

REVIEW ARTICLE

SELF DOUBLE EMULSIFYING DRUG DELIVERY SYSTEM (SDEDDS): A REVIEW

Padole Atul*, Bodhankar Mitali

Gurunanak College of Pharmacy, Nagpur University, Nagpur, India-440026

*Corresponding Author's Email: atulpadole05@gmail.com, mit21_bod@yahoo.co.in

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ABSTRACT:

Self emulsifying drug delivery systems (SEDDS) are well known for its potential to improve the aqueous solubility and oral absorption of lipophilic drugs. Self double-emulsifying drug delivery system (SDEDDS) are basically used for drugs having low solubility in water, but its potential application for the drugs defined as "high solubility low permeability class" or a biopharmaceutical classification system [BCS] class III drug is appreciable, in which gastrointestinal permeation is the rate controlling step in the absorption process. The most important factor affecting the oral absorption of a drug, besides dissolution, is the permeability of the drug across the gastrointestinal lining. Improving permeability may, therefore, potentially improve the bioavailability of a drug. In this review we discuss the preparation, stability, formulation and characterization of SDEDDS.

Key Words: Multiple emulsion, self emulsifying, Protein peptide drug delivery, High soluble poorly permeable drugs.

INTRODUCTION:

Many drugs are delivered orally as it is the most favorable route of drug administration. Nevertheless, many potential hydrophilic drugs such as protein and peptide drugs administered orally exhibit low oral bioavailability mainly due to their low intestinal permeability. For such kind of drugs defined as "high solubility low permeability class" or a biopharmaceutical classification system [BCS] class III drug, gastrointestinal permeation is the rate controlling step in the absorption process¹. 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 small oil globules are absorbed through lymphatic system their by bypass portal circulation and hepatic first pass effect.

Also the drugs which undergo hepatic first pass effect have low bioavailability which can be improved by absorption and transport through lymphatic system. Many approaches such as absorption enhancers², chemical modifications³ and pharmaceutical means were used to enhance oral bioavailability of those drugs. Among these approaches, water-in-oil-in-water emulsions show great potential for enhancing oral bioavailability of BCS class III drugs^{4,5}.

The majority of orally administered drugs gain access to the systemic circulation by direct absorption into the portal blood. However, highly lipophilic compounds may reach the systemic blood circulation via the intestinal lymphatic system. This alternative lymphatic absorption pathway from the gastrointestinal tract (GIT) has been shown to be a significant contributor to the overall bioavailability.

SDEDDS are poly dispersed systems where the dispersed phase contains the droplets of the continuous phase. These double emulsions are of two types: W/O/W types multiple emulsions and O/W/O types multiple emulsions⁶. Small water droplets are dispersed in bigger oil droplets and these oil droplets are again dispersed in continuous

aqueous phases⁷. Similarly in O/W/O type multiple emulsions, small oil droplets are dispersed in larger aqueous droplet and these aqueous droplets are again dispersed in continuous oil phase. Their potential pharmaceutical applications include uses such as taste masking, adjuvant vaccines and an immobilization of enzymes, sorbent reservoir of overdose treatments and for enhancement of enteral or dermal absorption⁸. Multiple emulsions have been formulated as cosmetics, such as skin moisturizer. Prolonged release can also be obtained by means of multiple structures. These systems have some advantages, such as the protection of the entrapped substances and the incorporation of several actives in the different compartments. Despite their potential usefulness, applications of multiple emulsions have been limited because of thermodynamic instability and their complex structure⁹. 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 system, control the drug release from these systems¹¹. Although multiple emulsions are still infrequently used, their potential applications are numerous and the investigation of these systems is now an active field research, especially in such product areas as pharmaceutical drug delivery systems, cosmetics and foods¹².

Approaches to improve the bioavailability of BCS Class III drugs are:

- Permeation enhancers
- Prodrug
- Chemical modification
- Pharmaceutical means
- Multiple / Double emulsions

COMPOSITION OF SDEDDS:

The self double emulsifying process is depends on

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

Emulsifying equipment:

The primary emulsion can be prepared using a laboratory mixer or homogenizer to provide a good dispersion of droplets within the appropriate continuous phase^{13,14}. The secondary emulsification stage must disperse the primary emulsion into droplets of suitable size for use in delivery vehicles. Excessive mixing, especially 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 must be used with care for the secondary emulsification step.

Nature of the 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 phase are often solution of encapsulated compound, such as sugar, salt and nutrient¹⁵. External aqueous phase are solutions of emulsifiers e.g. proteins and stabilizers e.g. polysaccharide. The volume fraction of the aqueous phase has large effect on stability of double emulsion.

Nature of the oil phase:

The oil phase to be employed in a pharmaceutical emulsion must be nontoxic and it also determines the encapsulation efficiency of emulsion. 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. However high hydrophobicity materials such as mineral oils or hydrocarbon solvents are commonly used as the oil phase in studies of w/o or w/o/w emulsion. The various oils of vegetable origin (soybean oil, corn oil, sesame, peanut, safflower, etc.) are acceptable if purified correctly. Refined hydrocarbons such as light liquid paraffin squalene, as well as esters of fatty acids (ethyl oleate and isopropyl myristate) have also been used in double emulsions¹⁶. Oils derived from vegetable sources are biodegradable, whereas those based on mineral oils are only removed from the body very slowly. The order of decreasing stability and percentage entrapment has been found to be light liquid paraffin > squalene > sesame oil > maize or peanut oil¹⁴.

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.

Nature and quantity of emulsifying agents:

Two different emulsifier (lipophilic and hydrophilic) are required to form a stable emulsion. In general, for a w/o/w

emulsion the optimal HLB value will be in the range 2-7 for the primary surfactant and in the range 6-16 for the secondary surfactant. The concentration of the emulsifiers can also be varied. Too little emulsifier may result in unstable system, whereas too much emulsifier may lead to toxic effect and can even cause destabilization¹⁷.

Added stabilizing components:

The stabilizer are added for improve the stability of multiple emulsion. These include gelling or viscosity – increasing agents added to the internal or external aqueous phases (e.g. 20% gelatin¹⁸, 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)¹³.

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. Phase Inversion Technique (One Step Technique)
3. Membrane Emulsification Technique

1. Two Steps Emulsification (Double Emulsification)^{19,20}:

Two steps emulsification methods involve re-emulsification of primary W/O or O/W emulsion using a suitable emulsifier agent. The first step involves, obtaining an ordinary W/O or O/W primary emulsion wherein an appropriate emulsifier system is utilized. In the second step, the freshly prepared W/O or O/W primary emulsion is re-emulsified with an excess of aqueous phase or oil phase. The finally prepared emulsion could be W/O /W or O/W/O respectively.

2. Phase Inversion Technique (One Step Technique)^{21,22}:

An increase in volume concentration of dispersed phase may cause an increase in the phase volume ratio, which subsequently leads the formation of multiple emulsions. The method typically involves the addition of an aqueous phase contains the hydrophilic emulsifier [Tween 80/ sodium dodecyl sulphate (SDS) or Cetyl trimethyl ammonium salt CTAB] to an oil phase consisted of liquid paraffin and containing lipophilic emulsifier (Span80). A well-defined volume of oil phase is placed in a vessel of pin mixer. An aqueous solution of emulsifier is then introduced successively to the oil phase in the vessel at a rate of 5 ml/min, while the pin mixer rotates steadily at 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.

3. Membrane Emulsification Technique²³:

In this method, a 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. The relation between membrane pore size and particle size of W/O/W emulsion exhibits good correlation as described by the following equation:

$$Y = 5.03 X + 0.19$$

Where X is the pore size and Y is the mean particle size of the multiple prepared using membrane emulsifier technique.

CHARACTERIZATION OF SDEDDS FORMULATIONS:

1. Viscosity analysis of SDEDDS formulations

The rheological measurements of the formulations can be performed with a programmable rheometer, (Brookfield viscometer) operating with cone plate geometry (cone diameter 60mm, angle 1°, and gap 0.058 mm). Samples transferred to the instrument and allowed to equilibrate to 25±1 °C for 10 min prior to the measurement. The apparent viscosity can be measured over a shear rate range of 0.1–300 s⁻¹. Viscosities (mPa s) of each formulation were measured at different shear rates; the mean constant shear viscosity may be determined from the data obtained at 300 s⁻¹. Six replicate analyses may be presented as means ± SD.

2. pH determination

The pH value of the freshly prepared emulsions and the emulsions kept at different conditions can be determined by a digital pH-meter. pH measurements were repeated for multiple emulsions after 1, 3, 7, 14, 21 and 28 days of preparation, may be used for adjustments in formulation parameter²⁴.

3. Microscopic tests

Multiple emulsions have to be analyzed under the microscope to confirm the multiple characters. A drop of multiple emulsions have to be placed on the glass slide, diluted with water and covered by a glass cover. A drop of immersion oil placed on the cover slide and to be observed under the microscope.

4. Entrapment efficiency

The amount of drug entrapped is the amount of total drug minus the amount of free drug separated in the lower phase of the emulsion by centrifugation. The entrapped efficiency of the drug is defined as,

$$\text{Efficiency of drug entrapped (\%)} = [(T_d - F_d) / T_d] \times 100$$

Where, T_d = Total drug added, F_d = free drug present in the separated oil or aqueous phase^{25,26}.

5. Release of drug from SDEDDS formulations in vitro

Release profiles from formulation filled in capsules have to be performed using the USP30 rotating paddle apparatus with 900 ml of simulated gastric fluid (SGF, pH 1.2) without pepsin as the medium at 37±0.5 °C. The speed of the paddle was adjusted to 75 rpm. Samples (5 ml) are to be withdrawn and replaced with fresh media after 5, 15, 30, 60, 120, 240, 360 and 480 min. Samples are filtered using a 0.45micrometer filter and analyzed

using an HPLC assay. Three replicate analyses are carried out for each formulation, and data presented as means ± SD.

6. Electrical conductivity tests

Conductivity tests are performed for the multiple emulsions immediately after preparation and for the samples kept at different conditions by using digital conductivity-meter. Conductivity tests are repeated for the multiple emulsions after 1, 3, 7, 14, 21 and 28 days of preparation^{27,28}.

7. Turbidity Measurement:

This is to identify efficient self-emulsification by establishing whether the dispersion reaches Equilibrium rapidly and in a reproducible time. Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter²⁹.

8. Emulsion droplet size analysis:

The droplet size distribution of double emulsions will influence the rheology, stability, color and test. These are generally measured by dynamic light scattering using a Malvern Particle Size Analyzers equipped with a He-Ne laser. SDEDDS are mixed with distilled water (200 ml) and stirred at mild agitation (75 rpm) in a magnetic stirrer for 5min at room temperature, forming the double emulsions. The particle size distribution of the double emulsions is determined after presentation. The refractive index of dispersed phase and continuous phase were calculated respectively, and the absorbance values of the emulsion droplets are calculated. The results are reported as the volume average diameter³⁰.

9. Stability studies:

Stability tests can be performed at different storage conditions for both primary and multiple emulsions. The tests are performed on samples kept at 2 ± 0.1 °C (in refrigerator), 25 ± 0.1°C 60%RH (relative humidity), 40 ± 0.1 °C at 75% (RH) (in stability chamber) and 50°C in oven.

10. In-vivo method:

Male Wister rats are used and acclimatized for 7 days and fed the solid feed for 6 weeks. Weights of the rats serving as recipients of the W/O/W emulsions were 200–250 g. Before feeding the sample solutions, the rats are fasted overnight for 17 h. After being anesthetized with ether, blood samples are collected from the coccygeal vein 5 min before the administration using 23–27 gauge needles and used as the reference blood-sugar level at 0 min. The sample solutions are fed at 50 IU/kg-weight using feeding tubes. Purified water as a control solution, which contained insulin at the same concentration as the other emulsions, is also fed. The blood samples are collected at 15, 30, 45, 60, 120, 180, and 240 min from the coccygeal vein under temporary ether anesthesia. The blood concentrations in the samples can be measured by spectrophotometry or HPLC determination³¹.

PHARMACEUTICAL APPLICATIONS OF MULTIPLE EMULSIONS:

1. They can mask the bitter taste and order of drug, e.g. chlorpromazine³².
2. Multiple emulsions are used in food³³.
3. They can be used to prolong the release of drug thereby providing sustained release action^{34,35}.
4. Essential nutrients like carbohydrates, fats and vitamins can all be emulsified and can be administered to bed ridden patient as sterile intravenous injection.
5. Emulsion provides protection to drugs which are susceptible to oxidation or hydrolysis^{36,37}.
6. Intravenous emulsions of contrast media have been developing to assist in diagnosis.
7. Increase in dosing interval.
8. Hydrophilic as well as hydrophobic drug can be entrapped.

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