AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Self-Microemulsifying Drug Delivery Systems: Formulation Design and Characterization

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ABSTRACT

Oral route has been considered as most convenient route but restricted to only hydrophilic compounds having GI stability and greater dissolution. The delivery of lipophilic compounds has been area of interest since most of the drugs under discovery shows limited bioavailability. Self-emulsifying delivery systems (SMEDDS) has drawn a greater attention in the formulation of poorly soluble compounds where increase in the absorption and permeation of the drug has observed. The self-emulsification which occurs in the case of SMEDDS has shown a potential advantage over conventional emulsion due to the fine globules formed upon dilution. The recent trends such as dry emulsion, s-SMEDDS, SNEDDS thoroughly investigated. This article, attempts to present the overview of the SMEDDS along with its formulation, application and characterization.

Keywords: Microemulsion, Self-emulsification, Surfactants, Bioavailability

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Received 01 April 2022, Accepted 29 May 2022

Please cite this article as: Sharvani K *et al*., Self-Microemulsifying Drug Delivery Systems: Formulation Design and Characterization. American Journal of PharmTech Research 2022.

INTRODUCTION

Among the various routes available, oral route has been considered as 'convenient' route due to patient compliance, cost effectiveness, non-invasiveness and ease of its administration. Nearly 35-40% of the drug discovered belong to practically insoluble category due to their lipoidal nature causing a problem in the solubility and thus bioavailability. The Biopharmaceutical classification system (BCS) categorized these into class 2 for low soluble and high permeable drugs and class 4 for low soluble and low permeable drugs (Figure 1). For this class of drugs, the gastrointestinal solubility or dissolution and intestinal permeability is the rate limiting steps. The effectiveness of these drugs is enhanced either by formulating them into solid dosage forms with the increase in their surface area and/or changing the physical form i.e., conversion into amorphous or molecular forms such as solid dispersions or solid solutions or lipid and surfactant-based drug delivery systems using various excipients where the drug is in solution form. This results in the improvement in the gastrointestinal solubilization with the increase in the solubility and dissolution thereby altering their pharmacokinetic profiles. [1,2]

The continuous study on lipid-based drug delivery system led to the development of simple oil solutions to complex formulations such as oily suspension, coarse or micro emulsion, liposomes, self-emulsifying drug delivery systems (micro or nano) etc. Incorporation of the drug in the inert lipid vehicles such as oils, surfactants and co-surfactants mixtures ensure that the drug does not show variable absorption pattern due to the precipitation or in other words drug remains in the solution form throughout the GIT. These formulatory additives also known as permeability enhancers has the ability to inhibit the first pass metabolism of the drug as well as the efflux mechanism mediated by the P-glycoprotein thereby enhancing the oral absorption of anti-cancer drugs. [3,4]

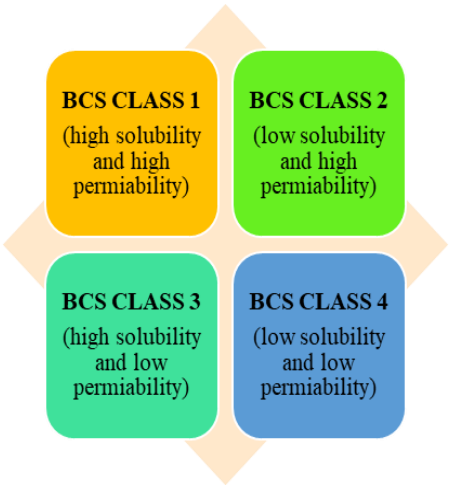

Figure 1: The bio-pharmaceutical classification system

LIPID FORMULATION CLASSIFICATION SYSTEM

Lipid formulations are the blend of oils such as triglycerides, mono and diglycerides, lipophilic surfactants, hydrophilic surfactants, co-surfactants and water soluble cosolvents. Colin W Pouton has classified the lipid formulations based on the polarity of the mixture (Table 1). Type 1 formulations are simple and biocompatible oily solutions such as triglycerides and/or mixed glycerides which required to be digested. The addition of lipophilic surfactants for the dispersion of the drug led to the development of type 2 formulations termed as water insoluble self-emulsifying drug delivery systems (SEDDS) by retaining its solvent capacity. Mixing of Hydrophilic surfactants or water-soluble co-solvents with the oils resulted in very fine dispersion of drug under the peristaltic movement in GIT introduced the type 3 formulations termed as self-micro emulsifying drug delivery system (SMEDDS). Recent class of the formulations are developed with no oils i.e., hydrophilic formulations containing the mix of surfactants with the co-solvents provides much greater solvent capacity [5,6].

Recently much attention has been given to Self micro-emulsifying drug delivery system (SMEDDS). These are defined as an 'isotropic mixture of oil, non-ionic surfactants and hydrophilic surfactants or hydrophilic co-solvents which forms oil-in-water type of emulsion upon mild agitation in aqueous environment in GIT'. SMEDDS are an optically clear or slightly opalescent dispersions with the droplet size less than 100nm in comparison with SEDDS formulations which are opaque in nature with the particle size greater than 100nm. A study by Xiong *et al* found that the optimized formulation of Ziyuglycoside I- loaded SMEDDS showed a 6.94-greater absolute bioavailability of 21.94 ± 4.67% in mice. In addition, SNEDDS are developed because of their thermodynamic stability and high drug loading. These are dispensed in the dosage forms such as self-emulsifying capsules, self-emulsifying sustained/controlled release tablets or pellets, solid dispersions for oral delivery [7,8]

Table 1: Oral lipid delivery system classification [4,6]

		Composition (% w/w)		Globule size(nm)	Characteristics
Type I		triglycerides or mixed mono and diglycerides	100%	Coarse	Non dispersible and non-digestible
Type II		triglycerides or mixed mono and diglycerides	40-80%	100-250nm	Solvent capacity gets unaffected upon dilution (SEDDS)
		Water-insoluble surfactants (HLB < 12)	20-60%		
Type III	Type III A	triglycerides or mixed mono and diglycerides	40-80%	100-250nm	Digestion is not essential for drug absorption and some loss of solvent capacity occurs upon dilution in git (SMEDDS)
		Water-soluble surfactants (HLB > 12)	20-40%		
		Hydrophilic co-solvents	0-40%		
	Type III B	triglycerides or mixed mono and diglycerides	<20%	50-100nm	
		Water-soluble surfactants (HLB > 12)	20-50%		
		Hydrophilic co-solvents	20-50%		
Type IV		Water-insoluble surfactants (HLB < 12)	0-20%	Micelles	Good solvent capacity and micellar formation occurs upon dilution
		Water-soluble surfactants (HLB > 12)	30-80%		
		Hydrophilic co-solvents	0-50%		

ADVANTAGES OF SMEDDS OVER CONVENTIONAL EMULSION:

1. The low oral bioavailability of lipophilic drugs enhanced by their micronized form which increases the area thereby increasing the solubility and permeability
2. The drug absorption of drug from SMEDDS is independent of presence of food
3. Ease of manufacture and scale up with simple formulation technique
4. The macromolecules such as proteins, peptides, enzymes can be easily delivered, as they can protect such drugs from acidic environment of git and enzymatic degradation
5. Increased drug loading capacity
6. SMEDDS are thermodynamically stable formulations thus can be easily stored at room temperature
7. Reduced inter and intra subject variability compared to other formulations. [9,10]

DISADVANTAGES OF SMEDDS:

1. High risk of drug precipitation in GIT upon dilution due to the presence of high amount of hydrophilic solvents
2. Since the formulatory additives are more the formulation becomes more challenging
3. Incompatibility of co-solvents with the soft or hard gelatin capsule shells
4. Predictive in-vitro models are less for the assessment of the formulation
5. The lipids used for the formulation may undergo oxidation or degradation. [10,11]

MECHANISM OF SELF-EMULSIFICATION:

Pounton[12] reported for the first time the occurrence of self-emulsification that is observed when the system is diluted thereby avoiding the dissolution step and improving the bioavailability of hydrophobic drugs. The microemulsions are often identified as optically clear solutions by the equilibrium phase studies due to the presence of the additional excipient which acts as a co-solvent for both oil and water. The force required to increase the interfacial area is lower than the force required for the conventional emulsions. Presence of smaller size globule in microemulsion increases the surface area of the bulk of the oil droplet thereby increasing the surface free energy and the entropy of the system.

Rees *et al* explained that the free energy involved in the microemulsion formation can be depicted as,

$$\Delta G_f = \gamma \Delta A - T \Delta S$$

Where,

ΔG_f – Free energy formation

γ – Surface tension between the oil-water interface

ΔA – Change in the area upon emulsification

ΔS – Change in the entropy of the system

T - Temperature

The larger reduction in the surface tension and significant entropic changes results in the negative free energy (ΔG) which is considered to be thermodynamically stable and the system formation is spontaneous [12,13,14]

FORMULATION DESIGN:

1. Selection of excipients
2. Construction of pseudo-ternary phase diagrams
3. Formulation of SMEDDS
4. Characterization of SMEDDS [15]

Excipients for the SMEDDS formulation:

The selection of excipients is very important in order to achieve the maximum drug loading, spontaneous emulsification, minimum droplet size and to prevent drug precipitation in GIT. These excipients may be natural, synthetic or semi-synthetic in nature. The physiological factors such as gastric emptying, bile flow, lipid fluidity and effect of efflux transporter influence the selection of excipients. The formulatary additives like oils, surfactants and co-surfactants are screened by the solubility studies generally by shake flask method. The excess amount of drug is added separately to various oils, surfactants and co-surfactants which are shaken at room temperature. The supernatant liquid of equilibrated sample is filtered and quantified by spectroscopic method [15,16]

Additives:

Oils:

Oils form the key element of SMEDDS which solubilizes the hydrophobic or lipophilic moiety thereby improving the bioavailability. At room temperature they can exists in liquid, semisolid, or solid form having saturated medium-/long-chain or a partially unsaturated or unsaturated hydrocarbon chain. Triglycerides vegetables oils are found to be completely digestible and absorbable thus, they are used most often in the formulation. These are further classified as long-chain triglycerides (LCT), medium-chain triglycerides (MCT) and mixed mono-, di-, and triglyceride small-chain triglycerides (SCT) (Table 2) [17,18]

Table 2: The classification lipids used in SMEDDS [17,18]

Sl.no	Triglycerides	Properties	Examples
1	Long-chain triglycerides (LCT)	Fatty acid chains of 1420 carbons High solubilizing capacity, easily digestible	Olive oil, jojoba oil, sesame oil, sunflower oil, castor oils
2	Medium-chain triglycerides (MCT)	Fatty acid chains of 612 carbons Resistant to oxidation, high solvent capacity	Labrafac CM 10, Capric/caprylic triglycerides (Velsan® CCT, CCT), Pecola (glycerol monooleate)
3	Small chain triglycerides (SMT)	Mono, di and triglycerides Self-dispersible amphiphiles with high solubilizing capacity	CC Capmul MCM EP (caprylic/ capric mono- and diglycerides) 49, Capryol®, Myrj®

Surfactants:

The hydrophilic groups in the surfactants categorizes them into anionic, cationic, non-ionic and ampholytic surfactants**.** They increase the permeability by partitioning between the cellular membrane and thus causing the disruption of the organization of the phospholipid bilayer thereby showing the enhancement in the permeability. The HLB value of a surfactant is an important factor for the selection of the surfactants. Since SMEDDS are the hydrophilic preparations 30-60% of non-ionic surfactants are most commonly used because of their high HLB value. These are preferred over other surfactants due to their low toxicity and high stability**.** These surfactants help in spontaneous emulsification and rapid distribution in the GI aqueous media. The use of surfactants mixture proved to show high emulsification power then the single use of the surfactant**.** Examples; Sorbitan esters (Spans), polysorbates (Tweens) [18,19]

Co-surfactant and co-solvents:

The combination of oil and hydrophilic surfactant increases the viscosity of the preparation which is an evident for the liquid crystal or lamellar formation. Further incorporation of the co-surfactants or co-solvents decreases the interfacial tension between the oil and water droplets and they break the liquid crystalline structure which is a characteristic of formation of an microemulsion. However, the addition these short chain alcohols are not mandatory. The co-solvents tend to dissolve the hydrophile of a surfactants or drug in lipid phase**.** The use of alcohol-free formulations is extensively studied since they show the capsule incompatibility but this results in low dissolution of the lipids**.** Examples; ethanol, propylene glycol (PG), polyethylene glycol(PEG) [20, 21]

CONSTRUCTION OF PSEUDO-TERNARY DIAGRAM:

Pseudo ternary phase diagrams are the equilateral triangles, used for the determination of the microemulsion region. The corner of these triangles represents the 100% of each component, they may be a binary mixture of surfactant and co-surfactant or water and drug or oil and drug typically representing more than three components. It is the most important step in the process of forming

the stable microemulsion even though it is a tedious method. This diagrammatic representation is divided into 100 parts when mass fractions of the additives are measured by percentage by weight. Different proportions of excipients are either titrated with the water or diluted with double distilled water which is followed by construction of the triangle the area and centroid of which is further calculated [22,23]

Water-titration method:

The initial step involves the preparation of surfactant mix by mixing surfactant and co-surfactant in different weight ratios. These mixtures are then combined with the oil to give various ratios varying from 1:9 to 9:1 which clearly defines the boundaries of the phase diagram. Water then added dropwise to the oil mixture under constant stirring until clear dispersion occurs; the point at which turbidity-to-transparency/transparency-to-turbidity transition visually observed and phase diagrams are prepared by using appropriate software [24,25]

Dilution method:

Varying compositions of surfactant mix and oil is prepared based on the need of the preparation so that the total composition of the mixtures always be 100%. The mixture is then diluted with double distilled water; the globule size of the dispersion is studied by the spectroscopic method. Further the desirable formulation can be achieved by selecting the appropriate region in the phase diagrams which defines the amount of oil, surfactant and co-surfactant [26,27]

FORMULATION OF SMEDDS:

The appropriate amount of drug is added to the SMEDD vehicle which is a combination of oil, surfactant and co-surfactant by constant stirring. Remaining excipients are added after the complete solubilization of the drug in the vehicle at room temperature. The preparation is equilibrated at atmospheric conditions for 48 hours [28,29]

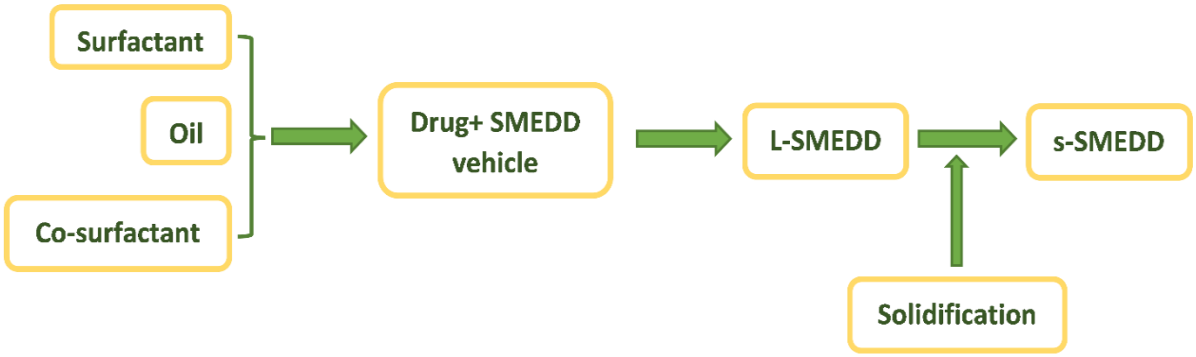

Figure 2: Formulation of solid self-emulsifying drug delivery system [30,31]

The problems such as stability and drug precipitation of L-SMEDDS can be overcome by converting them into solid dosage forms. Solidification of these liquid or semi-solid preparations

can be done by various techniques such as adsorption to water soluble or in-soluble carriers, spray drying, hot melt extrusion, lyophilization and melt granulation methods (Figure 2). These are then dispensed in the form of dry emulsion, SME capsules, SME tablets, SME pellets, SME suppositories, SME implants and SME solid dispersion. Despite of the toxicity or interaction of the carriers, the s-SMEDDS have gained the industrial attention [30,31]

CHARACTERIZATION OF SMEDDS:

Robustness to dilution:

Robustness to dilution can be studied by diluting the prepared formulation with 50, 100 and 1000 times with of various dissolution media i.e., water, buffer of pH 1.2, pH 4.5, pH 6.8. Diluted formulations are stored and observed for any physical changes like phase separation or drug precipitation [32]

Dispersibility and self-emulsification time:

Dispersibility and self-emulsifying efficiency of the formulation can be assessed by visually grading the preparation. Each ml of the preparation is added to 500 ml of distilled water at 37^0 C ± 0.5^0 C using standard USP XXIII dissolution apparatus II at rotation speed of 50 per minute.

The efficiency of the system is evaluated by following grading system (Table 3) [33,34]

Table 3: The classification lipids used in SMEDDS [33,34]

Grade	Emulsifying time	Appearance	Dispersibility
A	Within 1min	Clear transparent or bluish appearance	Rapidly forming
B	Within 1 min	less clear emulsion, having a bluish-white appearance	Rapidly forming
C	Within 2min	Fine milky emulsion	Intermediate
D	Longer than 2min	Dull, grayish-white emulsion having a slightly oily appearance	Slow emulsification
E	Longer than 2min	Formulation, exhibiting large oil globules present on the surface	Poor emulsification

The formulation which shows grade A and grade B will remain as nano emulsion/microemulsion whereas grade C formulations remain as SEDDS.

Globule size and poly-dispersibility determination:

The stability of the preparation depends on the globule size of the microemulsion prepared. The globule size of the emulsion can be determined by using dynamic light scattering principle or photon correlation spectroscopy by diluting the preparation with the distilled water. The size range of the globules are evaluated by using heterogenicity index or poly-dispersibility index by using photon correlation spectroscopy. The value found should be less or equals to 0.3[24,35]

Zeta potential determination:

The charge present on the surface of the globule is an important parameter determining the

stability of the system. Higher the electrostatic repulsion between the globules prevents the coalescence whereas low electrostatic repulsion shows the phase separation. The formulated SMEDDS are suitably diluted with the water; resulted microemulsion is analyzed by using the dynamic light scattering principle. With continual stirring samples are analyzed in triplicate [36,37]

Thermodynamic stability studies:

Heating-cooling cycle:

The formulations are stored between the temperatures between 4^0 and 45^0 for not less than 48hours. The formulations which can withstand these temperatures without any presence of cracking, creaming, phase-separation and coalescence are selected for centrifugation test.

Centrifugation:

The selected formulations are centrifuged at higher rotation for 30min. The formulation which shows no change in the physical appearance are selected for freeze thaw cycle.

Freeze-thaw cycle:

Three cycles are performed between -20^0 C and + 25^0 C for not less than 48hours. Each ml of the formulations is diluted with 25ml of double distilled water and observed for any physical instability. The selected formulations are further analyzed [38,39]

Cloud point measurement:

The occurrence of cloudiness in the formulation shows the effect of temperature and stable formulation shows the cloudiness above 60^0 C. 1ml of the prepared microemulsion is diluted with 100ml of the distilled water. These samples are kept on the water bath at room temperature. The analysis is carried out at a temperature range 40^0 to 60^0 by gradually increasing the temperature from room temperature at an interval of 10mins. The temperature at which cloudiness occurs is noted down [40,41]

Morphological examination by transmission electron microscopy:

The morphology of the SMEDDS can be studied by transmission electron microscopy by diluting the preparation with distilled water. One drop of this mixture placed on a film coated copper grid and negative stain phosphotungistic acid is added; allowed to dry at room temperature. Then finally this grid is observed under electron microscope and images of the microemulsion is captured by using the camera. [42,43]

Electro conductivity study:

The conductivity of the microemulsion is measured by using electro conductometer. The samples are diluted with Distilled water and 0.9% w/w isotonic sodium chloride solution. This test is used to confirm whether the formulation is O/W or W/O. Higher value of ion conductivity shows the

dispersion medium is a water. [44,45]

Differential scanning colorimetry:

Lipid content and thermal behavior of the excipients are studied by using differential scanning colorimetry. Samples are placed on the aluminum plate and thus any type of chemical interactions can be read through this test. [46]

Determination of percentage of transmittance:

By using UV-Visible spectroscopy the percentage of light transmitted by the microemulsion can be determined. The samples are diluted with 100, 1000 folds of distilled water, gastric fluid and intestinal fluid and transmittance can be recorded at specific lambda-max of the drug [47]

***In-vitro* drug release study:**

Estimated amount of preparation is filled in the capsules. These are then placed in the standard USP XXIII II dissolution apparatus containing either phosphate buffer or hydrochloric acid depending on the drug absorption as a dissolution medium. Test is carried out at $37^0 \pm 0.5^0$ C with the agitation rate of 50 rpm. Different aliquots are withdrawn at specific interval of time and replaced with the fresh medium. Percentage drug release is determined by using UV-Visible spectroscopy at specific lambda-max of the drug [47,48]

Stability studies:

The stability studies are conducted up to 3months for intermediate and acceralated; up to 6months for long term studies. Samples are exposed to different temperature and humidity conditions such as; 25°C/60% relative humidity (RH), 30°C/65% RH, and 40°C/75% RH in stability chamber. Samples are taken periodically and analyzed for their drug content, droplet size and *in-vitro* drug release [49,50]

FACTORS AFFECTING SMEDDS FORMULATION: [51,52]

Dose of the drug:

Drugs which require high dose for their action cannot be administered in the form of SMEDDS; unless solubility of that drug in any of the lipophilic phase is exceptionally good. Drugs which show limited solubility in both water and oil with less than 2 log P value are not suitable candidates for SMEDDS

Solubility of the drug in the oil phase:

The solubility of the drug in oil phase affected by the ability of the formulation to maintain the drug in soluble state. The precipitation of the drug is observed when the surfactant and co-surfactant are utilized for the solubilization purpose

Solubility equilibrium:

Equilibrium solubility measures the precipitation of the drug in GIT; however, crystallization could be slow in Gi environment. According to Pouton's research, the supersaturation of the drug occurs for 24hrs after emulsification occurs in the intestine and such emulsions take 5days to reach equilibrium

Polarity of the lipid droplets:

Polarity of the oil droplet provide evidence for the affinity of the drug for both oil and water and type of the force present. Higher amount of drug is released to the aqueous phase is observed when higher polarity of the oil phase which are affected by the HLB, molecular weight of the hydrophilic part and concentration of the emulsifier.

APPLICATION OF SMEDDS: [19,52]

Super saturable SMEDDS(SS-SMEDDS):

The high amount of surfactant leads to drug precipitation in GIT. This can be overcome by the new class of formulation i.e., super saturable SMEDDS which results in rapid drug absorption

Solid SMEDDS:

The liquid self-micro emulsifying drug delivery system shows some disadvantages in manufacturing process. Thus, alternative formulation is developed by solidifying the l-SMEDDS into solid forms using various approaches.

Solubilization in SMEDDS:

The high lipid content and high amount of surfactant in SMEDDS influence the solubilization of the drug. The fine globules are formed when the lipid phase interacts with the aqueous phase. These droplets deliver the drug to mucosal layer of the GIT which makes the drug ready for absorption

Sustain release of the drugs:

The lipophilic drugs which are solubilized in the oil droplets depending on its partition coefficient show slow release whereas hydrophilic drugs show faster release. Due to the dual nature of microemulsion, drugs can be tailored to release in a controllable manner.

Table 4: Some examples of past work on SMEDDS

Drug	Formulation design	Excipients used	Result	Reference
Tetrandrine	SNEDDS	Oleic acid SPC, cremophor RH 40 PEG 400	The dissolute rate of Tetrandrine SNEDDS in various dissolution media was remarkably faster than Tet commercial tablet.	37
Rilpivirin	s-SMEDDS	Cremophor RH 40 PEG 400 Transcutol 90	The in vitro dissolution rate of the drug from the s-SNEDDS was three folds than that of the plain drug and suspension	38
Andrographis paniculate Nees	SNEDDS	Capryol-90 Tween 20 PEG 400	The results suggested that SNEDDS formulation could enhance the dissolution and the bioavailability of andrographolide isolated from Andrographis paniculata Nees	39
Lercanidipine Hydrochloride	SMEDDS	Capmul MCM C8, cremophor EL propylene glycol	SMEDDS was found to be promising in improving solubility and permeability of lercanidipine hydrochloride that are proven by in vitro dissolution and permeation studies.	40
Setraline HCl	SMEDDS	Oleic acid Tween 80 PEG 400	In-vitro dissolution study indicates high dissolution rate of liquid SMEDDS over the pure drug	41

CONCLUSION:

Self-emulsifying drug delivery systems are the novel lipid drug delivery system used for the delivery of the hydrophobic drugs which improves their dissolution and pharmacokinetic profile of the drugs. Thermodynamic stability, ease of manufacturing, improved solubility and permeability and patient compliance thus preferred over a conventional emulsion. New modifications such as, s-SMEDDS, supersaturable SMEDDS, controlled release SMEDDS makes it an acceptable formulation approach.

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