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A COMPREHENSIVE REVIEW ON SELF DOUBLE EMULSIFYING DRUG DELIVERY SYSTEM (SDEDDS)

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ABSTRACT
Self-double-emulsifying drug delivery systems (SDEDDS) are novel formulation systems. This is a colloidal system where a primary water-in-oil emulsion is formed with lipophilic surfactants and dispersed in an aqueous phase containing hydrophilic surfactants. These are lipid-based formulations. A self-emulsifying drug delivery system (SEDDS) is used to deliver poorly aqueous-soluble drugs with dissolution-limited absorption. Double emulsions are reported to have good oral bioavailability for drugs with high solubility and low permeability (BCS class III). It enhances the oral bioavailability of drugs. The SDEDDS system is used to deliver drugs through the oral route. This review discusses the construction of a pseudo-ternary phase diagram, composition, methods of preparation, and characterization of SDEDDS in brief.

KEYWORDS: Self-double-emulsifying drug delivery systems (SDEDDS), Double emulsion.

INTRODUCTION

The oral route is the major route of drug delivery for chronic treatment of certain diseases. Many potential hydrophilic drugs, such as protein and peptide drugs are administered orally and exhibit low oral bioavailability, mainly due to their low intestinal permeability. Such kinds of drugs are defined as "high solubility, low permeability class" or a biopharmaceutical classification system [BCS] class III drug, where gastrointestinal permeation is the rate-controlling step in the absorption process. The transport of hydrophilic drugs across the intestinal epithelium is confined mainly to paracellular pathways. However, the limited surface area and the tight junctions present between the adjacent cells restrict the transport of the drugs and are responsible for the low bioavailability of hydrophilic drugs across the paracellular route. The lymphatic system is the route through which small oil globules are absorbed, bypassing portal circulation and the hepatic first-pass effect.

The drugs that undergo hepatic first-pass metabolism have low oral bioavailability, which can be improved by absorption and transport through the lymphatic system. To improve the oral bioavailability of those drugs, a variety of methods, including absorption enhancers, chemical modifications, and pharmaceutical means, were employed. Among these approaches, water-in-oil-in-water emulsions show great potential for enhancing the oral bioavailability of BCS class III drugs.[1]

Multiple emulsions generally called "emulsions of emulsion," a complex formulation. The most basic among these numerous emulsions is the double emulsion.

Self-double-emulsifying drug delivery systems (SDEDDS) are homogeneous and transparent solution composed of drug, oil phase, emulsifiers and co-emulsifier. Self-emulsifying drug delivery systems (SEDDS) have gained a huge attention in the field of pharmaceutical formulation development. These are isotropic mixtures containing oils, surfactants, solvents and co-solvents/surfactants that, upon dilution with the aqueous medium, form fine, relatively stable emulsions (o/w) owing to the gentle agitation of the gastrointestinal aqueous environment. Similar to SEDDS, SDEDDS could also spontaneously emulsify in the mixed aqueous gastrointestinal environment. Whereas the formed emulsions are water-in-oil-in-water (w/o/w) double emulsions, not o/w emulsions, and drugs are encapsulated in the internal water phase of the double emulsions. SDEDDS does not have an external water phase.

Compared to conventional thermodynamically unstable double emulsions, SDEDDS are more stable. It can be directly filled into hard or soft gelatin capsules which are easy to administrate and storage.[2]

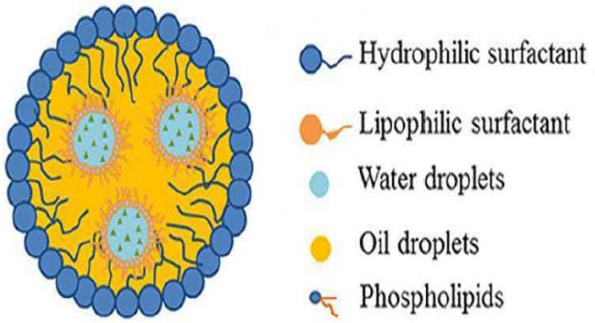

Fig. 1: Structure of W/O/W Double emulsion.

Classification of double emulsion:
Double emulsions are mainly classified into types:

I. **Water-in-oil-water (W/O/W) double emulsion**
II. **Oil-in-water-in-oil (O/W/O) double emulsion**

Fig. 2: (a) W/O/W multiple emulsion, (b) O/W/O multiple emulsion.

W/O/W double emulsions: The aqueous phase is dispersed in large oil droplets, which are further dispersed into a continuous external aqueous phase. The aqueous phase will be contained by the oil membrane, which will operate as a storage chamber for the hydrophilic medicines. W/O/W double emulsions are mostly used for oral drug administration.

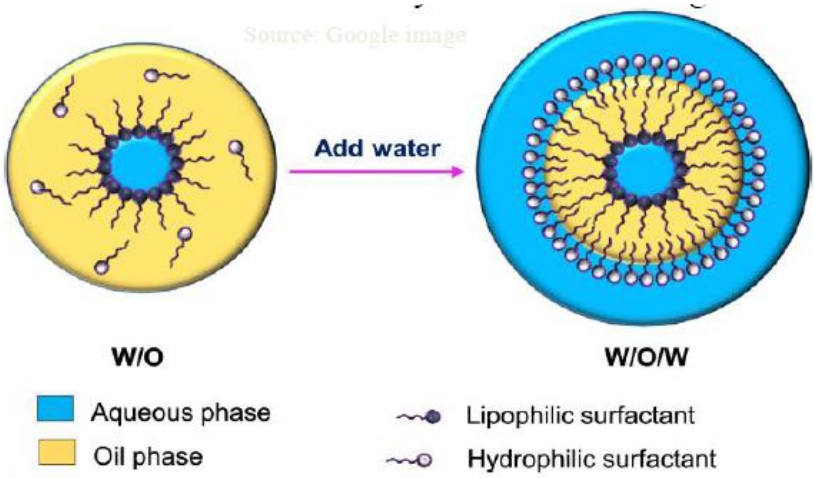

Fig. 3: Formation of W/O/W Double emulsion.

O/W/O double emulsions: The oil droplets are dispersed in water droplets, which are then emulsified with a continuous external oil phase. The internal phase, which is the oil phase, is enclosed in an aqueous membrane, which will be used as a storage chamber for hydrophobic medicines. O/W/O multiple emulsions are mostly used for topical administration.[3]

The basic rationale for the use of W/O/W and O/W/O type multiple emulsions as means of prolonged delivery of drugs is that the drug contained in the innermost phase of forced to partition itself through several phases prior to release at the absorption site10. Thus the partition and diffusion coefficient of the drug and the strength of the middle membrane phase, which is a multi-molecular layer of oil, water, and emulsifier molecules at both the

interfaces of multiple emulsion systems, control the drug release from these systems.

It is mentioned that solid self-emulsifying drug delivery systems can be prepared, by incorporating liquid or semisolid ingredients into powders utilizing diverse solidification techniques such as adsorption, spray drying, melt granulation, extrusion–spheronization and eutectic mixing. It has potential benefits such as the precision of dosage offered by solid filling, ease of transfer, portability and storage, better patient compliance as well as variety in solid dosage form options.[4]

Advantages

1. Controlled and sustained release of drug delivery can be achieved.
2. Enhances oral bioavailability by enabling reducing drug dose.
3. Both hydrophilic and lipophilic drugs can be entrapped and protected.
4. Versatility in the use of different oils and emulsifiers in one formulation.
5. Taste making of bitter drugs.
6. Protection of drugs from the hostile environment in the gut.

Construction of pseudo-ternary phase diagram

- Pseudo-ternary phase diagrams are constructed to identify self-double emulsifying regions for selected vehicles.
- Ternary phase diagrams are constructed by using the emulsifier titration method.
- Water-in-oil (w/o) emulsions are made by a one-step emulsification procedure where the Drug (BCS class III) is dissolved in distilled water.
- Oil phase contains a lipophilic surfactant and an emulsifying agent.
- Aqueous phase is added to the oil phase under moderate magnetic stirring.
- For w/o/w double emulsion preparation a series of mixtures are prepared by accurately weighing w/o emulsion and aqueous phase into vials at certain weight ratios 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10 (w/o : water) and then mixed uniformly under moderate magnetic stirring at room temperature.
- After the formation of w/o emulsions, hydrophilic surfactant was added quantitatively drop by drop.
- Simultaneously, the samples are agitated and observed under a microscope to identify the total mass of samples for which w/o/w double emulsion formation and disappearance values are recorded. These values are utilized to identify multiple emulsion regions.[5]

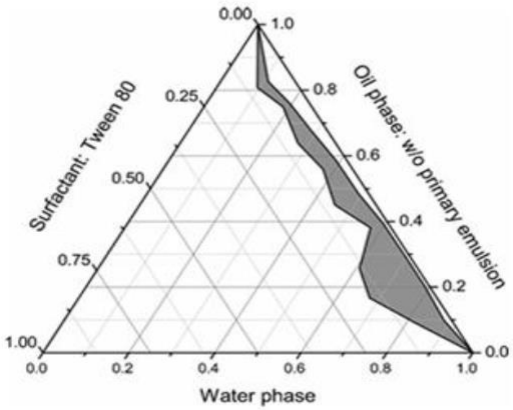

Fig. 4: Pseudo ternary phase diagram showing double emulsion region (W/O emulsion; Tween 80 and distilled water).[9]

Composition of sdedds:

The self-double emulsifying process is depends on

- Emulsification equipment
- Nature and quantity of emulsifying agents
- Nature of the aqueous phase
- Nature of the oil phase
- Volume of dispersed phase
- Added stabilizing component

Emulsifying equipment:

Equipment used to prepare SDEDDS homogenizer/ magnetic stirrer / Sonicator. The primary emulsions are prepared to ensure a good dispersion of droplets within the appropriate continuous phase. The secondary emulsification stage is responsible for dispersing the primary emulsion into droplets of suitable size for use in delivery vehicles. Excessive mixing, particularly at high shear, can cause the primary emulsion droplets to rupture. Low-speed, low-shear mixers should be used, or the system can be shaken by hand. Ultrasonic homogenizers should be used with care during the secondary emulsification step to ensure proper emulsion.[6]

Nature and quantity of emulsifying agents:

To form a stable emulsion, two different types of emulsifier/surfactant are required. One is a lipophilic

emulsifying agent; the other is a hydrophilic emulsifying agent.

For a w/o/w emulsion the optimal HLB value will be in the range of 2-7 for the primary surfactant and in the range 6-16 for the secondary surfactant. It is also possible to vary the emulsifier concentration. Emulsifiers can be used to stabilize a system, but too much can cause toxic effects and even destabilization.[6]

Nature of the aqueous phase:
Mainly distilled water is used as an aqueous phase. The aqueous phase is the dispersed phase in a w/o emulsion and a continuous phase in a w/o/w emulsion. Internal aqueous phases are often solutions of encapsulated compounds, like sugar, salt and nutrients. Drugs are dissolved in the internal aqueous phase. External aqueous phases are solutions of emulsifiers, such as proteins and stabilizers, such as polysaccharide. The volume fraction of the aqueous phase greatly influences the stability of double emulsion.[6]

Nature of the oil phase:
The oil phase used in a pharmaceutical emulsion must be nontoxic and it also determines the encapsulation efficiency of emulsion. Oils derived from vegetable sources are biodegradable, while oils made from mineral oils are only eliminated from the body very slowly. Vegetable oils usually have higher viscosity and higher solubility than mineral oil. Emulsion made from vegetable oil require a higher energy input and the resulting emulsion is less stable to the migration of water in and out of the internal aqueous phase.

Mineral oils or hydrocarbon solvents with high hydrophobicity are commonly used as the oil phase in studies of w/o or w/o/w emulsion. Different vegetable oils (soybean oil, corn oil, sesame, peanut, safflower, etc.) are acceptable if purified correctly. Refined hydrocarbons such as light liquid paraffin squalene, and esters of fatty acids (ethyl oleate and isopropyl myristate) have also been used in double emulsions. The order of decreasing stability and percentage entrapment has been found to be light liquid paraffin > squalene > sesame oil > maize or peanut oil.[6]

Volumes of the phases:
The quantity of water dispersed in the initial w/o emulsion [expressed as a phase volume ratio, (w/o/w)] can have an influence on both the yield and stability of the final emulsion system.[5]

Added stabilizing components:
The stabilizers are added to improve the stability of multiple emulsions. These include gelling or viscosity increasing agents which is added to the internal or external aqueous phases (e.g. 0.5% gelatin solution, 20% gelatin, methylcellulose and similar thickening agents, as well as complexing agent that will lead to liquid crystalline phase at the O/W interface (e.g. Cetyl alcohol) and gelling agent or the oil phase (e.g. aluminium monostearate).

Formulation aspects to form stable w/o/w emulsions, the emulsions can be incorporated in films by utilizing water vapour impermeable film-formers. Spray drying phenomenon can be utilized to form microspheres which yield emulsions on reconstitution. Adsorption of w/o/w emulsions on solid support enhances stability besides providing facilities of solid dosage form handling.[3]

Table 1: Excipients used in the preparation of sdedds.

Oil phase used	Surfactants used		Aqueous phase	Emulsifier for w/o emulsion
	Hydrophilic surfactants	Lipophilic surfactants		
Oleic acid	Tween 80	Span 80	Distilled water	Lecithin
Medium chain triglycerides (MCT)	Tween 60	Span 60	0.5% gelatin solution	Soy lecithin
Liquid paraffin	Labrasol	Polyglycerol Polyricinoleate (PGPR)		Bean phospholipids
Soybean oil	Polyethylene glycol dodecyl ether			
Corn oil	Octyl phenol ethoxylate			

Method of preparation of sdedds:
SDEDDS emulsions are best prepared by re-emulsification of primary emulsion. The following are the method of multiple emulsions:

1. Two Steps Emulsification (Double Emulsification)
2. Modified two step emulsification technique
3. Phase Inversion Technique (One Step Technique)
4. Membrane Emulsification Technique

1. Two steps emulsification (Double emulsification):
Two steps emulsification methods include re-emulsification of the primary W/O or O/W emulsion using a suitable emulsifying agent. The first step involves the preparing an ordinary W/O or O/W primary

emulsion by using an appropriate emulsifier system. The second step involves re-emulsifying the freshly prepared W/O or O/W primary emulsion with an excess of aqueous phase or oil phase. The final formulated emulsion could be W/O/W or O/W/O respectively.[6,7]

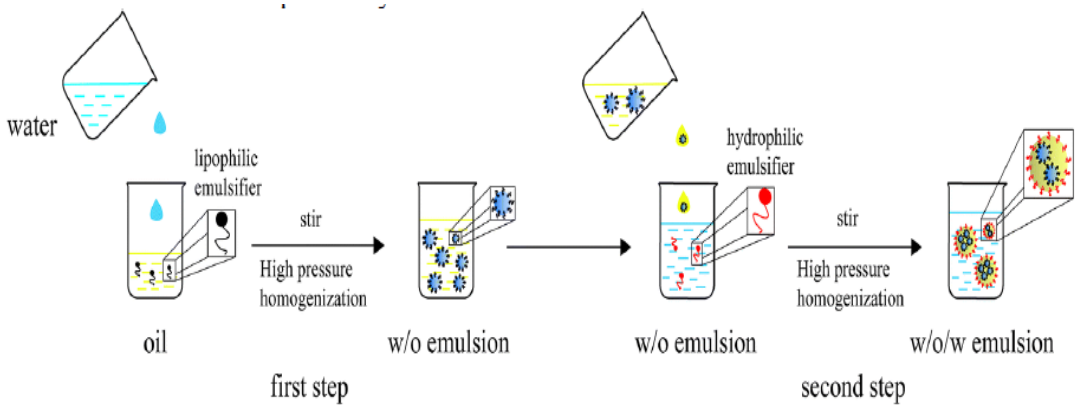

Fig. 5: Preparation process of w/o/w emulsions by two step emulsification method.[11]

2. Modified two step emulsification technique:

In this method both sonication and stirring are used to obtain fine, homogenous and stable w/o emulsion. Continuous phase is poured to the dispersed phase to obtain W/O/W emulsion.[8]

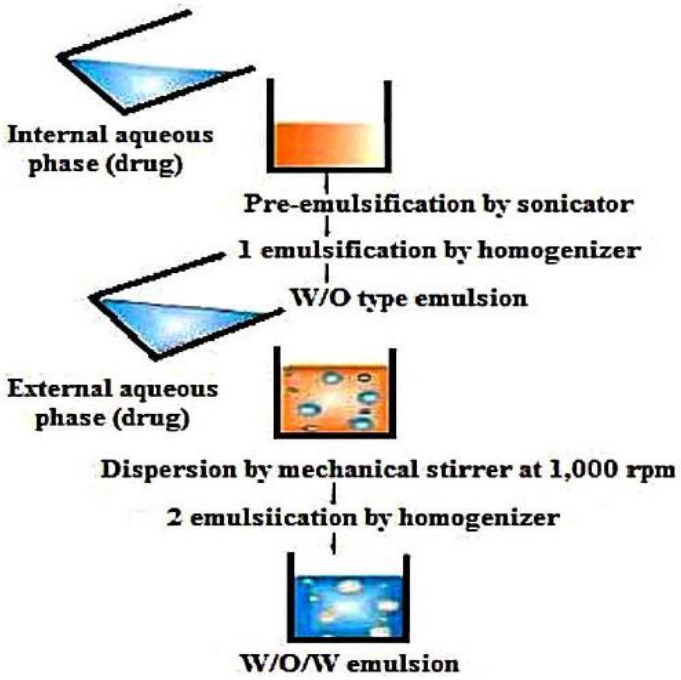

Fig. 6: Preparation of W/O/W double emulsion by modified two step emulsification.[7]

3. Phase inversion technique (One step technique):

In this method an aqueous phase containing hydrophilic emulsifier (Tween 80/ Tween 60/ sodium dodecyl sulphate (SDS) or Cetyl trimethyl ammonium salt CTAB) added to an oil phase containing liquid paraffin and lipophilic emulsifier (Span 80/ Span 60). Oil phase placed in vessel of pin mixer, an aqueous solution of emulsifier is introduced to the oil phase in the vessel at the rate of 5ml/min, with the rotation of 88 rpm at room temperature. When volume fraction of the aqueous solution of hydrophilic emulsifier exceeds 0.7, the continuous oil phase is substituted by the aqueous phase containing a number of the vesicular globules among the simple oil droplets, leading to phase inversion and formation of W/O/W multiple emulsion.[8]

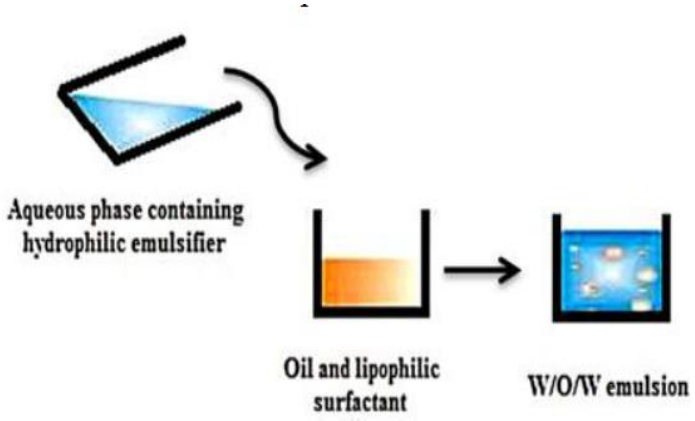

Fig. 7: Phase inversion technique.[7]

4. Membrane emulsification technique:

This method uses low shear forces to produce emulsions. In this method, W/O emulsion (a dispersed phase) is extruded into an external aqueous phase (A continuous phase) with a constant pressure through a porous glass membrane, which should have controlled and homogenous pores. The particle size of the resulting emulsion can be controlled with proper selection of porous glass membrane as the droplet size depends upon the pore size of the droplet size depends upon the pore size of the membrane.[6,8]

Characterization of sdedds formulation:

(i) Microstructure measurements: The morphology of SDEDDS formulations after transformation into water/oil/water multiple emulsions observed under optical microscopy/ inverted fluorescence microscope/ upright fluorescence microscope with an optical immersion microscope/ transmission electron microscope. A drop of multiple emulsion sample diluted with water was placed on the glass slide and covered with a coverslip and observed under the microscope. Multiple emulsions are analyzed under the microscope to confirm the multiple characteristics such as type emulsion & size distribution of droplets.[5]

(ii) Viscosity analysis: The rheological measurements of SDEDDS can be performed using Brookfield viscometer, operating with cone plate geometry (cone diameter 60mm, angle1◦, and gap 0.058mm). 5ml of the sample was transferred to the instrument and allowed to equilibrate to 25±1°C for 10min prior to the measurement. The apparent viscosity is measured over a shear rate range of 0.1–300s^{-1}. Viscosities (mPas) of each SDEDDS formulation were measured at different shear rates; the mean constant shear viscosity was determined from the data obtained at 300s−1. Six replicate analyses were carried out for each formulation, and data presented as means ±SD.[9]

(iii) Globule size or Particle size analysis: The particle size distribution of SDEDDS formulations after transformation into w/o/w multiple emulsions are determined by dynamic light scattering using Malvern Particle Size Analyzer. SDEDDS formulation mixed with 200ml of distilled water and stirred using magnetic stirrer at 75 rpm for 5min at room temperature to form w/o/w multiple emulsion and then the particle size distribution are determined. The results are reported as the volume average diameter.[5,10]

(iv) pH determination: The digital pH meter is used to determine the pH of the prepared emulsions.[6] SDEDDS formulation is mixed with distilled water and then the pH of the sample was determined.

(v) Zeta potential: The zeta potentials of w/o/w emulsions were determined by zeta potential analyzer. The samples were diluted with water prior to analysis; the ratio of sample to water was 0.0309: 1. In this process, the samples added slowly to avoid air bubbles. Each sample was analyzed at least in triplicate.[11]

(vi) Entrapment efficiency:

Freshly prepared W/O/W multiple emulsions are centrifuged at 4000rpm for 10min. Then 1ml aqueous phase (lower layer) was withdrawn through 2ml hypodermic syringe and diluted properly with required buffer. The solution was filtered through a millipore filter (0.22mm in pore size) and drug content was analysed on UV spectrophotometer. The Encapsulation Efficiency was determined by following equation:[12]

$$\% \text{ Entrapment efficiency} = \frac{Td-Fd}{Td} \text{ X } 100$$

Where,

T_d = total drug added to the formulation

F_d = free drug present in the separated aqueous phase

(vii) Drug content: The drug content is determined using UV Spectrophotometer. SDEDDS formulations after transformation into W/O/W multiple emulsions, a volume equivalent to dose

of the drug is dispersed in an appropriate amount of sample. The samples were measured at $\lambda_{max.}$ [13]

$$\text{Drug content} = \frac{\text{Concentration}}{1000} \text{ X dilution factor}$$

(viii) Self emulsification ability of SDEDDS: The gravimetric method was used to investigate the self-emulsification ability of SDEDDS. SDEDDS (0.5 g) was added into distilling flask with 10 ml distilled water, and the mixture was homogenized using a horizontal rotator at 100 rpm for 15 min under room temperature. The final step is to centrifuge the solution for 5 min, transfer 5 ml aliquot of supernatant liquor to a pre-weighed ceramic dish, and keep it in oven for 60°C till fully evaporation of water. This step was also practiced in triplicate.[14]

CSLM (Confocal Scanning Laser Microscope) used to observe the self-double emulsification performance/ behavior/ process of the SDEDDS formulation .One capsule of the stained formulation was added to 200ml of purified water at 37ºC. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 60 rpm. Immediately, 1min after the addition, the stained samples was withdrawn and dropped on a glass slide to observe the formation of w/o/w emulsion.[9]

(ix) *In-vitro* drug release: The *in-vitro* dissolution studies are carried out to assess drug release from the formulation. Release profiles drug from formulation filled in capsules are performed using the USP type II rotating paddle apparatus with 900 ml of suitable dissolution media at temperature 37º±0.5ºC. The speed of paddle adjusted to 100rpm. 5ml of samples are withdrawn at interval of 1hr to 8hrs. The samples were replaced by their equivalent volume of dissolution medium. Samples are filtered using a 0.45micrometer filter and subsequently analyzed by UV spectrophotometry. Three replicate analyses are carried out for each formulation, and data are used to calculate %cumulative drug release profile (CDR).[6,13]

$$\% \text{ Cumulative drug release} = \frac{\text{Cumulative drug release}}{\text{Drug Content}} \text{ X } 100$$

(x) Stability studies: Accelerated stability studies are performed as per ICH guidelines by storing the ready to use SDEDDS formulations in sealed amber glass vials at 40°C ± 2°C/ 70% RH ± 5% RH. Here time dependent changes in appearance, viscosity, self-emulsifying properties and droplet size of double emulsion are monitored for 0, 3 and 6 months.[13]

Applications of multiple emulsions:

i. Hydrophilic as well as hydrophobic drugs can be entrapped.
ii. They can be used to prolong the release of drugs thereby providing sustained release action.
iii. They can mask the bitter taste and order of the drug, e.g. chlorpromazine.
iv. Double emulsions are well known for their site-specific delivery.
v. Double emulsion provides protection to drugs which are susceptible to oxidation or hydrolysis.
vi. Double emulsion also used for enhancement of enteral or dermal absorption.[6]

Table 2: Reported Formulations of SDEDDS.

Drug	Excipients used	Conclusions	Reference
Pidotimod	0.5% Gelatin Solution, Oleic Acid, MCT, Span 80, Bean Phospholipids, Tween 80.	• 2.56-fold increase in oral bio- -availability compared to drug solution. • No serious local intestinal tissue damage seen. • Good stability for a period of 6 months.	[9]
Vancomycin HCl	Lecithin, Oleic Acid, Span 80, Tween 80.	• Sustained release effect. • Stable for a period of 3 months under 40ºC.	[13]
Hydroxysafflor yellow A	0.5% Gelatin Solution, Bean Phospholipid, Medium Chain Triglycerides, Tween 80, Oleic acid, Labrasol.	• Hydroxysafflor yellow A absorption was greatly improved. • Toxic effect seen on tissues but was not serious.	[15]
Stachydrine	0.5% Gelatin Solution, Span 80, atolein, Tween 80.	• 1.8-fold increase compared to the unformulated stachydrine. • Sustained release *in-vitro* and improved oral bioavailability *in-vivo.*	[16]

(-) Epigallocatechin-3-gallate	Water, MCT, Glyceryl monostearate, Polyglycerol Polyricinoleate, Glycerol, Tween	• Rapidly formed fine w/o/w emulsion, 1.93-fold greater area-under-curve value than that of the drug solution. • Solid form.	[17]
Nattokinase	MCT, Liquid Paraffin, Labrasol.	• Sustained release effect. • More effective *in-vivo* as compared to drug solution. • 2 mins emulsification time of optimized formulation.	[5]
Atenolol	Water, Span 80, Tween 80, Captex, Oleic Acid.	• SDEDDS exhibited 1.18-fold increase in drug permeation as compared to that of pure atenolol solution and 1.82 fold increase in permeability as compared to atenolol tartaric acid solution. b. • Toxic effect seen on tissues but was not serious.	[4]

CONCLUSIONS

This review provides a comprehensive overview of the SDEDDS, types of double emulsion, construction of the pseudo-ternary phase diagram, composition, types of preparation, and assessment of the SDEDDS. Pseudo-ternary phase diagrams are constructed to identify the self-double emulsifying region and from this, we can calculate the amount of hydrophilic surfactants required to add to form a double emulsion. Adding the SDEDDS formulation into water it converts into W/O/W double emulsion. Sustained release or controlled release drugs can be achieved. Drugs can be entrapped in the inner aqueous membrane. Solid SDEDDS can be formulated. SDEDDS is a promising technique for improving the oral absorption of drugs with high solubility and low permeability.

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