubilisation and modification of pharmacokinetic profile of hydrophobic drugs.

This system is clear, stable, isotropic mixture of drug, oil, water, surfactant and sometimes containing co-surfactant, which form fine emulsion/lipid droplets of size less than 50 nm when come in contact with gastrointestinal fluid. So the drug remains in solution in gut, therefore avoiding the rate limiting step i.e. dissolution and the small droplet size provides large surface area for the absorption of hydrophobic drugs. Some of the essential criteria for the effective use of this approach in pharmacy include tolerance towards additives, stability over wide temperature range, low viscosity, small size biodegradability, and easy elimination from the body and so on [12-16].

Advantages of this system involve reduction in inter, intra subject variability and food effects, protection from the gut environment, control of delivery of drug profile, reduction in dose, protection of sensitive drug substances, more consistence drug absorption, selective targeting of drug toward specific absorption window in gastro-intestinal tract (GIT), high drug payloads, high stability and longer self-life etc [2, 12, 17].

Self-Microemulsifying Drug Delivery System (SMEDDS):

Self Dispersing Lipid Formulation System [18]: Various delivery systems for the lipophilic drugs are available such as, microemulsion, lipid solution, lipid emulsion, dry emulsion, whose formulation involve large number of possible combination of excipient, so to understand these lipid based formulation a classification namely 'lipid formulation classification system have been introduced by Pouton in 2000 and recently updated (2006). According to the composition and the effect of dilution and digestion on the ability to prevent precipitation of drug, lipid based formulations are classified into four groups as discussed in **Figure 1**.

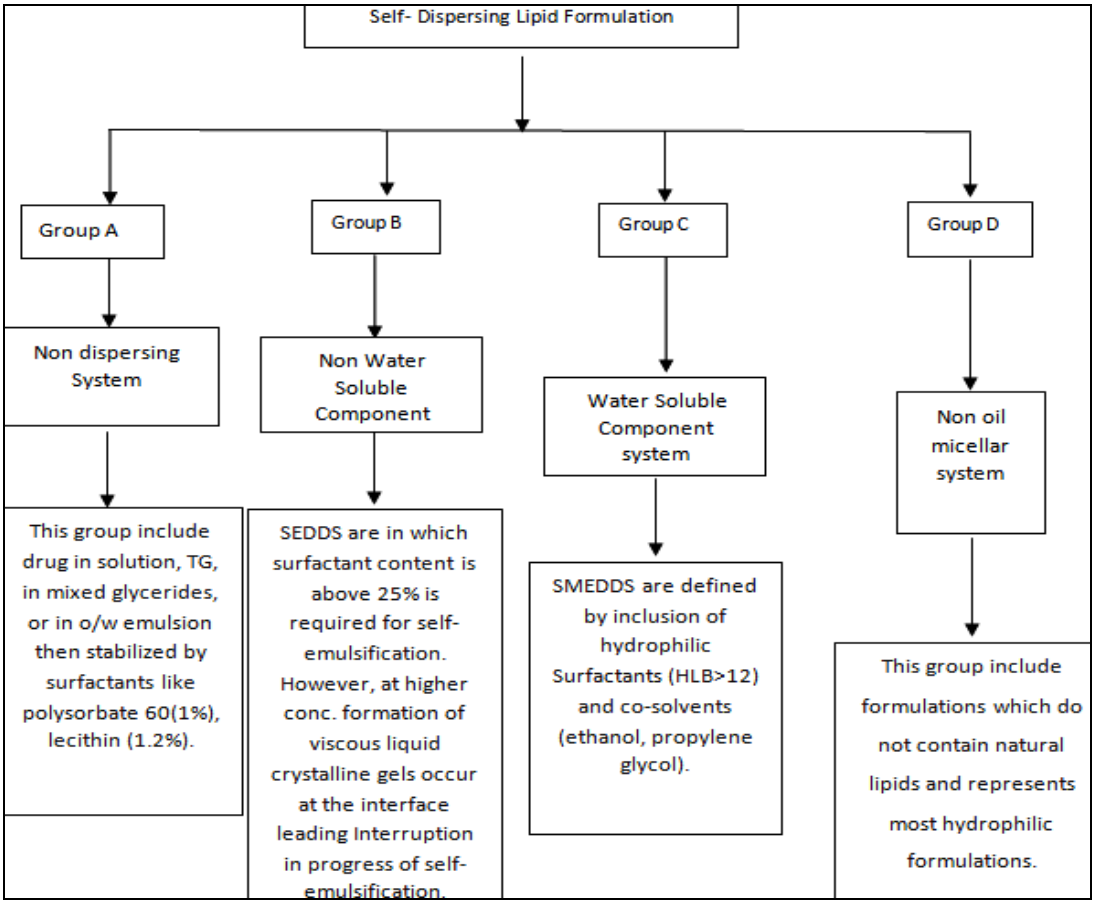

FIG. 1: CLASSIFICATION OF LIPID BASED FORMULATION

SMEDDS is the type of self dispersing lipid formulations (SDLFs) which contain mixture of oils and surfactants, ideally isotropic. Sometime it also contains co-surfactants. Drug is incorporated into this mixture. When the mixture of drug, oil and a surfactant comes in contact with the aqueous environment in GIT they form an emulsion under gentle agitation provided by digestive motility of stomach and intestine which is necessary for self-emulsification *in- vivo*.

Once an emulsion is formed then the drug is quickly distributed throughout the GIT as fine droplets, due to this dispersion and large surface area of fine droplets the bioavailability of drug enhanced. Presence of surfactant also influences absorption due to membrane induced permeation changes. The mechanism of self-emulsification is specific for parameters like, pair of oil and surfactant, type and concentration of surfactant, oil/surfactant ratio, and temperature at which self emulsification occur. Since the drug delivery should be biocompatible so the selection of excipient used in formulation is very important [17-21].

Formulation Design of SMEDDS: Pre-formulation studies are carried out for the selection of oil, surfactant and co-surfactant as these are specific for a particular SMEDDS. First we determine solubility of drug in various oils and surfactant/co-surfactant then prepare a series of SMEDDS containing drug in various oil and surfactant/co-surfactant. These formulations are analysed for self-emulsification properties and droplet size upon addition to water under mild agitation (*in- vitro*) studied. By constructing the pseudo-ternary phase diagram we identify the efficient self-emulsification region. So by doing such studies an optimized formulation is selected and its bioavailability also compared with a reference formulation [12, 22]. Parameters taken into consideration while formulating SMEDDS [12]:

- Solubility of drug in formulation as such and upon dispersion
- The rate of digestion (for digestion susceptible formulation)
- The solubilisation capacity of the digested formulation

Components of SMEDDS: Active pharmaceutical ingredient (API) includes (**table 1**);

- Oil
- Surfactant
- Co-surfactant
- Co-solvent
- Consistency Builder
- Enzyme Inhibitor
- Polymer
- Other Components

TABLE 1: SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM OF DIFFERENT API WITH THEIR COMPOSITION

API	Oil phase	Surfactant	Co surfactant	Reference
Xibornol	Labrafil M1944, Labrafil M2125 and Labrafac CC	Labrasol and Labrafac PG	Transcutol	[23]
Furosemide	Mygliol 812	Caprylocaproyl macrogolglycerides Labrasol	Polyglyceryl-6 dioleate plurol oleique	[24]
Candesartan cilexetil	Transcutol P	Capryol 90	Plurol Oleque	[25]
Nobiletin	Mixture of polyoxyethylene 35 castor oil and polysorbate 80 oil	Mixture of polyoxyethylene 35 castor oil and polysorbate 80	Polyethylene glycol 400	[26]
9-Nitrocamptothecin	Ethyloleat	Tween-80 and CremophoL EL	PEG-400	[27]
Fenofibrate	Labrafac CM10	Tween 80	PEG 400	[28]
Atorvastatin	Labrafil, Labrafac, Estol and IPM(Isopropyl myristate)	Cremophor EL, Cremophor RH40, Tween 80 and Labrasol	Ethanol, propylene glycol, PEG 400 and Transcutol	[29]
Oridonin	Labrafac CC	Cremopher EL	Transcutol P	[30]
Valproic acid	castor oil	Cremaphor RH 40	PEG 400	[31]
Curcumin	Isopropyl myristate, Aethylis oleas, Soybean oil	Tween 80, Cremophor RH40, Cremophor EL	Ethanol, PEG 400, 1,2-propylene glycol	[32]
Simvastatin	Capryol 90	Cremophor EL	Carbitol	[33]
Buparvaquone	Capryol 90	Cremophor EL	Labrasol	[34]
Valsartan	Capmul MCM	Tween 80	Polyethylene glycol 400	[35]
Glyburide	Capryol 90	Tween 20	Transcutol P	[36]

Vinpocetine	Ethyl Oleate	Solutol HS	Transcutol P	[37]
Danazol	Sesameoil,Maisine 35-1	Cremophor RH40	Ethanol	[38]
Halofantrine	Capex 355,Capmul MCM	Cremophor EL	Ethanol	[38]
Puerarin	Oleic acid	Tween 80	Propylene glycol(PG)	[38]
Tamoxifen citrate	Maisine 35-1,Capryol 90	Cremophor RH40	PG	[38]

Active Pharmaceutical Ingredient: Properties of drug suitable for loading in SMEDDS: Active pharmaceutical agent should be soluble in oil phase as this influence the ability of SMEDDS to maintain the API in solubilised form. Drugs which have low solubility in water or lipids are difficult to deliver through SMEDDS. Drugs which are administered in very high dose are not suitable for formulation unless they have extremely good solubility in at least one of the components of SMEDDS, preferably oil phase. High melting point drugs with log P values of about 2 are poorly suited to SEMDDS. At the other end of the spectrum, lipophilic drugs, such as cinnarizine with log P values greater than 5, are good candidate for SMEDDS [18, 39].

Oil: Oil is the most important excipient in the formulation of SMEDDS as it solubilizes the lipophilic drug in a required quantity or facilitates self-emulsification and also enhances the absorption through the GIT by increasing fraction of lipophilic drug transported through it. The main criterion for selecting the oil is that the drug should have high solubility in it so this will minimize the volume of the formulation for the delivery of effective dose. Lipid part of SMEDDS formulation forms core of the emulsion particle and is typically composed of non-polar lipids.

Long chain triglycerides (LCTs) and medium chain triglycerides (MCTs) oils with different degree of saturation have been used as oil phase in the formulation of SMEDDS. Unmodified edible oils are the most biocompatible lipid vehicles but they are enable to dissolve large dose of lipophilic drug and less efficient self-emulsification limits their use in formulation of SMEDDS, whereas modified and hydrolysed vegetable oils are successful in these formulations as they shows formulative and physiological advantages. MCTs were preferred over LCTs because according to Deckelbaum (1990) MCT is more soluble and have a higher mobility at the lipid/water interfaces than LCT associated with a more rapid hydrolysis of MCT and more concentration of surfactant (Cremophore RH40) is required when LCTs were used as oil phase as compared to MCTs. Now the novel approach includes use of semi-synthetic medium chain derivatives which exhibit surfactant properties and also known as amphiphilic compounds. In such type of cases more lipophilic surfactants may play the role of hydrophilic oil in the formulation. By blending the triglycerides with mono- and di-glycerides solvent capacity for hydrophobic drugs can be improved [12, 16, 18, 40-43].

Surfactant: Surfactant molecules consist of two part, polar head group region and non-polar tail region. They are classified into four categories according to the nature of hydrophilic group within the molecule [43]:

- Anionic surfactant
- Cationic surfactant
- Non-ionic surfactant
- Ampholytic surfactant

Surfactant reduces the interfacial tension between two immiscible liquids and makes them miscible. When surfactants are incorporated in oil and water mixture then their polar heads is self associated towards water phase and non-polar tails towards oil phase or they can locate at the interface, which is thermodynamically very favourable. Some of the possible self-association structures that surfactant can form in the presence of oil, water or combination of all three are shown [41] in **Figure 2**.

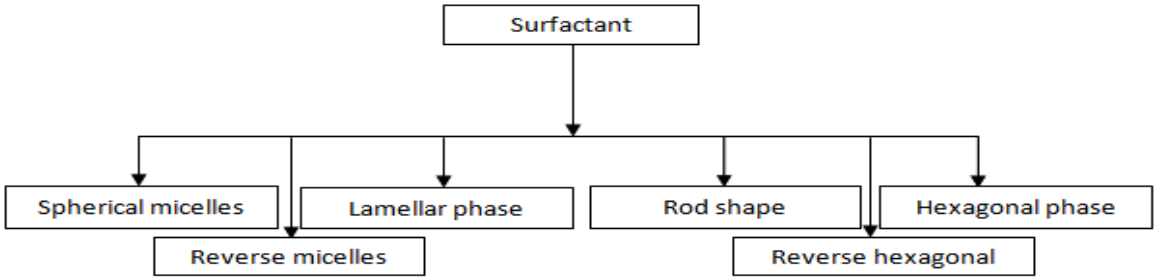

FIG. 2: FLOW CHART OF THE MOST COMMONLY ENCOUNTERED SELF-ASSOCIATION STRUCTURES THAT SURFACTANT CAN FORM IN WATER, OIL OR A COMBINATION OF ALL THREE

Surfactants in solution below their critical micellization concentration (CMC) improve drug solubility by providing regions for hydrophobic drug interactions in solution. Above the CMC, surfactants self-aggregate in defined orientation to form micelles with a hydrophobic core and a hydrophilic surface. The hydrophobic core enhances the entrapment of drug, thus increasing its solubility. In the presence of a significant amount of oil, surfactants concentrate on the oil/water interface forming emulsions, wherein the drug is solubilised in the internal oil phase. When the oil content is low, minute oil-entrapped surfactant globules are produced, which are known as swollen-micelles or microemulsion. Drug may be solubilised in the oily core and/or on the interface of these structures. The predominant location of drug solubilization depends on its hydrophobicity and interactions with the surfactant and/or co- surfactant [44].

The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased/inhibited p-glycoprotein drug efflux. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GIT. The effect of formulation and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case [16, 17].

Among all types of surfactants only few surfactants are orally acceptable. The most widely preferred surfactants for the design of SMEDDS are non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) value. High HLB value and subsequent hydrophilicity of surfactant is necessary for a good self-microemulsifying performance. Emulsifiers of natural origin are safer than the synthetic one as they are non-toxic or bio-compatible, despite their limited ability of self-emulsification.

Concentration range for preparation of stable SMEDDS lie b/w 30 to 60%. Example of surfactants used in SMEDDS formulation are, Tween 80, Labrafac CM10, Sodium dodecyl benzene sulfonate, Quaternary ammonium salts etc., [12, 16-48].

Co-surfactant: For the production of an optimum SMEDDS, high concentration of surfactant is required in order to reduce interfacial tension sufficiently, which can be harmful, so co-surfactants are used to reduce the concentration of surfactants. Co-surfactants together with the surfactants provide the sufficient flexibility to interfacial film to take up different curvatures required to form micro-emulsion over a wide range of composition. Selection of proper surfactant and co-surfactant is necessary for the efficient design of SMEDDS and for the solubilization of drug in the SMEDDS.

Generally co-surfactant of HLB value 10-14 is used. Organic solvents like ethanol, propylene glycol, polyethylene glycol are able to dissolve large amount of either drug or hydrophilic surfactant in lipid base and are suitable for oral delivery, so they can be used as co-surfactant for SMEDDS. Alternately alcohols and other volatile co-solvents show a disadvantage that by evaporation they get entered into soft/hard gelatin capsule shells resulting in precipitation of drug. On the other hand formulations which are free from alcohols have limited lipophilic drug dissolution ability. Hence, proper choice of components has to be made for formulation of efficient SMEDDS [17, 18, 45, 49].

Co-solvents: High concentration of surfactant (generally more than 30%) is required for optimum production of SMEDDS. Organic solvents enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in oil phase. Examples include ethanol, butanol, propylene glycol etc., esters such as ethyl propionate, tributyl citrate and amides as 2-pyrolidine, caprolactum and polyvinyl pyrollidine [50].

Consistency Builder: To alter consistency of emulsion, beeswax, cetyl alcohol can be added [50, 51].

Enzyme Inhibitors: If the active pharmaceutical agent is prone to enzymatic degradation, then enzyme inhibitors can be added to SMEDDS e.g. amino acids and modified amino acids- aminoborinine derivatives,

peptides and modified peptides - bacitracin, amastatin [50, 51, 52].

Polymers: The polymer matrix after ingestion in contact with GI fluid forms a gelled polymer making it possible to release the microemulsified therapeutic agent by diffusion in continuous and sustained manner e.g. hydroxy propyl methyl cellulose and ethyl cellulose [53].

Other components: Other components include pH adjusters, flavours, and antioxidants. Some unsaturated lipids show peroxide formation with oxidation. Free radicals like ROO` RO` and `OH can damage drug and induce toxicity pH of solution also accelerate hydrolysis of lipid content of SMEDDS. Therefore, lipophilic antioxidants can be added for stabilization of oil part of SMEDDS e.g. α-tocopherol, ascorbyl palmitate, propyl gallate and BHT [43].

Screening of Oil/Saturation Solubility in different Oils: In order to find out appropriate oil with good solubilizing capacity of API, the saturation solubility of API was investigated in some oils by shake flask method. An excess amount of API was added to vial containing 0.5 g of each solvent. After sealing, the mixture was vortexed using a cyclomixer for 10 min in order to facilitate proper mixing of API with the vehicles. Mixtures were kept for 72 hr at ambient temperature to attain equilibrium, and afterwards, mixtures were centrifuged at suitable rpm for 15 min. Aliquots of supernatant was filtered through membrane filter (0.45 µm) and diluted with mobile phase. Drug content was quantified directly by using high performance liquid chromatography (HPLC) technique [36, 54-56].

Screening of Surfactant: In order to find appropriate surfactant with good solubilizing capacity, after screening of oil emulsifying ability of different surfactants with the screened oil was investigated. 0.3 g of surfactant and 0.3 g of oil phase were weighed and vortexed for two minutes followed by warming at 40-45^{0}C for 30 seconds, so we can obtain an isotropic mixture. 50 mg of isotropic mixture was taken and diluted with double distilled water previously filtered through (0.45 µm) membrane filter in a volumetric flask. Number of volumetric flask inversions was observed visually to form a clear emulsion. The resulting emulsions allowed standing for 2 hours after that transmittance were observed at 638 nm. The surfactant which forms a clear emulsion with lesser number of inversions and with more transmittance was selected [37, 57].

Screening of Co-Surfactant: In order to find appropriate co-surfactant with good solubilizing capacity, after screening of oil emulsifying ability of different co-surfactants with the screened oil was investigated. 0.2 g of co-surfactant and 0.3 g of oil phase were weighed and vortexed for two minutes followed by warming at 40-45^{o}C for 30 seconds, so we can obtain an isotropic mixture. 50 mg of isotropic mixture was taken and diluted with double distilled water previously filtered through (0.45 µm) membrane filter in a volumetric flask. Number of volumetric flask inversions was observed visually to form a clear emulsion. The resulting emulsions allowed standing for 2 hours after that transmittance were observed at 638 nm. The co-surfactant which forms a clear emulsion with lesser number of inversions and with more transmittance was selected [57].

Construction of Phase Diagram: Phase diagrams were constructed to obtain the proportion of components that can result in maximum microemulsion existence area. These diagrams were constructed with oil, surfactant/co-surfactant and water using water titration method at room temperature. The procedure consisted of preparing solutions of different ratio of surfactant to co-surfactant by weight such as: 1:1, 2;1, 3:1 etc, these solutions then vortexed for 5 min and placed at 50^{o}C for 1 h so that an isotropic mixture was obtained. Each of these solutions was then used for preparing a mixture containing oil and smix (mixture of surfactant and co-surfactant) in the following ratios by weight: 1:9, 2:8, 3:7, 4:6,5:5, 6:4, 7:3, 8:2, 9:1 and after preparation vortexed for 5 min followed by placing in oven at 50^{o}C for 1 hr.

All the mixtures were then placed at room temperature for 24 h. Water from 5% to 95% of the mixture was added at 10-15 min interval to each of the mixture under stirring on magnetic stirrer. After each addition the mixtures were observed for their appearance (turbid or clear).Turbidity of the samples would indicate formation of a coarse emulsion, whereas a clear isotropic solution would indicate the

formation of a microemulsion. Percentage of oil, smix and water at which clear mixture was formed were selected and the values were used to prepare ternary phase diagram. [28, 36, 58]

Preparation of SMEDDS: From the ternary phase diagram ratio of surfactant to co-surfactant (K_m) was optimized. Then by varying ratio of oil to S_{mix}, different formulations were prepared with and without drug. Formulations were prepared by preparing optimized ratio of s_{mix} first, for this surfactant and co-surfactant were accurately weighed and then vortexed for 5-10 min. After that s_{mix} was placed in oven at 50^0C for 1 h. Oil with different ratio was added to s_{mix} (oil:s_{mix}, 2:8, 2.5:7.5, 3:7, 3.5:6.5, 4:6, 4.5:5.5, 5:5, 5.5:4.5, 6:4 etc) then these formulations were vortexed for 5-10 min and placed in oven at 50^0C for 1 h so that an isotropic mixture was formed. Drug was loaded to these isotropic formulations at the end and vortexed by vortex shaker until clear solution was obtained [26, 34, 59].

Evaluation of SMEDDS:

Determination of Droplet Size/Distribution and Zeta-Potential: Determination of droplet size of SMEDDS is crucial factor for the performance of self-emulsification because the rate and extent of drug release as well as absorption depends on droplet size. Smaller droplet size provides larger interfacial surface area for drug absorption and permits faster release rate. Method use for the determination of droplet size include photon correlation spectroscopy (which analyses fluctuations in light scattering due to Brownian moment of particles) using a zeta sizer able to measure size in range 10-5000nm. This technique can only be employed at relatively low dilutions for accurate droplet size evaluation [2, 17, 18, 60-65].

Oil droplets possess some charge on their surface due to presence of some groups like conventional SMEDDS is negative due to presence of free fatty acids; however, incorporation of cationic lipids in concentration range 1-3% will yield cationic SMEDDS Thus, such systems have a positive n-potential value of about 35-45 mV. This positive n-potential value is preserved following the incorporation of the drug compounds [65].

Rheological Determination: Viscosity determination is very important as SMEDDS systems are generally administered in either soft or hard gelatin capsules so, for easy to pour in capsules these systems should not be too thick. Brookfield viscometer, rotational viscometer Rheomat 108 can be use for evaluation of rheological properties of microemulsion. This study confirms whether the system is o/w or w/o. It should be performed in triplicate [43, 61]

- Low viscosity-o/w type system
- High viscosity-w/o type system

Polarity: Polarity of the lipid phase governs the drug release from the micro-emulsion it means polarity characterizing emulsification efficiency. Polarity of oil droplet is governed by some parameters such as, the HLB, chain length and degree of unsaturation of the fatty acids, molecular weight of the hydrophilic portion and concentration of the emulsifier. Polarity has an impact on affinity of the drug for oil and/or water, and the type of forces formed. Highest release will be obtained with the formulation that have oil phase with highest polarity [17, 60, 61].

Thermodynamic Stability Studies: For the optimum performance of the lipid based formulations physical stability also plays an important role and this will be adversely affected by the precipitation of the drug in the excipient matrix. Poor physical stability can lead to phase separation of excipient, which have an impact on formulation performance as well as visual appearance. In addition, brittleness or deformation, delayed disintegration and incomplete drug release occur due to incompatibility between the formulation and the gelatin capsule shells. There are three steps for the thermodynamic stability studies and they are-

- **Heating Cooling Cycle:** Six cycles between refrigerator temperature (4°C) and 45°C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.
- **Centrifugation:** Passed formulations are centrifuged thaw cycles between 21°C and 25°C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that does not show any phase

separation are taken for the freeze thaw stress test.

- **Freeze Thaw Cycle:** Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking [2, 12, 64].

Dispersibility Test: The efficiency of self-emulsification of oral nano or micro emulsion is assessed by using a standard USP XXII dissolution apparatus 2 for Dispersibility test. One millilitre of each formulation was added in 500 mL of water at 37 ± 1^0C. A standard stainless steel dissolution paddle is used with rotating speed of 50 rpm provided gentle agitation. The *in-vitro* performance of the formulations is visually assessed using the following grading system:

- **Grade A:** Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.
- **Grade B:** Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
- **Grade C:** Fine milky emulsion that formed within 2 min
- **Grade D:** Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).
- **Grade E:** Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulations falling in Grade C could be recommend for SEDDS formulations [2, 12, 15, 43, 64].

Turbidimetric Evaluation: Growth of emulsion can be monitored by doing Nephaloterbidimetric evaluation. Fixed quantity of Selfemulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification) [2, 12, 43, 62, 63].

Refractive index and Percent Transmittance: Transparency of the formulation is proved by the refractive index and percent transmittance. Refractive index is measured by Refractometer by placing a drop of solution on slide and then by comparing with water (1.333). The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent, then formulation have transparent nature [2, 12, 43, 62, 63].

Electro Conductivity Test: This test is performed for measurement of the electro conductive nature of system. The electro conductivity of resultant system is measured by electro conductometer. In conventional SMEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids [2, 12, 66].

Drug Content: Drug from pre-weighed SMEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug [2, 12].

Drug Encapsulation Efficiency: The quantities of the drugs theoretically contained in the SMEDDS were compared with the quantity actually obtained, from the drug content studies i.e. the quantity loaded into the SMEDDS formulated. To get the drug encapsulation efficiency equation used for calculation is [43, 61]

$$EE\ (\%) = ADC \times 100 \,/\, TDC$$

Where, ADC is the actual drug content, TDC is the theoretical drug content.

Yield of the SMEDDS: The SMEDDS formed is filtered from the solvent, dried in the desiccators and weighed to get the yield of the SMEDDS formulated per batch. Percentage yield can be calculated by formula [43, 61]

$$\%\ recovery = [W1/W2+W3]100$$

Where, W1 is the weight of the SMEDDS formulated, W2 weight of the drug added, W3 is the weight of the lipid and surfactant, used as the starting material.

***In- vitro* Dissolution Testing:** The quantitative *in- vitro* release test is performed in US Pharmacopoeia XXIV Dissolution apparatus 2, using 900 mL of buffer with pH (given in pharmacopoeia for particular drug) as

dissolution media, the paddles are set to rotate at 100 rpm and temperature is set at 37°C. The SMEDDS formulations are put in hard gelatin capsules (size 0), during the drug release studies 5 mL sample of dissolution media is to be taken out for analysing the sample using HPLC. The removed volume is to be replaced each time with 5 mL of fresh medium.

Dissolution studies are also performed in other media (buffer with different pH) to study the effect of pH on drug release [35].

***In- vivo* Studies:** The appropriate model, depending on drug is to be selected for *in- vivo* studies. Proper environment is provided in concern with humidity, temperature, food and water. The animals models are distributed in experimental groups and the SMEDDS formulation are administered orally by intubation using 18 gauge feeding needle (the volume to be fed is to be equal in all groups). The placebo group can also be introduced for examining the effect of components of formulation. Blood samples are drawn at predetermined time intervals as at 0 hours, 24 hours and 48 hours and analysed [35].

Lymphatic Transport: Intestinal lymphatic transport is responsible for portion of total uptake of lipophilic drugs. In association with chylomicrons and very low density lipoproteins (VLDL), poorly aqueous soluble drugs are transported to systemic circulation, also bypasses the first pass hepatic metabolism, which further boosts the bioavailability [67, 68].

Applications:

Enhancement in Solubility and Bioavailability: Improvement in solubility observed if a drug is loaded in SMEDDS because it circumvents the solubilization or dissolution step in case of class-2 drugs (low solubility/high permeability). A moderately hydrophobic drug ketoprofen (Non-steroidal anti-inflammatory drug), is a drug of choice for sustain release formulation has a side effect of gastric irritation during chronic therapy. Ketoprofen shows incomplete release from sustain release formulation due to its low solubility. Vergote et al. (2001) shows complete release of ketoprofen from sustains release formulation by loaded it in nano crystalline form [2, 69]

Various formulation approaches have been used to achieve sustain release, improvement in bioavailability, and decrease in side effect of gastric irritation of ketoprofen include preparation of matrix pellets of nano-crystalline ketoprofen, sustained release ketoprofen microparticles and formulations, floating oral ketoprofen systems, and transdermal systems of ketoprofen [70, 71, 72]

Different problems like processing, stability and economic problem arises during preparation and stabilization of nanocrystalline or improved solubility forms of drug so by loading drug in SMEDDS such problems can be overcome. SMEDDS formulation enhances the bioavailability by increasing solubility of drug and also decreases the gastric irritation. Also incorporation of gelling agent in SMEDDS sustains the release of ketoprofen [2, 12].

In SMEDDS, by the interaction b/w lipid matrix and water a fine particulate oil-in-water emulsion will form and this emulsion droplet will deliver the drug in dissolved form to the gastro intestinal mucosa readily accessible for absorption. Therefore, increase in AUC i.e. bioavailability and Cmax is observed with many drugs when presented in SMEDDS [2, 12].

Supersaturable SMEDDS (S-SMEDDS): S-SMEDDS have been developed to overcome the toxic effect of surfactant or GI side effects produced by surfactant when used in very high concentration as typically used in SMEDDS. When the formulation is released from an appropriate dosage form into an aqueous medium, S-SMEDDS forms a protected supersaturated solution of drug and this supersaturation is intended to enhance the thermodynamic activity to the drug inspite its solubility limit, therefore enhancement in driving force for transit into and across the biological membrane will be obtain.

Reduced level of surfactant and a polymeric precipitation inhibitor (HPMC and related cellulose polymers) to yield and stabilize a drug in a temporarily supersaturated state are contents of S-SMEDDS formulation. S-SMEDDS of paclitaxel in which HPMC used as precipitation inhibitor was developed.

Formation of a microemulsion, followed by slow crystallization of paclitaxel on standing occur in *in-*

vitro dilution study of S–SMEDDS formulation. This result indicated that the system was supersaturated with respect to crystalline paclitaxel, and the supersaturated state was prolonged by HPMC in the formulation. In the absence of HPMC, the SMEDDS formulation underwent rapid precipitation, yielding a low paclitaxel solution concentration. A pharmacokinetic study showed that the paclitaxel S-SMEDDS formulation produced approximately a 10-fold higher maximum concentration (Cmax) and a 5-fold higher oral bioavailability (F ˜ 9.5%) compared with that of the orally administered Taxol formulation (F ˜ 2.0%) and the SMEDDS formulation without HPMC (F ˜ 1%).Reduced quantity of surfactant can be used with HPMC in order to produce a temporarily supersaturated state with reduced solubilisation by applying this approach.

Thus a high free drug concentration would be obtained through generating and maintaining a supersaturated state *in- vivo* and to increase the driving force for absorption. Better toxicity/safety profile than the conventional SMEDDS formulation will be obtained by using this approach as S-SMEDDS contain reduced amount of surfactant. However, the underlying mechanism of the inhibited crystal growth and stabilized supersaturation by means of these polymers is poorly understood even although several studies have been carried out to investigate this [14, 16, 18, 43, 61, 73].

Solid SMEDDS: SMEDDS are normally prepared as liquid dosage forms that can be administrated in soft or hard gelatin capsules, which have some disadvantages especially in manufacturing process for soft and leakage problem with hard gelatin capsules. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules). A pellet formulation of progesterone in SEDDS has been prepared by the process of extrusion/spheronization to provide a good *in- vitro* drug release (100% within 30 min, T_{50}% at 13 min).

The same dose of progesterone (16 mg) in pellets and in the SEDDS liquid formulation resulted in similar AUC, Cmax and Tmax values. A method of producing self-emulsifying pellets by wet granulation of a powder mixture composed of microcrystalline cellulose, lactose and nimesulide as model drug with a mixture containing mono- and diglycerides, polisorbate 80 and water has been investigated. The pellets produced with oil to surfactant ratio of 1:4 (w/w) showed improved performance in permeation experiments [18, 43, 66, 74].

TABLE 2: METHOD AND CARRIER EMPLOYED FOR SOLIDIFICATION OF SMEDDS OF VARIOUS DRUGS

Drug	Carrier employed	Solidification technique	Title	Reference
Nimodipine	Dextran	Spray Drying	A new solid Self Microemulsifying formulation to improve the oral bioavailability of poorly soluble drugs	[75]
Cyclosporine	Neusilin® (Magnesium aluminometasilicate)	Direct compression	Porous Magnesium Aluminometasili-cate Tablets as carrier for cyclosporine self emulsifying formulation.	[76]
Simvastatin	Silicon Dioxide	Adsorption to solid carriers	Optimized microemulsions and solid microemulsion system of Simvastatin: characterization and *in- vivo* evaluation.	[77]
Carvedilol	Gelucire® 44/14	Capsule Filling	Use of solid SMEDDS in delivery of carvedilol	[78]

Protection from Biodegradation: Drugs for which both solubility and degradation is low in the GI tract contribute to a low oral bioavailability, SMEDDS is useful for such drugs due to ability to reduce degradation as well as improve absorption. Drugs which undergo degradation in physiological system due to some reasons like acidic PH in stomach, enzymatic degradation or hydrolytic degradation can be protected from these degradation processes by loading them in SMEDDS, as liquid crystalline phase in SMEDDS act as a barrier between degrading environment and the drug.

Acetylsalicylic acid (log P = 1.2, M_w=180) is a drug readily hydrolyzed to salicylic acid in an acid environment and because of this it degrades in GI tract. When this drug is loaded in SMEDDS formulation and compare with commercial formulation, good plasma profile will be observed with SMEDDS formulation as compare to reference formulation.

Bioavailability enhancement (73%) also occurs when SMEDDS formulation used. This suggests that the SMEDDS formulation has a capacity to protect drugs from degradation in the GI tract [2, 12, 16].

Sustain Release from SMEDDS: Due to the wide range of structures occurring in them, SMEDDS display a rich behaviour regarding the release of solubilised material. Thus in case of O/W microemulsion, hydrophobic drugs solubilised mainly in the oil droplets, experience hindered diffusion and are therefore released rather slowly (depending on the oil/water partitioning of the substance).

Water soluble drugs, on the other hand, diffuse essentially without obstruction (depending on the volume fraction of the dispersed phase) and are release fast. For balanced microemulsion, relatively fast diffusion and release occur for both water soluble and oil soluble drugs due to the bicontinious nature of microemulsion "structure". Apart from the microemulsion structure, the microemulsion composition is important for the drug release rate [39, 79]

Advantages of SMEDDS:

1. Reduction in dose by the enhancement in bioavailability [66].
2. Temporal profile of drug absorption is more consistent [15, 43].
3. Targeted delivery of drug towards specific absorption window in GIT [15].
4. Drug is not affected by the hostile environment in gut [80].
5. Reduced variability including food effects [81]
6. Protection of sensitive drug substances [43].
7. Easy manufacture and scale up [18].
8. In SMEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore increase in AUC i.e. bioavailability and Cmax is observed with many drugs when presented in SMEDDS [15].
9. Fine oil droplets empty rapidly from the stomach and promote wide distribution of drug throughout the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of drugs and gut wall [80].
10. SMEDDS has potential to deliver peptides that are processed to enzymatic hydrolysis in GIT [43].
11. When polymer is incorporated in composition of SMEDDS it gives prolonged release of Medicament [51]
12. SMEDDS formulation is composed of lipids, surfactants and co-solvents. The system has the ability to form an oil-on-water emulsion when dispersed by an aqueous phase under gentle agitation. SMEDDS present drugs in a small droplet size and well-proportioned distribution and increase the dissolution and permeability.

    Furthermore, because drugs can be loaded in the inner phase and delivered to the lymphatic system, can bypass first pass metabolism. Thus SMEDDS protect drugs against hydrolysis by enzymes in the GI tract and reduce the presystemic clearance in the GI mucosa and hepatic first-pass metabolism [43].

Drawback of SMEDDS: Lack of good predicative *in vitro* models for assessment of the formulation is the most important problem in the development of SMEDDS and other lipid-based formulation. These formulations are dependent on digestion prior to release of the drug so traditional dissolution method do not work. To mimic this, *in vitro* model simulating the digestive processes of the duodenum has been developed. This *in vitro* model needs further development and validation before its strength can be evaluated. Further development will be based on *in vitro*, *in vivo* correlations and therefore different prototype lipid based formulations need to be developed and tested *in vivo* in a suitable animal model [43].

TABLE 3: PATENTS ON SMEDDS

Patent no.	Patent name	Inventor
US 2010/0331356	Self-microemulsifying drug delivery systems	Igor Legen, Janez Kerc, Polona Jurkovic
US 2007/0104740	Self-microemulsifying drug delivery systems of a HIV protease inhibitor	Jody Firmin Marceline Voorspoels
US 1999/5,993,858	Method and formulation for increasing the bioavailability of poorly water-soluble drugs	Crison; John R., Amidon; Gordon L.
US 2006/0275358	Self-microemulsifying dosage forms of low solubility active	Lin, Jing

	ingredients such as co-enzyme Q10	
US 2001/6309665	Composition with sustained release of active principle, capable of forming a microemulsion	Barthelemy, Philippe, Benameur, Hassan
US 2004/0248901	Compositions containing itraconazole and their preparation methods	Lee, Beom Jin (Kangwon-do, KR) Lee, Dong Won (Seoul, KR) Choi, Choon Young (Kangwon-do, KR)

TABLE 4: COMMERCIALLY AVAILABLE SMEDDS

Drug	Indications	Brand name	Manufacturer	Ref
Cyclosporine A	Immunosuppressant	SandimmuneNeoral®	Biochem, Cipla, Novartis etc	[82]
Ritonavir	Anti-HIV	Norvir®	Abbott Laboratories	[82]
Amprenavir	Anti HIV	Agenerase®	Glaxosmithkline	[82]
Saquinavir	Anti HIV	Fortovase®	Hoffman-La Roche inc	[82]
Valproic acid	Antiepileptic	Convulex®	Pharmacia	[82]
Bexarotene	Antineoplastic	Targretin®	Ligand	[82]

CONCLUSION: For Lipophilic drugs, which have dissolution rate limited absorption, SMEDDS are proved to be promising strategy to increase solubility and bioavailability of drug. The oral delivery of hydrophobic drugs now, is not a tough task when formulated in SMEDDS. Also problems associated with many drugs like causing GI irritation, having high first pass metabolism, short half life and stability issues are solved when incorporated in SMEDDS. In Future Sight, novel development technology will enable SMEDDS to solve more problems associated with other routes of administration along with oral route.

REFERENCES:

1. Stegemanna S and Leveillerb F: When poor solubility becomes an issue: From early stage to proof of concept. European Journal of Pharmaceutical Sciences 2007; 31:249-61.
2. Sachan R, Khatri K and Kasture SB: Self-emulsifying drug delivery system: A novel approach for enhancement of bioavalibility. International Journal of PharmTec Research 2010; 2:1738-1745.
3. Aungst BJ: Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. Journal of Pharmaceutical Sciences 1993; 81:979-986.
4. Burcham DL, Maurin MB, Hausner EA and Huang SM: Improved oral bioavailability of the hypocholesterolemic DMP 565 in dogs following oral dosing in oil and glycol solutions. Biopharmaceutics & Drug Disposition 1997; 18:737-742.
5. Serajuddin AT, Sheen PC, Mufson D, Bernstein DF and Augustine MA: Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water soluble drug from solid dispersion. Journal of Pharmaceutical Sciences 1988; 77:414-417.
6. Aungst BJ, Nguye N, Rogers NJ, Rowe S, Hussain M, Shum L and White S: Improved oral bioavailability of an HIV protease inhibitor using gelucire 44/14 and labrasol vehicles. Bulletin Technique Gattefosse 1994; 87:49-54.
7. Wakerly MG, Pouton CW, Meakin BJ and Morton FS: Self-emulsification of vegetable oil-non-ionic surfactant mixtures. ACS Symposium Series 1986; 311:242-255.
8. Craig DQM, Lievens HSR, Pitt KG and Storey DE: An investigation into the physicochemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis. International Journal of Pharmaceutics 1993; 96:147-155.
9. Toguchi H, Ogawa Y, Iga K, Yashiki T and Shimamoto T: Gastro-intestinal absorption of ethyl 2 chloro-3-(4-(2- methyl-2-phenylpropyloxy) phenyl) propionate from different dosage forms in rats and dogs. Chemical & Pharmaceutical Bulletin 1990; 38:2792-2796.
10. Kararli TT, Needham TE, Griffin M, Schoenhard G and Ferro LJ: Alcorn L oral delivery of a renin inhibitor compound using emulsion formulations. Pharmaceutical Research 1992; 9:888-93.
11. Schwendener RA and Schott H: Lipophilic 1-beta-darabinofuranosyl cytosine derivatives in liposomal formulations for oral and parenteral antileukemic therapy in the murine L1210 leukemia model. Journal of Cancer Research & Clinical Oncology 1996; 122:723-726.
12. Patel PA, Chaulang GM, Akolkotkar A, Mutha SS, Hardikar SR and Bhosale AV: Self-emulsifying drug delivery system: A review. Research Journal of Pharmacy & Technology 2008; 1:313-324.
13. Corbo DC, Liu JC and Chein YW: Characterization of the barrier properties of mucosal membranes, Journal of Pharmaceutical Sciences 1990; 79:202-206.
14. Wakerly MG, Pouton CW and Meakin BJ: Evaluation of the self–emulsifying performance of a non-ionic surfactant-vegetable oil mixture. Journal of Pharmacy & Pharmacology 1987; 39:6p.
15. Constantinides PP: Lipid microemulsion for improving drug dissolution and oral absorption: Physical and biopharmaceutical aspect. Pharmaceutical Research 1995; 12:1561-1572.
16. Shah NH, Carvagal MT, Patel CI, Infild MH and Malick AW: Self-emulsifying drug delivery system (SEDDS) with polyglycolyzed glycerides for improving *in vitro* dissolution and oral absorption of lipophilic drugs. International Journal of Pharmaceutics 1994; 106:15-23.
17. Gupta RN, Gupta R and Singh RG: Enhancement of oral bioavailability of lipophilic drugs from self-microemulsifying drug delivery system (SMEDDS). International Journal of Drug Development & Research 2009; 1:10-18.
18. Kyatanwar AU, Jadhav KR and Kadam VJ: Self micro-emulsifying drug delivery system (SMEDDS): Review. Journal of Pharmaceutical Research 2010; 3:75-83.
19. Wakerly MG, Pouton CW, Meakin BJ and Morton FS: Self-emulsification of vegetable oil-non-ionic surfactant mixtures: A proposed mechanism of action. ACS symposium Series 1986; 311:242-255.
20. Pouton CW: Effects of the inclusion of a model drug on the performance of self-emulsifying formulations. Journal of Pharmacy & Pharmacology 1985; 37:1p.

21. Tang JL, Sun J and He ZG: Self-emulsifying drug delivery system: Strategy for improving oral delivery of poorly soluble drugs. Current Drug Therapy 2007; 2:85-93.
22. Pouton CW and Charman WN: The potential of oily formulations for drug delivery to the gastro-intestinal tract. Advanced Drug Delivery Review 1997; 25:1-2.
23. Cirri M, Mura P and Mora PC: Liquid spray formulations of xibornol by using self-microemulsifying drug delivery systems. International Journal of Pharmaceutics 2007; 340: 84-91.
24. Zvonar A, Berginc K, Kristl A and Gasperlin M: Microencapsulation of self-microemulsifying system: Improving solubility and permeability of furosemide. International Journal of Pharmaceutics 2010; 388:151-158.
25. Shukla JB and Patel SJ: Formulation and evaluation of self-microemulsifying system of candesartan cilexetil. International Journal of Pharmaceutical Sciences 2010; 2:143-146.
26. Yao J, Lu Y and Zhou JP: Preparation of nobiletin in self-microemulsifying systems and its intestinal permeability in rats. Journal of Pharmaceutical Sciences 2008; 3:22-29.
27. Lu JL, Wang JC, Zhao SX, Liu XY, Zhao H, Zhang X, Zhou SF and Zhang Q: Self-microemulsifying drug delivery system improves anticancer effect of oral 9-nitrocamptothecin on human cancer xenografts in nude mice. European Journal of Pharmaceutics & Biopharmaceutics 2008; 69:899-907.
28. Patel AR and Vavia PR: Preparation and *in vivo* evaluation of self-microemulsifying drug delivery system containing fenofibrate. AAPS Journal 2007; 3:344-352.
29. Shen HR and Zhong MK: Preparation and evaluation of self-microemulsifying drug delivery systems containing atorvastatin. Journal of Pharmacy & Pharmacology 2006; 58:1183-1191.
30. Zhang P, Liu Y, Feng N and Xu J: Preparation and evaluation of self-microemulsifying drug delivery system of oridonin. International Journal of Pharmaceutics 2008; 355:269-276.
31. Patro MN and Yadav AV: Formulation design and evaluation of self-microemulsifying drug delivery system of valproic acid. Jordan Journal of Pharmaceutical Sciences 2010; 2:117-125.
32. Wu X, Xu J, Huang X and Wen C: Self-microemulsifying drug delivery system improves curcumin dissolution and bioavailability. Drug Development & Industrial Pharmacy 2010; 37:1-10.
33. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, Lee HB and Cho SH: Development of self-microemulsifying drug delivery systems for oral bioavailability enhancement of simvastatin in beagle dogs. International Journal of Pharmaceutics 2004; 274:65-73.
34. Venkatesh G, Majid MIA, Mansor SM, Nair NK, Croft SL and Navaratnam V: *In vitro* and *in vivo* evaluation of self-microemulsifying drug delivery system of buparvaquone. Drug Development & Industrial Pharmacy 2010; 36:735-743.
35. Dixit AR, Rajput SJ and Patel SG: Preparation and bioavailability assessment of SMEDDS containing valsartan. AAPS Pharmaceutical Sciences & Technology 2010; 1:314-321.
36. Bachhav YG and Patravale VB: SMEDDS of glyburide: Formulation, *in vitro* evaluation and stability studies. AAPS Pharmaceutical Sciences & Technology 2009; 2:481-487.
37. Cui SX, Nie SF, Wang CG and Pan WS: Preparation and evaluation of self-microemulsifying drug delivery system containing vinpocetine. Drug Development & Industrial Pharmacy 2009; 35:603-611.
38. Mullertz A, Ogbonna A, Ren S and Rades T: New perspectives on lipid and surfactant based drug delivery systems for oral delivery of poorly soluble drugs. Journal of Pharmacy & Pharmacology 2010; 62:1-15.
39. Patel MJ, Patel SS, Patel NM and Patel MM: A self-microemulsifying drug delivery system. International Journal of Pharmaceutical Sciences Review & Research 2010; 4:29-35.
40. Tolle S, Zuberi T and Lawrence MJ: Physiochemical and der-solubilisation properties of N, N-dimethyl-N-(3-dodecyloxy propyl) amine oxide: a biodegradable nonionic surfactant. Journal of Pharmaceutical Sciences 2000; 89:798-806.
41. Lawrencea MJ and Reesb GD: Microemulsion-based media as novel drug delivery systems. Adv. Drug Deliv. Rev 2000; 45:89-121.
42. Kimura M, Shizuki M, Miyoshi K, Sasai T, Hidaka H, Tatakamura H and Matoba T: Relationship between the molecular structures and emulsification properties of edible oils. Bioscience Biotechnology Biochemistry 1994; 58:1258-1261.
43. Kamble AV, Jagdale DM and Kadam VJ: Self-micro emulsifying drug delivery system. International Journal of Pharma & Bio Sciences 2010; 1:2-8.
44. Narang AS, Delmarre D and Gao D: Stable drug encapsulation in micelles and microemulsions. International Journal of Pharmaceutics 2007; 345:9-25.
45. Crison JR and Amidon GL, 1999. Methods and formulation for increasing the bioavailability of poorly water-soluble drugs. US Patent 5993858.
46. Hauss DJ, Fogal SE, Ficorilli JV, Price CA, Roy T, Jayaraj AA and Keirns JJ: Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor. Journal of Pharmaceutical Sciences 1998; 87:164-169.
47. Yuasa H, Sekiya M, Ozeki S and Watanabe J: Evaluation of milk fat globule membrane (MFGM) emulsion for oral administration: absorption of α-linolenic acid in rats and the effect of emulsion droplet size. Biological & Pharmaceutical Bulletin 1994; 17:756-758.
48. Georgakopoulos E, Farah N and Vergnault G: Oral anhydrous nonionic microemulsions administrated in softgel capsules. Bulletin Technique Gattefosse 1992; 85:11-20.
49. Bose S and Kulkarni PK: Self emulsifying drug delivery systems: A review. Indian Journal of Pharmaceutical Education 2002; 36:184-190.
50. Ganesh S, Shantanu K, Pravin K, Ashwin K, Rajesh K and Bhanudas K: Self-microemulsifying drug delivery system: A novel approach for hydrophobic drugs. International Journal of Pharmaceutical Sciences 2011; 3:988-1005**.**
51. Shaji J and Joshi V: Self-microemulsifying drug delivery system (SMEDDS) for improving bioavailability of hydrophobic drugs and its potential to give sustain release dosage form. Indian Journal of Pharmaceutical Education 2005; 39:130-135.
52. Patel M.V. and Chen F.J., 2002. Compositions and methods for improved delivery of hydrophobic agents. United States Patent 6451339.
53. Barthelemy P. and Benameur H., 2001. Composition with sustained release of active principle capable of forming microemulsion. United State Patent 6309665.
54. Zhang P, Liu Y, Feng N and Xu J: Preparation and evaluation of self-microemulsifying drug delivery system of oridonin. International Journal of Pharmaceutics 2008; 355:269-276.
55. Fregonezi-Nery MM: Determination of albendazole in oral suspension. Analytical Letters 2001; 34:1255–1263.
56. Borhade V, Nair H and Hegde D: Design and evaluation of self-microemulsifying drug delivery system (SMEDDS) of tacrolimus. AAPS Pharmaceutical Sciences & Technology 2008; 9:13–21.
57. Mukherjee T and Plakogiannis FM: Development and oral bioavailability assessment of a supersaturated self-microemulsifying drug delivery system of albendazole. Journal of Pharmacy & Pharmacology 2010; 62:1112-1120.
58. Patrick H, Nigel MD and Uwe V: Pseudo-ternary phase diagram of aqueous mixtures of Quil A cholesterol and phospholipids prepared the lipid film hydration method. International Journal of Pharmaceutical Sciences 2004; 270:229-39.

59. Martin A, "A book on physical pharmaceutical sciences", Lippincott Williams, UK, Fourth Edition., 1999, 156-71.
60. Pouton CW: Self-emulsifying drug delivery system: Assessment of the efficiency of emulsification. International Journal of Pharmaceutics 1985; 27:335.348.
61. Craig DQM, Barker SA, Banning D and Booth SW: An investigation into mechanism of size analysis and low frequency dielectric spectroscopy. International Journal of Pharmaceutics 1995; 114:103-110.
62. Patil P, Joshi J and Paradkar P: Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen. AAPS Pharmaceutical Sciences & Technology 2004; 5:34-42.
63. Patil P, Vandana P and Paradkar P: Formulation of self-emulsifying drug delivery system for oral delivery of simvastatin: *In vitro* and *in vivo* evaluation. Acta Pharmaceutica 2007; 57:111-122.
64. Myers RA and Stella VJ: Factors affecting the lymphatic transport of penclomedine (NSC-338720), a lipophilic cytotoxic drug: Comparison to DDT and hexachlorobenzene. International Journal of Pharmaceutics 1992; 80:511-62.
65. Khoo SM, Porter CJ, Edwards GA and Charman WN: Intestinal lymphatic transport is the primary route for halofantrine after oral postprandial administration. Pharmaceutical Sciences 1999; 1:S-624.
66. Gershanik T and Benita S: Positively-charged self-emulsifying oil formulation for improving oral bioavailability of progesterone. Pharmaceutical Development & Technology 1996; 1:147–157.
67. Khoo SM, Shackleford DM and Porter CJ: Intestinal lymphatic transport of halofantrine occurs after oral administration of a unit dose lipid-based formulation to fasted dogs. Pharmaceutical Research 2003; 20:1460-65.
68. Patro MN, Bankar AS, Rakesh SU, Yadav AV: Oral lipid based formulation: A review. International Journal of Pharma & Bio Sciences 2010; 1:1-14.
69. Vergote GJ, Vervaet C, Van DI, Hoste S, De SS, Demeester J, Jain RA, Ruddy S and Remon J P: An oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen. International Journal of Pharmaceutics 2001; 219:81-87.
70. Yamada T, Onishi H and Machida Y: Sustained release ketoprofen microparticles with ethyl cellulose and carboxy methyl ethyl cellulose. Journal of Control Release 2001; 75:271-281.
71. Roda A, Sabatini L, Mirasoli M, Baraldini M and Roda E: Bioavailability of a new ketoprofen formulation for once-daily oral administration. International Journal of Pharmaceutics 2002; 241:165-172.
72. El-Kamel AH, Sokar MS, Al Gamal SS and Naggar VF: Preparation and evaluation of ketoprofen floating oral delivery system. International Journal of Pharmaceutics 2001; 220:13-21.
73. Gursoy N, Garrigue JS, Razafindratsita A, Lambert G and Benita S: Excipient effects on *in vitro* cytotoxicity of a novel paclitaxel selfemulsifying drug delivery system. Journal of Pharmaceutical Sciences 2003; 92:2420–2427.
74. Gershanik T, Benzeno S and Benita S: Interaction of the self-emulsifying lipid drug delivery system with mucosa of everted rat intestine as a function of surface charge and droplet size. Pharmaceutical Research 1998; 15:863-869.
75. Yi T, Wan J, Xu H and Yang X: A new solid self-microemulsifying formulation prepared by spray-drying to improve the oral bioavailability of poorly water soluble drugs. European Journal of Pharmaceutics &. Biopharmaceutics 2008; 70:439-44.
76. Sander C and Holm P: Porous magnesium aluminometasilicate tablets as carrier of a cyclosporine self-emulsifying formulation. AAPS Pharmaceutical Sciences & Technology 2009; 10:1388-1395
77. Dixit RP and Nagarsenker MS: Optimized microemulsion and solid microemulsion systems of simvastatin: Characterization and *in vivo* evaluation. Journal of Pharmaceutical Sciences 2010; 99:4892-4902.
78. Wei-san P, Lei T, Xin T, Ting-ting Y, Lan-lan W and Pei-nan S: Use of solid smedds in delivery of carvedilol. Journal of Chin Pharmaceutical Sciences 2006; 15:223-227.
79. Kumar P and Mital K L: Handbook of microemulsion: Science and Technology. Marcel Dekker, New York, Basel, First Edition 1999.
80. Farah N, Laforet JP and Denis J: Self-microemulsifying drug delivery systems for improving dissolution of drugs: in vitro evaluations presented by Gattefosse patented technology, AAPS annual meeting in San Diego, 1994, pp 41.
81. Charman WN, Porter CJ, Mithani S and Dressman JB: Physiochemical physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. Journal of Pharmaceutical Sciences 1997; 86:269-82.
82. Shukla JB, Koli AR,. Ranch KM and Parikh RK: Self-microemulsifying drug delivery. International Journal of Pharmacy & Pharmaceutical Sciences 2010; 1(2):15-33.
83. Legen I., Kerc J. and Jurkovic P., 2010. Self-microemulsifying drug delivery systems. US 2010/0331356.
84. Voorspoels J.F.M., 2007. Self-microemulsifying drug delivery systems of a HIV protease inhibitor. US 0104740 A1.
85. Crison J. R. and Amidon G. L., 2009. Method and formulation for increasing the bioavailability of poorly water-soluble drugs. US 1999/5,993,858.
86. Jing L., 2006. Self-microemulsifying dosage forms of low solubility active ingredients such as co-enzyme Q10. US 0275358.
87. Philippe B. and Hassan B., 2001. Composition with sustained release of active principle, capable of forming a microemulsion. US 6309665.
88. Lee B. J., Lee D. W. and Choi C. Y., 2004. Compositions containing itraconazole and their preparation methods. US 0248901.

****