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An Analysis of the Self-Double Emulsifying Drug Delivery System (SDEDDS)

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Abstract: *The potential of self-emulsifying drug delivery systems (SEDDS) to enhance the aqueous solubility and oral absorption of lipophilic pharmaceuticals is widely recognized. Self-diluent drug delivery systems (SDEDDS) are predominantly employed for pharmaceuticals that exhibit low solubility in water. However, their potential utility extends to biopharmaceutical classification system (BCS) class III drugs, which have gastrointestinal permeation as the rate-determining step in the absorption process and are therefore classified as "high solubility low permeability class" substances. In addition to solubility, the primary determinant of oral drug absorption is the drug's permeability through the intestinal mucosa. Thus, enhancing permeability has the potential to augment the bioavailability of a pharmaceutical compound. The preparation, stability, formulation, and characterization of SDEDD S. are covered in this article*

Keywords: Self-emulsification, Nanoemulsions, Lipid-based delivery systems

I. INTRODUCTION

Numerous medications are administered orally, as this is the most effective route. However, numerous hydrophilic medications with potential, including protein and peptide pharmaceuticals, demonstrate inadequate oral bioavailability when administered orally. This is primarily attributed to their low intestinal permeability. For pharmaceuticals classified as "high solubility, low permeability class" or biopharmaceutical classification system [BCS] class III, the rate-regulating phase in the absorption process is gastrointestinal permeation [1]. The predominant mode of transport for hydrophilic medications across the intestinal epithelium is via paracellular pathways. Nonetheless, the transport of hydrophilic drugs across the paracellular route is impeded due to the constrained surface area and the tight junctions that exist between adjacent cells. As a consequence, the drugs have a low bioavailability. By traversing the lymphatic system, the minute oil globules circumvent portal circulation and the hepatic first pass effect.

Additionally, pharmaceuticals that experience a hepatic first pass effect have a diminished bioavailability that can be enhanced via lymphatic system absorption and transport. A variety of methods, including chemical modifications, absorption enhancers, and pharmaceutical interventions, were employed to augment the oral bioavailability of those medications. Water-in-oil-in-water emulsions exhibit significant promise among these methodologies in augmenting the oral bioavailability of BCS class III medications.4, 5.

A significant proportion of medications that are administered orally enter the systemic circulation via direct absorption into the portal blood. Conversely, compounds with a high lipophilic content have the potential to enter the systemic bloodstream via the intestinal lymphatic system. It has been demonstrated that this alternative lymphatic absorption pathway from the gastrointestinal tract (GIT) contributes significantly to the overall bioavailability.

SDEDDS are polydispersed systems in which the particles of the continuous phase are contained within the dispersed phase. Two varieties of double emulsions are present: multiple emulsions of the W/O/W type and multiple emulsions of the O/W/O type. In O/W/O type multiple emulsions, small water droplets are dispersed within larger oil droplets, which are subsequently dispersed within continuous aqueous phases (7). Likewise, in these emulsions, small oil droplets are dispersed within larger aqueous droplets, which are subsequently dispersed within continuous oil phases. The potential pharmaceutical applications of these substances encompass a range of uses, including but not limited to taste concealing, adjuvant vaccines, enzyme immobilization, sorbent reservoirs for toxicity treatments, and enteral or cutaneous absorption enhancement [8]. Emulsions have been developed in various forms to serve as cosmetics,

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including moisturizers for the epidermis. Extended release can also be achieved through the utilization of various structures. The protection of the entrapped substances and the incorporation of multiple actives in the various compartments are a few of the benefits of these systems. The utilization of multiple emulsions has been constrained in practice due to their intricate structure and thermodynamic instability, notwithstanding their potential utility [9]. The fundamental justification for employing W/O/W and O/W/O type multiple emulsions as methods of extended drug delivery is that the drug, which is concentrated in the innermost phase, must undergo partitioning across multiple phases before reaching the absorption site (10). Therefore, the intensity of the middle membrane phase, a multimolecular layer composed of emulsifier molecules, oil, and water situated at both interfaces of multiple emulsion systems, and the partition and diffusion coefficient of the drug, dictate the rate of drug release from these systems (11). Despite their limited utilization, multiple emulsions possess a multitude of prospective applications; thus, their research is currently an active area of study, particularly in the domains of pharmaceutical drug delivery systems, cosmetics, and foodstuffs (12).

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 generated by employing a laboratory mixer or homogenizer in order to achieve a uniform distribution of droplets throughout the suitable continuous phase [13,14]. For use in delivery vehicles, the secondary emulsification stage must disperse the primary emulsion into particles of suitable size. Particularly when subjected to high shear, excessive mixing can induce rupture in the primary emulsion particles. Mixers with minimal shear and low speed should be utilized, or the system can be manually agitated. When utilizing ultrasonic homogenizers for the secondary emulsification phase, caution is required.

Nature of the aqueous phase:

In a water-only emulsion, the aqueous phase is the dispersed phase; in a water-only/w emulsion, it is the continuous phase. Frequently, the internal aqueous phase comprises a solution of the encapsulated substance, including sugar, salt, and feed (15). Solutions of emulsifiers (e.g., proteins) and stabilizers (e.g., polysaccharide) comprise the external aqueous phase. The volume fraction of the aqueous phase significantly impacts the double emulsion's stability.

Nature of the oil phase:

The nontoxicity of the oil phase is a determining factor in the encapsulation efficacy of the pharmaceutical emulsion. In general, vegetable oils are more soluble and have a greater viscosity than mineral oil. Producing an emulsion using vegetable oil necessitates a greater input of energy and results in a substance that is less resistant to water migration into and out of the internal aqueous phase. As the oil phase, however, substances with a high hydrophobicity, such as mineral oils or hydrocarbon solvents, are frequently employed in w/o or w/o/w emulsion research. If properly purified,

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the various vegetable oils (soybean oil, maize oil, sesame, peanut, safflower, etc.) are permissible. Additionally, light liquid paraffin squalene and esters of fatty acids (ethyl oleate and isopropyl myristate) have been employed in the production of double emulsions (16). Oils derived from vegetable sources decompose rapidly in the body, in contrast to those composed of mineral oils, which are eliminated considerably more slowly. It has been determined that light liquid paraffin is the medium through which stability and percentage entrapment decrease, followed by squalene, sesame oil, maize, and peanut oil (14).

Volumes of the phases:
As expressed as a phase volume ratio (w/o/w), the amount of water disseminated in the initial w/o emulsion can affect the yield and stability of the final emulsion system.

Nature and quantity of emulsifying agents:
It is necessary to use two distinct emulsifiers (hydrophilic and lipophilic) in order to create a stable emulsion. Typically, the optimal HLB value for a w/o/w emulsion falls within the intervals of 2-7 for the primary surfactant and 6-16 for the secondary surfactant. Additionally, the emulsifier concentration can be altered. An inadequate amount of emulsifier can cause a system to become unstable, while an excess of emulsifier can have deleterious effects and potentially cause destabilization.

Added stabilizing components:
In order to increase the stability of multiple emulsions, stabilizer is applied. These encompass viscosity-enhancing or gelling agents introduced into the internal or external aqueous phases (e.g., 20% gelatin, methylcellulose, and analogous thickening agents), in addition to complexing agents (e.g., cetyl alcohol) that induce a liquid crystalline phase at the interface of the oil and water (e.g., aluminum monostearate) and gelling agents or the oil phase (e.g., cetyl alcohol)13.

Preparation of Sdedds:
In order to create SDEDDS emulsions, re-emulsification of the initial emulsion is optimal. The procedure for producing multiple emulsions is as follows:

- Two Steps Emulsification (Double Emulsification)
- Phase Inversion Technique (One Step Technique)
- Membrane Emulsification Technique

Two Steps Emulsification (Double Emulsification)
Emulsification procedures consisting of two stages require re-emulsification of the initial W/O or O/W emulsion with an appropriate emulsifier agent. The initial stage entails generating a standard W/O or O/W primary emulsion by employing a suitable emulsifier system. The newly prepared W/O or O/W primary emulsion is re-emulsified in the second step using an excess of aqueous phase or oil phase. The resulting emulsion may be W/O/W or O/W/O in composition.

Phase Inversion Technique (One Step Technique):
A phase volume ratio increase may result from an increase in the volume concentration of the dispersed phase; this, in turn, may contribute to the formation of multiple emulsions. The conventional procedure entails the introduction of a hydrophilic emulsifier (Tween 80/sodium dodecyl sulfate (SDS) or cetyl trimethyl ammonium salt CTAB) into an aqueous phase. This phase is then combined with an oil phase comprising liquid paraffin and a lipophilic emulsifier (Span80). A precise quantity of oil phase is incorporated into a pin mixer vessel. 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 consistently at 88 rpm at room temperature. Phase inversion occurs and a W/O/W multiple emulsion is formed when the volume fraction of the aqueous solution of the hydrophilic emulsifier surpasses 0.7. This results in the substitution of the continuous oil phase with the aqueous phase containing a number of vesicular globules among the simple oil droplets.

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Membrane Emulsification Technique:

A W/O emulsion (a dispersed phase) is extruded under constant pressure through a Porous Glass Membrane, which should have regulated and uniform pores, into an external aqueous phase (a continuous phase). By selecting a porous glass membrane appropriately, it is possible to regulate the particulate size of the resulting emulsion, since the size of the droplets is proportional to the pore size of the membrane. The correlation between the pore size of the membrane and the particulate size of the W/O/W emulsion is strong, as indicated by the subsequent equation:

$Y = 5.03 X + 0.19$

In the set Y, the mean particle size of the multiple that was prepared via the membrane emulsifier technique, denotes X, the pore size.

Characterization of Sdedds Formulations:

Viscosity analysis of SDEDDS formulations

The rheological properties of the formulations were assessed using a programmable rheometer, specifically a Brookfield viscometer, equipped with a cone plate configuration (60mm cone diameter, 1◦ cone angle, and 0.058mm gap). Using an HPLC assay, samples were transferred to the instrument and permitted to equilibrate to. Each formulation is subjected to three replicate analyses, and the results are presented as means ± standard deviation.

Electrical conductivity tests

Conductivity tests are conducted on various emulsions both promptly following preparation and on samples stored under different conditions. Digital conductivity meters are utilized for this purpose. Conductivity experiments are replicated at 1, 3, 7, 14, 21, and 28 days post-preparation for the various emulsions.

Turbidity Measurement:

The purpose of this is to determine whether self-emulsification is effective by observing whether the dispersion reaches equilibrium quickly and consistently. The purpose of nepheloturbidimetric analysis is to track the development of emulsification. The increase in turbidity is measured using a turbidimeter after a fixed quantity of self-emulsifying system is added to a fixed quantity of suitable medium (0.1N hydrochloric acid) while agitating continuously at 50 rpm on a magnetic plate at room temperature.

10 minutes at 25±1 C prior to the measurement. Aperture viscosity can be determined within the range of 0.1–300 s^{-1} of shear rate. The formulation viscosities (measured in mPa s) were assessed under varying shear rates. The data collected at 300 s^{-1} can be utilized to calculate the mean constant shear viscosity. The results of six replicate analyses may be displayed as means ± standard deviation.

pH determination

An electronic pH-meter can be utilized to ascertain the pH value of both freshly prepared emulsions and emulsions maintained under varying conditions. The pH measurements that were replicated for several emulsions 1, 3, 7, 14, 21, and 28 days post-preparation can be utilized to modify formulation parameters.

Microscopic tests

Under the microscope, multiple emulsions must be examined to corroborate the presence of multiple characters. A glass slide must be coated with a drop of multiple emulsions that have been diluted with water and sealed with a glass cover. A single droplet of immersion oil is applied to the cover slide in preparation for microscopic examination.

Entrapment efficiency

The quantity of drug entrapped is calculated by subtracting the amount of unbound drug that is separated by centrifugation in the lower phase of the emulsion from the total amount of drug. Defined as follows is the entrapped efficacy of the drug,

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.

Release of drug from SDEDDS formulations in vitro

The USP30 rotating paddle apparatus must be utilized to generate release profiles for formulations loaded into capsules. This apparatus requires 900 ml of simulated gastric fluid (SGF, pH 1.2) at 37±0.5 ◦C, without pepsin as the medium. The paddle's rotational speed was modified to 75 revolutions per minute. After a duration of 480 minutes, samples (5

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ml) are to be withdrawn and substituted with new media at the following time points: 5, 15, 30, 60, 120, 240, and 360. Samples are analyzed after being purified through a 0.45 micrometer filter.

Emulsion droplet size analysis:

The rheology, stability, color, and test of double emulsions are all impacted by the particle size distribution. In general, these are assessed through the utilization of dynamic light scattering on Malvern Particle Size Analyzers that are outfitted with a He–Ne laser. The double emulsions are formed by combining SDEDDS with distilled water (200 ml) and stirring at room temperature for 5 minutes with a magnetic agitator at a low speed of 75 revolutions per minute. Following presentation, the particle size distribution of the double emulsions is ascertained. Both the dispersed phase and continuous phase refractive indices were computed, as were the absorbance values of the emulsion particles. The results are presented as the average diameter of the volume.

Stability studies:

Stability assessments can be conducted on primary and multiple emulsions under varying storage conditions. The experiments were conducted on specimens maintained at the following relative humidity levels: 25 ± 0.1oC (relative humidity), 40 ± 0.1oC (at 75% RH) (in the stability chamber), and 50^0c (in the oven).

In-vivo method:

After seven days of acclimation to solid food, male Wister rodents are provided with it for six weeks. The weights of the rodents that were administered the W/O/W emulsions ranged from 200 to 250 g. Prior to consuming the sample solutions, the rodents undergo a 17-hour fasting period. Following ether anesthesia, blood samples are obtained from the coccygeal vein utilizing 23–27 gauge catheters, five minutes prior to administration. These samples serve as the reference blood-sugar level at the 0 minute mark. Using feeding tubes, the sample solutions are dosed at a rate of 50 IU/kg-weight. In addition, purified water is utilized as a control solution, comprising the same concentration of insulin as the other emulsions. At 15, 30, 45, 60, 120, 180, and 240 minutes, blood samples are collected from the coccygeal vein while under transient ether anesthesia. Methods for determining the blood concentrations in the samples include spectrophotometry and HPLC.

Pharmaceutical Applications of Multiple Emulsions:

- They are capable of masking the acrid flavor and odor of drugs such as chlorpromazine.
- Food products may contain multiple emulsions.
- They have the capability to extend the duration of drug release, thus facilitating sustained release action.
- By emulsifying vital nutrients such as carbohydrates, lipids, and vitamins, a bedridden patient can receive a sterile intravenous injection.
- Substratile medications are safeguarded by emulsion against oxidation and hydrolysis.
- For diagnostic purposes, intravenous emulsions of contrast media have been developed.
- Implement a longer dosing interval.
- Both hydrophilic and hydrophobic drugs are capable of entrapment.

II. CONCLUSION

Injectable formulations have been the only viable method for delivering specific proteins, peptides, and anticancer drugs for the past century. The oral administration of such highly soluble pharmaceuticals is of critical commercial importance in terms of patient adherence, product stability, formulation simplicity, and manufacturing considerations. The purpose of this investigation is to define the function of the oral route in systemic delivery of these extremely water-soluble (BCS Class-III) pharmaceuticals. The investigation will also establish a method for administering life-saving drugs that are extremely water-soluble and impermeable through the lymphatic system; such drugs will be utilized to treat diseases such as cancer, diabetes, and vaccines. The assessment of these products will undeniably contribute to the advancement of drug delivery in the future.

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