IJMPR 2024, 8(4), 01-08

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 6.669

SELF DOUBLE EMULSIFYING DRUG DELIVERY SYSTEM: A NOVEL APPROACH TO ENHANCE BIOAVAILABILITY

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Article Received on: 22/01/2024
Article Revised on: 11/02/2024
Article Accepted on: 03/03/2024

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ABSTRACT
Self-emulsifying drug delivery (SEDDS) are well-known technique for improving the aqueous solubility and oral bioavailability of different classes of drugs. Self-double emulsifying drug delivery system (SDEDDS) is a modified form of self-emulsifying drug delivery system (SEDDS) primarily designed to deliver BCS Class III drugs defined as “high soluble and low permeable” drugs. Gastrointestinal permeability is the rate-limiting step in the absorption of Class III drugs (high soluble and low permeable drugs). 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 the hepatic first-pass effect also have low bioavailability, which can be improved by absorption and transport via the lymphatic system. Many methods, including absorption enhancers, chemical modifications, and pharmaceutical means, were used to improve the oral bioavailability of those drugs. Among these approaches, water-in-oil-in-water emulsions have the greatest potential for increasing the oral bioavailability of BCS Class III drugs. Therefore, increasing the permeability of low permeable drugs may improve the bioavailability of “high soluble and low permeable” drugs i.e., BCS Class III drugs. This review briefly discusses the composition, mechanism, advantages, disadvantages, method of preparation, formulation, and evaluation of Self double emulsifying drug delivery system (SDEDDS).

KEYWORDS: Self-emulsifying, double-emulsifying, high solubility, low permeability, SEDDS (self-emulsifying drug delivery system), SDEDDS (self-double emulsifying drug delivery system).

INTRODUCTION

The oral route of drug administration is the most favorable route of drug delivery for both patients and manufacturers. More than 35-40% of newly introduced potential hydrophilic drugs such as protein and peptide drugs administrated orally exhibit low oral bioavailability mainly due to their high solubility and low intestinal permeability.[1] In Which Gastrointestinal permeation is the rate-controlling step in drug absorption. These kinds of drugs are classified as "high solubility and low permeability" or a biopharmaceutical classification system [BCS] class III drugs.[2]

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 might help improve the bioavailability of BCS Class III drugs.[3] 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 the hepatic first-pass effect also have low bioavailability, which can be improved by absorption and transport via the lymphatic system. Many methods, including absorption enhancers, chemical modifications, and pharmaceutical means, were used to improve the oral bioavailability of those drugs.[4] Among these approaches, water-in-oil-in-water emulsions have the greatest potential for increasing the oral bioavailability of BCS Class III drugs.[2]

Most drugs that are taken orally enter the systemic circulation by absorption directly into the portal blood. However, highly lipophilic compounds may enter the systemic circulation through the intestinal lymphatic system. It has been determined that the alternative lymphatic absorption pathway from the gastrointestinal

system (GIT) significantly contributes to overall bioavailability.[1]

SDEDDS is a mixture of water-in-oil emulsions and hydrophilic emulsifiers that can self-emulsify into water/oil/water multiple emulsions after dilution with aqueous media at room temperature under gastrointestinal motility or light agitation. This form of drug delivery method has several significant benefits, which are as follows. On the one hand, SDEDDS can prevent peptide and protein medication inactivation and enzymatic degradation in the gastrointestinal tract. Meanwhile, the absorption of drugs and pharmacological activity can be substantially enhanced as compared to alternative formulations. Rather than producing artificial emulsification in vitro, SDEDDS can produce spontaneous emulsification in vivo due to gastrointestinal motility. As a result, SDEDDS is more stable than standard multiple emulsions that are thermodynamically unstable, and it can successfully prevent the lack of stability of multiple emulsions during formulation and storage in vitro. Also, SDEDDS significantly benefits patients by reducing the dose volume.[4]

Among these approaches, Self-double emulsifying drug delivery systems (SDEDDS) have great potential for increasing the oral bioavailability of BCS class III drugs.[3] SDEDDS are polydisperse systems in which the dispersed phase contains droplets of the continuous phase. There are two types of double emulsions: W/O/W multiple emulsions and O/W/O multiple emulsions. Small water droplets are dispersed in larger oil droplets, which are then dispersed again in continuous aqueous phases. Similarly, in O/W/O type multiple emulsions, small oil droplets are dispersed in larger aqueous droplets, which are then dispersed in the continuous oil phase.[5] Some potential pharmaceutical applications used are taste masking, adjuvant vaccinations, enzyme immobilization, sorbent reservoir of overdose therapies, and increase of enteral or superficial absorption—for example, skin moisturizer. Multiple structures of SDEDDS can also be used to achieve prolonged release of drugs. These methods show some advantages, including protecting the entrapped substances and incorporating multiple actives into the various compartments. Despite their potential usage, multiple emulsions' applications have been limited due to thermodynamic instability and their complicated structure.[6]

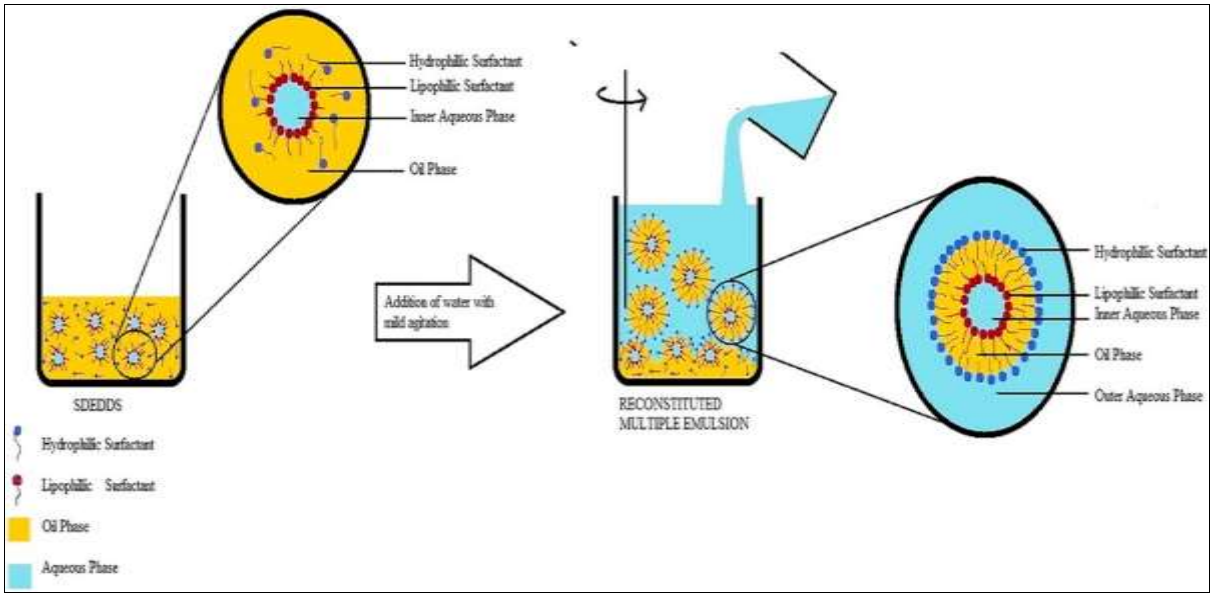

Figure 1.

❖ Approaches for increasing the bioavailability of BCS Class III drugs are as follows [1]:

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

ADVANTAGES OF SDEDDS

- Increase oral bioavailability enabling reduction of dose.
- Protection of drug from hostile environment in the gut.
- Both hydrophilic and lipophilic drugs can be entrapped and protected.
- Drug targeting to the reticulo-endothelial system (RES) can be achieved.
- They can mask the bitter taste and order of the drug, e.g., chlorpromazine.
- Controlled and sustained delivery of drugs can also be achieved.
- Multiple emulsions are used in food.[7]

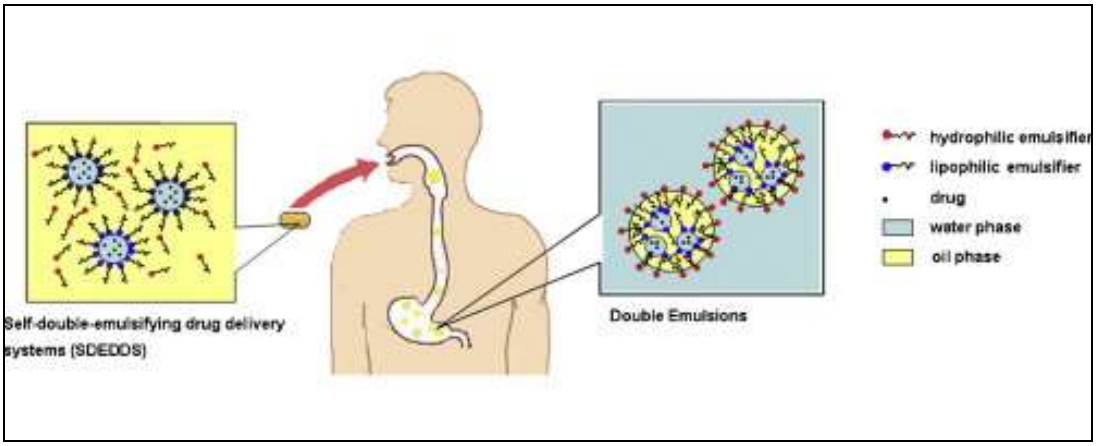

Figure 2.

Composition

The self-double emulsifying process depends on:

- Emulsification equipment.
- Nature of aqueous phase.
- Nature of oil phase.
- Volume of dispersion phase.
- Nature and quality of emulsifying agent.
- Added stabilizing component.

a) Emulsification equipment

The initial emulsion can be prepared by employing a laboratory mixer or homogenizer to ensure an effective dispersion of droplets within the relevant continuous phase.[9] The subsequent emulsification phase is tasked with dispersing the primary emulsion into droplets of the appropriate size for utilization in delivery vehicles. Excessive mixing, particularly at elevated shear levels, may lead to the rupture of the primary emulsion droplets. To mitigate this risk, it is advisable to use low-speed, low-shear mixers, or manually shake the system. Caution should be exercised when employing ultrasonic homogenizers during the secondary emulsification step.[10]

b) Nature of the Aqueous Phase

In a water-in-oil (w/o) emulsion, the aqueous phase serves as the dispersed component, while in a water-in-oil-in-water (w/o/w) emulsion, it functions as the continuous phase. The internal aqueous phase commonly comprises solutions containing encapsulated compounds, such as sugar, salt, and nutrients. On the other hand, external aqueous phases consist of solutions containing emulsifiers (e.g., proteins) and stabilizers (e.g., polysaccharides). The stability of a double emulsion is significantly influenced by the volume fraction of the aqueous phase.[11]

c) Nature of oil phase

The choice of oil phase in pharmaceutical emulsions is crucial, as it not only needs to be nontoxic but also plays a key role in determining the encapsulation efficiency. Vegetable oils, despite their higher viscosity and solubility compared to mineral oil, necessitate greater energy input for emulsion preparation. Consequently, emulsions formulated with vegetable oils exhibit lower stability against the ingress and egress of water from the internal aqueous phase. Nevertheless, hydrophobic materials like mineral oils or hydrocarbon solvents are commonly utilized as the oil phase in studies involving water-in-oil (w/o) or water-in-oil-in-water (w/o/w) emulsions. Various vegetable oils such as soybean oil, corn oil, sesame, peanuts, and safflower are acceptable if properly purified. Refined hydrocarbons like light liquid paraffin and squalene, along with esters of fatty acids such as ethyl oleate and isopropyl myristate, have also found application in double emulsions. Oils derived from vegetable sources boast biodegradability, whereas those based on mineral oils are eliminated from the body at a slower rate. The order of decreasing stability and percentage entrapment has been observed as follows: light liquid paraffin > squalene > sesame oil > maize or peanut oil.[12]

d) Volume of dispersion phase

The amount of water dissolved in the initially formed w/o emulsion (shown as a phase volume ratio, (w/o/w)) can affect the final emulsion system's stability and yield.[8]

e) Nature and quantity of emulsifying agents

The formation of a stable emulsion necessitates the use of two distinct emulsifiers, one lipophilic and the other hydrophilic. Specifically, for a water-in-oil-in-water (w/o/w) emulsion, the optimal Hydrophilic-Lipophilic Balance (HLB) value typically falls within the range of 2-7 for the primary surfactant and 6-16 for the secondary surfactant. It is also possible to adjust the concentration of the emulsifiers. Insufficient emulsifier amounts may result in an unstable system, while excessive emulsifier quantities can lead to toxic effects and, in extreme cases, provoke destabilization.[13]

f) Added stabilizing components

Stabilizers are introduced to enhance the stability of multiple emulsions. These stabilizers encompass substances such as gelling or viscosity-enhancing agents incorporated into either the internal or external aqueous phases (e.g., 20% gelatine, methylcellulose, and

comparable thickening agents).[14] Additionally, complexing agents capable of inducing a liquid crystalline phase at the oil-in-water (O/W) interface are employed, such as cetyl alcohol. Furthermore, gelling agents may be added to the oil phase, exemplified by substances like aluminium monostearate.[15]

MECHANISM OF DRUG RELEASE FROM SDEDDS

After the formation of delf double emulsion through various methods, the drug is released from the internal to external phase through the different layers following the development of the double emulsion from SDEDDS. Release rates are affected by several factors, including viscosity, phase volume, pH, and droplet size.[16]

1. Diffusion Mechanism

The diffusion mechanism is a highly popular transport method in which unionized hydrophobic drugs diffuse through the oil layer, in stable multiple emulsions. Therefore, Drug transport complies with both Fick's law of diffusion and first-order kinetics.[17]

2. Micellular transport

The formation of a water-swollen inverse micelle, acting as a carrier for both ionized and non-ionized medications, is enabled by the inclusion of both lipophilic and hydrophilic surfactants in the oil phase. The exterior lipophilic character of inverse micelles, characterized by a surfactant with its polar part inside and non-polar part outside, allows the hydrophilic medication to be housed within the core and traverse the oil membrane.[18]

3. Thinning of the oil membrane

Differences in osmotic pressure lead to the thinning of the oil membrane, facilitating the diffusion of drugs and water. Additionally, this pressure variance serves as a driving force for molecular movement.[19]

4. Rupture of oil phase:

This process asserts that the rupture of the oil membrane results in the merging of the aqueous phase, facilitating the straightforward release of the drug.[7]

5. Facilitated diffusion (carrier-mediated transport)

This technique makes use of a unique molecule (carrier) that interacts with the drug to help it pass through the oil membrane.[8]

6. Solubilization of the internal phase in the oil

This mechanism of transport is widely recognized, involving the transportation of minute quantities of materials through the solubilization of the internal phase within the membrane phase.[20]

METHOD OF PREPARATION OF SDEDDS

The optimal method for preparing SDEDDS emulsions involves the re-emulsification of a primary emulsion. Multiple emulsions can be created using various techniques, including:

1. Two-Step Emulsification (Double Emulsification)
2. Phase Inversion Technique (One-Step Technique)
3. Membrane Emulsification Technique

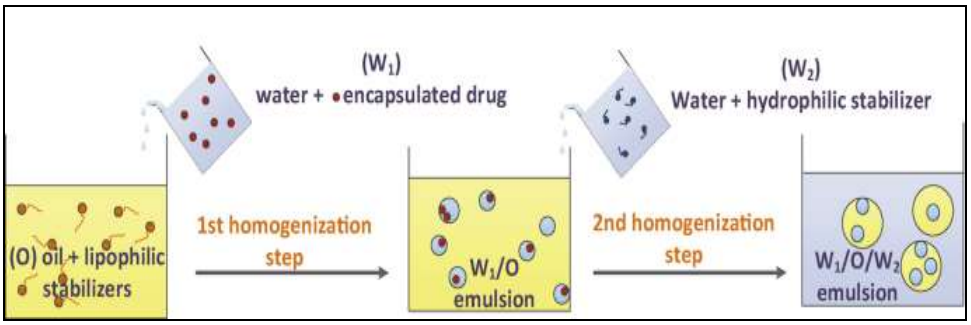

Figure 3.

1. Two-Step Emulsification (Double Emulsification)

The two-step emulsification process includes re-emulsifying a primary W/O or O/W emulsion using a suitable emulsifying agent. In the initial step, an ordinary W/O or O/W primary emulsion is obtained, employing a suitable emulsifier system. The subsequent step involves re-emulsifying the freshly prepared W/O or O/W primary emulsion with an excess of either aqueous phase or oil phase. The resulting emulsion can ultimately be W/O, O/W, or O/W/O, depending on the specific process [21].

2. Phase Inversion Technique (One-Step Technique)

An increase in the concentration of the dispersed phase can result in a higher phase volume ratio, ultimately triggering the formation of multiple emulsions. The procedure typically involves adding an aqueous phase containing a hydrophilic emulsifier (such as Tween 80, sodium dodecyl sulfate (SDS), or Cetyl trimethyl ammonium salt (CTAB)) to an oil phase composed of liquid paraffin and a lipophilic emulsifier (Span 80). A defined volume of the oil phase is placed in a pin mixer vessel. Subsequently, an aqueous solution of the emulsifier is introduced sequentially into the oil phase in the vessel at a steady rate of 5 ml/min, while the pin mixer rotates consistently at 88 rpm at room temperature. When the volume fraction of the aqueous solution of the hydrophilic emulsifier surpasses 0.7, the continuous oil phase is replaced by the aqueous phase containing

vesicular globules among the simple oil droplets, resulting in phase inversion and the formation of W/O/W multiple emulsion.[22]

3. Membrane Emulsification Technique

In this approach, a W/O emulsion (dispersed phase) is forced into an external aqueous phase (continuous phase) under constant pressure through a Porous Glass Membrane characterized by controlled and homogeneous pores. The resulting emulsion's particle size can be regulated by carefully selecting the Porous Glass Membrane, as the droplet size is dependent on the membrane's pore size. The correlation between membrane pore size and the particle size of the W/O/W emulsion is well-represented by the equation: Y = 5.03X + 0.19, where X is the pore size and Y is the mean particle size of the multiple emulsion prepared using the membrane emulsifier technique.[23]

EVALUATION OF SDEDDS FORMULATIONS

1. Physical stability of emulsion formulations

The organoleptic characteristics are examined to detect any visible signs of instability, including manifestations like creaming, cracking, phase separation, or alterations in colour.

2. Viscosity analysis of SDEDDS formulations

The SDEDDS formulations' rheological characteristics can be evaluated using a programmable rheometer, specifically a Brookfield viscometer, with a cone-plate geometry (cone diameter of 60mm, angle of 1◦, and a 0.058 mm gap). Following a 10-minute equilibration period at 25±1 ◦C, samples are introduced into the instrument. The apparent viscosity can then be assessed across a shear rate range of 0.1–300 s−1. Viscosities (in mPa s) for each formulation are recorded at various shear rates, and the mean constant shear viscosity can be derived from the data obtained at 300 s−1. Six replicate analyses can be presented as means ± SD.[24]

3. pH determination

Utilizing a digital pH meter, the pH values of freshly prepared emulsions and emulsions subjected to various conditions can be ascertained. pH measurements can be conducted repeatedly on multiple emulsions at intervals of 1, 3, 7-, 14-, 21-, and 28-days post-preparation, providing valuable information for potential adjustments in formulation parameters.[25]

4. Microscopic test

The confirmation of multiple characteristics in emulsions necessitates microscopic analysis. A drop of the emulsion is applied to a glass slide, diluted with water, and covered with a glass cover. Subsequently, a drop of immersion oil is placed on the cover slide, and the emulsion is observed under the microscope.

5. Turbidity Measurement

The objective is to determine the effectiveness of self-emulsification by verifying if the dispersion attains equilibrium quickly and consistently. Nepheloturbidimetric assessment is employed to observe the emulsification progression. A set amount of the self-emulsifying system is introduced to a fixed quantity of a suitable medium (0.1N hydrochloric acid) while being continuously stirred at 50 rpm on a magnetic plate at room temperature. The rise in turbidity is then measured using a turbidimeter.[26]

6. Entrapment Efficiency

The drug entrapment is calculated by subtracting the amount of free drug separated in the lower phase of the emulsion through centrifugation from the total drug quantity. The efficiency of drug entrapment is expressed as a percentage and is defined by the formula:

Efficiency of drug entrapped (%) = [(Td - Fd) / Td] X 100

Where, Td = Total drug added, Fd = free drug present in the separated oil or aqueous phase.[27]

7. Emulsion droplet size analysis

The size distribution of double emulsions plays a crucial role in affecting rheology, stability, color, and testing outcomes. Typically, dynamic light scattering is employed for measurement using a Malvern Particle Size Analyzer equipped with a He–Ne laser. SDEDDS is combined with distilled water (200 ml) and gently stirred at 75 rpm on a magnetic stirrer for 5 minutes at room temperature to create double emulsions. Subsequently, the particle size distribution of the double emulsions is determined. The refractive indices of the dispersed phase and continuous phase are calculated, and absorbance values of the emulsion droplets are computed. The results are presented as the volume average diameter.[28]

8. Electric conductivity test

The stability of emulsions is directly linked to the charge present on the mobile surface, known as zeta potential. Instruments such as Zetasizer and Mastersizer are commonly utilized for determining zeta potential. These tools assess both globule size and zeta potential to optimize the stability and shelf life of the formulation. The calculation of zeta potential and surface charge is based on the mobility and electrophoretic velocity of dispersed globules using a zeta potentiometer. The apparatus employed comprises a cylindrically bored micro-electrophoresis cell equipped with platinum-iridium electrodes, measuring the electrophoretic mobility of the diluted emulsion.

The zeta potential is determined using the following formula:

$$\zeta = \frac{4\pi\eta\mu \times 10^{3}}{E\varepsilon}$$

- (ζ) represents the zeta potential,
- (η) is the viscosity of the dispersion medium measured in poise,
- (μ) denotes the migration velocity in centimeters per second,

- (ε) stands for the dielectric constant of the dispersion medium, and
- (E) is the potential gradient, calculated as the applied voltage divided by the distance between electrodes.[29]

9. Self emulsification time

The self-emulsification time is assessed utilizing a USP type II dissolution apparatus operating at 50 rpm. In this procedure, 0.5 gm of the SDEDDS formulation is introduced into 250 ml of a suitable medium (either 0.1N HCl or 0.5% SLS solution). The duration for emulsification at room temperature is then documented as the self-emulsification time for the given formulation.[30]

10. Stability studies

Stability assessments can be conducted under various storage conditions for both primary and multiple emulsions. The examinations are carried out on samples stored at 2 ± 0.1 ^{0}C (in a refrigerator), 25 ± 0.1^{0}C with 60%RH (relative humidity), 40 ± 0.1 ^{0}C at 75%RH (relative humidity) (in a stability chamber), and 50^{0}C in an oven.[15]

11. *Invitro drug release*

In-vitro dissolution studies are conducted to evaluate the release of the drug from the formulation. The release profiles from formulations encapsulated in capsules are determined using the USP type II rotating paddle apparatus with 900 ml of appropriate dissolution media at 37±0.5 ◦C. At specified time intervals, samples (5 ml) are drawn, filtered using a 0.45 micrometer filter, and then analyzed through either UV or HPLC assay. Three replicate analyses are performed for each formulation, and the data obtained is utilized to calculate the cumulative drug release profile.[31]

12. *In vivo Method*

Male Wister rats, weighing 200–250 g, undergo a 7-day acclimatization period and are fed solid feed for 6 weeks. To ensure fasting, the rats are deprived of food overnight for 17 hours before the administration of sample solutions. Following anesthesia with ether, blood samples are collected from the coccygeal vein 5 minutes before administration, using 23–27-gauge needles, to establish the baseline blood sugar level at 0 min. The sample solutions, administered at 50 IU/kg-weight through feeding tubes, are compared with a control solution of purified water containing insulin at an equivalent concentration. 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 quantified through spectrophotometry or HPLC determination.[32]

PHARMACEUTICAL APPLICATIONS OF SDEDDS[33]

SDEDDS demonstrates a wide range of potential applications in fields such as chemistry, pharmaceutics, cosmetics, and food. These formulations have been explored for their utility as controlled-release drug delivery systems, enabling simultaneous extraction and stripping of metals, organic acids, and antibiotics. Additionally, they have been studied for their role as microcapsules, providing protection and controlled release of functional food ingredients, as well as contributing to the formulation of reduced-calorie food emulsions. Furthermore, double emulsions have found applications as intermediate products in the preparation of inorganic particles, lipid nanoparticles, polymeric microspheres, biodegradable microspheres, gel microbeads, and vesicles like polymerosomes.

Some notable applications of Self Double Emulsifying Drug Delivery System (SDEDDS)

1. Controlled and Sustained Drug Delivery

SDEDDS holds significant promise in clinical therapeutics for achieving prolonged and controlled drug release. In these systems, the drug, initially situated in the innermost phase, undergoes several phases before becoming available for absorption within the system.

2. Targeted Drug Delivery Systems

Achieving site-specificity is a crucial requirement for effective pharmacotherapy. An optimal strategy for a drug delivery system involves delivering the drug exclusively to the diseased tissue or organ without impacting healthy tissues. Drug targeting aims to concentrate the drug specifically in the diseased tissue, thereby minimizing adverse effects on non-diseased tissue. This targeted approach proves particularly advantageous for cytotoxic drugs, such as anti-cancer agents, due to their high toxicity towards non-diseased tissue. Double emulsions are recognized for their efficacy in achieving site-specific drug delivery.[34]

3. Vaccine Adjuvant

Double emulsions (w/o/w) are under scrutiny as potential vaccine adjuvants due to their suitable consistency for administration and their ability to elicit an antibody response. These emulsions are not only sterile, safe, and potent but studies also indicate that vaccination with double emulsion induces both humoral and cell-mediated immune responses.

4. Enzyme Immobilization

The primary aim of the liquid surfactant membrane is to facilitate enzyme immobilization. Enzymatic conversion of water-insoluble, highly lipophilic substrates, such as steroids, can be effectively conducted within a double emulsion (w/o/w). The immobilized enzyme maintains its catalytic activity, which can be easily recovered through straightforward mechanical disruption of the liquid membrane. There have been documented instances of reducing and separating nitrates and nitrites using both liquid membrane-encapsulated enzymes and whole cells. This technique for eliminating nitrates and nitrites holds promise for application in wastewater treatment.

5. Drug Overdosage Treatment/Detoxification

Double emulsions of the w/o/w variety find application in the treatment of drug overdosing. A w/o/w system has been devised to eliminate acidic drugs, such as barbiturates and salicylates, from the gastrointestinal tract. This is achieved by trapping the unionized drug, allowing it to permeate through the oil membrane into the inner basic phase, where it undergoes conversion into an oil-insoluble anion.

6. Taste Masking

Double emulsions have been utilized to mask the taste of drugs such as chlorpromazine HCl and chloroquine, both known for their bitter taste. The strategy involves dissolving the drug in the inner aqueous phase of the emulsion, ensuring good shelf stability. This formulation is designed to release the drug through the oil phase in the presence of gastric fluid. Various biocompatible and edible oils have also been employed to enhance taste masking potential.

7. Miscellaneous

Emulsions of the w/o/w type, functioning as liquid membrane systems, demonstrate the capability to extract heavy metals and contaminants from wastewater, acting as an external phase. Notably, metals such as Cu, Ni, and Zn have been effectively extracted from wastewater plants utilizing the liquid membrane emulsion system. Conversely, the o/w/o type system has found application in separating hydrocarbons, employing the aqueous phase as the membrane and a solvent as the external phase.

CONCLUSION

The current review underscores the potential applications of the Self Double Emulsifying Drug Delivery System (SDEDDS) in the realms of pharmaceuticals and food materials. The prospect of encapsulating active substances within liquid membranes opens up intriguing possibilities across various fields. For the past century, the primary avenue for delivering certain proteins, peptides, and anti-cancer drugs has been injectable methods. Therefore, introducing these highly soluble drugs through the oral route carries significant commercial importance, addressing factors such as patient compliance, product stability, ease of formulation, and manufacturing considerations. This study aims to delineate the role of the oral route in delivering extremely water-soluble drugs, classified as BCS Class III. The investigation explores the delivery of such drugs via the lymphatic system, offering a means to administer highly water-soluble, poorly permeable life-saving drugs relevant to diseases like cancer, diabetes, vaccines, etc. The assessment of these products holds promise for enhancing the future delivery of such drugs.

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