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SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEMS: ADVANCES AND EMERGING TRENDS

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Abstract:
Most modern medicines don't dissolve well in water, which often leads to poor absorption after they're taken. This is especially typical with lipophilic medicines—drugs that stick to fat more than water. A solid solution to this limitation in lipid-based drug delivery is the Self-Micro emulsifying Drug Delivery System, or SMEDDS. The blend of oil, surfactant, co-surfactant, and drug in equal proportions is called SMEDDS. When swallowed, it mixes with stomach fluids and instantly forms a tiny oil-in-water mixture. This method boosts the drug's surface area, making it more soluble—and that helps it absorb better in the gut and become more available in the body. SMEDDS work especially well for drugs that don't dissolve easily in water or break down poorly. They usually come in soft or firm gelatin capsules. Surfactants like Tween 80 help medications cross the intestinal barrier by boosting absorption through better membrane penetration. A lot of newly discovered drugs don't dissolve well in water, and that's holding back progress in modern medicine. That's why SMEDDS are a great way to boost the solubility, dissolution, absorption, and bioavailability of poorly soluble drugs.

Key Words: *SMEDDS, Poorly water-soluble drugs, Lipophilic drugs, Solubility enhancement, Dissolution enhancement, Microemulsion, Lipid-based drug delivery, Drug absorption*

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INTRODUCTION:

One big hurdle in developing new drugs is that lots of drug candidates just don't dissolve in water. Over half of all newly made drugs with pharmacological activity fall into this category. Because lipophilic drugs don't dissolve well in water, scientists use tricks like salt formation, pH tweaks, β-cyclodextrin binding, or microemulsions to get them absorbed by the body. But the Self-Micro emulsifying Drug Delivery System (SMEDDS)—a new way to boost bioavailability for hard-to-absorb drugs—is quickly gaining popularity. SMEDDS is a type of emulsion specifically made to help drugs that don't absorb well in the gut get into the bloodstream more effectively. These formulas typically rely on oil and surfactants, and occasionally include co-surfactants. These formulations mix easily with water to create smooth emulsions, needing little energy to get started. There's also a similar formulation called Self-Emulsifying Drug Delivery Systems (SEDDS). Natural and synthetic oils, along with surfactants—and occasionally hydrophilic solvents or co-solvents—are blended into isotropic mix They'll gently mix in the stomach or intestines, blending with digestive fluids to form tiny microemulsions or fine oil-in-water droplets. Spreading the medication evenly across the GI tract helps reduce irritation, since small droplets avoid harsh, prolonged contact with sensitive gut lining. The increased surface area presented for absorption which enhances the rate and consistency of drug absorption into the circulation system is one of the major advantages of using SMEDDS and SEDDS. For drugs with low solubility, the improved absorption translates into enhanced drug absorption and blood level consistency.[2,3]One of the benefits associated with microemulsions is their thermodynamic stability, excellent solubilizing potentiality and protection of drugs from enzymatic degradation. A disadvantage of using microemulsions is their high lipid and water content which makes them bitter tasting and challenging to formulate in capsule formulation and thus impairs patient compliance.[4]An approach which has been proposed to overcome these limitations is through the development of anhydrous SMEDDS formulation.This dry form retains all the benefits of self-emulsification and allows for the easy encapsulation of the formulation. Since no external mixing and energy is needed for the emulsification process, these emulsions exploit These dry formulations retain all the advantages of auto-emulsification while being capable of encapsulation and convenient handling and dosing. They utilize the natural peristalsis of the stomach for the process of emulsification; hence, there is no need for any external mixing.[5]

To sum up, SMEDDS are a great substitute for traditional tablets or capsules, particularly for lipophilic medications with weak dissolving properties. Better outcomes are made possible by SMEDDS's enhanced medication absorption and dissolution.

MECHANISM OF SELF EMULSIFICATION

Self-emulsification is a phenomenon in which the energy saved from spreading one liquid in another (such as oil in water) is more than the energy required for making new surfaces between the two. This means that the energy released is sufficient to make small droplets without the help of any external energy.[6,7]

In traditional emulsions, the free energy (ΔG\Delta GΔG) needed to form new droplets depends on how much energy it takes to create new surfaces between oil and water. It can be expressed by the equation:

$$\Delta G=\sum N \prod r\, 2\, \sigma$$

Where, ΔG is the free energy (ignoring the free energy of mixing)
N is the number of droplets,
r is the radius of droplet,
σ is interfacial energy with time,

Since energy minimization is inherent to any system, there is a tendency for the two components of an ordinary emulsion to get separated due to the absence of stabilization elements. For this reason, the emulsifiers create a film around the droplets, minimize the surface tension and prevent merging. Self-emulsification, in turn, means that either a small amount of energy is needed for the formation of the emulsion, or the process can happen without any additional energy, with just a slight agitation in the stomach or intestine. This possibility arises because the system was designed to facilitate the easy and spontaneous creation of droplets, and the ingredients—such as oils and surfactants—were chosen to be compatible and simple to combine on a molecular level. Some preliminary studies indicate that the rate at which water can enter organised liquid phases formed at the oil-water interface affects the emulsification process.

In case when oil and a non-ionic surfactant mixture is applied to water, a layer is formed at the interface of these phases. Water begins entering the oil layer until it achieves the limit of dissolution. Further, a liquid crystalline layer begins to be formed. As more water seeps in, crystals start to form and eventually divide into tiny droplets. A stable emulsion is created through spontaneous disintegration aided by minimal mechanical treatment. The liquid crystal layers that surround each droplet are thought to be related to the stability of such droplets.[8,9]

For instance, investigations conducted with the use of particle size analyzer and dielectric spectroscopy

have demonstrated the role of liquid crystal formation in creation of the emulsions of systems, such as Imwitor 742 (glyceride) and Tween 80. Nevertheless, this process is quite complicated and the introduction of drug in a mixture could influence it.[10,11]

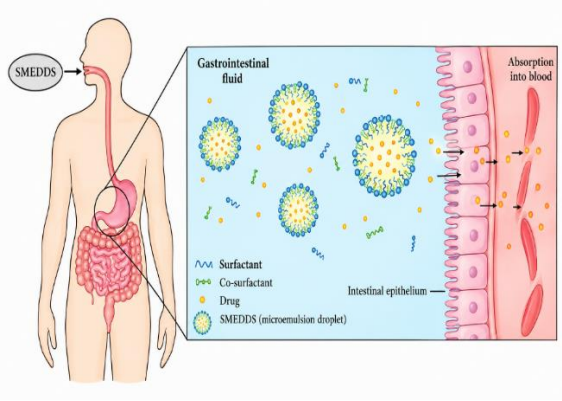

Figure 1: Mechanism of self-emulsification

ENHANCING ORAL ABSORPTION THROUGH SMEDDS

The Self-Microemulsifying Drug Delivery System (SMEDDS) improves the oral absorption of drugs that are poorly soluble in water and hydrophobic by forming fine oil droplets in gastrointestinal fluids. The small droplet size of SMEDDS enhances the surface area available for drug delivery, and the lipophilic nature of the formulation aids in dissolving and absorbing the drug. In comparison to typical oil-in -water emulsion systems, SMEDDS are physically stable, easy to administer, and suitable for use in soft gelatin capsules. Preclinical and clinical studies have shown that drug absorption via SMEDDS is improved with higher values of Cmax and AUC. Thus, SMEDDS can enhance the solubilization, dissolution, and absorption of poorly water-soluble drugs.[12]

DRUG INCORPORATION INTO SMEDDS

Developing drugs that have low water solubility presents multiple difficulties, particularly because their high hydrophobicity renders them insoluble in most common pharmaceutical solvents. Fortunately, newer synthetic hydrophilic oils and surfactants seem to dissolve hydrophobic drugs more effectively than traditional vegetable oils. Additionally, to enhance the drug's solubility in the formulation, solvents like ethanol, PG, and PEG are commonly included. How easily the drug can be incorporated into a Self-Microemulsifying Drug Delivery System (SMEDDS) largely depends on its interactions with the formulation. Each drug is distinct and will likely exhibit different levels of compatibility with SMEDDS formulations, depending on its physical and chemical characteristics. This type of interference can arise via several mechanisms: the drug might interact with certain components and affect charge movement, or it could form complexes with the LC phase of the system. Additionally, it may pass through the surfactant layer at the oil-water interface, influencing the creation of monodisperse droplets. Therefore, the distribution of droplet sizes will vary based on the quantity of the drug. The most significant point is that SMEDDS systems generating small, complex oil droplets are more susceptible to such interferences. Thus, to successfully prepare SMEDDS, a preformulation study including solubility assessment and phase diagram development is essential.[12]

CONSTRUCTION OF PHASE DIAGRAM

Understanding how different ingredients in a formulation interact and behave is crucial for preparing effective microemulsions, and this can be accomplished by constructing a phase diagram. Phase diagrams are useful in indicating the relation between the composition of the mixture and the physical phase that is formed. Even though different temperatures and pressures may be applied in the analysis of these systems, most pharmaceutical microemulsion investigations are conducted at room temperature and ambient pressure unless special solvents such as supercritical fluids and HFA propellants are used. In ternary system comprising of only oil, water, and surfactant, ternary phase diagram is normally used. However, in the real-life situations where the pharmaceutical formulations consist of more than three components such as co-surfactants and the drug itself, the situation becomes more complicated. Co-surfactants are additives that help stabilize microemulsions and make them easier to prepare. They are amphiphilic, similar to surfactants, and thus exhibit both hydrophobic and oleophobic properties. They may not always aggregate to form micelles and other aggregates, but assist the primary surfactant at oil-water interface. Some of the common co-surfactants include alcohols, fatty acids, diols, and amines.

Notably, despite most drugs being surface-active agents and hence capable of influencing the behavior of the system, little has been done to explore the impact of drugs on phase behavior (as mentioned by Kawakami in 2002). This is a phenomenon that should be explored further considering its influence on the performance of the mixture. In the case where there are four or more components – such as oil, water, surfactant, co-surfactant and drug – the pseudo-ternary phase diagram is applied. Pseudo-ternary phase diagram has corners where different combinations of the ingredients can be placed, such as oil/drug, surfactant/co-surfactant and water/drug. This helps to understand how the system will behave in terms of the behavior of the ingredients and the possibility of obtaining stable microemulsions depending on

their compositions. It is noteworthy that not all compositions of ingredients result in the production of microemulsions across the entire range. In many cases, the microemulsion region is limited.[13]

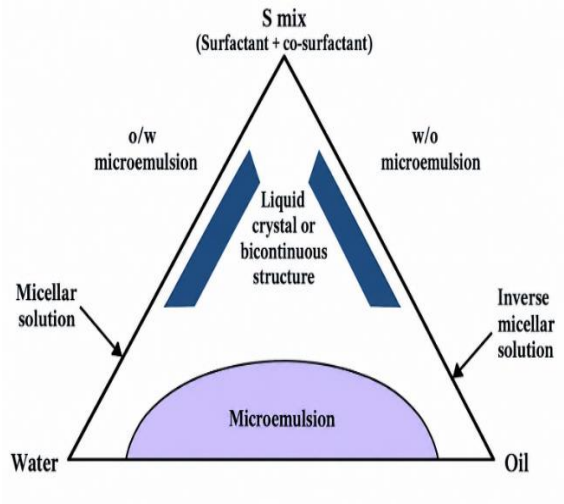

Figure 2: Phase diagram

FORMULATION OF SMEDDS

SMEDDS consist of several carefully chosen components that work together to improve the absorption of drugs with poor water solubility in the body. Let us examine the role of each component:

1. Oils

These are the key components of the SMEDDS formulation. They not only dissolve lipophilic drugs but also help form the emulsion and enhance drug absorption, particularly via the intestinal lymphatic system, thereby boosting bioavailability the proportion of the drug that reaches the bloodstream.

Types of oils:

- Long-chain triglycerides (LCTs)
- Medium-chain triglycerides (MCTs)

- Modified vegetable oils (like semi-synthetic or hydrolyzed oils) are often used because they combine solubilizing power with better stability.
- Some semi-synthetic MCTs also work like surfactants, so they serve more than one purpose.[14]

2. Co-solvents

Co-solvents assist in dissolving drugs and surfactants within the oil phase, which is particularly helpful when the drug does not readily mix with oil by itself.

Common co-solvents include:

- Transcutol® (diethylene glycol monoethyl ether)
- Propylene glycol
- Polyethylene glycol (PEG)
- Propylene carbonate
- Glycofurol

Some co-solvents can function similarly to co-surfactants, offering additional flexibility in the formulation.

3. Surfactants

Surfactants play a crucial rolethey reduce the surface tension between oil and water, enabling the creation of small oil-in-water droplets known as microemulsions.

- Preferably non-ionic surfactants with high HLB values (Hydrophilic-Lipophilic Balance)

Common examples:

- Tween
- Labrasol
- Labrafac CM 10
- Cremophor

- These make up 30–60% of the formulation.
- They also help keep the drug dissolved and prevent it from precipitating out inside the gut.[15,16]

4. Co-surfactants

Co-surfactants work alongside surfactants to further reduce interfacial tension, making the emulsion process even easier and more efficient.

- Ideal HLB range: 10–14
- They expand the interfacial layer, allowing more surfactant to stay active and stabilize the emulsion.
- In some cases, if the surfactant is powerful enough, a co-surfactant may not be necessary.

5. Consistency Builders

Although commonly employed in solid SMEDDS, consistency agents help regulate the viscosity and stability of the formulation. This is especially pertinent when converting a liquid SMEDDS into a more convenient solid dosage form.

6. Polymers

Polymers provide structure and control in solid SMEDDS. They help form a stable matrix that can affect how the drug is released over time.

- These are usually non-ionizable at physiological pH, which makes them stable in the body.
- Typically used in 5–40% of the formulation.
- Common examples:
  - Hydroxypropyl Methylcellulose (HPMC)
  - Ethyl Cellulose

Overall, each of these components contributes uniquely and is vital to creating a stable and effective SMEDDS. By carefully choosing and blending them, scientists can develop oral formulations that greatly enhance the absorption of difficult-to -dissolve, poorly water-soluble drugs.[17]

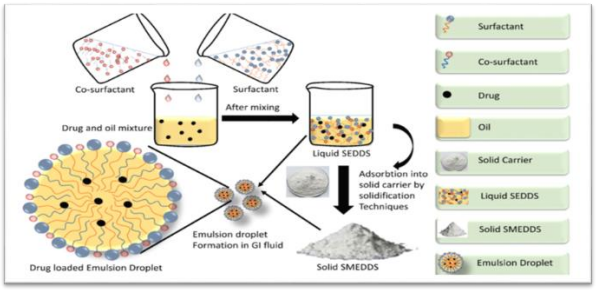

Figure 3: Pictorial Representation of SMEDDS

ADVANTAGES

1. Enhanced Oral Bioavailability

The key advantage of SMEDDS is their capacity to significantly improve the oral bioavailability of drugs. As is well known, SMEDDS are formulated as microemulsions, consisting of droplets with sizes between 1 and 100 nanometers. This feature increases the surface area available for absorption by the intestinal wall, thereby enhancing permeability through it.

Example: The antimalarial drug halofantrine showed 6 to 8 times greater bioavailability when given as SMEDDS rather than standard tablets.[18]

2. Cost-effectiveness and Simplicity of Production

SMEDDS can be manufactured using standard equipment like mixers and liquid fillers. Therefore, SMEDDS are both inexpensive and easy to scale. Minimizes variation both between and within individuals. Some drugs vary significantly in how well they are absorbed from person to personor even within the same individual at different times. Food can also affect how well many drugs work. But SMEDDS reduce these variations. Many studies have shown that SMEDDS can provide a consistent drug absorption profile, regardless of food intake or individual differences.[19]

3. Can Deliver Fragile Peptides and Proteins

These usually break down easily in the stomach. But SMEDDS can protect these delicate molecules and help them reach the bloodstream. They do this by shielding them from enzymes and acidic conditions in the gut.

For example, Polysorbate 20 in SMEDDS can protect peptide drugs from being broken down by digestive enzymes like cholinesterase.

Also, since SMEDDS form without needing heat or high energy, they are suitable for heat-sensitive (thermolabile) drugs like peptides.

4. Not Affected by Lipid Digestion

Unlike certain other lipid-based drug delivery systems, SMEDDS do not depend on digestion by bile salts or enzymessuch as pancreatic lipasesto function. This increases their predictability and reliability.[20]

5. Higher Drug Loading Capacity

SMEDDS can hold more drug compared to traditional oil-based systems. This is because many poorly water-soluble drugs dissolve better in the surfactants, co-surfactants, and co-solvents used in SMEDDS, rather than in natural oils.

6. Controlled or Extended Release with Polymers

Adding polymers to the SMEDDS formulation can delay the drug's release. This implies the drug remains in the body for a longer duration, which could mean it needs to be taken less frequently.

7. Protection from the Harsh Gut Environment

SMEDDS can shield drugs from breakdown due to the acidic and enzymatic environment in the gastrointestinal tract, thereby helping more of the active drug reach the bloodstream unchanged.[21]

DISADVANTAGES

While SMEDDS offer many benefits, they also come with a few challenges that researchers and formulators need to be aware of:

1. Lack of in Vitro Testing Models

One of the main drawbacks is that good laboratory models (in vitro tests) for predicting how SMEDDS will perform in the body are still lacking. This makes it difficult to know how well a formulation will work before testing it in animals or humans.

- These lab models need more research, development, and validation to become reliable tools.
- A lot of progress in SMEDDS depends on in vitro–in vivo correlation (IVIVC)

2. Need for Animal Testing During Development

Because of the limited lab models, different versions of SMEDDS must often be tested in animals to find the most effective one. This makes more time-consuming and costly.

3. Possible Chemical Instability and Irritation

Some drugs can be chemically unstable when mixed into SMEDDS, especially if the formulation includes high concentrations of surfactants (typically 30–60%). These high surfactant levels can also irritate the gastrointestinal tract, leading to discomfort or side effects in some patients.

4. Volatile Co-Solvents Can Cause Issues in Capsules

Many conventional SMEDDS employ volatile co-solvents that readily evaporate. These co-solvents may migrate into the shell of soft or hard gelatin capsules, potentially resulting in:

- Weakening of the capsule structure, and
- Precipitation of the drug takes place

5. Drug May Precipitate Upon Dilution

When SMEDDS mix with body fluids (especially water), there's a risk that the drug may come out of solution and precipitate, especially if hydrophilic (water-attracting) solvents are used. This limits how

much of the drug can be absorbed and could decrease its effectiveness.

EVALUATION OF SMEDDS

1. **Thermodynamic stability studies:**

Physical stability of SMEDDS is very critical for proper functioning and consumer acceptability of the drug. If the drug begins to precipitate from the formulation or if there is separation of the components from each other, then it can:

- Lower the effectiveness of the drug
- Cause visual defects like cloudiness or uneven texture
- Lead to problems with the capsule shell (like brittleness or delayed disintegration)
- Potentially reduce safety and consistency during use

To ensure the formulation remains stable under different environmental conditions, thermodynamic stress tests are performed. These tests help simulate real-storage and handling conditions.

2. **Heating–Cooling Cycle:**
   - The formulation undergoes six temperature cycles, alternating between refrigerator temperature (4 °C) and an elevated temperature (45 °C).
   - At each temperature, it is stored for at least 48 hours.
   - This checks how the formulation holds up under extreme temperature changes.
   - Only formulations that stay stable (no clouding or separation) are moved to the next test
3. **Centrifugation Test:**
   - The formulation is centrifuged at 3500 rpm for 30 minutes.
   - This mimics the force that could cause separation during shipping or handling.
   - If the formulation shows no phase separation, it passes and moves on to the freeze–thaw test
4. **Freeze–Thaw Cycle:**
   - The formulation undergoes three freeze thaw cycles, with storage alternating between freezing and room temperatures (typically ranging from -20 °C to +25°C).
   - Each stage lasts at least 48 hours.
   - A stable formulation will show no signs of:
     - Phase separation
     - Creaming (oil floating to the top)
     - Cracking (breaking of emulsion structure)[23]
5. **Dispersibility test:**

The Dispersibility Test is used to check how efficiently a SMEDDS (or SEDDS) formulation can self-emulsify—basically, how well it mixes with digestive fluids once swallowed.

- Dispersibility test is performed using a USP Dissolution Apparatus II.
- 1 mL of the SMEDDS formulation is added to 500 mL of water at body temperature (37 ± 0.5 °C).
- A paddle rotates at 50 rpm, gently stirring the solution—just like how food and medicine are mixed in the stomach.
- The way the formulation disperses is visually observed and graded.

Grading system:

- **Grade A:** Forms quickly (within 1 minute) a clear or faintly bluish nanoemulsion.
- **Grade B:** Forms a slightly less distinct emulsion quickly, appearing bluish-white and cloudy.
- **Grade C:** A fine milky emulsion forms within 2 minutes.
- **Grade D:** Produces a dull, greyish-white emulsion with a faint oily sheen, requiring more than 2 minutes to fully emulsify.
- **Grade E:** Poor or minimal emulsification, with oil droplets visible on the surface.

This test helps predict how well the formulation will behave inside the body. The faster and clearer the emulsion forms, the better the drug is likely to be absorbed.[23]

6. **Turbidimetric Evaluation:**

Turbidimetric analysis is a technique that allows assessment of how effectively and quickly an emulsion forms using a Self-Micro Emulsifying Drug Delivery System (SMEDDS). The turbidimetric analysis is performed in an aqueous phase to determine the rate at which the emulsion forms.

1. A fixed amount of the SMEDDS formulation is added to a set volume of a suitable aqueous medium, typically 0.1 N hydrochloric acid (to mimic gastric conditions).
2. The solution is kept for strring at 50 rpm using a magnetic stirrer at room temperature.
3. As the SMEDDS begins to emulsify, the mixture turns cloudy or milky depending on droplet size and dispersion.
4. A Nephloturbidimeter is used to measure turbidity, which indicates how much light is scattered by the droplets in the emulsion.[24,25,26]

7. **Droplet Size:**

In SMEDDs, droplet size isn't essentially a number that's a parameter whose value can affect the drug's effectiveness and absorption rate. As droplet size decreases, the surface area available

for drug release increases significantly, thereby enhancing the dissolution rate and overall bioavailability of the drug. Smaller droplets possess larger surface areas, allowing them to interact more effectively with the body's absorption sites, like the intestines. Several scientific tools and techniques are used to accurately measure the size of droplets in a SMEDDS formulation:

- Photon Correlation Spectroscopy (PCS), also known as Dynamic Light Scattering (DLS) – a common and precise method.
- Microscopy – helps visualize droplet shape and size.
- Coulter Nanosizer – used to count and determine size of droplets.

In SMEDDS, the droplet size is generally less than 50 micrometres (μm). At this scale, the system produces a well-defined, stable, and uniformly distributed oil-in-water (o/w) emulsion that improves both drug solubility and absorption particularly for drugs with low water solubility. [27]

8. Viscosity Measurement:

Viscosity tells us how "thick" or "flowy" the formulation is, which affects:

- Encapsulation in soft/hard gelatin capsules
- Ease of manufacturing
- Performance in the body

A Brookfield Viscometer is used to assess viscosity and flow behaviour.

- Low viscosity: Likely an oil-in-water (o/w) emulsion—ideal for oral delivery.
- High viscosity: Suggests a water-in-oil (w/o) emulsion—less suitable for oral use.[28]

9. Zeta potential measurement:

For self-emulsifying drug delivery systems (SMEDDS), maintaining emulsion stability is crucial to ensure consistent drug delivery. Zeta potential: an indicator of the electrical charge on the surface of emulsion droplets.

To measure zeta potential in SMEDDS:

- The formulation is first diluted in distilled water at a 1:2500 (v/v) ratio.
- It's gently stirred to allow the formation of a microemulsion.
- This mixture is then analysed using an instrument called a Zetasizer (such as those from Malvern Instruments), which calculates the zeta potential based on how the droplets move in an electric field.

In general, a zeta potential greater than ±30 mV (that's either more negative than −30 mV or more positive than +30 mV) is considered a sign of strong electrostatic repulsion. This means the emulsion droplets are less likely to merge or settle over time—making the formulation physically stable and more reliable.[30]

10. In vitro release:

The method most commonly used is based on the USP XXIV dissolution procedure.

- The test is conducted in 900 mL of purified distilled water, kept at body temperature (around 37°C).
- The SMEDDS formulation is placed inside a dialysis bag. This bag acts like a selective barrier—allowing the drug to diffuse out while holding back the rest of the formulation.
- Over a set period, researchers take 10 mL samples from the surrounding water at specific time points.
- Each sample is passed through a 0.45 μm membrane to eliminate any undissolved particles and is then diluted to the correct concentration.
- The drug concentration in each sample is then measured using a UV spectrophotometer.

To ensure accurate results, every time a sample is removed, an equal amount of fresh dissolution medium is added. This keeps the system in what's called "sink conditions"—making sure the drug continues to dissolve without reaching saturation.[31]

APPLICATIONS

- **Bioavailability:** One key advantage of SMEDDS is its ability to improve a drug's solubility, thereby boosting bioavailability, that is, the quantity of drug present in the body. This is beneficial for highly lipophilic drugs, since they typically exhibit low absorption rates.
- **Mitigation of Gastric Irritation:** Certain medications may cause gastric irritation, which could result in undesirable effects for patients. In such cases, SMEDDS can be very useful since they will ensure that the medication is contained within an emulsion, minimizing its interaction with the stomach.
- **Protecting the Drug against Biodegradation:** The GIT can sometimes be a very hostile place for medications since some of them are biodegradable. However, in certain cases, SMEDDS can form a barrier around the drug, which can protect it from biodegradation.
- **Enhanced Oral Drug Delivery:** SMEDDS are particularly useful for oral delivery of complex or sensitive drugs, such as those used in: Cancer therapy, Antiviral treatments, Migraine relief. By improving solubility and absorption, SMEDDS make it possible to deliver effective doses without requiring invasive methods like injections.

- **Conversion into Solid Dosage Forms:** Although SMEDDS are generally liquid, they can be transformed into solid dosage forms such as tablets, capsules, or pellets by incorporating solid carriers. This offers several advantages:
  - Improved long-term stability
  - Easier handling and storage
  - Protection from environmental factors

This flexibility makes SMEDDS attractive for commercial pharmaceutical products.

- **Nose-to-Brain Drug Delivery:** One of the more innovative applications of SMEDDS is in nasal delivery for brain targeting. By formulating SMEDDS for intranasal use, drugs can bypass the blood-brain barrier and reach the brain directly through the olfactory pathway. This approach shows promise for treating neurological disorders such as:
  - Alzheimer's disease
  - Parkinson's disease
  - Epilepsy [32,33,34,35]

RECENT ADVANCEMENTS IN SMEDDS

- **Self-micro emulsifying mouth dissolving film (SMMDF):** A new drug delivery formulation called the Self-Micro emulsifying Mouth Dissolving Film (SMMDF), proposed by Xiao et al. was developed to enhance the oral bioavailability of drugs that have poor solubility. This drug delivery system has been engineered by embedding self-micro emulsifying units into a solid carrier matrix made of microcrystalline cellulose (MCC), low-substituted hydroxypropyl cellulose (L-HPC), and Hypromellose (HPMC). Within 20 seconds, the SMMDF formulation broke apart and released the drug within 5 minutes in the disintegration medium. The mean globule size of the formed emulsion was 28.81 ± 3.26 nm, fulfilling the criteria specified in the Chinese Pharmacopeia 2010. In a pharmacokinetic study comparing SMMDF, fluid SMEDDS, and conventional formulations, it was observed that the SMMDF formulation significantly enhanced both Cmax (maximum plasma concentration) and AUC (area under the curve). In addition, the time to reach maximum concentration (Tmax) was notably shortened, indicating a quicker onset of action. Therefore, SMMDF is regarded as an advanced and convenient dosage form.[36]
- **Sponges Carrying SMEDDS:** A promising approach to address the limitations of liquid SMEDDS formulations involves using sponges as solid carriers. Although SMEDDS are very effective at improving the solubility of lipophilic drugs, their liquid form presents difficulties in storage, handling, and adherence by patients. To tackle this, researchers have created a sponge-like delivery system made from common hydrophilic polymers, capable of absorbing and holding SMEDDS within a solid structure. Using electron microscopy, this nano-sponge structure was analyzed, showing a porous framework containing finely distributed oil droplets. After drying, droplets of SMEDDS with an average size of 9 nm were observed on the surface of the dry sponge. Crucially, following rehydration, the sponge maintained its capacity to release the SMEDDS, demonstrating that its structure and function remained intact. To assess drug delivery performance, Nile Red, a lipophilic fluorescent dye, was included in the system. The dye was evenly distributed in both the dry and rehydrated sponges and was released slowly from the nano sponge structure. The drying method used had a significant effect on the release rate and also affected the sponge's ability to absorb water. This sponge-based system serves as a reliable foundation for SMEDDS, offering a practical and efficient method for delivering hydrophobic drugs. It enhances the stability, portability, and ease of dosing in SMEDDS formulations without compromising their solubilization efficiency.[36]
- **Herbal SMEDDS**: Besides the previously mentioned methods, Self-Microemulsifying Drug Delivery Systems (SMEDDS) have been suggested as a novel delivery approach for herbal extracts to enhance their poor solubility and bioavailability. Typically, SMEDDS systems are liquid formulations encapsulated in hard gelatin capsules. The development and optimization of herbal SMEDDS typically involve studying solubility and pseudo-ternary phase diagrams. For example, in the study carried out by Warke et al., The optimized formulation included Cremophor RH 40 at 40%, Plurol Oleique at 30%, and herbal extract at 30%. The optimized formulation was found to achieve full drug release within 10 minutes in the in vitro dissolution test. Under ICH storage conditions over a 3-month period, the formulation maintained its physical stability and solubilization capacity without any decline. Therefore, SMEDDS enhanced the dissolution profile of the herbal extract compared to conventional dosage forms. SMEDDS can be regarded as a highly promising approach for enhancing herbal medicine.[37]
- **Self-micro–Emulsifying Floating Dosage form:** Self-Micro- Emulsifying Floating Dosage Form: Some drugs with poor solubility, significant pre-systemic first-pass

metabolism, and inconsistent absorption throughout the gastrointestinal tract often exhibit reduced oral bioavailability. To address this challenge, self-micro emulsifying drug delivery systems in floating form (SMEDDS-based floating forms) have been developed. These drug delivery systems are capable of extending gastric residence time, thereby enabling sustained drug release in the stomach. One such system entails adsorbing the self-microemulsion onto a blend of functional excipients and matrix polymers, including HPMC E50LV, HPMC K4M, and sodium bicarbonate ($NaHCO_3$), which acts as a gas-generating agent. This approach results in the creation of a floating matrix system that ensures sustained drug release. In a separate study, floating alginate beads loaded with tetrahydro curcumin in SMEDDS formulation have been created to enhance solubility and prolong gastric retention. The formulation was fine-tuned by varying the concentrations of sodium alginate, calcium chloride (as a cross-linker), and a water-soluble pore-forming agent. They play a crucial role in influencing the floating behavior and in vitro drug release from the beads, as well as gastric retention. [38]

- **SE Capsules:** Conventional SE formulations face challenges in optimizing drug absorption due to the persistent phase separation in the microemulsion, which reduces the drug's bioavailability. To resolve this problem, some formulations include sodium dodecyl sulphate to increase stability of the emulsion and better solubilization of the drug. One step further in the advancement of traditional SE formulations is to develop Supersaturated Self-Emulsifying Drug Delivery Systems (S-SEDDS). This approach involves adding a small quantity of hydroxypropyl methylcellulose (HPMC) or similar polymers to avoid drug precipitation, thereby creating a supersaturated state in the body and enhancing absorption while reducing gastrointestinal side effects. To eliminate the disadvantages of liquid SMEDDS including high cost of manufacturing, incompatibility with soft gelatin capsules and low stability during storage, some researchers propose solid and semi-solid SMEDDS. This method implies transformation of the components of liquid self-emulsifiable system into solid or semi-solid state by using solid carriers such as polymers or adsorbents. For example, inclusion of the formulation into the solid PEG matrix allows preserving its self-emulsifying properties and drug solubility. For semi-solid formulations, the excipients are first melted, then filled into capsules, and finally solidified at room temperature. This approach improves handling, storage stability, and manufacturability, while still retaining the benefits of conventional liquid SMEDDS.[39]
- **SE implants:** Another use of self-emulsifying drug delivery systems in drug delivery devices stems from their capacity to enhance the stability of therapeutic agents released from implantable devices and also modulate their release rate. In the case of one such device, carmustine (BCNU)an anticancer drug with low water solubility was embedded into PLGA (polylactic-co -glycolic acid) wafers via SE technology. The SE system comprised of Cremophor RH 40, tributyrin, Labrafil MC 1944, and carmustine. This technology helped reduce the contact between BCNU and aqueous environment, thus minimizing its hydrolysis. SE-PLGA wafers were produced using compression moulding technique and had uniform smooth surfaces. In vitro studies demonstrated that BCNU release from SE wafers lasted longer than seven days and persisted more than with non-SE wafers. In addition, these SE-based implants demonstrated strong antitumor activity and were resistant to hydrolytic breakdown. Specifically, the in vitro half-life of carmustine was extended to 2 hours and 10 minutes, indicating improved drug stability.

CONCLUSION:

Using Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) represents an innovative method to enhance the oral bioavailability of drugs that are poorly water-soluble but highly lipid-soluble and potent. In addition to benefiting BCS Class II and IV drugs, SMEDDS can enhance the performance of all BCS classes by bypassing the dissolution step, thereby increasing absorption rate, reducing onset time, and improving bioavailability. The system enables the drug to be dissolved in lipid-based excipients, and in certain cases, supports the lymphatic delivery of highly hydrophobic drugs that dissolve well in triglycerides. The review covers multiple facets of formulation development, including solubility testing, creation of the pseudo-ternary phase diagram, and additional evaluation methods. Each of these steps is essential for successfully designing SMEDDS. Future studies should focus on creating non-toxic surfactants and more reliable in vitro techniques that better mimic in vivo conditions.

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