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ORIGINAL ARTICLE

Self-Emulsifying Drug Delivery Systems for Improving Oral Bioavailability of Poorly Soluble Drugs

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ABSTRACT

The administration of hydrophobic drugs by the oral route was presents a major challenge due to low water solubility drugs show their poor dissolution, which results in higher variability related to intra & inter subject and lack of dose congruence so solubility of orally administered drug a very task for the effective improvement and Introduce of newly launched medicines in the pharmaceutical industry. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oils, surfactants/ solvents and co-solvents/co-surfactants and can be utilize to design such preparations which expand the oral absorption of more lipophilic drug molecules. Self-emulsification mechanism depends upon entropy change. The oral absorption efficiency of API molecules from the SEDDS, depends on various parameters which relates with formulation such as, concentration of surfactant, it's ratio with oil phase, types of surfactant, and co-solvents, and viscosity enhancer. Present review provides an updated account of mechanism of self-emulsification of SEDDS with regard to its advantages, disadvantages, composition, solidification techniques to convert liquid SEDDS, evaluation.

Key-words: *Self-emulsifying, Drug delivery systems, Oral, Bioavailability, Poorly Soluble, SEDDS.*

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INTRODUCTION

The oral administration is a preferable route in chronic drug therapy. More than 40% of novel API molecules have low aqueous solubility so the oral route for such drugs is usually related Physiological aspect expressed in **[Fig. 1]** with properties such as: less bioavailability, higher variation and a lack of dose affinity. To overwhelm above issues, several approaches were oppressed with usage of surface-active agents, micronization, salt formation, penetration enhancers, lipids, cyclodextrins, nanoparticles and solid dispersions (1, 2).

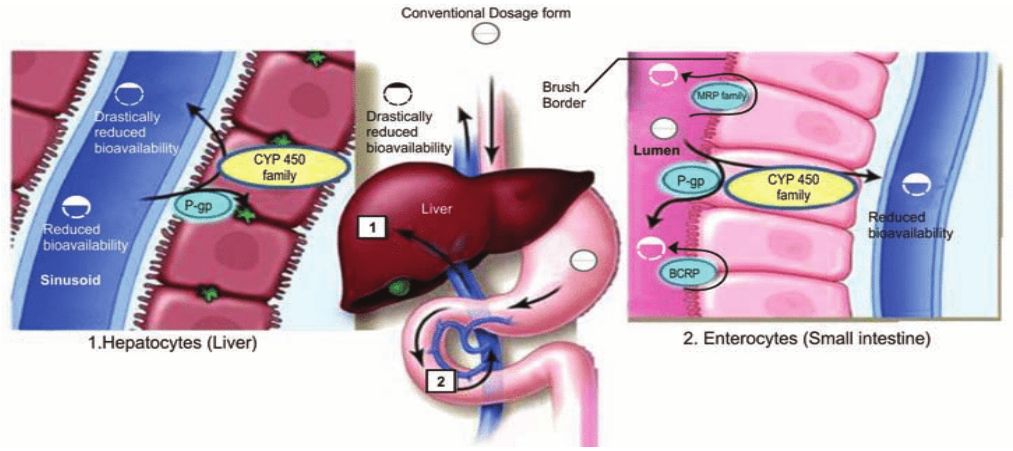


FIG. 1. Physiological Pathways To Decrease Drug Bioavailability By Oral Conventional Dosage Forms [1, 2].

Self-emulsifying drug delivery system (SEDDS) formulations are natural dual systems: oil phase and drug or oil phase, surfactant and drug (3). In SEDDS formulations are used co-surfactant for converting it into microemulsions. Such kinds of formulations can evaluate with the help of oil droplet sizes that is 200 nm - 5 mm (*in-vitro*), and diffusion has a grubby form. O/W type emulsion is the combination of oils and surfactants preferably isotropic and at times enclosing co-surfactant, which emulsify it when mixed into aqueous phase under adequate agitation (6-10). Currently, SEDDS prepared by tri-glyceride oils having medium chain and non-ionic surfactants, less toxic. In oral route delivery, Self-emulsifying systems form emulsions (or microemulsions) in the GI tract, with slight agitation provided by gastrointestinal mobility [4-6, 11, 12].

If these formulations is release in GI tract lumen, than comes in contact with the fluid of GI and formulate to uniform and adequate emulsions either microemulsions or nanoemulsions, So it is called as In-situ emulsification or which promote solubilization of such drugs which absorbed from lymphatic pathways, through hepatic first-pass metabolism. This bioavailability enhancing attribute associated with various *in-vivo* properties of the lipid formulations **[Fig. 2]** (13) such as-

- It prevents precipitation and re-crystallization process of active moiety by formation of fine dispersion and micellar suspensions.
- Lipids and their metabolites having the ability to initiate change in the GI fluid that improved the drug absorption
- It keeps drug out of circulation by Inhibition mechanism of cellular efflux

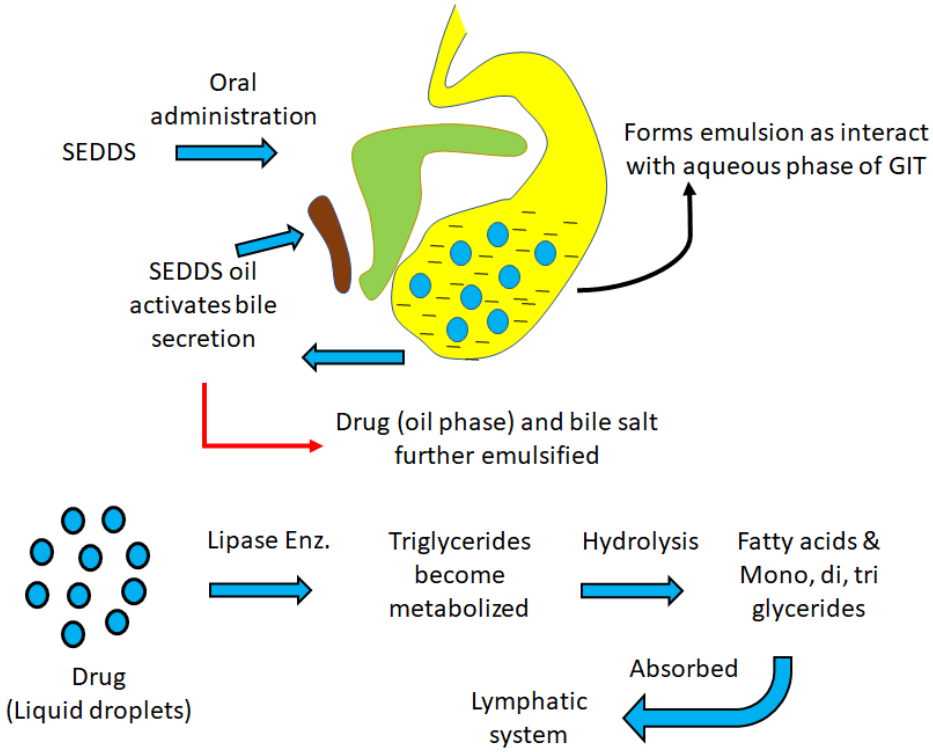


FIG. 2. PROCESS OF SELF EMULSIFICATION [13].

ADVANTAGES OF SEDDS OVER CONVENTIONAL DDS (14, 15)

- Protection of drugs from the hostile environments in gut
- High Drug-loading capacity
- increase in oral bioavailability
- Reduced variability including food effects
- Protective against sensitive pharmaceutical drug substances.

DISADVANTAGES OF SMEDDS (16)

- Old dissolution approaches were unable to give response properly because these dependent on earlier drug release at the time of digestion.
- Insufficient relevant predictive in-vitro models for evaluation of the formulation

- Volatile co-solvents can migrate on capsule shell
- Expensive.
- Low drug incompatibility.

These formulations are help to produce emulsion of droplet size range 100-300 nm, while SMEDDS is used to prepare less than 50 nm droplet size microemulsion. These microemulsions are thermodynamically stable, less viscos colloidal dispersion of oil- water steadied by interfacial film by using gangling surfactant and co-surfactant.

TABLE 1. CLASSIFICATION AND PROPERTIES OF SOME DIFFERENT LIPID FORMULATIONS

Parameters	Type			
	I	II	III A	III B
Triglyceride/ mixture of glycerides (%)	100	40-80	40-80	<20
Percentage of Surfactants	-	20-60 (HLB> 12)	20-40 (HLB<11)	20-50 (HLB<11)
Water soluble co-solvents (%)	-	-	0-40	20-50
Particle size (nm)	Coarse	100- 250	100- 250	50- 100

Therefore, Self-emulsifying system is an effective carrier for drugs lies under BCS class II, III and IV.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM OF DRUG

BCS is helps in categorizing drugs on the bases of their solubility profile and permeability, the classification of such type drugs is expressed in **[Table 2]** (17, 18).

TABLE 2. BIOPHARMACEUTICAL DRUG CLASSIFICATION.

Class	Solubility	Permeability	Hurdles overawed by SEDDS
I	High	High	Gut wall efflux, Enzymatic degradation
II	Low	High	Bioavailability, Solubilization
III	High	Low	Gut wall efflux, Enzymatic degradation,
IV	Low	Low	Solubilization, enzymatic degradation

The composition and characteristics of different type of formulations are expressed in **[Table 3]**. Drugs that having high water solubility and high GI Tract permeability come in Class I. Due to this administered orally because it does not have solubility problems or oral bioavailability of the drug. While those drugs having solubility or permeability problem are called classes II, III and IV drugs are those which reproduces bioavailability in blood when taken orally. Approx. 75% of the medications from Classes II, III and IV are accessible in the market.

TABLE 3. COMPOSITION AND CHARACTERISTICS OF DIFFERENT TYPE OF FORMULATION

Formulation Types	Composition of formulations	Characteristics
Type I	Oils having no surfactants	Low solvent efficiency excepts, extremely lipid soluble drugs which require digestion for drug release.
Type II	Oils and water insoluble surfactants	SEDDS, is not clear o/w dispersion (particles size 0.25-2 μm), unlikely the low solvent capacity on dispersion, possible loss of solvent capacity on digestion
Type III	Oils and water-soluble surfactants or Co-solvents	SEDDS/SEMDDS, slightly bluish to pure dispersion, on dispersion it lost of solvent capability, not easy to digested, likely loss of solvent capability on digestion
Type IV	Water soluble surfactants or Co-solvents (Oils free)	Produce a pure micellar solution on dispersion, likely on dispersion it lost of solvent capability, not likely to be digested

SELF-EMULSIFICATION MECHANISM

Reiss suggest that, Moreover, the free energy of an emulsion formation is an immediate role of the energy for grow novel superficial between oil and aqueous phases (19, 20). In this manner the free energy (ΔG) related is represented as follows.

$$\Delta G = \Sigma N i \pi r i^2 \sigma$$

Where, in the above equation

ΔG = free energy associated with the process, N = No of droplets, r = radius, and σ = interfacial energy.

With time, two different phases of emulsion separated due to the exemption in surface area and surface free energy of the systems. Then, the emulsions prepared after aqueous dilution can be stabilized by using an emulsifier, due to this a single layer of droplets forms around the emulsion which leads reduction in the interfacial energy and form an obstacle to coalescence (21). Potential Mechanism for Absorption Enhancement shown in **[Fig. 3]** (20)

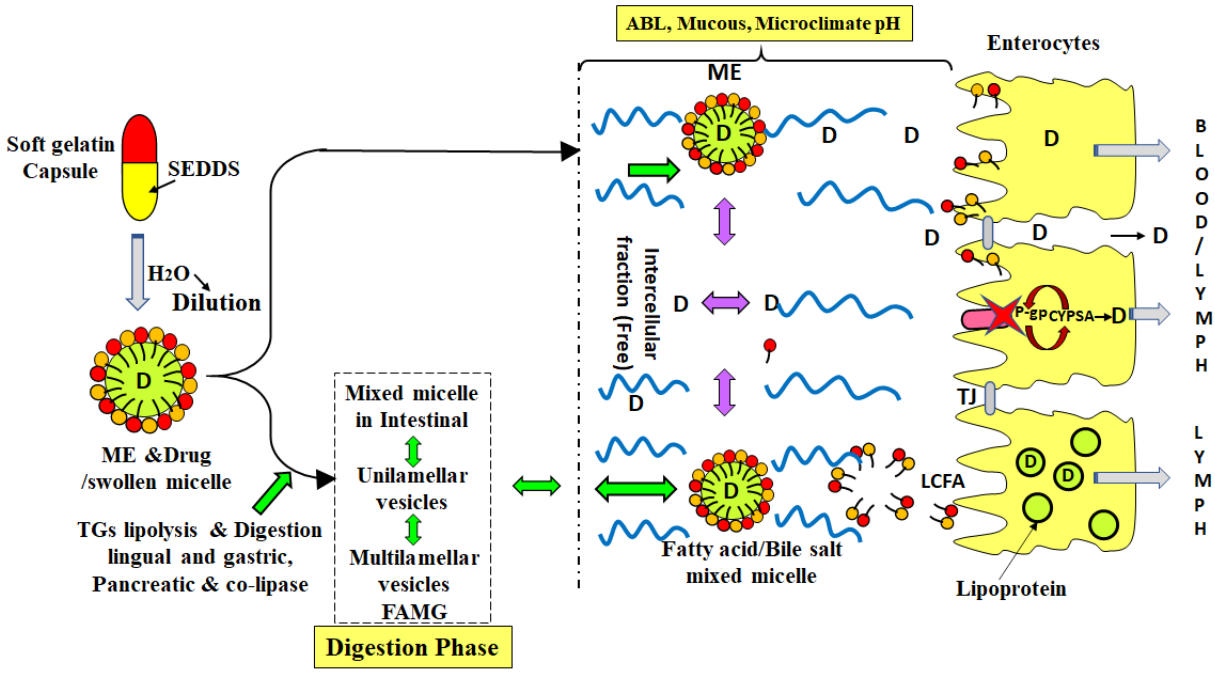


FIG. 3. MECHANISM OF SELF-EMULSIFYING DRUG DELIVERY SYSTEM [20].

DILUTION PHASES

This mechanism is used in SEDDS formulations, the precipitate curving of the surfactant layer modifications through various liquid crystalline states. The various droplets pass from a retreated spherical droplet to a, hexagonal phase.

SELECTION OF EXCIPIENTS

Various polymers are utilized in the preparation of self-emulsifying system, but the choice of suitable excipients has vital for the development of an efficient formulation. Because the most efficacious formulation is suitable for use, due to a smaller number of excipients are used in formulation (22-24). Factors which should be considered at the selection time of excipients are-

- Self-dispersibility
- Mixable
- Chemically constancy
- Budget
- compatibility
- Pureness
- Non-irritant, nontoxic, etc.

COMPONENTS OF SEDDS

These are the basic substance

- Drug or Active Pharmaceutical Ingredients (API)
- Oil
- Surfactant
- Co-solvent
- Viscosity Enhancers
- Polymers

- Antioxidant Agents

DRUG OR ACTIVE PHARMACEUTICAL INGREDIENTS (API)

It is having following properties (25, 26)-

- Drugs go through extensive hepatic metabolism
- Adequate half-life.
- Low dose.
- Drug should have higher log P value means high lipophilicity.
- BCS class II Drugs (low water solubility)
- Bioavailability of the drug should be low.

OILS

The oil most effectively used in the formulation of the SEDDS, such as vegetable oil and its derivatives. Vegetable oil means the oil which containing a mixture of triglycerides (more than 90%), free fatty acids, Phospholipids and steroids, Ex carotenoids. The oils are very important excipient because it helps in the self-emulsification which improves the drug transported portion of lipophilic from lymphatic system of intestine, thus absorption from GI tract also enhanced (27). Medium chain triglycerides are utilizes most frequently expressed in **[Table 4]**. Glycerides having long chain are often used like oils of peanut, olive, castor, sesame, corn. But these are not suitable for SEDDS formulations. These are usually substituting to regular medium chain triglycerides (28).

TABLE 4. CHEMICAL NAME OF MEDIUM CHAIN TRIGLYCERIDES.

Medium chain triglyceride	Chemical Name
Capryol 90	Polyethylene glycol monocaprylate
Capryol PGMC	Polyehtylene glucol caprylate
Labrafac PG	Polyethylene glycol di-caprylocaprate

SURFACTANT

The various chemical compounds are having surfactant properties which play important role in the designing of SEDDS but few of them are used in the orally administrated formulation. Non-ionic surfactants as presented in **[Table 5]**, having high HLB value (more than 12) most widely recommended for the formulation of the SEDDS from the class II, III, and IV. These non-ionic surfactants are use because it promotes the instant formation of o/w droplets with low toxicity.

TABLE 5. SURFACTANTS/CO-SURFACTANTS USED FOR SEDDS FORMULATION NAMES.

Surfactant/ Co-surfactant	Chemical Name
Cremophore EL	Polyoxyl 35 castor oil
Cremophore RH 40, 60	Polyoxyl 40, 60 hydrogenated castor oil
Tween 20, 80	Polysorbate 20, 80
Span 20	Sorbitan monooleate
Labrafil M 2125 CS	Polyoxyethylated linoleic glyceride
Labrafil M 1944 CS	Polyoxyethylated oleic glyceride
PEG 400 monostearate	Polyoxyl 8 stearate
PEG 1750 monostearate	Polyoxyl 40 stearate
Labrasol	Caprylocaproylmacrogol glyceride
Transcutol P	Diethylene glycol monoethyl ether

CO-SURFACTANT

Surfactants that having high HLB value are utilize for making optimized self-emulsifying formulation it is used orally because it helps in improve the dissolution, Ex: ethanol, propylene glycol, PEG-400, glycerol etc.

VISCOSITY ENHANCERS

Acetyl alcohol, stearic acids, tragacanth, and beeswax etc. are act as viscosity modifier of emulsion.

Polymers

Approximately 5-40% w/w inert matrix Polymer matrix (inert) is present in SEDDS, which is not ionisable at biological pH are capable to make matrix. Ethyl cellulose, HPMC, are used as polymers in SEDDS.

ANTIOXIDANT AGENTS

These antioxidants, such as: ascorbic palmitate, propyl gallate, α-tocopherol,) stabilize the oily content of SEDDS formulations.

BIOPHARMACEUTICAL ASPECTS

The rate and extent in plasma, of hydrophobic and low water-soluble drugs can be improved by using various mechanisms (29, 30), including:

GASTRIC TRANSIT REDUCTION (ALTERATION)

Here through reducing delivery at absorption site the dissolution time increase.

ENHANCED EFFECTIVE LUMINAL DRUG SOLUBILITY

Lipids in GI can promote the secretion of bile salts and endogenous biliary lipids (phospholipids and cholesterol), which leads the formulation of Bile salt/Phospholipids/Cholesterol intestinal mixed micelles and solubilization capacity of GI tract may improve. The exogenous lipids into the bile salts can be either administered by injection directly (if adequately polar), or secondary to digestion, results swell micellar structures with enhanced solubility (31).

STIMULATION OF INTESTINAL LYMPHATIC TRANSPORT

The drug having high lipophilic in nature, the lymphatic transport may enhance by the lipids and directly or indirectly increase the bioavailability with reduce in the first pass metabolism (32-34).

MODIFICATION IN GI BIOCHEMICAL BARRIER FUNCTION

The surfactants are used for reduction in of intestinal efflux transporters/extant of enterocyte-based metabolism such as p-glycoprotein efflux pump (35-37).

TRANSFORMATION IN GI PHYSICAL BARRIER UTILITY

Different mixtures of lipids, surfactants act as permeability enhancer. But passive intestinal penetrability is not obstacle to the bioavailability for hydrophobic, and in lipophilic drugs particularly (38, 39).

SOLIDIFICATION METHODS FOR CHANGING LIQUID/SEMI-SOLID

These solidification techniques are used:

CAPSULE FILLING FOR LIQUID AND SEMISOLID SELF-EMULSIFYING FORMULATIONS

This technique is mostly used for the encapsulation of semi-solid and liquid SE formulations for the oral administration. For semisolid preparation, it follows 4 step process (40).

Semisolid excipients melt at above 20˚C

↓

Mix active substances by continuous stirring

↓

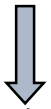
This mixture filled in Capsule shell at room temp. For liquefied preparations, it involves a two-step process

↓

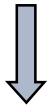
Sealing of capsule (body and cap) by banding /microspray sealing technique.

Spray Cooling or spray congealing:

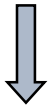
Composition of lipids, surfactants and drug are



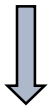
Blend is sprayed for maintaining the chamber cool



Molten droplets



Coagulate and recrystallize
solid particles (sphere-shaped)



Collect as fine powder in collecting chamber

This powder further utilizes for preparation of solid dosage form such as capsule, tablets etc. The ultrasonic atomizer is used to atomize the liquid blend and to produce droplets. The excipients used for this purpose are steryl polyoxyl glycerides, gelucire 50/13 e.g. Praziquantel & diclofenac (41, 42).

Spray Drying:

Lipids + Surfactants + Drug + Solid carriers

Mixed and solubilization of the mixture

Spray drying

Above mixture atomize into a spray of
droplets

These droplets are used into a drying chamber, for preparing tablet
by evaporation the volatile phase by dry chamber

By using of this self-micro emulsified formulation of Nimodipine (spray drying method) and dextran is use as a solid carrier (43). This method also used for preparation of self-emulsifying curcumin (44) and dexibuprofen (45).

Melt Granulation: In melt granulation, the accumulation of the powder by adding binder that liquefies at low temperatures.

Melt Extrusion/Extrusion Spheronization: This technique allows drug having loading approx. (60%) and content uniformity (46). It produces identical forms and maintain density of product by pushing it through a die under exact temperature, pressure and flow of products (47, 48).

EVALUATION

Thermodynamic stability studies

The precipitation of the API in carrier matrix may reduce the effectiveness of SEDDS formulations. The phase separation of the excipient may affect performance and visual form of SEDDS preparation. Due to incompatibilities in API and capsule shell can lead to brittleness and deformation and the drug is not release completely form the carrier matrix (49-53).

Heating cooling cycle

In this process using 6 cycles between refrigerator temperatures 40- 45ºC, for producing stable formulation these are store on each temperature for not less than 48 hours than centrifugation test was done.

Our freeze thaw cycle

In this test store the prepared formulation in freezer due to this the emulsion showing good stability without phase separation.

Dispersibility test

USP XXII dissolution apparatus-II can be used for the oral efficacy testing of self-emulsify microemulsion/Nano-emulsion. In this method One ml sample of every formulation was taken and mixed in 500 ml of water at 37 ± 0.5°C. Paddle of dissolution apparatus rotate at 50 rpm to achieve gentle agitation. The In-vitro qualities of such systems can visually assess with the help of these methods (49-50).

Table 6. Grading system.

Grade	Formation speed and time	Appearance
A	Nanoemulsion within 1 min	Clear or bluish
B	Slightly clear emulsion repid (1-2 min)	Bluish white
C	Fine emulsion (within 2 min)	Milky
D	Slow emulsification (more than 2 min)	Dull, greyish white
E	Large oil globules very poor emulsification	Muddy

The formulations come under Grade A and B when dispersed in the GIT it will remain as a nanoemulsion, while formulations falling in Grade C can be uses as self-emulsion formulation, expressed in **[Table 6]**.

Turbidimetric evaluation

For the evaluation and to monitor the emulsification growth, Nepheloturbidimetric method is used.

Fixed amounts of self-emulsification system, add in suitable medium (0.1 N HCL) with continuous agitation (50 rpm) on a magnetic plate, increase in turbidity and evaluate by turbidimeter.

Viscosity determination

The SEEDDS systems are generally poured into hard or soft gelatin capsules. Such types of systems are not too thick; hence they reduce the problems associated with their structure. The viscosity of microemulsions helps to determination of its types and rheological properties of emulsion. There are various types of viscometer used for viscosity measurement but Brookfield viscometer is suitable for this purpose. The various research studies perorate that the o/w emulsions have low viscosity and the w/o type emulsions have high viscosity.

Droplet and particle size analysis

The photon correlation spectroscopy determines the droplet size by using a Zeta-Sizer. Brownian movement of particles of emulsion is able to measure sizes between 10 and 5000 nm.

Marketed Formulations of SEDDS

The different formulations present in market are expressed in **[Table 7]**.

Table 7. Marketed formulations of SEDDS.

Product Name	API	Dosage Form	Company
Gengraf®	Cyclosporine	Hard gelatin capsule	Abott Laboratories
Sandimmune Neoral®	Cyclosporine	Soft gelatin capsule	Novartis
Juvela®	Tocopherol, Nicotinate	Soft gelatin capsule	Eisai Co.
Fortovase®	Saquinavir	Soft gelatin capsule	Hoffman-La Roche
Agenerase®	Amprenavir	Soft gelatin capsule	GSK
Lipirex®	Fenofibrate	Hard gelatin capsule	Sanofi-Aventis

CONCLUSION

It is mixture of the Drug, surfactant, lipids and co-surfactant. The SEDDS is most efficient approach for low water-soluble drug. This system is most appropriate for BCS class II and IV drugs for oral administration. SEDDS is use hydrous moiety from the surroundings and naturally forms oil/water type of emulsion which disperses in fine globules due to this system suitable for drug showing gastric irritation. SEDDS is also shown controlled and sustain release of poor water drugs. It also improved the dissolution by increasing the absorption of drug due to this the increase the bioavailability of the drug. The drug having poor oral water-soluble drug may administered by SEDDS. In future prospective SEDDS work as novel application or delivery system for the poor aqueous soluble drugs. Thus, SEDDS system need explored and research so the self-emulsifying formulation can come the pharmaceutical markets.

CONFLICT OF INTEREST

The author has no conflict of interest on this article.

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REFERENCES

1. Gursoy, R.N., Benita, S. (2004) Self-emulsifying drug delivery systems for improved oral delivery of lipophilic drugs. Biomedicine and Pharmacotherapy, 58:173-182.
2. Abdalla, A., Klein, S., Mader, K. (2008) A new Self emulsifying drug delivery system for poorly soluble drugs. European Journal of Pharmaceutical Sciences, 35:357-464.
3. Groves, M.J., Mustafa, R.M.A., Carless, J.E. (1947) Phase studies of mixed phosphated surfactants, n-hexane and water. J. Pharm. Pharmacol., 26:616-623.
4. Pouton, C.W. (1985) Self-emulsifying drug delivery systems: Assessment of the efficiency of emulsification. Int. J. Pharm., 27:335-348.
5. Wakerly, M.G., Pouton, C.W., Meakin, B.J. (1985) Evaluation of the self-emulsifying performance of a non-ionic surfactant-vegetable oil mixture. J. Pharm. Pharmacol., 6-39.
6. Pouton, C.W., Wakerly, M.G., Meakin, B.J. (1987) Self-emulsifying systems for oral delivery of drugs. Proc. Int. Symp. Control. Releases. Bioact. Mater., 14:113-114.
7. Serajuddin, A.T., Shee, P.C., Mufson, D., Bernstein, D.F., Augustine, M.A. (1988) Effect of vehicle amphiphilicity on the dissolution and bioavailability of poorly water-soluble drug from solid dispersions. J. Pharm. Sci., 77:414-417.
8. Tarr, B.D., Yalkowsky, S.H. (1989) Enhanced intestinal absorption of cyclosporine in rats through the reduction of emulsion droplet size. Pharm. Res., 6:40-43.
9. Charman, S.A., Charman, W.N., Rogge, M.C., Wilson, T.D., Dutko, F.J., Pouton, C.W. (1992) Self-emulsifying drug delivery systems: Formulation and biopharmaceutic evaluation of an investigational lipophilic compound. Pharm. Res., 9:87-93.
10. Craig, D.Q. (1993) The use of self-emulsifying systems as a means of improving drug delivery. BT Gattefosse, 86:21-31.
11. Garrigue, J.S., Lambert, G., Benita, S. (2005) Self-emulsifying oral lipid-based formulations for improved delivery of lipophilic drugs. In: Drugs and the Pharmaceutical Sciences. Microencapsulation Methods and Industrial Applications. 2nd ed. Chap. 13. Benita S, editor. Switzerland: Informa Healthcare, pp. 429-80.

12. Craig, D.Q., Lievens, H.S., Pitt, K.G., Storey, D.E. (1993) An investigation into the physico-chemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis. Int. J. Pharm., 96:147-155.
13. Mistry, R., Sheth, N.S. (2011) Self emulsifying drug delivery system. International Journal of Pharmacy and Pharmaceutical Sciences, 3(2):23-28.
14. Shah, N.H., Carvajal, M.T., Patel, C.I., Infeld, M.H., Malick, A.W. (1994) Self-emulsifying drug delivery system (SEDDS) with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. Int. J. Pharm. 106:15-23.
15. Constantinides, P.P. (1994) Lipid microemulsion for improving drug dissolution and oral absorption: Physical and biopharmaceutical aspects. Pharm. Res. 1994; 12:1561-1572.
16. Shukla, J.B., Koli, A.R., Ranch, K.M., Parikh, R.K. (2010) Self micro emulsifying drug delivery system. Pharma science monitor, An International Journal of Pharmaceutical Sciences, 1(2): 13-33.
17. Karalis, V., Macheras, P., Peer, A.V., Shah, V.P. (2008) Bioavailability and bioequivalence: focus on physiological factors and variability. Pharm. Res., 25(8):1956-1962.
18. Craig, D.Q., Lievens, H.S., Pitt, K.G., Storey, D.E. (1993) An investigation into the physico-chemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis. Int. J. Pharm., 96:147-55.
19. Craig, D.Q.M., Barker, S.A., Banning, D., Booth, S.W. (1995) An Investigation into the Mechanisms of Self-Emulsification Using Particle Size Analysis and Low Frequency Dielectric Spectroscopy. Int. J. Pharm., 114:103-110.
20. Wakerly, M.G., Pouton, C.W., Meakin, B.J., Morton, F.S. (1986) Self-emulsification of vegetable oil-nonionic surfactant mixtures. ACS Symp. Ser., 311:242-255.
21. Gershanik, T., Benita, S. (2000) Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. European Journal of Pharmaceutics and Biopharmaceutics, 50:179-188.
22. Pouton, C.W., Porter, C.J. (2008) Formulation of Lipid-Based Delivery Systems for Oral Administration: Materials, Methods and Strategies. Adv. Drug. Deliv. Rev., 60:(6):625-637.
23. Shaji, J., Jadhav, D. (2010) Newer approches to self emulsifying drug delivery system. International Journal of Pharmacy and Pharmaceutical Sciences, 2(1):37-42.
24. Strickley, R.G. (2004) Solubilizing Excipients in Oral and Injectable Formulations. Pharm Res., 21(2):201-230.
25. Kumar, S., Malviya, R., Sharma P.K. (2011) Solid Dispersion: Pharmaceutical Technology for the Improvement of Various Physical Characteristics of Active Pharmaceutical Ingredient. African Journal of Basic and Applied Science, 3(4):116-125.
26. Kumar, S., Gupta, S., Sharma P.K. (2012) Self-Emulsifying Drug Delivery Systems (SEDDS) for oral delivery of lipid based formulations. African Journal of Basic & Applied Science, 4(1):07-11.
27. Nigade, P.M., Patil, S., Tiwari S.S. (2012) Self Emulsifying drug delivery system (SEDDS): A review. International Journal of Pharmacy and Biological Sciences, 2(2):42-52.
28. Sharma, V., Singh, J., Gill, B., Harikumar, S.L. (2012) SMEDDS: A novel approach for lipophilic drugs. International Journal of Pharmaceutical Science and Research, 3(8):2441-2450.
29. United States Pharmacopoeia 24th National Formulary 19, 2000. Asian ed., United States Pharmacopoeia Convention, Inc., pa. 1342, 2231-2232, 2254.
30. Jain, N.K., Jain, S., Singhai, A.K. (1997) Enhanced Solubilization and Formulation of an Aqueous Injection of Piroxicam. J. Global, 52(12):942-946.
31. Odeberg, J.M., Kaufmann, P., Kroon, K.G., Hoglund, P. (2003) Lipid Drug Delivery and Rational Formulation Design for Lipophilic Drugs with Low Oral Bioavailability, Applied to Cyclosporine. Eur. J. Pharm. Sci., 20(4-5):375-82.
32. Ana, R., Mendes, M., Sousa, J., Pais, A., Falcão, A., Fortuna, A., Vitorino, C. (2019) Rethinking carbamazepine oral delivery using polymer-lipid hybrid nanoparticles. Int. J. Pharm., 554:352-365.
33. Da Silva, R.C., Spitzer, M., Da Silva, L.H.M., Loh, W. (1999) Investigations on the Mechanism of Aqueous Solubility Increase Caused by Some Hydrotropes. Thermochim Acta, 328(1/2):161-168.
34. Maheshwari, R.K., Chaturvedi, S.C., Jain, N.K. (2005) Application of hydrotropic solubilization phenomenon in spectrophotometric analysis of hydrochlorothiazide tablets. Indian Drugs, 42:541-544.
35. Maheshwari, R.K. (2006) Titrimetric Analysis of Aceclofenac in Tablets Using Hydrotropic Solubilizing Technique. Indian drugs, 43:516-518.
36. Saleh, A., Khordagui, L. (1985) Hydrotropic Agent a New Definition. Int. J. Pharm., 24:231-238.
37. Ueda, S. (1966) The Mechanism of Solubilization of Water Insoluble Substances with Sodium Benzoate Derivatives. I. The Interaction between Water Insoluble Substances and Sodium Benzoate Derivatives in Aqueous Solution. Chem Pharm Bull, 14(1):22-29.
38. Maheshwari, R.K., Joshi, G., Mahajan, S.C. (2010) Novel application of hydrotropy in thin layer chromatography. The Indian Pharmacist, 57-59.
39. Maliwal, D., Jain, A., Maheshwari, R.K., Patidar, V. (2008) Simultaneous Spectrophotometric Estimation of Metronidazole and Norfloxacin in Combined Tablet Formulations using Hydrotropy. Research J. Pharm. and Tech., 1(4):357-361.
40. Sapra, K., Sapra, A., Singh, S.K., Kakkar S. (2012) Self Emulsifying Drug Delivery System: A Tool in Solubility Enhancement of Poorly Soluble Drugs. Indo Global Journal of Pharmaceutical Sciences, 2(3):313-332.

41. Passerini, N., Albertini, B., Perissutti, B., Rodriguez, L. (2006) Evaluation of melt granulation and ultrasonic Spray congealing techniques to enhance dissolution of praziquantel. International Journal of Pharmaceutics, 318:92-102.
42. Cavallari, C., Rodriguez, L., Albertini, B., Passerini, N., Rosetti, F., Fini, A. (2005) Thermal and Fractal analysis of diclofenac/Gelucire 50/13 micro particles obtained by ultrasound assisted atomization. Journal of Pharmaceutical Sciences, 94:1124-1134.
43. Yi, T., Wan, J., Xu, H., Yang, X. (2008) A new solid self-micro emulsifying formulation prepared by Spray drying to improve the oral bioavailability of poorly water soluble drugs. European Journal of Pharma and Biopharma, 70:439-444.
44. Yan, Y.D., Kim, J.A., Kwak, M.K., Yoo, B.K., Yong, C.S., Choi, H.G. (2011) Enhanced oral bioavailability of curcumin via a solid lipid based self-emulsifying drug delivery system using a spray drying technique. Biological and Pharmaceutical Bulletin, 34:1179-1186.
45. Balkrishan, P., Lee, B.J., Oh, D.H., Kim, J.O., Hong, M.J., Jee, J.P., Kim, J.A., Yoo, B.K., Yong, C.S., Choi, H.G. (2009) Enhanced Oral bioavailability of Dexibuprofen by a novel solid self-emulsifying drug delivery system. European Journal of Pharma and Biopharma, 72:539-545.
46. Hauss, D.J., Fogal, S.E., Ficorilli, J.V., Price, C.A., Roy, T., Jayaraj, A.A., Keirns, J.J. (1998) Lipid-based delivery systems for improving the bioavailability and lymphatic transport of poorly water-soluble LTB4 inhibitor. J. Pharm. Sci., 87:164-169.
47. Pillay, V., Fassihi, R. (1999) Unconventional dissolution methodologies. J. Pharm. Sci., 88:843-851.
48. Gupta, J., Km, Rachna. (2020) Nanotechnology approach in Targeting and Treatment of Neurological Disorders by Overcome Blood Brain Barrier. Int. J. Adv. Sci. Technol., 29(8):2852-2870.
49. Gupta, P., Kumar, P., Sharma, N.K., Pawar, Y., Gupta, J. (2014) Self nano emulsifying drug delivery system: A strategy to improve oral bioavailability. World J. Pharm. Pharm. Sci., 3(5):506-512.
50. Gupta, J., Prabakaran, L., Gupta, R., Mohan, G. (2011). Nanoparticles formulation using counter-ion induced gelification technique: In-vitro Chloramphenicol Release. Int. J. Pharm. Pharm. Sci., 3(3):66-70.
51. Patel, P.A., Chaulang, G.M., Akolkotkar, A., Mutha, S.S., Hardikar, S.R., Bhosale, A.V. (2008) Self emulsifying drug delivery system: A review. Research. J. Pharm. and Tech., 1:313-323.
52. Jannin, V., Musakhanian, J., Marchaud, D. (2008) Approaches for the development of solid and semi-solid lipid-based formulations. Adv. Drug. Deliv. Rev., 60:734-746.
53. Tang, B., Cheng, G., Gu, J.C., Xu, C.H. (2008) Development of solid self-emulsifying drug delivery systems: Preparation techniques and dosage forms. Drug Discov. Today, 13:606-612.