

Review on Self Emulsifying Drug Delivery System: Novel Approach for Solubility Enhancement

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Abstract:

Oral route still remains the favorite route of drug administration in many diseases and till today it is the first way investigated in the development of new dosage forms. The major problem in oral drug formulations is low and erratic bioavailability due to poor aqueous solubility. It is estimated that 40% of active substances are poorly soluble in water. The improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations. Lipophilic drugs can be solubilized to increase the bioavailability by using several methods as micro emulsion, nano suspension, liposome, solid lipid nanoparticles (SLN), self emulsifying drug delivery system (SEDDS), complexation with cyclodextrin etc. Self emulsifying drug delivery system has gained more attention due to enhanced oral bio-availability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT. SEDDS are liquid to semisolid in nature, but it has drawbacks as formulation development, quality control, stability etc. These liquid SEDDS can be converted into solid dosage form without affecting drug release property. After administering the drug gets released and self emulsify in the GI tract.

Keywords: *Self emulsifying drug delivery system, surfactant, oil, co-surfactant, technique of solid Sedds development, dosage form, marketed formulation of Sedds*

INTRODUCTION:

Self-emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. The oral route is one of the preferred routes for chronic drug therapy. Approximately 35-40% of new drug candidates have poor water solubility. The oral delivery of such drugs is frequently associated with low bioavailability, high inter and intra subject variability and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. To overcome these problems, new strategies were reported to increase solubility and bioavailability including complexation with cyclodextrins, solid dispersion (suspension), co precipitation, micronisation, salt formation, emulsion, use of micelles, and co grinding.¹⁻⁴

Emulsions are used as vehicles for the administration of drugs, especially due to its

potential of enhancing the oral bioavailability of poorly absorbed drugs.⁵

SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SEDDS requires the use of a co-surfactant to generate a micro emulsion. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200nm-5µm and the dispersion has a turbid appearance. Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation. Recently, SEDDS have been formulated using medium chain tri-glyceride oils and non-ionic surfactants, the latter being less toxic. Upon per oral administration, these systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility.

Biopharmaceutical drug classification system:

Table 1: Biopharmaceutical drug classification

Class	Permeability	Solubility
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Class I includes drugs that are water soluble and gastrointestinal tract permeable. This class does not suffer from absorption or permeation problems that may affect oral drug bioavailability. While classes II, III and IV contain drugs having problems in solubility and/or permeability that may reflect on their bioavailability in the blood after the drug is taken orally. Classes II, III and IV form approximately 80% of the drugs available in the market.

NEED OF SEDDS:

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that pre-dissolving the compound over comes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets.⁵ Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, Poly Vinyl Pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favor a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetric or X-ray crystallography. In this type of case SEDD system is a good option.

POTENTIAL ADVANTAGES OF THESE SYSTEMS INCLUDE:

1. Enhanced oral bioavailability enabling reduction in dose,

Biopharmaceutical drug classification is a fundamental guideline classifying drugs based on the solubility and permeability, as shown in Table 1

2. More consistent temporal profiles of drug absorption,
3. Selective targeting of drug(s) toward specific absorption window in GIT,
4. Protection of drug(s) from the hostile environment in gut.
5. Control of delivery profiles
6. Reduced variability including food effects
7. Protective of sensitive drug substances
8. High drug payloads
9. Liquid or solid dosage forms

COMPOSITION OF SEDDS:

The self-emulsifying process is depends on

1. The nature of the oil–surfactant pair
2. The surfactant concentration
3. The temperature at which self-emulsification occurs.

OILS:

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract⁷. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages.⁶ Novel semisynthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride.⁷

SURFACTANT:

Nonionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules.⁸

COSOLVENTS:

Cosolvents like diethylene glycol monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the co surfactant in the microemulsion systems.

FORMULATION OF SEDDS: ⁹

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble co-solvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions. The following should be considered in the formulation of a SEDDS:

1. The solubility of the drug in different oil, surfactants and co-solvents.
2. The selection of oil, surfactant and co-solvent based on the solubility of the drug and the preparation of the phase diagram
3. The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and co-solvent.

The addition of a drug to a SEDDS is critical because the drug interferes with the self-emulsification process to a certain extent, which leads to a change in the optimal oil-surfactant ratio. So, the design of an optimal SEDDS requires pre formulation-solubility and phase-diagram studies. In the case of prolonged SEDDS, formulation is made by adding the polymer or gelling agent .

THE EMULSIFICATION PROCESS:

1) MECHANISM OF SELF-EMULSIFICATION:

The process by which self-emulsification takes place is not yet well understood. However, according to Reiss, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. In addition, the free energy of a conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by equation.¹⁰

$$\Delta G = \sum_i N_i \pi r_i^2 \sigma$$

Where, G is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius, r, and s represents the interfacial energy. With time, the two phases of

the emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the systems. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to coalescence. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously). Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing.¹¹ In earlier work, it was suggested that the ease of emulsification could be associated with the ease by which water penetrates into the various LC or gel phases formed on the surface of the droplet.^{12,13} According to Wakerly et al.¹⁴, the addition of a binary mixture (oil/nonionic surfactant) to water results in interface formation between the oil and aqueous-continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interface. Further aqueous penetration will result in the formation of the dispersed LC phase. As the aqueous penetration proceeds, eventually all material close to the interface will be LC, the actual amount depending on the surfactant concentration in the binary mixture. Once formed, rapid penetration of water into the aqueous cores aided by the gentle agitation of the self-emulsification process, causes interface disruption and droplet formation. The high stability of these self-emulsified systems to coalescence is considered to be due to the LC interface surrounding the oil droplets. The involvement of the LC phase in the emulsion formation process was extensively studied by Pouton et al.^{13, 14, 15, 16} Later, Craig et al. used the combination of particle size analysis and low frequency dielectric spectroscopy (LFDS) to examine the self-emulsifying properties of a series of Imwitor 742 (a mixture of mono- and di glycerides of capric and caprylic acids)/ Tween 80 systems^{16,19, 20}. The dielectric studies provided evidence that the formation of the emulsions may be associated with LC formation, although the relationship was clearly complex. The above technique also pointed out that the presence of the drug may alter the emulsion characteristics, possibly by interacting with the LC phase⁴¹. However, the correlation between the spontaneous emulsification and LC formation is still not definitely established²⁰

b) Dilution phases:

Upon dilution of a SMEDDS formulation, the spontaneous curvature of the surfactant layer changes via a number of possible liquid crystalline phases. The droplet structure can pass from a reversed spherical droplet to a reversed rod-shaped droplet, hexagonal phase, lamellar phase, cubic phase and various other structures until, after appropriate dilution, a spherical droplet will be formed again dilution.

ROLE OF EXCIPIENT USED IN SOLID SELF EMULSIFICATION SYSTEM:

Self emulsifying solid dosage form mainly contains oil, surfactant, co surfactant, filler etc. A wide range of oils has been studied either as model system or as potential vehicles for the dosage forms, with many of the oils under study being medium chain fatty acid ester or a medium/long chain saturated, partially unsaturated or unsaturated hydrocarbon, in liquid, semisolid or solid form at room temperature. In SEDDS we can use different types of oil for examples mono, di, triglycerides of fatty acids, fatty alcohols, vegetable oils, mineral oils, refined animal oils etc.²¹

Nature of oil is very important in the formation of SEDDS. Chemicals structure of the oil components and interactions of these components with the various enzymes, surfactants and proteins associated with digestion and absorption process, for example, fatty acid chain length is important factor for chylomicron formation. Short and medium chain acids are predominantly absorbed by portal blood

system while longer chain fatty acid may be re-esterified in the cell lining the small intestine and absorbed via the lymphatics.²²⁻²³

The absorption enhancement is greater when using unsaturated fatty acids. Figure 1 showed digestion of lipid and subsequent absorption via the portal blood and intestinal lymphatics.²³

M. Cheema et al reported that a greater degree of unsaturation led to a more rapid onset of lipoprotein synthesis as a result of faster absorption or greater affinity of fatty acid binding to protein because unsaturated fatty acids have lower melting points as compared to saturated with increasing fluidity.²⁴

Liquid crystal formation from oil depends on oil polarity, which would influence the emulsification process. Very polar or non polar oils tend to form poor emulsions. Miglyol 812 and 840 both have intermediate polarity which shows favourable emulsification properties with Tween85. Solubility of the drug in the oil surfactant mixture is very important whereas solubility of drug in vegetable oil is not a problem. The simplest and most desirable formulation may well be a simple oil solution which is self emulsified in the gut during digestion.²⁵ For toxicity reason, these days research focuses on the use of non ionic surfactant with relatively high hydrophilelipophile balance (HLB) value. Surfactants possess properties to inhibit the digestion of oils, so selection of surfactant is very important. Pouton and Wakerley et al have screened arrange of surfactants, finding that in general molecules with unsaturated acyl chains were most efficient emulsifiers.²⁶⁻²⁷

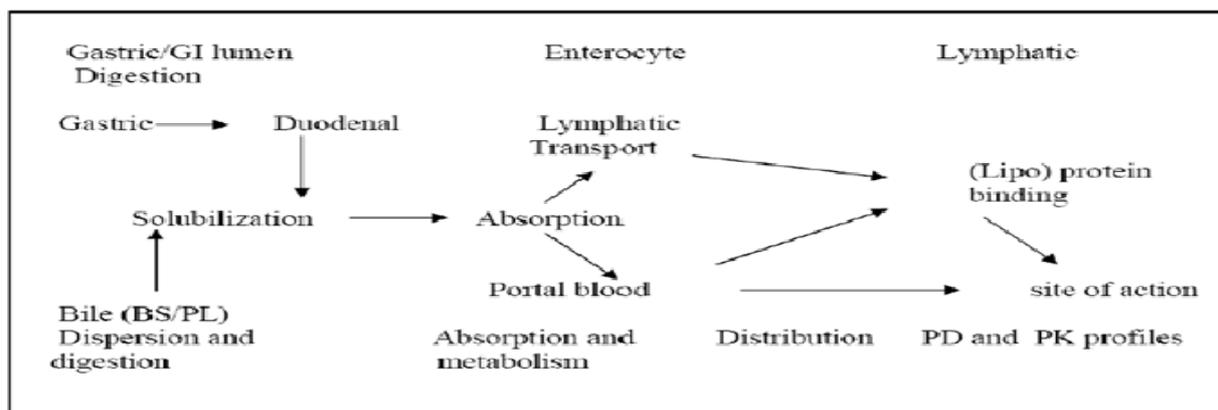


Fig 1. Processing of lipid and co- administered drug

TECHNIQUE OF SOLID SEDDS DEVELOPMENT:

Solid SEDDS were developed mainly by adsorption of solid carriers, spray drying, melt extrusion, dry emulsion, solid dispersion etc. These solid SEDDS can be converted into pellets, tablets and capsule

METHOD OF PREPARATION:²⁸

A) Solidification techniques for transforming liquid/semisolid:

Various solidification techniques are as listed below;

1) Capsule filling with liquid and semisolid self-emulsifying formulations:

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four-step process:

- A) Heating of the semisolid excipient to at least 20°C above its melting point.
- B) Incorporation of the active substances (with stirring).
- C) Capsule filling with the melt cooling to room temperature. For liquid formulations, it involves a two-step process.
- D) Filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by micro spray sealing.

B) Spray drying:

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets.

The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates into tablet pattern and the drying chamber design are selected according to the drying characteristic the product and powder specification.

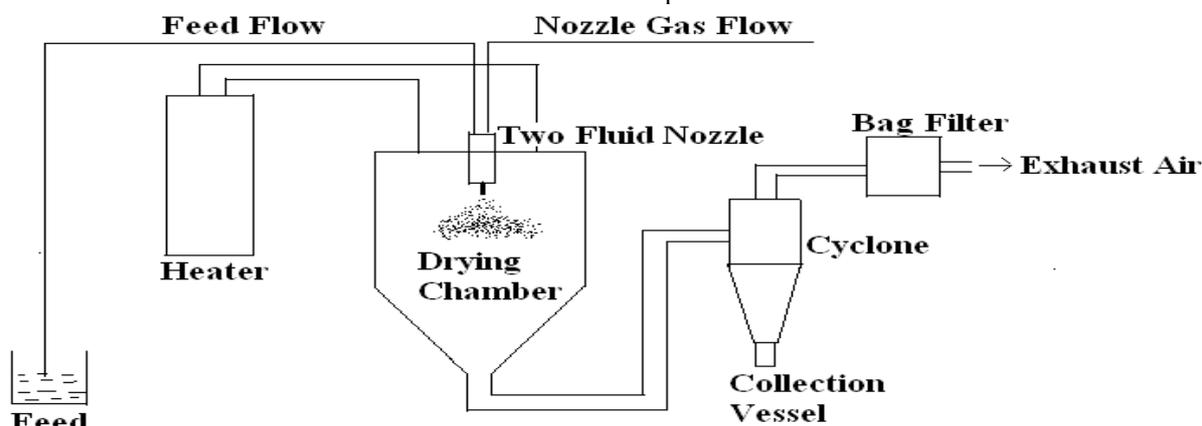


Fig 2. Spray Drying.

C) Adsorption to solid carriers:

Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid on to carriers by mixing in a blender.

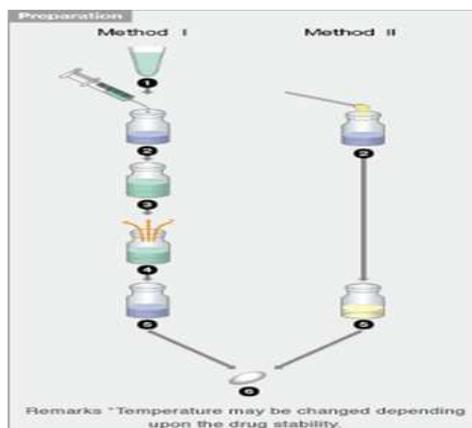
D) Melt granulation:

Melt granulation is a process in which powder agglomeration is obtained through the addition of a

binder that melts or softens at relatively low temperatures.

E) Melt extrusion/extrusion spheronization:

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions.



Method: 1

- (1) Dissolve drug in suitable solvent such as ethanol etc.
- (2) Add the drug solution prepared in (1) to Solubilizer SL-11 thoroughly mix to completely dissolve the content
- (3) Drug/SL11 solution with solvent is made
- (4) Evaporate the solvent at 50°C for about 1 hour to remove the solvent. Remove the solvent under a nitrogen stream
- (5) The complex of SL-11 and the drug is made.
- (6) Soft capsule can be prepared by using the concentrated solution in (5)

Method: 2

- (2) Depending on the drug; drug can be dissolved directly in SL-11. If required warm this to about 50°C to allow complete dissolution
- (3) The complex of SL-11 and the drug is made
- (4) Soft capsule can be prepared by using the concentrated solution in (5)

DOSAGE FORMS FROM SELF EMULSIFYING SYSTEM:

(1) Oral delivery:

Self emulsifying capsule: It is a capsules containing liquid or semisolid form of self emulsifying system. In the GIT, the capsules get dispersed to SES uniformly in the fluid to micron size, enhancing bioavailability. Second type of self emulsifying capsule is solid SES filled into capsule.

Self emulsifying tablets : S.Nazzal et al developed self nanoemulsified tablet dosage form of Ubiquinone. The main objectives of this study were to study effect of formulation ingredients on the release rate of Ubiquinone and to evaluate an optimized self nanoemulsified tablets formulation. The first prepared self nanoemulsion system containing Ubiquinone was prepared as nanoemulsion, this nanoemulsion was adsorbed by granular materials and then compressed to form tablets. The optimized formulation of coenzyme Q10 self nanoemulsified tablet dissolution profile showed that 80-90% drug release took place in 45 minute.²⁹

A.A. Attama et al formulated the solid self emulsifying systems in the delivery of diclofenac. This solid self emulsifying system was developed using goat fat and tween. The fatty material and surfactant were heated together to melt and added to weighted quantity of drug and dissolved in the melt, this molten mass was then poured into plastic mould and cooled. This tablets will liquify at body temperature without agitation and at gastrointestinal conditions, agitation as peristaltic movement will lower the liquification time, resulting in faster emulsification with increased plasma concentration.

Different formulation ratio shows varying dissolution profile at constant speed/agitation. These tablets showed good release profiles with acceptable tablet properties.³⁰

Self emulsifying pellets: C. Tuleu et al presented comparative bioavailability study in dogs of a self – emulsifying formulation of progesterone presented as in pellets and the liquid form was compared with an aqueous suspension of progesterone. The in vitro dissolution tests showed that nearly 100% of progesterone dissolved within 30 min and within 5 min from capsules containing the progesterone dissolved in self emulsifying system. From the aqueous suspension, 50% of the dose was released within 60 min. They also showed that pellets administered orally to dogs were tested versus the same dose of progesterone dissolved in liquid SES in capsules or a suspension of micronized progesterone. In that SES pellets and SES solution had higher plasma levels of progesterone at each time point as compared to the aqueous suspension of progesterone.³¹ E. Franceschinis et al developed a method of producing self emulsifying pellets by wet granulation. Here they first developed a binder solution containing an oil (mono and diglycerides), polysorbate80 and model drug nimesulide in different proportion. This oil-surfactant mixture was stirred then added to water to form Self- emulsifying system. Second step was to prepare granules from microcrystalline cellulose and lactose in a granulator. These binder solutions were sprayed on to the granules and pellets were formed by increasing the speed of the granulator. Pellets were able to generate significantly smaller droplets with respect to corresponding emulsions.³² M.Serratori et al presented controlled drug release from self-emulsifying pellets. The prepared self emulsifying system were formed by mixing oil- surfactant within solubilised drug in appropriate concentrations, because higher quantity of drug incorporated into SES, could be precipitated when diluted with water. This SES was added into damp mass of microcrystalline cellulose and lactose monohydrate, water was then added to the prepared wet mass for extrusion spheronization to form pellets. These pellets were coated by hydrophilic polymers namely ethyl cellulose then coated by aqueous.³³ Solution of hydroxypropylmethyl cellulose in a fluid bed coater. The ability of this formulation to enhance dissolution of the model drug, where dissolution results for the uncoated pellets containing methyl or propyl parabens with and without the addition of self emulsifying system were compared. Ahmed abdalla and Karsten Mader investigated preparation and characterization of self emulsifying pellets formulation. They formulated three self emulsifying

systems separately by melting Cithrol GMS (mono and diglycerides) and solutol HS 15, to this was added drug, dye and spin probe. Then added water to the molten lipid blend until creamy mass was formed, then added dry MCC into it to form suitable mass for extrusion. The dye was added for assessment of self emulsification and spin probe was added for the release kinetics and microenvironment of pellets, during release process, which were assessed using electron spin resonance spectroscopy. The dissolution profile showed complete release of drug as diazepam from the non self emulsifying GMS/MCC pellets. It had a 3 fold duration of action. Nearly 90% of the drug was released after an hour while only 55% was released from the GMS/MCC pellets. Pellets composed of MCC/GMS were only capable of releasing diazepam until the saturation solubility reached.³⁴ T. Iosio et al prepared bi layered self emulsifying pellets, SEP was formed by co extrusion sponification with two cohesive layers, in that, type 1 pellets had formulation A (a matrix made of lactose and MCC loaded with a SES dispersion) in the inner part and formulation B (a inert matrix containing in lactose, MCC, and water) in the outer and type 2 having formulation B in the inner core and formulation A externally. SEP were formulated in two steps, first prepared oil surfactant mixture then added to water to form self emulsifying system and this mixture was then loaded into MCC and lactose to form suitable extrusion sponification mass for pellets. Pellets of type I plus 2% of croscarmellose sodium released 90% of vinpocetine as a model drug within 30 min, pellets of type II were release in 20 min and from the physical mixture only 25% of drug was released after 60 min.³⁵

Self emulsifying beads: Self emulsifying system can be formulated as a solid dosage form by using less excipient. Patil and Paradkar discovered that deposition of SES into microporous polystyrene beads was done by solvent evaporation. Porous polystyrene beads with complex internal void structures were typically produced by co polymerising styrene and divinyl benzene. It is inert and stable over a wide range of pH, temperature and humidity. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES loaded PPB.³⁶

Self emulsifying microsphere: You et al. formulated solid SE sustained-release microspheres using the quasi emulsion solvent diffusion method for the spherical crystallization technique. Zedoary turmeric oil release behavior could be controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma concentration time profiles were achieved after oral administration of such microspheres into

rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS.³⁷

Selfemulsifying nanoparticle: Nanoparticle technology can be applied to the formulation of self emulsifying nanoparticle. One of the solvent was injection, in this method the prepared molten lipid mass contained lipid, surfactant and drug. This lipid molten mass was injected drop wise into a non solvent system. This is filtered and dried to get nanoparticles. By this method 100 nm size particle with 70-75% drug loading efficiency was obtained.³⁸ Second technique is sonication emulsion diffusion evaporation; by this method co load 5-fluorouracil and antisense EGFR (epidermal growth factor receptor) plasmids into biodegradable PLGA/O]CMC nanoparticles. The mixture of PLGA (poly lactide co- glycolide) and O -CMC (O-carboxymethyl chitosan) had a SE effect, with no additional surfactant required. Trickler et al. developed a novel nanoparticle drug delivery system consisting of chitosan and glycerylmonooleate (GMO) for the delivery of paclitaxel (PTX). These chitosan/ GMO nanoparticles, with bioadhesive properties increased cellular association and was prepared by multiple emulsion (o/w/o) solvent evaporation methods.³⁹

(2) **Topical Delivery:** Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drugs and related toxicity effects.⁴⁰

(3) **Oculars and Pulmonary delivery:** For the treatment of eye disease, drugs are essentially delivered topically o/w microemulsion have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.⁴⁰

(4) **Parenteral delivery:** Parenteral administration of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered as target site.⁴⁰

FACTOR AFFECTING OF SEDDS: ⁴¹

A) Nature and dose of the drug: Drugs which are administered at very high dose are not suitable for unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately are most difficult to deliver by SMEDD.

B) Polarity of the lipophilic phase: The polarity of the lipid phase is one of the factors that govern the drug release from the micro emulsions. The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of micronized for their propensity to inhibit crystallization and, thereby,

generate and maintain the supersaturated state for prolonged time period.

EVALUATION:

(A) Thermodynamic stability studies

The physical stability of a lipid-based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

1. 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.

2. 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 3500rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

3. Freeze thaw cycle: Three freezes for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.⁴²

(B) Dispersibility test: The efficiency of self-emulsification of oral nano or microemulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500mL of water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 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) nano emulsion, 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 with in 2 min.

Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2min).

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 formulation falling in Grade C could be recommend for SEDDS formulation.⁴²

(C) Turbidimetric Evaluation

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self

emulsifying 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).⁴³⁻⁴⁴

(D) Viscosity Determination

The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. So it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosities then it is w/o type of the system.⁴³⁻⁴⁴

(E) Droplet Size Analysis Particle Size Measurements

The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nano metric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water.⁴³⁻⁴⁴

(F) Refractive Index and Percent Transmittance

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare 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.

(G) Electro conductivity Study

The SEDD system contains ionic or non-ionic surfactant, oil, and water. So, this test is used to measure the electroconductive nature of system. The electro conductivity of resultant system is measured by electroconductometer.

(H) In Vitro Diffusion Study

In vitro diffusion studies is performed to study the release behavior of formulation from liquid crystalline phase around the droplet using dialysis technique.⁴⁴

(I) Drug content

Drug from pre-weighed SEDDS 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.⁴⁵

DISADVANTAGES OF SEDDS: ⁴⁶

- ✓ Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
- ✓ 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 needs to be developed and tested in vivo in a suitable animal model.
- ✓ The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.

APPLICATION:

1) Improvement in Solubility and bioavailability: 47-49

If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of Class-I drug (Low solubility/high permeability). Ketoprofen, a moderately hydrophobic (log P 0.979) non steroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation has high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained release formulations. Vergote et al. (2001) reported complete drug release from sustained release formulations containing ketoprofen in nano crystalline form.⁴⁵ Different formulation approaches that have been sought to achieve sustained release, increase the bioavailability, and decrease the gastric irritation of Ketoprofen include preparation of matrix pellets of nano-crystalline ketoprofen, sustained release Ketoprofen microparticles and formulations, floating or ketoprofen systems, and transdermal systems of ketoprofen. 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.

Preparation and stabilization of nano-crystalline or improved solubility forms of drug may pose processing, stability, and economic problems. This problem can be successfully overcome when Ketoprofen is presented in SEDDS formulation. This formulation enhance bioavailability due to increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent

in SEDDS sustained the release of Ketoprofen. In SEDDS, 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 C max is observed with many drugs when presented in SEDDS.

2) Protection against Biodegradation:

The ability of self emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, may be because of acidic PH in stomach, enzymatic degradation or hydrolytic degradation etc. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might be an act as barrier between degrading environment and the drug. Acetylsalicylic acid (Log P = 1.2, Mw=180), a drug that degrades in the GI tract because it is readily hydrolyzed to salicylic acid in an acid environment. When the drug was formulated in a Galacticles™ Oral Lipid Matrix System (SEDDS formulation) and compare with a commercial formulation, it showed the good plasma profile as compare to reference formulation. The oral bioavailability of undegraded acetylsalicylic acid is improved by 73% by the Galacticles™ Oral Lipid Matrix System formulation compared to the reference formulation. This suggests that the SEDDS formulation has a capacity to protect drugs from degradation in the GI tract⁴³ Supersaturable SEDDS contain a reduced amount of a surfactant and a water-soluble cellulosic polymer (or other polymers) to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. The S-SEDDS formulations can result in enhanced oral absorption as compared with the related self-emulsifying drug delivery systems (SEDDS) formulation and the reduced surfactant levels may minimize gastrointestinal surfactant side effects. Oral drug delivery systems are designed address the varied challenges in oral delivery of numerous promising compounds including poor aqueous solubility, poor absorption, and large molecular size. These are both liquid and powder-in-capsule products comprising our self-emulsifying liquid crystalline nano-particles (LCNP) technology (featuring Cubosome®, Hexosome®, and Flexosome™). Liquid crystalline nano-particles (LCNPs) are excellent solubilizers. Compared with conventional lipid or non lipid carriers, LCNPs show high drug carrier capacity for a range of sparingly water-soluble drugs. For drugs susceptible to in vivo degradation, such as peptides and

proteins, LCNP vehicles protect the sensitive drug from enzymatic degradation. The LCNP systems also address permeability limitations by exploiting the lipid-mediated absorption mechanism. For water-soluble peptide typical bioavailability enhancements range from twenty to more than one hundred times. In an alternative application large proteins have been encapsulated for local activity in the gastrointestinal tract. LCNP carriers can be combined with controlled-release and targeting functionalities. The particles are designed to form in

situ at a controlled rate, which enables an effective in vivo distribution of the drug. LCNP carriers can also be released at different absorption sites, for example in the upper or lower intestine, which is important for drugs that have narrow regional absorption windows. SMEDDS' composition of PNU156804 that showed a good chemical stability and a higher bioavailability with respect to a conventional formulation.⁵⁰

Marketed formulations of SEDDS

Active moiety	Trade name	Dosage forms
Tretinoin	Vesanoid (Roche)	Soft gelatin capsule, 10 mg
Isotretinoin	Accutane (Roche)	Soft gelatin capsule, 10, 20 and 40 mg
Cyclosporine	Panimum bioral (Panacea Biotec)	Capsule, 50 and 100 mg
Cyclosporin A	Gengraf (Abbott)	Hard gelatin capsule, 25 and 100 mg
Cyclosporin A	Sandimmune (Novartis)	Soft gelatin capsule, 25, 50 and 100 mg
Lopinavir and Ritonavir	Kaletra (Abbott)	Soft gelatin capsule, Lopinavir 133.33 mg and Ritonavir 33.3 mg
Sanquinavir	Fortovase (Roche)	Soft gelatin capsule, 200 mg
Tipranavir	Aptivus (Boehringer Ingelheim)	Soft gelatin capsule, 250 mg
Amprenavir	Agenerase (GSK)	Soft gelatin capsule

Type of delivery system	Drug	Oil	Surfactant	Cosolvent / Cosurfactant	Improvement
SEDDS (gelled)	Ketoprofen	Captex 200	Tween 80	Capmul MCM	Silicon dioxide was used for the gelling agent. As the concentration of silicon dioxide increases, it causes an increase in the droplet size of the emulsion and slows the drug diffusion
SMEDDS	Atorvastatin	Labrafil, Estol and Isopropyl myristate	Cremonophor EL, Cremonophor RH40	Propylene glycol, PEG 400 and Transcutol	It improves the solubility and permeability of atorvastatin through the mucous membrane, and it improves bioavailability. Oral bioavailability was increased nearly 1.5 times more than conventional tablets
SEDDS	Carvedilol	Labrasol	Labrafil M 1944CS	Transcutol P	It improves the oral bioavailability of carvedilol up to 413% when compared to conventional tablets.
SMEDDS	Simvastatin	Caproyl 90	Cremonophore EL	Carbitol	The release rate of simvastatin from SMEDDS was higher than conventional tablets. The oral bioavailability of SMEDDS is about 1.5-fold higher than conventional tablets.
SEDDS	Itraconazole	Tocopherol acetate	Pluronic L64	Transcutol	Itraconazole SEDDS formulation shows greatly enhanced bioavailability without the influence of food.
SEDDS	1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU)	Tributyrin	Cremonophore RH 40	Labrafil 1944	SEDDS increases the <i>in vitro</i> half-life of BCNU up to 130 min compared to 45 min of intact BCNU. Self-emulsified BCNU was fabricated into wafers and the self-emulsion system increased the stability of BCNU after release from a PLGA wafer.
SEDDS	Coenzyme Q ₁₀	Myvacet 9-45 and Captex-200	Labrafac CM-10 and Labrasol	lauroglycol	Medium-chain oils and Myvacet 9-45 provided higher solubility for Coenzyme Q ₁₀ than long-chain oils. SEDDS provided a two-fold increase in the bioavailability compared to a powder formulation.
Self-Emulsifying Tablet	Diclofenac sodium	Goat fat	Tween 65	---	SEDDS tablets were formulated by pour molding using a plastic mold. Tablets containing higher Tween 65:goat fat content ratios gave better release rates.
Self-Emulsifying Pellet	Methyl and Propyl Parabens	Mono- and diglycerides of capric and caprylic acids	Tween 80	---	The self-emulsifying formulation improves the rate of drug release from the pellets. By applying a water-insoluble polymer containing a water soluble plasticiser, it reduces the rate of drug release.
SMEDDS	Seocalcitol	Viscolec (MCT), Sesame oil (LCT)	Cremonophor RH40	Akoline	There was no improvement in bioavailability by the use of SMEDDS, compared to the bioavailability achieved from simple MCT and LCT solutions. After three months of storage at accelerated conditions (40 °C/75% RH), a decrease in concentration of seocalcitol of 10–11% was found in MC-SMEDDS and LC-SMEDDS compared with a degradation of less than 3% for the simple lipid solutions of MCT and LCT. So, the simple lipid solutions seem to be a better choice compared with the developed SMEDDS due to a slightly higher bioavailability and a better chemical stability of seocalcitol.
SMEDDS	Silymarin	Ethyl linoleate	Tween 80	Ethyl alcohol	Release of silymarin from SMEDDS was limited, incomplete, and typical of sustained characteristics. Relative bioavailability of SMEDDS was dramatically enhanced in an average of 1.88- and 48.82-fold that of silymarin PEG 400 solution and suspension, respectively.
Self-nano-emulsifying drug delivery system (SNEDDS)	Cefpodoxime proxetil (CFP)	Caproyl 90	Cremonophore EL, Solutol HS	Akoloino MCM	SNEDDS of CFP could accommodate a high dose of CFP (130 mg) and exhibited rapid release independent of pH of dissolution media. The optimized SNEDDS released CFP completely within 20 min irrespective of the pH of dissolution medium.
SNEDDS	All-trans-retinol acetate	Soybean oil	Cremonophor EL	Capmul MCM-C8	The optimum surfactant to cosurfactant ratio was found to be 2:1 (37.5–50% for Cremonophor EL, and 18.75–25% for Capmul MCM-C8). With this ratio, the resulting nanoemulsions obtained have a particle size range of 0.103–0.051µm. SNEDDS of all-trans-retinol acetate increased its dissolution rate and has the potential to enhance its bioavailability.

Application of self emulsifying drug delivery system

Future Trend

In relation to formulation development of poorly soluble drugs in the future, there are now techniques being used to convert liquid/semi-solid SEDDS and SMEDDS formulations into powders and granules, which can then be further processed into conventional powder-fill capsules or even compressed into tablets. Hot melt granulation is a technique for producing granules or pellets, and by using a waxy solubilising agent as a binding agent, up to 25% solubilising agent can be incorporated in a formulation. There is also increasing interest in using inert adsorbents, such as the Neusilin (Fuji Chemicals) and Zeopharm (Huber) products for converting liquids into powders which can then be processed into powder fill capsules or tablets. But to obtain solids with suitable processing properties, the ratio of SEDDS to solidifying excipients must be very high, which seems to be practically non feasible for drugs having limited solubility in oil phase. In this regard, it was hypothesized that the amount of solidifying excipients required for transformation of reducing the amount of solidifying excipients required and aiding in slowing drug release.

Conclusion:

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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REFERENCES

1. York P, The design of dosage forms, In: Aulton M.E. (eds.), *Pharmaceutics The science of dosage form design* Churchill Livingstone, Edinburgh; 1988.p 1-13.
2. Sugimoto M, Okagaki T, Narisawa S, Koida Y, and Nakajima K. Improvement of dissolution characteristics and bioavailability of poorly water soluble drugs by novel cogrinding method using water soluble polymer. *Int. J. Pharma*, 1998;160:11-19.
3. Pong CH, Kearney AS, Patel K, Palepu NR, Zuber G. Investigation of formulation approaches to improve the dissolution of SB-210661, a poorly water soluble 5-lipoxygenase inhibitor. *Int. J. Pharma*, 1998; 176: 31-38

4. Nazzal S, Guven N, Reddy IK, Khan MA. Preparation and characterization of Coenzyme Q10 – Eudragit solid dispersion. *Drug Dev. Ind. Pharm.* 2002; 28: 49-57

5. Amidon, G., et.al. A theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, *Pharm. Res.* 1995; 12: 413-420.

6. Charman SA, Charman WN, Rogge MC, Wilson TD, Dutko FJ, Pouton C W. Self-emulsifying drug delivery system: formulation and biopharmaceutical evaluation of an investigational lipophilic compound. *Pharm. Res.* 1992; 9: 87-93.

7. NH Shah, Carvajal M T, Patel CI, Infiled M H, Malick AW. Self- emulsifying Drug Delivery systems (SEDDS) with polyglycolized glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. *Int. J. Pharm.* 1994; 106: 15-23.

8. Khoo S M, Humberstone A J, Porter CJH, Edward GA, Charman WN. Formulation Design and bioavailability assessment of lipidic self emulsifying formulation of halofantrine. *Int.J. Pharm.* 1998; 167: 155-164.

9. Amidon GL, Lennernas H, Shah VP, Crison JRA. Therotical basis for a biopharmaceutical classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res*, 1995; 12: 413-420.

10. Reiss H., Entropy-induced dispersion of bulk liquids, *J.Colloids Interface Sci.* 1975; 53:61-70

11. Dabros T., et al. Emulsification through area contraction, *J. Colloids Interface Sci.*1999; 210:222-230

12. M J. Groves, R.M.A. Mustafa, J.E. Carless, Phase studies of mixed phosphated surfactants n-hexane and water, *J. Pharm. Pharmacol.*1974; 26: 616-623.

13. M. J. Rang, C.A. Miller, Spontaneous emulsification of oils containing hydrocarbon, non-ionic surfactant, and oleyl alcohol, *J. Colloids Interface Sci.* 1999; 209: 179-192.

14. M. G.Wakerly, C.W. Pouton, B.J.Meakin , F.S. Morton, Self-emulsification of vegetable oil-non-ionic surfactant mixtures. *ACS Symp. Ser.* 1986; 311: 242-255.

15. M.G. Wakerly, C.W. Pouton, B.J. Meakin, Evaluation of the self emulsifying performance of a non-ionic surfactant vegetable oil mixture, *J. Pharm. Pharmacol.* 1987; 39: 6P

16. C. W. Pouton, M.G. Wakerly, B.J. Meakin, Self emulsifying systems for oral delivery of drugs, *Proc. Int.Symp.Control. Release Bioact. Mater.*1987; 14: 113-114.

17. D.Q.M. Craig, et al. An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy, *Int. J. Pharm.* 1995; 114: 103-110

18. C.W. Pouton, Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification, *Int. J.Pharm.* 1985; 27: 335-348.

19. D.Q.M. Craig, et al. An investigation into the physicochemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surfacetension measurements and particle size analysis. *Int. J. Pharm.*1993; 96: 147- 155

20. D.Q.M. Craig, The use of self-emulsifying systems as a means of improving drug delivery, *B.T. Gattefosse* 1993;86; 21-31.

21. Friedman D, Non-aqueous compositions for oral delivbery of insoluble bioactive agents. *US Pat* 20070190080 Ockner RK, Manning JM, Fatty acid

- binding protein in the small intestine; identification, isolation and evidence for its role in cellular fatty acid transport. *Journal. Clinical Invest.* 1974; 54: 326-338.
22. Greenberger NJ, Rodgers JB, Isselbacher KJ. Absorption of medium and long chain triglycerides: factors influencing their hydrolysis and transport. *Journal of. Clinical Invest.* 1966; 45: 217-227.
23. Porter CJH, Charman WN, Uptake of drug into the intestinal lymphatic after oral administration. *Adv. Drug Del. Rev.* 1997; 25: 71-89.
24. Cheema M, Palin K., Davis SS. Lipid Vehicles for intestinal lymphatic drug transport. *J. Pharm Pharmacol.* 1987; 39: 55-56.
25. Embleton JK, Pouton CW. Structure and function of gastro intestinal lipase, *Adv. Drug Del. Rev.* 1997; 25:15-32.
26. Pouton CW. A study of self- emulsifying oil/surfactant mixture. Ph.D.thesis, University of London, 1982.
27. Wakerley MG, Pouton CW, Meakin BJ, Morton FS. Self emulsification of vegetable oil-nonionic surfactant mixtures: a proposed mechanism of action. *American Chemical Society Symp Series.* 1986; 311: 242-255
28. *European Journal of Pharmaceutical Sciences*, Volume 35, Issue 4, 15 November 2008, Pages 257- 263.
29. Nazzal S, Nutan M, Palamakula Shah AR, Zaghoul AA, Khan MA, Optimization of a self nano emulsified tablets dosage form of Ubiquinone using response surface methodology: effect of formulation ingredients. *Int.J. Pharm.* 2002; 240: 103-114.
30. Attama AA, Nzekwe IT, Nnamani PO, Adikwu MU, Onugu CO. The use of solid self emulsifying system in the delivery of diclofenac. *Int. J. Pharm* , 2003; 262: 23-28.
31. Tuleu C. et al. Comparative bioavailability study in Dogs of a self-emulsifying formulation of progesterone presented in a pellets and liquid form compared with an aqueous suspension of progesterone. *J. Pharm Sci*, 2004; 93(6): 1495-1502.
32. Franceschini E, et al. Self emulsifying pellets by wet granulation in high -shear mixer: influence of formulation variables and preliminary study on the in vitro absorption. *Int. J.Pharm.* 2005;291 :87-97.
33. Serratori M, Newton M, Booth S, Clarke A. Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system. *Eur. J. Pharm. Biopharm* . 2007; 65: 94-98.
34. Abdalla A, Mader K. Preparation and characterization of a self- emulsifying pellets formulation. *Eur. J. Pharm Biopharm.* 2007; 66:220-226.
35. Iosio T., et al. Bi layered self emulsifying pellets prepared by co-extrusion and sponification: Influence of formulation variables and preliminary study on the in vivo absorption. *Eur.J. Pharm. Biopharm.* 2008; 69(2): 686-697.
36. Patil, P. and Paradkar, A Porous polystyrene beads as carriers for self emulsifying system containing loratadine. *AAPS Pharm. Sci.Tech.* 10.1208/ pt070128. 2006
37. You J, Fu de Cui, Qingpo Li, X. Han, Ying Wei Yu. A novel formulation design about water insoluble oily drug: preparation of zedoary turmeric oil microspheres with self emulsifying ability and evaluation in rabbits. *Int. J. Pharm.* 2005; 288(2): 315-325.
38. Attama AA, Nkemnele MO. In vitro evaluation of drug release from self micro emulsifying drug delivery systems using a biodegradable homo lipid from *Capra hircus*. *Int. J. Pharm* 10. 44. Hu YX. Et al., Preparation and evaluation of 5-FU/PLGA/gene nanoparticles. *Key Eng. Mat.* 2005; 288-289 147-150.
39. Trickler WJ. et al. A novel nanoparticle formulation for sustained paclitaxel delivery. *AAPS Pharm. Sci. Tech.*, 2008; 10 1208/s1224900890637.
40. *International Journal of Pharmaceutics*, Volume 352, Issues 1-2, 20 March 2008, Hazem Ali, Mahmoud Nazzal, Abdel-Azim A. Zaghoul, and Sami Nazzal, Pages 104-114
41. D.Q.M. Craig, et al. An investigation into the physicochemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis. *Int. J. Pharm.* 1993; 96: 147- 155
42. Shafiq S., et al. Development and bioavailability assessment of ramipril nanoemulsion formulation *Eur. J. Pharm. Biopharm* 2007; 66: 227-243
43. Patil p, Vandana p, paradkar p formulation of self emulsifying drug delivery system for oral delivery of simvastatin: In vitro and in vivo evaluation. *Actapharma.* 2007; 57: 111-122
44. Patil P, Joshij, paradkar. Effect of formulation variable preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen. *AAPS Pharm Sci Tech.* 2004;5(3):34-42
45. Vergote GJ, et al. An oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen. *Int J Pharm.* 2001; 219:81-87.
46. Hauss, D.J. (2007) Oral Lipid Based Formulation *Advanced drug Delivery Rev.* 59; 667-676.
47. Yamada T, Onishi H, Machida Y. Sustained release ketoprofen microparticles with ethylcellulose and carboxymethylcellulose. *J Control Release.* 2001;75: 271-282.
48. Imran K. Tadwee, Sourabh Gore, Prashant Giradkar "Advances in Topical Drug Delivery System: A Review" *Int. J. of Pharm. Res. & All. Sci.* 2012; Volume 1, Issue 1, 14-23
49. Roda A, et al. Bioavailability of a new ketoprofen formulation for once-daily oral administration. *Int J Pharm.* 2002; 241: 165-172.
50. El-Kamel AH, et al. Preparation and evaluation of ketoprofen floating oral delivery system. *Int J Pharm.* 2001; 220: 13-21
51. P.Gao, et al. Enhanced oral bioavailability of a poorly water soluble drug PNU- 91325 by supersaturable formulations, *Drug Dev. Ind. Pharm.* 2004;30:221-229