Vol 5, Issue 4, 2018 ISSN 2349-7041

Review Article

A PROMISING APPROACH TO ENHANCE SOLUBILITY AND BIOAVAILABILITY BY SELF EMULSIFYING DRUG DELIVERY SYSTEM: A BRIEF REVIEW

SRINIVASA RAO BARATAM[1*], VEERABHADHRA SWAMY PADAVALA[2], J. VIJAYA RATNA[3]

[1*]Department of Pharmaceutical Technology, St. Ann's College of Pharmacy, Cantonment, Vizianagaram 535003, Andhra Pradesh, India.Department of Pharmaceutical Technology, Shri Vishnu College of Pharmacy, Bhimavaram 534202, Andhra Pradesh, India. [3]Department of Pharmaceutical Technology, A.U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam 530003, Andhra Pradesh, India.

Email: srinivas.baratam077@gmail.com

ABSTRACT

Objective: The formulation of self-emulsifying drug delivery system of drugs is to enhance the solubility and bioavailability. More than 40% of available drugs exhibit poor water solubility, resulting in unsatisfactory oral drug delivery.Increasing the bioavailability of drugs is one of the challenges in oral formulations. SEDDS is one of the formulation design to improve the absorption process.SEDDS are the mixture of oil, surfactants and cosolvent/co-surfactants. After administration, the drug remains entrapped/solubilized in the oil phase of the emulsion that is formed in the gastrointestinal tract upon self-emulsification lead to increased solubilization and absorption resulting in increased bioavailability. **Conclusion:** The review focuses on SEDDS formulating design and characterization along with the technique by which the bioavailability can be improved.

KEYWORDS: Self emulsifying drug delivery system, solubility, bioavailability, Characterization.

INTRODUCTION

Drawbacks to intravenous administration, together with extravasations of the drug or blood, tube infections, and occlusion may be prevented by administering the drug orally, creating the oral delivery the foremost well-liked route of administration [1]. However, oral administration is restricted by issues relating to physical-chemical properties of the drug, together with poor solubility, low permeability, instability, and speedy metabolism all of that decrease oral bioavailability [2]. With the appearance of drug style, numerous molecules are created that have a possible for therapeutic action. However, most of the freshly discovered chemical entities are of high mass and belong to biopharmaceutical system (BCS) – II, with poor binary compound solubility and high membrane permeability. Hence, these two characteristics limit the bioavailability of orally- administered drugs [3]. These drugs have low solubility, which results in low dissolution and limits absorption. This poor solubility not solely provides slow oral bioavailability however conjointly results in high inter-and intra-subject variability and lack of dose proportionality [4]. Also, a number of these drugss have increased bioavailability once co-administered in conjunction with food, e.g., halofantrine [5]. The evident increase in bioavailability of poorly water soluble drug with a fatty meal is that the baseline within the style of lipid based mostly formulations [6-8]. Oral delivery of poorly water soluble medicine victimization lipid because the vehicle could be a new and up to date approach to beat the same issues. Formulation excipients like surfactants employed in the lipid based mostly formulations can aid in achieving the goal. Stimulation of body secretions that facilitate in digestion of lipids: administration of lipid will stimulate the biliary and duct gland secretions that are useful within the digestion of lipids. The enzymes gift within the secretions is water soluble and act at water/lipid interface. Fatty acids liberated from the lipids digestion method move with the gall salts and lead to the formation of mixed micelles and micelles during which the drug gets solubilized. Prolongation of GI residence time: administration of lipids in conjunction with the drug permits the drug to be a gift for the prolonged period of the amount within the rat that facilitates the absorption of the drug [9,10]. Lipid-based drug delivery (LBDD) systems have gained a lot of importance within the recent years because of their ability to boost the solubility and bioavailability of medicine with poor water solubility [11]. The absorption of the drug from lipid based mostly formulation depends on various factors, together with particle size, the degree of emulsification, the speed of dispersion and precipitation of the drug upon dispersion [10,12]. Lipid based formulations might embrace oil answer or suspensions, emulsions, self-micro, self nano emulsifying drug delivery systems (SMEDDS/SNEDDS)[12,13]. Among numerous lipids based mostly formulations (liposomes, solid lipid nanoparticles, self-dispersing tablets, and solid solutions), self-micro emulsifying formulations are receiving additional attention by formulation scientists as these are advantageous within the facet of their stability, self-dispersing nature, easy preparation, and scale-up. SMEDDS are the isotropous, clear mixtures of oils and surfactants and generally embrace co solvents/co surfactants. These are designed to make O/W micro emulsions with gentle agitation made by the motility of rat followed by solubilization and absorption of the drug. SMEDDS sometimes turn out micro emulsions of drop size below 100nm upon dilution [14].

SMEDDS OFFER THE FOLLOWING ADVANTAGES

- Irritation caused by prolonged contact between the drug and also the wall of the rat may be head by the formulation of SMEDDS because the microscopic droplets shaped facilitate within the wide distribution of the drug on the rat and these are transported quickly from the stomach[15].
- Upon dispersion in water, these formulations turn out fine droplets with huge surface space because of that the simple partition of the drug from the oil section into the binary compound section is feasible that can't be expected just in case of oily solutions of lipophilic drugs[15].
- Poor water soluble medicine that has dissolution rate restricted absorption may be absorbed expeditiously by the formulation of SMEDDS with sequent stable plasma-time profile[14].
- Drugs that have a propensity to be degraded by the chemical and protein suggests that in rate may be protected by the formulation of SMEDDS because the drug is conferred to the body in oil droplets [14].
- Micro emulsion pre concentrate is advantageous over micro emulsion to dispense within the type of liquid stuffed soft gelatine capsules [16].
- SMEDDS are advantageous over SEDDS because the former is a smaller amount obsessed with gall salts for the formation of

droplets by that higher absorption of the drug is predicted compared to SEDDS [17].

- The Surfactants of high HLB like Tween 80 are used to extend the permeability of the drug once administered in conjunction with the formulation because of the loosening impact of those on tight junctions [18].

COMPOSITION OF SEDDS

Lipid based excipients

The lipid based excipients encompass vegetable oils and their derivatives.

- Vegetable oils: Vegetable oils contain a mixture of triglycerides (90-95% w/w) and also free fatty acids, phospholipids and non saponifiable products such as pigments and sterols or fat soluble vitamins like tocopherol and carotenoids that act as natural antioxidants [19].
- Oil derivative: the most oil derivatives ar alter oil, partial animal oil, polyoxyglyceride, ethoxylated animal oil and esters of edible fatty acids and numerous alcohols normally used oil phases within the lipid based mostly drug delivery system were shown in Table No. 1.

Table 1: Commonly used oily phases [20,21]

General class	Examples	Commercial name
Medium chain triglyceride	Triglycerides of capric/caprylic acids	Miglyol 810, 812, Labrafac CC
	Triacetin	Crodamol GTCC, Captex 300, 355, Captex 500
Medium-chain mono- and di-glycerides	Mono- and diglycerides of capric/caprylic acids	Capmul MCM, Imwitor 742, Akoline MCM
Long-chain mono-glycerides	Glyceryl monooleate	Peceol, Capmul-GMO
Propylene fatty acid esters	PG monocaprylate	Capryol 90, Capmul PG-8, Sefsol 218
	PGmonolaurate/dilaurate	Lauroglycol 90, Capmul PG-12, Lauroglycol FCC
	PG dicaprylate/caprate	Miglyol 840, Captex 200

Surfactants

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, however, the selection is restricted, as only a few surfactants are acceptable orally [22, 23]. The most widely recommended ones are the non-ionic surfactants with a relatively high HLB 34. Safety could be a major determinant considers selecting a wetting agent. The four main teams of surfactants are outlined as follows

1. Anionic surfactants wherever the deliquescent cluster carries a charge cherish carboxyl, salt or salt. Examples are potassium laurate and sodium lauryl salt.

2. Cationic surfactants herever the deliquescent cluster carry a charge. the instance is quaternary ammonia salt.

3. Ampholytic surfactants (Also referred to as zwitterionic surfactants) contain each a negative and a charge the instance is sulfobetaines.

4. Non-ionic surfactants where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene. Examples are sorbitan esters (Spans) and poly sorbates (Tweens). Some of the surfactants were shown in the following Table No.2.

Table 2: Commonly Used Surfactants [21, 24]

General class	Examples	Commercial name
Polysorbates	Polyoxyethylene-20-sorbitan monooleate	Tween® 80, Crillet 4
	Polyoxyethylene-20-sorbitan monolaurate	Tween 20, Crillet 1
Sorbitan esters	Sorbitan monooleate	Span® 80, Crill 4
	Sorbitan monooleate	Span 20, Crill 1
	Sorbitan monooleate	Span 60, Crill 3
Polyoxyethylene castor oil	Polyoxyethylene castor oil	Cremphor® EL, Etocas 35 HV
Polyoxyethylene-stearate	Polyethylene glycol-660-12-hydroxy stearate	Solutol HS 15®
Polyglycolyzed glycerides	Linoleoyl macrogol glycerides	Labrafil® 2125 CS
	Oleoyl macrogol glycerides	Labrafil 1944 CS
	Polyglyceryl oleate	Plurol® oleique CC 497
	Lauroyl macrogol glycerides	Gelucire® 44/14

Co solvents

Co solvents facilitate the dissolution of wetting agent and hydrophobic drug within the oil section thanks to their ability to access the entry of water into the formulation. These excipients play the role of co surfactant in micro emulsion system. a number of the normally used co solvents ar short chain alcohols like grain alcohol, n-butanol, humectants, and synthetic resin glycol. The addition of co solvents cherish short chain alcohols imparts flexibility to the interface that's useful for the free movement of the hydrophobic tails of the wetting agent at the interface that successively imparts dynamic behavior to micro emulsions[21,25]. Samples of co solvents were shown in Table No.3.

Table 3: List of Commonly Used Co solvents.

General class	Examples
Short-chain alcohols	Ethanol, benzyl alcohol
Alkane diols and triols	Propylene glycol Glycerol
Polyethylene glycols	Polyethylene glycol 400
Glycol ethers	Diethylene glycol monoethyl ether (Transcutol®)

MECHANISM OF SELF EMULSIFICATION

The free energy of the emulsion can be described by the Following equation

$$\Delta G = \Sigma \pi r 2 \sigma$$

ΔG is the free energy, N is the number of droplets, r is the radius of droplets, and σ is the interfacial energy. From this equation, it's evident that the lower the surface energy the lower the free energy. Self-emulsification happens once the energy concerned within the dispersion is larger than the energy needed for the formation of droplets [26]. The free energy of typical emulsion is incredibly high as high energy is needed to make a brand new surface between two unmixable phases like oil and water. Because of high free energy, the emulsion might not be stable and also the two phases tend to separate. However just in case of SMEDDS, emulsion formation happens outright as a result of the free energy of the system is incredibly low and generally negative because of the presence of a versatile interface. On combining oil and wetting agent/co surfactant mixture with water, upon gentle agitation, An interface is made between two phases. Then, binary compound section penetrates through the interface and gets solubilized inside the oil section up to the solubilization limit. Redoubled water penetration causes the formation of the spread liquid crystalline section. the quantity of liquid crystalline section depends on the wetting agent concentration. Upon gentle agitation of SMEDDS, water penetration

happens apace and results in the disruption of the interface and droplets are formed [14].

PREPARATION OF SEDDS

Choice of oils, co solvent, and wetting agent supported the solubility of the drug. The preparation of the SEDDS formulation by dissolving the drug during a mixture of oil, wetting agent and co solvents. The addition of the drug to SEDDS is essential as a result of the drug interferes with the self-emulsifying method to a particular extent, that results in an amendment in best oil – wetting agent ratio; thus, the planning of best SEDDS needs pre formulation solubility and section diagram studies. Due to their low binary compound solubility and low permeability, dissolution rate from the delivery system forms the speed limiting step in their absorption and general availability [27].In some cases, the drug is dissolved in any one of the excipients and also the remaining excipients are more to the drug solution[28]. Then, the answer ought to be properly mixed and tested for the signs of muddiness. Once stabilization at close temperature for 48 hours ought to be heated for the formation of the clear solution if needed. Reckoning on the ultimate volume, the formulation ought to keep in capsules of appropriate size [29].

CHARACTERIZATION OF SEDDS

Ternary phase diagram

Pseudo ternary diagrams are usually created for the event of SEDDS that facilitate in determinant the optimum concentration of various excipients necessary to get homogenous pre concentrates, self-emulsification ability, and drug loading in this technique, water is incorporated into the SMEDDS (Self micro emulsifying Drug Delivery System) pre concentrate in a drop wise manner, with a mild stirring to permit stabilization. Addition of water results in the formation of a fancy system starting from gels to a system containing lamellar, polygon phases to micro emulsions. The mixture is visually examined for transparency [30]. At totally different compositions, totally different structures could also be shaped like emulsions, micro emulsions, micelles, inverted micellar forms, then forth and also the extent of formation of those structures may be far-famed with the development of the section diagram. This section diagram helps within the determination of diluteness and in obtaining info concerning the various compositions that form monophasic clear solutions[31]. Then pseudo ternary diagram ought to be planned with the assistance of appropriate software package. The samples that shaped clear answer ought to be denoted by appropriate symbols within the section diagram [32].

Droplet size analysis and particle size measurements

The drop size of the emulsions is set by gauge boson correlation spectrometry (which analyses the fluctuations in light-weight scattering because of the Brownian movement of the particles) employing a Zetasizer able to live sizes between 10 and 5000nm. Light-weight scattering is monitored at 25°C at a 90° angle. The nano size varies of the particle is maintained even once one hundred times dilution with water, that proves the system's compatibility with excess water [33,34].

Zeta potential

This is often wont to establish the charge on the droplets. The charge on the oil droplets is because of in typical SMEDDS, and is negative because of the presence of free fatty acids; but, incorporation of an ion lipid cherish oleyamine at a level vary of 1-3% can yield ion SMEDDS. Later potential helps to predict the soundness and also the activity impact in emulsion systems. If the letter potential falls below a particular level, the mixture cans combination because of enticing forces. Conversely, a high letter potential maintains a stable system[35]. Zeta potential is usually measured by letter potential analyzer [34] or letter meter system thirty seven. price of letter potential indicates the soundness of emulsion once acceptable dilution. Higher letter potential indicates the great stability of formulation [37].

Emulsification rate

The speed of self-emulsification is typically determined by adding a dose of the SMEDDS pre concentrates, ideally during a capsule, to a relevant quantity of water or bio relevant media. the speed of dispersion is set by visual observation. The time required for self-emulsification for various formulations may be assessed typically victimization dissolution apparatus USP II during which the formulation is more drop wise to the basket containing water and observant the formation of the clear answer below agitation provided by a paddle at 50 rpm[36,27]. A speedy rate of emulsification is discovered with higher wetting agent concentration thanks to the speedy ejection of oil droplets by penetration of water into the interface. The emulsification time also can be determined by visual analysis once inserting the formulation in 0.1N HCI below stirring at the vital sign by that the Gastro intestinal conditions may be simulated [38].

Visual evaluation

The assessment of self-emulsification is feasible by visual analysis. Once dilution of SMEDDS with water, the opaque and opaque white look indicates the formation of macro emulsion whereas the clear, isotropic, clear answer indicates the formation of micro emulsion [14, 39, 40].Assessment of precipitation of the drug in diluted SMEDDS is also possible by visual evaluation. The formulations can be considered as stable when drug precipitation is not evident. Precipitation is common if the formulation contains water soluble co solvents and can be avoided by increasing the concentration of surfactant [41].

Thermodynamic stability studies [42]

The physical stability of a lipid based formulation is additionally crucial to its performance, which may be adversely laid low with precipitation of the drug within the excipient matrix. Additionally, poor formulation, physical stability will result in section separation of the excipient, poignant not solely formulation performance, however visual look similarly. Additionally, incompatibilities between the formulation and also the gelatin capsule shell will result in crispness or deformation, delayed disintegration, or incomplete unharness of the 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 hours 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 48h is done at 3500 rpm for 30 min. Those formulations that do not show any phase separation are taken for the freeze thaw stress test.

3. **Freeze thaw cycle**

Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

Dispersibility test

Take a look at the potency of self-emulsification of oral nano emulsion is assessed employing a commonplace USP XXII dissolution II. One ml of every formulation added to 500 ml of water at 37.5°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 within 2 minutes

Grade D: Dull, greyish white emulsion having a 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 nano emulsion when dispersed in GIT. While formulation falling in Grade C could be recommended for SNEDDS formulation [43].

Refractive index

Refractive index is the property by which the isotropic nature of diluted SMEDDS that is micro emulsion can be determined. Karamustafa and Celebi performed refractive index measurements of the optimized formulation at 4°C and 25°C up to 6 h at different time intervals and concluded that there is no significant change in a refractive index indicating the constant micro emulsion structure [44]. The constant refractive index also indicates the thermodynamic stability of the formulation [45]. Usually, the refractive index measurements are carried out using refractometers[46].

***In vitro* dissolution profile**

Drug release from formulation can be evaluated after filling the formulation in a hard gelatin capsule using USP XXIII apparatus II at 50 rpm[28,36] or with dialysis method[47]at 37± 0.5°C. Samples at regular intervals should be withdrawn from the medium and drug content is estimated and compared with the control. The polarity of oil droplet has an impact on drug release from the diluted SMEDDS. The higher the polarity, the faster the drug release from the oil droplet into the aqueous phase. Polarity is mainly dependent on the HLB of surfactant, the molecular weight of the hydrophilic part of the surfactant, and its concentration along with the degree of un saturation of fatty acid lipid phase[14,48].

***In vitro* diffusion study**

In vitro diffusion studies were performed for all the formulations developed, using a dialysis technique. The dialysing medium was phosphate buffer pH 6.8. One end of pretreated cellulose dialysis tubing (7 cm in length) was tied with thread, and then 1 ml of self-nano emulsifying formulation was placed in it along with 0.5 ml of dialyzing medium. The other end of the tubing was also secured with thread and was allowed to rotate freely in 200 ml of dialyzing medium and stirred continuously at 100 rpm with a magnetic bead on the magnetic plate at 37°C. Aliquots of 1 ml were removed at different time intervals and diluted further. The volume of the aliquots was replaced with fresh dialyzing medium each time. These samples were analyzed quantitatively for drug dialyzed across the membrane at the corresponding time by using UV Visible spectrophotometer[42].

***In vivo* studies**

The impact of excipients on the bioavailability and the pharmacokinetic profile of drugs can be estimated by designing appropriate *in vivo* studies. A detailed study of intestinal lymphatic absorption is required since lipid-based formulations enhance bioavailability by improving the intestinal uptake of the drug. Due to insufficient clinical data and differences in methods and animal models used, studies related to the drug transport by the lymphatic system have become difficult [51]. Hence, further work has to be carried out to establish an *in vivo* method and model to predict lymphatic drug transport. A lipid-based formulation of saquinavir mesylate (For- tovases) enhanced the bioavailability of the drug up to threefold when compared to Invirases (saquinavir in hard gelatin capsules)[52]. Lipid-based drug delivery system a report on bioavailability enhancement using self-emulsifying formulation by different workers is presented in [53] Table No. 4.

Table 4: Enhancement of bio availability of drugs by Lipid based drug delivery system.

Drug	Enhancement	With reference to	Species
Acyclovir	3.5 fold	Pure drug solution	Male albino rats
Anethole trithione	2.5 fold	Tablets	Rabbits
Bicalutamide	2 fold	Suspension	Rats
Mitotane	3.4 fold	Lysodren	Rabbits
Carvedilol	4.13 fold	Commercial tablet	Beagle dogs
Nimodipine	2.6-6.6fold	Conventional tablet	New Zealand Male rabbits
Simvastatin	1.5 fold	Zocor tablets	Beagle dogs
Ketoprofen	1.13 fold	Pure drug	Humans

STABILITY ASSESSMENT

Stability studies are performed as per the ICH guidelines on the formulation which is filled in Stability studies are performed as per the ICH guidelines on the formulation which is filled in gelatin capsules. At regular intervals, the samples should be collected and tested for appearance, color, drug content, pH of the diluted formulation, and dissolution profile. If there is no change in all these properties during storage conditions, the formulation can be concluded as stable formulation [49,28,37,50].

CONCLUSION

Self-emulsifying drug delivery systems are a promising approach for the formulation of drugs with poor water solubility. SEDDS also an effective formulation for drugs having poor solubility in the GI fluids resulting from less drug exposure to GIT. SEDDS are a novel technology for formulating lipophilic compounds and represent an alternative for improving the oral absorption of lipophilic drugs. SEDDS are usually explored to improve the bioavailability of hydrophobic drugs. Currently, several formulations have been developed to produce modified emulsified formulations as alternatives to conventional SEDDS. Table No.5 indicates the list of commercially available marketed products In this review, we focused on the patents reviewed showing an assortment of the SEDDS and their delivery based on the less aqueous solubility of the drug compounds were shown in Table No.6. It is well demonstrated that SEDDS promotes lymphatic delivery of highly hydrophobic drugs (with high octanol: water partition coefficient) with good solubility in triglycerides. The present review highlighted the developmental steps (solubility studies, construction of pseudo ternary phase diagrams, and various evaluation tests) involved in obtaining a robust and stable dosage form.

Table 5: Commercially Available SEDDS Formulations in Market[63]

Trade name	Year of Approval	Drug	composition	Company
Vesanoid	1995	Tretinoin	beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils, soybean oil, glycerin, yellow iron oxide, red iron oxide, titanium dioxide, methylparaben, and propylparaben	Hoffmann La Roche
Norvir	1996	Ritonavir	butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil, and titanium dioxide	Abbott
Fortovase	1997	Saquinavir	medium chain mono- and diglycerides, povidone, dl-alpha tocopherol, gelatin, glycerol, red iron oxide, yellow iron oxide, and titanium dioxide	Hoffmann La Roche
Gengraf	2000	Cyclosporine A	alcohol USP absolute, FD&C Blue No. 2, gelatin NF, polyethylene	Abbott

Aptivus	2005	Tipranavir	glycol NF, polyoxyl 35 castor oil NF, polysorbate 80 NF, propylene glycol USP, sorbitan monooleate NF, and titanium dioxide. polyethylene glycol 400, vitamin E polyethylene glycol succinate, purified water, and propylene glycol	Boehringer

Table 6: Patents of SEDDS Formulation [63]

Title	Patent number	Published year	Ref
Methods of forming a self-supporting film for delivery of therapeutic agents	US8632839B2	2014	54
Self-micro emulsifying mitotane composition	US8486445	2013	55
Rhizoma corydalis total alkaloids self-emulsifying drug delivery system and preparation method and application thereof	CN101912447B	2013	56
Self-emulsifying pharmaceutical composition with enhanced bioavailability	EP2062571B1	2012	57
Oil-in-water emulsion and its use for the delivery of functionality	AU2006316507B2	2012	58
Coated capsules and tablets of a fatty acid oil mixture	CA2781525A1	2011	59
Process for dosing self-emulsifying drug delivery systems	EP2136785B1	2011	60
Formulation of self-emulsifying matrix type mucosal and transdermal absorbent	KR20010093728A	2010	61
New self -emulsifying drug delivery system	US20100266683	2010	62

REFERENCES

1. Roger E, LagarceF, Benoit JP. Development and characterization of a novel lipid nano capsule formulation of Sn38 for oral administration. European Journal of Pharmaceutics and bio pharmaceutics. 2011;79:181–188.
2. Sunil P, MaruO, ChanM. Novel lipid-based formulations enhancing the in vitro dissolution and permeability characteristics of a poorly water-soluble model drug piroxicam. International journal of pharmaceutics. 2005;301: 209–216.
3. Amidon GL, LennernasH, ShahVP, CrisonJR. A theoretical basis for a biopharmaceutic drug classification: the correlation in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research. 1995;12: 413–420.
4. Porter CJ, Charman WN. In vitro assessment of oral lipid based formulations. Advanced Drug Delivery Review. 2001;50(1):127–147.
5. CharmanWN, RoggeMC, BoddyAW, BergerBM. Effect of food and a monoglyceride emulsion formulation ondanazol bioavailability. Journal of Clinical Pharmacology. 1993;33:381–386.
6. Pouton CW, Charman WN. The potential of oily formulations for drug delivery to the gastrointestinal tract: preface. Advanced drug delivery reviews.1997;25(1):1–2.
7. Humberstone AJ, Charman WN.Lipid-based vehicles for the oral delivery of poorly water soluble drugs. Advanced drug delivery reviews. 1997; 25(1):103–128.
8. DiMaio S, Carrier RL.Gastrointestinal contents in fasted state and post-lipid ingestion: in vivo measurements and in vitro models for studying oral drug delivery. Journal of controlled release. 2011;151(2):110–122.
9. Chakraborty S, Shukla D, Mishra B, Singh S.Lipid an emerging platform for oral delivery of drugs with poor bioavailability. European journal of pharmaceutics and bio pharmaceutics. 2009; 73(1):1–15.
10. Porter CJ,Charman WN. In vitro assessment of oral lipid based formulations. Advanced drug delivery review. 2001;50 (1):127–147.
11. Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. Advanced drug delivery review. 2008;60:734–746.
12. Pouton CW. Lipid formulations for oral administration of drugs: non emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. European journal of pharmaceutical sciences. 2000;11(2) 93–98.
13. Hauss DJ, Fogal SE, Ficorilli JV, PriceCA, RoyT, JayarajAA, etal. 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.
14. Gursoy RN,Benita S.Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomedicine and pharmacotherapy .2004 ;58(3):173–182.
15. Tang JL, Sun J, He ZG. Self-emulsifying drug delivery systems: strategy for improving oral delivery of poorly soluble drugs. Current drug therapy. 2007; 2(1): 85–93.
16. .Kim J, Yoon KA, Hahn M, Park ES, Chi SC. Preparation and in vitro evaluation of self-micro emulsifying drug delivery systems containing idebenone. Drug development and industrial pharmacy.2000;26(5):523–529.
17. Jadhav KR, Shaikh IM, Ambade KW, Kadam VJ. Applications of micro emulsion based drug delivery system. Current drug delivery.2006;3(3): 267–273.
18. Buyukozturk F, Benneyan JC, Carrier RL. Impact of emulsion-based drug delivery systems on intestinal permeability and drug release kinetics. Journal of controlled release. 2010.vol 142, no. 1, pp. 22–30.
19. Kimura M, Shizuki M, Miyoshi K, Sakai T, Hidaka H, Takamura H, et al. Relationship between the molecular structures and emulsification properties of edible oils. Bioscience, biotechnology, and biochemistry.1994;58: 1258‑1261.
20. Strickley RG. Solubilizing excipients in oral and injectable formulations.Pharmaceutical research.2004; 21: 201–230.
21. Date AA, Nagarsenker MS. Parenteral micro emulsions: an over view. International journal of pharmaceutics.2008; 355: 19–30.
22. Meinzer A, Mueller E, Vonderscher J. Micro emulsion a suitable galenical approach for the absorption enhancement of low soluble compounds. B T Gattefosse.1995;88:21‑26.
23. Craig DQ, Barkar SA, Banning D, Booth SW. An investigation into the mechanisms of self emulsification using particle size analysis and low frequency dielectric spectroscopy. International journal of pharmaceutics. 1995;144:103‑110.
24. Ren F, Jing Q, Cui J, Chen J, Shen Y. Self-Nano emulsifying drug delivery system (SNEDDS) of anethole trithione by combined use of surfactants. Journal of dispersion science and technology. 2009; 30: 664–670.
25. Strickley RG. Solubilizing excipients in oral and injectable formulations. Pharmaceutical research. 2004; 21: 201–230.
26. Gershanik T Benita S. Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. European journal of pharmaceutics and biopharmaceutics.2000;50(1): 179–188.
27. Singh A, Singh V, Juyal D, Rawat G. Self emulsifying systems: A review. Asian J Pharm.2015;9:13-8.
28. Singh K, Chaurasiya A, Singh M, Upadhyay SC, Mukherjee R, Khar RK. Exemestane loaded self micro emulsifying drug delivery system (SMEDDS): development and optimization. American association of pharmaceutical scientist. 2008;9(2): 628–634.
29. Y.Wang, J. Sun, T. Zhang, H. Liu, F. He, He Z, Enhanced oral bioavailability of tacrolimus in rats by self micro emulsifying drug delivery systems. Drug development and industrial Pharmacy.2011;37(10):1225–1230.
30. Rang MJ, Miller CA. Spontaneous emulsification of oils containing N hydrocarbon, non ionic surfactant and oleyl alcohol. Journal of colloid interface science.1999;209:179-192.
31. Narang AS., Delmarre D, Gao D. Stable drug encapsulation in micelles and micro emulsions. International journal of pharmaceutics.2007; 345(2):9–25.

32. Zhang H, Cui Y, Zhu S, Feng F, Zheng X. Characterization and antimicrobial activity of a pharmaceutical microemulsion. International journal of pharmaceutics.2010;395(2):154–160.
33. Patil P, Joshij, Paradkar P. Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen. American association of pharmaceutical scientist. 2004; 5(3): 34-42.
34. Patil P, Vandana P, 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.
35. Wasan KM. Drug development and industrial pharmacy .2001; 27:267‑276.
36. Balakrishnan P, Lee BJ, OhDH, et al. Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. International journal of pharmaceutics.2009:374(2): 66–72.
37. Atef E, Belmonte AA.Formulation and in vitro and in vivo characterization of a phenytoin self-emulsifying drug delivery system (SEDDS).European journal of pharmaceutical sciences. 2008; 35(4) 257–263.
38. Basalious EB, Shawky N, Badrldin SM.SNEDDS containing bioenhancers for improvement of dissolution and oral absorption of lacidipine. Development and optimization. International journal of pharmaceutics.2010; 391(2): 203–211.
39. Kohli K, Chopra S, Dhar D, Arora S, Khar RK. Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug discovery today. 2010;15:(21-22): 958–965.
40. Parveen R, Baboota S, Ali J, Ahuja A, Vasudev SS,Ahmad. Oil based nanocarrier for improved oral delivery of silymarin: In vitro & In vivo studies. International journal of pharmaceutics.2011;413:(1-2): 245–253.
41. Patel AR, Vavia PR. Preparation and in vivo evaluation of SMEDDS (self-microemulsifying drug delivery system) containing fenofibrate. American association of pharmaceutical scientist. 2007;9(3):344– 352.
42. Hiral M, Makadia A. Self-nano Emulsifying Drug Delivery System (SNEDDS): Future Aspects. Asian journal of pharmaceutics. 2013;3:(1): 21-27.
43. Shafiq S. Development and bioavailability assessment of ramipril nanoemulsion formulation. European journal of pharmaceutics and bio pharmaceutics.2007; 66: 227–243.
44. .Karamustafa F, Celebi N. Development of an oral microemulsion formulation of alendronate: Effects of oil and cosurfactant type on phase behavior. Journal of microencapsulation.2008; 25(5):315–323.
45. Bali V, Ali M, Ali J. Nanocarrier for the enhanced bioavailability of a cardiovascular agent: in vitro, pharmacodynamic, pharmacokinetic and stability assessment. International journal of pharmaceutics.2011;403(1-2): 45–56.
46. DeCampos LMP, Araujo JA. Thomazine, Lopez RFV. Development of microemulsions to topically deliver 5-aminolevulinic acid in photodynamic therapy. European Journal of Pharmaceutics and Bio pharmaceutics.2010; 75(1): 48–55.
47. Huang Y, Zhou Y, Liu Y. Development of silymarin self microemulsifying drug delivery system with enhanced oral bioavailability. American association of pharmaceutical scientists.2010; 11(2): 672–678.
48. Kim HJ, Yoon KA, Hahn M, Park ES, Chi SC. Preparation and in vitro evaluation of self-micro emulsifying drug delivery systems containing idebenone. Drug development and industrial pharmacy.2000; 26(5):523–529.
49. Borhade V, Nair H, Hegde D. Design and evaluation of self-microemulsifying drug delivery system (SMEDDS) of tacrolimus. American association of pharmaceutical scientist. 2008; 9[1]:13–21.
50. Kale AA, Patravale VB. Design and evaluation of self-emulsifying drug delivery systems (SEDDS) of nimodipine. American association of pharmaceutical scientists. 2008(9):191–196.
51. Edwards GA, PorterCJH, CaliphSM, KhooSM, CharmanWN. Animal models for the study of intestinal lymphatic drug transport. Advanced drug delivery review. 2001;50:45–60.
52. Perry CM, Noble S. Saquinavir soft-gel capsule formulation. A review of its use in patients with HIV infection. Drugs 1998;55:461–86.
53. Priya T, Vrushali M, Pankaj B, Jaydeep D, Sanjay KA review on self-emulsified drug delivery system. Pharmaceutical and biological evaluations.2016;3 (2): 140-153.
54. Joshua, S, Garret, E, Amin, E, Daniel, B. Methods of forming self-supporting film for delivery of therapeutic agents. US8632839B2 (2014).
55. Florian B, Emad H, Lionel S. Self-microemulsifying mitotane composition. US8486445 (2013).
56. Ma, H, Guo T. Rhizoma corydalis total alkaloids self-emulsifying drug delivery system and preparation method and application thereof. CN101912447B (2013).
57. Hao WH., Wang, JJ, Hsu, C.S. Self-emulsifying pharmaceutical composition with enhanced bioavailability. EP2062571B1 (2012).
58. Laurent, S, Martin L, Martin M, Heribert JW, Simone A, Raymond B, Birgit H, Fabien R. Oil-in-water emulsion and its use for the delivery of functionality. AU2006316507B2 (2012).
59. Klaveness JEJ, Berge G, Hustvedt SO, Olesen PH, Muellertz A. Coated capsules and tablets of a fatty acid oil mixture. CA2781525A1 (2011).
60. Schwarz, FX. Process for dosing self-emulsifying drug delivery systems. EP2136785B1 (2011).
61. Hong, CIL, Ki MH, Kwon DS, Lee SG, Shin HJ. Formulation for self-emulsifying matrix type mucosal and transdermal absorbent. KR20010093728 A (2010).
62. Holmberg C, Siekmann B. New self-emulsifying drug delivery system. US20100266683 (2010).
63. Zanchetta B, Chaud MV, Santana MHA . Self-Emulsifying Drug Delivery Systems (SEDDS) in Pharmaceutical Development. Journal of advanced chemical engineering. 2015; 5 [3]:1-7.