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Self-Double Emulsifying Drug Delivery System for The Enhancement of Bioavailability: A Review

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ABSTRACT

The oral route of drug administration is the one that is used most commonly, and more than 40% of new chemical entities have low water solubility, which leads to inadequate oral drug delivery. As a result, self-emulsifying drug delivery systems (SEDDS) are receiving significantly greater attention when it comes to the delivery of pharmaceuticals that are poorly aqueously soluble and have restricted absorption due to dissolution rate. SDEDDS (Self-double emulsifying drug delivery system), a modified form of SEDDS, is primarily intended to distribute BCS Class III drugs, which are characterized as having a "high aqueous solubility and low permeability class" and whose rate of absorption is controlled by gastrointestinal permeation. Consequently, increasing permeability might help improving the bioavailability of BCS Class III drugs. The Composition, mechanism, techniques of preparation, and evaluation of SDEDDS are briefly discussed in this review.

INTRODUCTION

Since oral administration is the most effective method of drug delivery, many medications are administered this way. Yet, due to their low intestinal absorption, many potentially hydrophilic drugs, such as protein and peptide medications taken orally, have low oral bioavailability mainly due to their low intestinal permeability. Gastrointestinal permeation is the rate-regulating step in the absorption process for the drugs that are classified as "high solubility low permeability class" or a biopharmaceutical categorization system [BCS] class III drug[1].

Hydrophilic drug transport across the intestinal epithelium is primarily restricted to paracellular pathways. However, the limited surface area and tight junctions between adjacent cells limit drug transport and are responsible for the low bioavailability of hydrophilic drugs across the paracellular route. Small oil globules are absorbed via the lymphatic system bypassing portal circulation and the hepatic first pass effect. Drugs that undergo hepatic first pass effect also have low bioavailability, which can be improved by absorption and transport via lymphatic system. Many methods, including absorption enhancers, chemical modifications, and pharmaceutical means, were used to improve the oral bioavailability of those drugs[2]. Among these approaches, water-in-oil-in-water emulsions have the greatest potential for increasing the oral bioavailability of BCS Class III drugs[3].

Most medications taken orally enter the systemic circulation by directly absorbing into the portal blood. Nevertheless, extremely lipophilic substances might travel through the intestinal lymphatic system to enter the systemic blood circulation. It has been demonstrated that the alternative lymphatic absorption pathway from the intestinal system (GIT) significantly contributes to the total bioavailability[5].

The combination of hydrophilic emulsifiers and water-in-oil emulsions is known as SDEDDS, and it can self-emulsify into water/oil/water emulsions, followed by dilution with aqueous media under gastrointestinal motility or mild agitation at the ambient temperature. The following are important benefits of a particular drug delivery technology, such as it helps to prevent the inactivation and enzymatic breakdown of peptide and protein medications in the digestive tract. In the meantime, the medications' pharmacological activity and absorption can be markedly improved when compared to alternative preparations. Instead of achieving artificial emulsification *in vitro*, SDEDDS can achieve spontaneous emulsification because of gastrointestinal motility *in vivo*. As a result, SDEDDS is more stable than traditional multiple

emulsions that are thermodynamically unstable, and it can successfully prevent the lack of stability of multiple emulsions during production and storage *in vitro*. Moreover, SDEDDS significantly helps the patients by lowering the dose volume[4].

SDEDDS are polydisperse systems that have the droplets of the continuous phase in the dispersed phase. There are two varieties of these double emulsions: multiple emulsions of the W/O/W and O/W/O types. Tiny water droplets are dispersed in larger oil droplets, which are then dispersed once more in a continuous aqueous phase. Similarly in O/W/O type multiple emulsions small oil droplets spread in larger aqueous droplets, which then disperse in continuous oil phase. They could be used as adjuvant vaccines, taste maskers, enzyme immobilisers, sorbent reservoirs for overdose therapies, and to improve cutaneous or enteral absorption, among other medicinal applications like a moisturiser for the skin. Moreover, numerous structures can be used to achieve prolonged release, such as the safeguarding of the chemicals that are entrapped and the inclusion of various actives in the various compartments. Applications of multiple emulsions have been restricted despite their potential utility due to thermodynamic instability and their complex structure[5].

The main justification for using several emulsions of the W/O/W and O/W/O types as a form of delayed drug delivery is that the medication forced to partition itself through several stages before releasing at the absorption site. Although multiple emulsions are still rarely employed, they have a wide range of potential uses, and research into these systems is currently underway, particularly in the fields of foods, cosmetics, and pharmaceutical drug delivery systems[5].

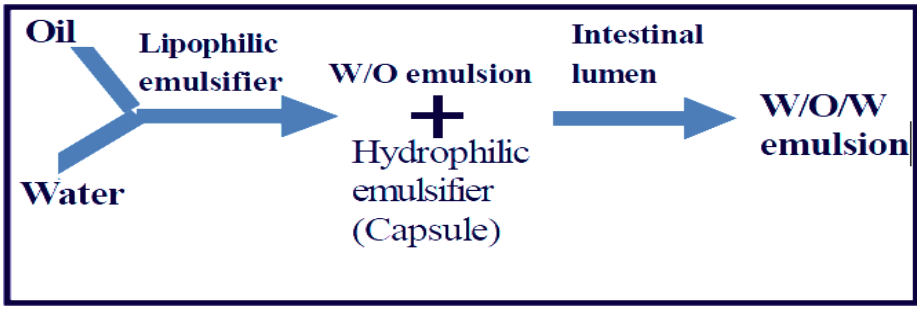

Figure 1: Process for the preparation of SDEDDS

ADVANTAGES OF SDEDDS

- Improved oral bioavailability enabling reduction of dose.
- Versatility in the employment of several oils and emulsifiers in one formulation.

- Drugs that are lipophilic and hydrophilic both can be entrapped and protected.
- The reticuloendothelial system (RES) can be targeted by drugs.
- Taste making of bitter drugs.
- Controlled and sustained delivery of drugs can also be achieved.
- Protection of drug from the hostile environment in gut[6].

COMPOSITION OF SDEDDS

The self-double emulsifying process depends on:

- Emulsification equipment
- Nature of the aqueous phase
- Nature of the oil phase
- The volume of the dispersed phase
- Nature and quantity of emulsifying agents
- Added stabilizing components

a. Emulsification equipment:

To ensure a proper dispersion of droplets within the suitable continuous phase, the primary emulsion can be made by using a laboratory mixer or homogenizer. The primary emulsion must be divided during the secondary emulsification stage into droplets that are appropriate for use in delivery vehicles. The primary emulsion droplets may break apart under conditions of excessive mixing, particularly when shear is strong. It is recommended to utilise low speed, low shear mixers, or to shake the system by hand. The second emulsification process requires the careful use of ultrasonic homogenizers[5].

b. Nature of the aqueous phase:

In a w/o emulsion, the aqueous phase is a dispersed phase, while in a w/o/w emulsion, it is a continuous phase. Internal aqueous phase solutions of encapsulated substances including sugar, salt, and nutrients are common. Solutions of emulsifiers, such as proteins, and

stabilisers, such as polysaccharides, make up the external aqueous phase. The stability of the double emulsion is significantly impacted by the volume fraction of the aqueous phase[5].

c. Nature of the oil phase:

The oil phase that will be used in a pharmaceutical emulsion must be nontoxic, and it also affects how well the emulsion encapsulates particles. In comparison to mineral oil, vegetable oils often have higher viscosities and solubilities. Vegetable oil emulsions need more energy to produce and are less stable to the movement of water into and out of the internal aqueous phase. However, in research of w/o or w/o/w emulsions, strong hydrophobicity materials as mineral oils or hydrocarbon solvents are frequently utilised as the oil phase. The different oils of Vegetable origin (soybean, corn, sesame, peanut, safflower, etc.) are suitable as long as they have been properly purified. Double emulsions have also been made using refined hydrocarbons such isopropyl myristate and ethyl oleate, esters of fatty acids, and light liquid paraffin squalene. Biodegradable oils are those made from plant sources, whereas mineral oil-based oils are slowly expelled from the body. Light liquid paraffin > squalene > sesame oil > maize or peanut oil has been determined to have the lowest stability and highest proportion of entrapment[5].

d. Volumes of the phases:

The yield and stability of the final emulsion system can be affected by the amount of water dispersed in the initial w/o emulsion [represented as a phase volume ratio, (w/o/w)][7].

e. Nature and quantity of emulsifying agents:

To create a stable emulsion, two distinct emulsifiers (lipophilic and hydrophilic) are needed. The ideal HLB value for a w/o/w emulsion will typically fall between 2 and 7 for the primary surfactant and between 6 and 16 for the secondary surfactant. The emulsifiers' concentration can also be changed. A system that has too little emulsifier may become unstable, whereas a system that has too much emulsifier may become poisonous or potentially destabilise[7].

f. Added stabilizing components:

To increase the stability of multiple emulsions, stabilisers are added. They include complexing agents that will result in a liquid crystalline phase at the O/W interface (such as cetyl alcohol) and gelling agents or the oil phase added to the internal or external aqueous

phases, such as 20% gelatin, methylcellulose, and similar thickening agents (e.g. aluminium monostearate)[7].

MECHANISM OF DRUG RELEASE FROM SDEDDS

The drug is released from the internal to external phase through the various layers after the formation of the double emulsion from SDEDDS using a variety of mechanisms. Factors like droplet size, pH, phase volume, and viscosity, among others, have an impact on release rates[8].

a. Diffusion Mechanism:

Unionized hydrophobic drugs most frequently diffuse through the oil layer in stable multiple emulsions by the diffusion mechanism. As a result, drug transport follows Fick's law of diffusion and first order kinetics[9].

b. Micellar Transport:

The creation of a water-swollen inverse micelle, which serves as a carrier for both an ionised and unionised medication, is facilitated by the presence of both lipophilic and hydrophilic surfactants in the oil phase. Due to the exterior lipophilic nature of inverse micelles, which have a polar part of surfactant inside and a non-polar part outside, the hydrophilic medication is contained within the core and can pass through the oil membrane[10].

c. Thinning of the oil membrane:

Osmotic pressure differences cause the oil membrane to thin, making it easier for drugs and water to diffuse. Moreover, this pressure difference acts as a force for the movement of molecules[11].

d. Rupture of oil phase:

This process states that when the oil membrane ruptures, the aqueous phase unites allowing for simple drug release[6].

e. Facilitated diffusion (carrier-mediated transport):

This mechanism uses a unique molecule (carrier), which when combined with the drug, allows it to pass through the oil membrane[6].

f. Solubilization of the internal phase in the oil:

It is a well-known transport mechanism. In this, very little quantities of materials are transported as a result of the internal phase's solubilization in the membrane phase[12].

PREPARATION OF SDEDDS

SDEDDS emulsions are best prepared by re-emulsification of primary emulsion. The following is 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):

Re-emulsifying the initial W/O or O/W emulsion with an appropriate emulsifier ingredient is a step in the two-step emulsification process. The first stage entails acquiring a standard W/O or O/W primary emulsion using the proper emulsifier equipment. The freshly made W/O or O/W primary emulsion is then re-emulsified with an excess of aqueous phase or oil phase in the second step. The final emulsion that is created can either be W/O/W or O/W/O[13].

2. Phase Inversion Technique (One Step Technique): An increase in the dispersed phase volume concentration might result in an increase inthe phase volume ratio, which would then lead to the production of multiple emulsions. The process usually entails mixing an aqueous phase with a hydrophilic emulsifier, such as Tween 80, sodium dodecyl sulfate (SDS), or cetyl trimethyl ammonium salt (CTAB), with an oil phase consisting of liquid paraffin and a lipophilic emulsifier (Span80). In a pin mixer vessel, an accurately measured volume of oil phase is added. Then, while the pin mixer rotates steadily at 88 rpm at room temperature, an aqueous solution of emulsifier is added 5 ml/min at a time to the oil phase in the vessel. When the volume percentage of the hydrophilic emulsifier's aqueous solution surpasses 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[14].

3. Membrane Emulsification Technique:

In this procedure, a W/O emulsion (a dispersed phase) is extruded into an external aqueous phase (a continuous phase) under constant pressure through a porous glass membrane. The pores of the membrane should be uniformly regulated. With the right choice of porous glass membrane, the resulting emulsion's particle size can be regulated because the size of the droplet is dependent on the pore size of the membrane[14].

CHARACTERIZATION OF SDEDDS FORMULATIONS

1. Physical Stability of Emulsion Formulations:

Organoleptic characteristics are observed for any visible indications of instability, such as creaming, cracking, phase separation, or changes in colour[15].

2. Viscosity analysis of SDEDDS formulations:

The rheological measurements of the SDEDDS formulations are performed with a Brookfield viscometer[15].

3. pH Determination:

The pH of fresh sample and samples kept in different storage conditions can be determined by a digital pH meter[16].

4. Microscopic test:

The optical microscopy methods are used to analyze and confirm the multiple characters of double emulsions such as type of emulsion, size distribution of droplets etc. Various other techniques used are coulter-counter, freeze-fracture electron microscopy[6].

5. Emulsion Droplet size analysis:

The droplet size distributions of double emulsions are measured by dynamic light scattering by using a suitable Particle Size Analyzer. SDEDDS are mixed with distilled water and stirred at required agitation in a magnetic stirrer for several min at room temperature, forming the double emulsions. The particle size distribution of the double emulsions is determined[17].

6. Stability studies:

Stability study is performed by storing the ready-to-use SDEDDS Formulation in the sealed amber glass vials at room temperature. The stability is evaluated by monitoring the time-

dependent changes in appearance, viscosity, self-emulsifying properties and double emulsion droplet size of the SDEDDS formulation within the capsules for required months[17].

7. 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,

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

Where, Td = Total drug added, Fd = free drug present in the separated oil or aqueous phase[18].

8. Electrical conductivity test:

By Using a digital conductivity-meter, conductivity tests are performed on multiple emulsions immediately after preparation and on samples kept at different temperatures[19.]

9. Dissolution study:

In-vitro dissolution studies are carried out to assess drug release from the formulation. Release profiles from formulation filled in capsules are performed using the USP type II rotating paddle apparatus with 900 ml of suitable dissolution media at 37±0.5◦C. Samples are withdrawn at specified interval of time, filtered and subsequently analyzed by either UV or HPLC assay[20].

10. *In-vivo* method:

Male Wister rats are used and acclimatised for specific interval of days and fed the solid food for required weeks. The rats used as recipients of the W/O/W emulsions weighed and rats are fasted for specific interval of hours before being fed the sample solutions. Blood samples are collected from the coccygeal vein for several minutes before administration by using gauge needles and used as the reference blood sugar level at zero min after being anaesthetized with suitable solvent. By using feeding tubes, the sample solutions are fed at suitable IU/kg-weight. Purified water is also fed as a control solution, containing insulin at the same concentration as the other emulsions. Blood samples are taken at different minutes[21].

PHARMACEUTICAL APPLICATIONS OF SDEDDS

- Hydrophilic as well as hydrophobic drug can be entrapped[5].

- Essential nutrients like carbohydrates, fats and vitamins can all be emulsified and can be administered to bed ridden patient as sterile intravenous injection[5].
- Increase in dosing interval[5].
- Intravenous emulsions of contrast media have been developing to assist in diagnosis[5].
- They can mask the bitter taste and odor of drugs such as chlorpromazine[12].
- Multiple emulsions are used in food[22].
- They can be used to prolong drug release, resulting in sustained release action[23].
- Emulsion protects the drugs which are susceptible to oxidation or hydrolysis[24].

CONCLUSION

The present review clearly shows the potential utility of the Self double emulsifying drug delivery system (SDEDDS) for pharmaceuticals. The ability to encapsulate active substances within liquid membranes may open up new opportunities in a variety of fields. Since the last century, the only route available for the delivery of certain proteins, peptides, and anticancer drugs has been via injection. The oral administration of such highly soluble drugs has significant commercial implications in terms of patient compliance, product stability, ease of formulation, and manufacturing consideration. The present study has an attempt to describe the role of oral route for systemic delivery of such highly water soluble (BCS Class-III) drugs. The investigation provides a method for delivering such drugs via the lymphatic system, as well as a method for delivering highly water soluble, poorly permeable life-saving drugs used in diseases such as cancer, diabetes, and vaccines. The evaluation of such products will undoubtedly be advantageous in the future.

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