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REVIEW ON DEVELOPMENT AND CHARACTERIZATION OF SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM OF LORATADINE

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ABSTRACT

Loratadine is a second-generation antihistamine with poor aqueous solubility, which limits its dissolution rate and oral bioavailability. Self-Microemulsifying Drug Delivery Systems (SMEDDS) have emerged as an effective lipid-based formulation approach to overcome these limitations by enhancing drug solubility, dissolution, and gastrointestinal absorption. This review summarizes the formulation strategies, mechanism of self-emulsification, composition, preparation methods, characterization, and evaluation of SMEDDS for poorly water-soluble drugs, with a focus on loratadine. The roles of oils, surfactants, co-surfactants, and solid carriers in the development of stable and efficient SMEDDS formulations are discussed. The review also highlights formulation techniques such as phase titration and phase inversion, along with essential evaluation parameters including particle size, zeta potential, self-emulsification time, drug content, percentage transmittance, and in vitro drug release studies. Overall, SMEDDS represent a promising oral drug delivery platform capable of significantly improving the dissolution behavior, bioavailability, and therapeutic performance of loratadine and other Biopharmaceutics Classification System (BCS) Class II drugs. Future research should focus on optimizing formulation components, establishing robust in vitro–in vivo correlations, and exploring large-scale manufacturing to facilitate successful clinical translation.

KEYWORDS: Loratadine, Self-Microemulsifying Drug Delivery System (SMEDDS), Oral Drug Delivery, Solubility Enhancement, Bioavailability, Lipid-Based Drug Delivery, Microemulsion, Surfactants, Dissolution Rate, Poorly Water-Soluble Drugs, Drug Delivery System, Formulation Development.

INTRODUCTION

Oral administration is one of the most widely used routes for drug delivery; however, it presents significant challenges for drugs with poor aqueous solubility. Drug solubility is a critical factor in achieving therapeutic concentrations in vivo. Many newly developed drug candidates are highly lipophilic, resulting in limited aqueous solubility, poor bioavailability, and difficulties in oral administration. Lipophilic drugs such as atorvastatin, simvastatin, seocalcitol, and carvedilol exhibit poor water solubility, leading to inadequate absorption in the small intestine and reduced bioavailability. Self-microemulsifying drug delivery systems (SMEDDS) have emerged as an effective strategy to overcome these limitations by enhancing the aqueous solubility and dissolution of lipophilic drugs. Consequently, SMEDDS improve gastrointestinal absorption and increase the oral bioavailability of these poorly soluble drugs.

SMEDDS can be formulated and filled into either hard or soft gelatin capsules, making them suitable for convenient oral administration. Conventional emulsions typically produce droplets with diameters ranging from 100 to 500 nm, whereas self-microemulsifying drug delivery systems generate much smaller droplets, generally below 50 nm, upon dilution. These systems spontaneously form fine oil-in-water microemulsions at physiological temperature and can be sterilized by filtration due to their small droplet size. As a result,

SMEDDS are considered highly effective oral drug delivery systems that enhance the solubility, dissolution, and bioavailability of poorly water-soluble drugs.

Self-microemulsifying drug delivery systems (SMEDDS) are isotropic mixtures of oil, surfactant, and co-surfactant that spontaneously form fine oil-in-water microemulsions upon dilution with an aqueous medium under gentle agitation (1). These systems enhance the solubility and dissolution of lipophilic drugs, thereby improving their oral absorption and bioavailability.

ADVANTAGES

1.) **Storage:** SMEDDS offer the same advantage as conventional emulsions by enhancing the solubility of hydrophobic drugs. However, unlike macroemulsions, which are prone to creaming and phase separation during storage, SMEDDS are thermodynamically stable systems. This inherent stability minimizes physical instability, allowing them to be stored for extended periods without significant changes in their properties.

2.) **Stability:** Unlike conventional microemulsions and nanoemulsions, SMEDDS are anhydrous systems and do not contain water, which contributes to their superior physical and chemical stability during long-term storage. Studies have demonstrated that self-nanoemulsifying tablets containing carvedilol successfully incorporated the drug into the SNEDDS formulation, resulting in enhanced stability upon dilution with aqueous media in the presence of cellulosic polymers.

3.) **Effect of Food:** Drug absorption from SMEDDS formulations is generally less influenced by food intake compared with conventional oral dosage forms. The lipid components of a high-fat meal may further enhance the absorption of lipophilic drugs from these systems. For example, food has been reported to significantly affect the absorption of itraconazole from the marketed formulation (Sporanox® capsules), whereas its effect was considerably less pronounced with the self-emulsifying itraconazole formulation (ITRA-GSMP capsules) in human volunteers. This reduced food effect contributes to more consistent drug absorption and improved oral bioavailability.

4.) **Rapid Onset of Action:** SMEDDS facilitate rapid oral absorption of drugs, leading to a faster onset of therapeutic action. Their ability to form fine microemulsions upon contact with gastrointestinal fluids enhances drug dissolution and absorption. For example, studies have shown that vitamin A formulated as self-nanoemulsifying drug delivery system (SNEDDS) capsules and tablets exhibited a shorter time to reach maximum plasma concentration (T_{max}) and higher bioavailability compared with conventional vitamin A oily solution-filled capsules without formulation additives.

5.) **Ease of Manufacturing and Scale-Up:** SMEDDS are well suited for large-scale production because they require simple and cost-effective manufacturing processes. Their preparation involves straightforward mixing of the formulation components using conventional equipment, such as mixers with agitators, followed by filling into dosage forms using standard volumetric liquid-filling equipment. This simplicity facilitates scale-up and supports cost-efficient industrial manufacturing.

DISADVANTAGES

1.) **Lack of Predictive *In Vitro* Models:** Reliable predictive *in vitro* models for evaluating the performance of SMEDDS are currently limited.

2.) **Need for Model Validation:** Existing *in vitro* evaluation methods require further development and validation before they can be used as dependable tools for formulation assessment.

3.) **Limited *In Vitro–In Vivo* Correlation (IVIVC):** Improved *in vitro–in vivo* correlation can be achieved by developing and evaluating different prototype lipid-based formulations in suitable animal models.

4.) **Chemical Instability:** Certain drug molecules may undergo chemical degradation within SMEDDS formulations, affecting their stability and therapeutic efficacy.

5.) **High Surfactant Concentration:** SMEDDS typically contain high concentrations of surfactants (approximately 30–60%), which may cause gastrointestinal irritation and reduce patient tolerability.

MECHANISM OF SELF-EMULSIFICATION

In Self-Microemulsifying Drug Delivery Systems (SMEDDS), the free energy of formation may be very low, zero, or even negative, enabling thermodynamically spontaneous emulsification. When a binary mixture of oil and a non-ionic surfactant is introduced into an aqueous phase, an interface is formed between the oil and water. Self-emulsification occurs due to the penetration of water into the liquid crystalline (LC) phase that develops at the oil–water/surfactant interface. This LC phase readily allows water penetration, which is facilitated by gentle agitation. As water continues to infiltrate the LC phase beyond a critical level, the interfacial structure becomes unstable, leading to its disruption and the subsequent formation of fine emulsion droplets.

According to the theory proposed by Reiss, self-emulsification occurs when the increase in entropy associated with dispersion exceeds the energy required to create a new interfacial surface. The free energy change

associated with the emulsification process can be expressed as:

$$\Delta G = \Sigma N_i \pi r^2 \sigma$$

where:

- **ΔG** = Free energy associated with the emulsification process (excluding the free energy of mixing)
- **N** = Total number of droplets
- **r** = Radius of the droplets
- **σ** = Interfacial energy (surface tension) between the oil and aqueous phases.

COMPONENTS OF SMEDDS

OIL

Oil is a key component of Self-Microemulsifying Drug Delivery Systems (SMEDDS) as it dissolves lipophilic drugs, facilitates self-emulsification, and enhances gastrointestinal absorption by promoting lymphatic drug transport. The choice of oil significantly influences drug solubility and nanoemulsion formation. Medium-chain triglycerides (MCTs) are commonly preferred due to their high solubilization capacity, oxidative stability, and excellent emulsification properties. Other oils, such as olive oil, soybean oil, sesame oil, corn oil, palm oil, and oleic acid, are also used. Typically, oils constitute 40–80% of the formulation, with modified and hydrolyzed vegetable oils being favored because of their superior solubilization potential, compatibility with surfactants, and safety for oral administration.

SURFACTANTS

Surfactants play a crucial role in Self-Microemulsifying Drug Delivery Systems (SMEDDS) by enhancing the solubility of hydrophobic drugs in the oil phase and facilitating the dispersion of the formulation upon dilution with gastrointestinal (GI) fluids. They also improve drug bioavailability by increasing membrane permeability, preventing drug precipitation within the GI lumen, and maintaining the drug in a solubilized state for an extended period, thereby promoting efficient absorption. Typically, surfactants are incorporated at concentrations ranging from 30% to 60% of the formulation. By accumulating at the oil–water interface and orienting themselves around the internal oil phase, surfactants reduce interfacial tension and stabilize the microemulsion, resulting in the formation of a thermodynamically stable and finely dispersed system.

COSURFACTANTS

In Self-Microemulsifying Drug Delivery Systems (SMEDDS), high concentrations of surfactants are often required to significantly reduce interfacial tension; however, excessive surfactant levels may cause gastrointestinal irritation. To overcome this limitation, cosurfactants are incorporated to reduce the amount of surfactant needed while enhancing the solubilization of both lipophilic drugs and hydrophilic surfactants within the lipid phase. Cosurfactants also further lower the oil–water interfacial tension, facilitating the rapid and spontaneous formation of microemulsions upon aqueous dilution. Generally, cosurfactants with hydrophilic–lipophilic balance (HLB) values ranging from 10 to 14 are used in combination with surfactants to achieve a substantial reduction in interfacial tension, often resulting in transient negative interfacial free energy, while imparting sufficient flexibility to the interfacial film for the formation of a stable microemulsion.

4. SOLID CARRIER

For **Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS)**, solid carriers are used to convert liquid SMEDDS into powders, granules, pellets, or tablets by adsorption or solidification. Commonly used solid carriers include.

- Neusilin® – High adsorption capacity, excellent flow properties, and widely used for S-SMEDDS.
- Aerosil® 200 – High surface area adsorbent that improves powder flow and converts liquid formulations into free-flowing powders.
- Microcrystalline Cellulose (MCC) – Commonly used as a filler and adsorbent in tablet and capsule formulations.

Among these, **Neusilin®**, **Microcrystalline Cellulose®** and **Aerosil® 200** are the most widely used solid carriers for preparing S-SMEDDS because of their high adsorption capacity, good flowability, and ability to maintain self-emulsifying properties after solidification.

SOLUBILITY STUDY

The solubility of tacrolimus in various vehicles, including oils, surfactants, and co-surfactants, was evaluated using the shake-flask method. An excess amount of tacrolimus was added to vials containing 1 mL of each selected vehicle. The vials were sealed, and the mixtures were vortexed at maximum speed for 10 minutes to ensure thorough mixing. Subsequently, the samples were placed in an orbital shaker and maintained at room temperature for 24 hours to achieve equilibrium. After equilibration, the mixtures were centrifuged at 15,000 rpm for 10 minutes, and the supernatant was filtered through Whatman filter paper. The filtered samples were analyzed using a validated high-performance liquid chromatography (HPLC) method. The chromatographic analysis was performed using 100% acetonitrile as the mobile phase at a flow rate of 0.9 mL/min, with UV detection at 213 nm. Quantification was carried out using a calibration curve prepared with tacrolimus concentrations ranging from 5 to 250 µg/mL, which demonstrated excellent linearity.

SCREENING OF SURFACTANTS AND COSURFACTANTS BASED ON EMULSIFYING ABILITY

The emulsifying efficiency of the selected surfactants and co-surfactants was assessed based on their emulsification capacity using a previously reported method. Briefly, oil, surfactant, and co-surfactant were mixed in a ratio of 1:2:1, followed by cyclomixing for 5

minutes. The mixtures were then heated to 40°C to obtain a homogeneous blend. An accurately weighed 50 mg portion of each mixture was diluted with double-distilled water to a final volume of 50 mL to form a fine emulsion. The prepared emulsions were visually evaluated for physical appearance, optical clarity, and phase separation over a period of 12 hours. In addition, the percentage transmittance of each emulsion was measured at 638.2 nm using a UV–Visible spectrophotometer to assess its emulsifying performance.

METHOD OF PREPARATION

Recently reported methods can be used to prepare self-microemulsifying drug delivery systems (SMEDDS). This approach involves adding predetermined quantities of oil, surfactant, and co-surfactant into a vial, followed by gentle mixing to obtain a homogeneous mixture. Upon complete dissolution of the components, a clear and transparent SMEDDS formulation is formed. In some cases, the drug is first dissolved in one of the excipients, after which the remaining excipients are added to the drug solution. The resulting mixture is then thoroughly blended and carefully examined for any signs of turbidity. Finally, the formulation is allowed to equilibrate at room temperature for 48 hours before further evaluation. necessary to apply heat to facilitate the production of a clear solution. The selection of appropriate capsule size (26) for storage of the formulation is contingent upon the ultimate volume.

Phase Titration Method

The phase titration method, also referred to as the spontaneous emulsification technique, is widely used for the preparation of microemulsions. The resulting microemulsion systems are commonly characterized and illustrated using phase diagrams, which provide valuable insight into the interactions among the formulation components. Depending on the composition and concentration of the constituents, various self-assembled structures may form, including emulsions, micelles, lamellar, hexagonal, cubic phases, as well as gel-like and viscous dispersions.

The construction of phase diagrams requires a thorough understanding of the equilibrium conditions of the system and the identification of phase boundaries. In practice, pseudo-ternary phase diagrams are preferred over quaternary phase diagrams because they are simpler to construct, less time-consuming, and easier to interpret. In a pseudo-ternary phase diagram, each apex represents 100% of one formulation component or component mixture, enabling clear visualization of different phase regions, including the microemulsion region. Furthermore, the diagram facilitates the classification of microemulsions as either water-in-oil (w/o) or oil-in-water (o/w) systems based on their composition. Careful evaluation of the phase diagram is essential to distinguish thermodynamically stable microemulsions from metastable systems.

Phase Inversion Method

Phase inversion in microemulsions occurs when an excess amount of the dispersion medium is added or when the system temperature is increased. This phenomenon results in significant physicochemical changes, particularly alterations in droplet size, which can influence drug release both *in vitro* and *in vivo*. Phase inversion is achieved by modifying the spontaneous curvature of the surfactant film.

One of the most widely used approaches is the phase inversion temperature (PIT) method, which employs non-ionic surfactants. As the temperature increases, the surfactant affinity shifts, causing the microemulsion to transition from an oil-in-water (o/w) system at lower temperatures to a water-in-oil (w/o) system at higher temperatures. During the subsequent cooling process, the system passes through a phase of near-zero spontaneous curvature and ultra-low interfacial tension, promoting the formation of finely dispersed oil droplets and a stable microemulsion.

In addition to temperature, phase inversion can also be induced by altering factors such as pH, salt concentration, or water content. Gradual addition of water to an oil phase initially results in the formation of water droplets dispersed within the continuous oil phase (w/o microemulsion). As the water content increases, the spontaneous curvature of the surfactant changes, eventually reaching the inversion point where the system transforms into an oil-in-water (o/w) microemulsion. Surfactants with shorter hydrocarbon chains form flexible interfacial monolayer.

PREPARATION OF LIQUID SMEDDS

The formulations were prepared by dissolving the required amount of tacrolimus in the mixture of oil, surfactant and co-surfactant, at 40°C in a water bath. This mixture was mixed by vortexing until a transparent preparation was obtained. Then, a formulation equivalent to 5 mg tacrolimus was manually filled in a hard gelatin capsule of size “1”.

PREPARATION OF SOLID SMEDDS

Thermodynamically stable liquid SMEDD was converted to solid SMEDDS to get the advantage of the solid dosage form. Theprepared liquid formulation of tacrolimus was added drop-wise on a solid carrier in glass mortar. The mixture was physically mixed until uniform free-flowing powder was obtained. This powder was screened through a 40# sieve. Then the powder was filled in a “00” size hard gelatin capsule shell.

CHARACTERIZATION AND EVALUATION OF SMEDDS

1.) Particle Size

The particle size of the prepared formulation can be determined using proton correlation spectroscopy (PCS), also known as dynamic light scattering (DLS), or

scanning electron microscopy (SEM). These techniques are capable of measuring particle diameters within the range of 10–5000 nm, providing information on the size distribution and homogeneity of the formulation.

2) Zeta Potential Measurement

The zeta potential of the formulation is determined to evaluate the surface charge and predict the physical stability of the microemulsion. Zeta potential, also known as electrokinetic potential, represents the electrical potential at the slipping plane of dispersed particles and serves as an indicator of colloidal stability. The analysis is performed using a Zetasizer HAS 300 instrument. Before measurement, the disposable zeta cell is thoroughly cleaned with methanol and rinsed with the sample to eliminate contaminants. The sample is then transferred into the zeta cell, and the instrument records the zeta potential values under the specified experimental conditions.

3) Visual Assessment

The self-emulsification performance of the formulation was evaluated by introducing an appropriate quantity of the formulation into 100 mL of distilled water contained in a glass Erlenmeyer flask maintained at 25 °C. The contents were gently mixed by manual agitation, and the emulsification behavior was visually observed. The efficiency of self-emulsification was assessed based on the ease of emulsion formation and the appearance of the resulting dispersion. Formulations that rapidly produced a clear or transparent emulsion were considered to exhibit good self-emulsifying properties, whereas those showing slow emulsification or poor emulsion formation were regarded as having inferior

4) Determination of Self-Emulsification Time

The USP 22 dissolution apparatus is employed for the assessment of the emulsification duration of self-micro emulsifying drug delivery systems (SMEDDS). A quantity of 300mg of the sample composition is introduced into 500ml of distilled water at a temperature of 30°C. The mixture is subjected to mild agitation using a standard stainless steel dissolution paddle revolving at a rate resulting in an emulsion time of 50 ppm.

5.) Drug content

SMEDDS equivalent to 25 mg CVD were weighed, suitably diluted with methanol and estimated for drug content by developed and validated HPLC method. The analysis was performed in triplicate.

6) In-Vitro Study

The in-vitro drug release study is carried out to compare the release profile of Metformin from SMEDDS with that of the pure drug. The test is performed using a USP dissolution apparatus II (paddle method), with the dissolution medium set to Simulated Gastric Fluid (pH 1.2).

7) %Transmittance

Transmittance is measured using a UV spectrometer to verify the stability of the optimised for emulsion formation with regard to dilution (UV-1700nm).

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