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Invitro Digestion Models of Self Emulsifying Drug Delivery Systems

Madhuri Pullemla, Dr. K. Annie Vijetha

Dept of Pharmaceutics, Centre for Pharmaceutical Sciences, UCEST,
Jawaharlal Nehru Technological University, Kukatpally, Hyderabad, Telangana ,500085
pullemlamadhuri1874@gmail.com

ABSTRACT

Self-emulsifying drug delivery systems (SEDDS) have a significant attention in recent years owing to their potential to improve the solubility and bioavailability of poorly water-soluble drugs. Understanding the behaviour of these systems during gastrointestinal transit is crucial for optimizing drug delivery efficacy. In vitro digestion models serve as valuable tools for studying the performance of SEDDS formulations under simulated physiological conditions. SEDDS formulation involves advantages in improving drug absorption. Subsequently, it discusses the physiological aspects of gastrointestinal digestion, highlighting the challenges encountered by SEDDS formulations during transit through the gastrointestinal tract. The role of in vitro digestion models in simulating the complexities of gastrointestinal digestion is thoroughly explored, encompassing static and dynamic models that mimic the physiological conditions of the stomach and intestine. It begins by explaining how SEDDS are made and how they help drugs enter the body more easily.. They focus on how the fats in SEDDS are broken down and which work best to ensure that the drug is absorbed and stays in the body. They are also working on new techniques to mimic real digestion using things like pH levels, enzymes and bile salts. These laboratory models are very important for designing SEDDS-based drug delivery systems that work well in real life and make drugs work better for patients.

Keywords: invitro digestion , SEDDS , gastrointestinal digestion , effi

INTRODUCTION

SEDDS, also called self-emulsifying drug delivery systems, are becoming very popular in medicine. They are like handy tools that improve medicines, especially those that don't mix well with water. This is a big deal because finding good treatments is very important.

These systems employ an emulsion, which is a blend of oil and water, to help the body absorb medications more efficiently, particularly those that are difficult to take orally. SEDDS is especially effective for medications in class II of the biopharmaceutical categorization system. These medications are poorly absorbed because they do not dissolve well in water, typically 10-40 milligrams. Transforming these systems into self-nanoemulsifying or self-microemulsifying drug delivery systems can improve their performance even more.

Simply put, SEDDS are made of oil, a soap-like substance called a surfactant, and another substance called co. -surfactant When they enter the body and mix with fluids, such as in the intestines, they form small oil droplets. These drops help dissolve medications and facilitate their absorption into the body. Different oils and surfactants can be used for different drugs to make these systems work better.

The use of SEDDS has many advantages over older drug delivery methods, especially for poorly water-soluble drugs. By encapsulating these types of drugs in tiny emulsion droplets, SEDDS helps them interact better with cell membranes, meaning they are absorbed more efficiently. This solves the problem of poor drug efficacy and unpredictable behavior often seen with poorly soluble drugs.

SEDDSs are also very flexible and can be adapted to different drugs and their uses. This flexibility extends to factors such as droplet size, types of surfactants and oils used, enabling tailored drug release and stability under different body conditions.

In addition to making drugs better, SEDDS also makes it easier for patients. that they take their medicine correctly. They can be made in liquid or semi-solid forms, which are easier to administer to people, especially children and older adults. This makes it more likely that people will adhere to their treatment plans, which ultimately means better outcomes for patients.

The development of self-emulsifying drug delivery systems is an important step forward in making medicine more effective. Through careful design and refinement, SEDDS offers a promising way to revolutionize drug delivery methods and improve patient care. They are versatile enough to work with many different types of drugs, including poorly soluble drugs, making it easier for patients to get the treatment they need.

IMPORTANCE OF SELF EMULSIFYING DRUG DELIVERY SYSTEMS IN ENHANCING ORAL BIOAVAILABILTY:

Self-emulsifying drug delivery systems (SEDDS) help oral drugs work better, especially those that do not dissolve well in water. These systems make small mixtures called emulsions or microemulsions in the intestine. This process helps the drug dissolve faster and be better absorbed. SEDDS can increase the amount of drug reaching the bloodstream by improving drug dissolution and crossing the intestinal mucosa, potentially leading to stronger effects. In addition, the SEDDS can be adapted to different doses and frequency of medication administration, which can facilitate patient adherence to the treatment plan. Because SEDDS can effectively deliver drugs that are fatty or poorly soluble in water, they have become very important in the development of new drugs and help ensure that the drugs work as well as possible.

One of the big challenges Many drugs that are; poorly water-soluble depends on how quickly they dissolve to be absorbed by the body. Self-microemulsifying drug delivery systems (SMEDDS) solve this problem by converting the drug into a dissolved and microemulsified form, where small spheres are typically 1-100 nanometers in size. This creates a much larger surface area for the drug, which facilitates the passage of the aqueous layer of the intestine and the intestinal mucosa. This improved transport means that more of the drug enters the bloodstream, resulting in greater effectiveness. For example, for a drug called halofantrine, using SMEDDS increased the amount of drug that entered the bloodstream about 6-8 times compared to taking tablets.

METHOD OF PREPARATION OF SEDDS:

The methods of preparation of SEDDS include,

1.High energy approach

2.High pressure homogenizer

3.Sonication method

4.Spontaneos emulsification method

5.Phase inversion method

High energy approach

The preparation of nanoemulsions usually requires a lot of energy. You have to use machines that mix things like surfactants, oil and another liquid called a co-solvent. This high-energy process is important because it helps break large droplets into really small ones, creating high-energy nanoemulsions. However, with nanoemulsifying drug delivery systems (SNEDDS) itself, it is a different story. They work on low power with a nice self-emulsifying trick. SNEDDS uses special ingredients that naturally form emulsions when they come into contact with water, so they don't need big machines or a lot of energy to mix them.

High pressure homogenizer

Nanoemulsions are usually made by using high pressure to mix ingredients such as surfactants, oil and another liquid called a cosolvent. This high-pressure method is important because it creates strong forces that break large droplets into very small ones, creating high-energy nanoemulsions. This method is based on two basic ideas: turbulence and cavitation. When the mixture is pressed under high pressure, it can form emulsions with tiny droplets of less than 100 nanometers. Many things, such as the type of machine used, the content of the mixture and the long and difficult process, can change the size of the drop. High-pressure homogenization is a common way to prepare these small emulsions for, for example, food, pharmaceutical and biotechnological applications.

Microfluidization is another way to prepare nanoemulsions. It uses a special device with small channels and a pump that pushes the mixture through. These channels help form small droplets. The droplets then undergo further processing in the device, making them even smaller and forming a truly fine nanoemulsion. Initially, the mixture forms a rough emulsion when water and oil are mixed together. However, after passing through the device, it becomes a clear and uniformly stable nanoemulsion.

Sonication method

Using sound waves, called sonication, is a great way to make self-nanoemulsifying drug delivery systems (SNEDDS). Compared to other methods that need a lot of energy, like high-pressure mixing, sonication has some advantages. It's cleaner and uses less energy. In this method, the sound waves create tiny bubbles in the mixture, which then burst and break down big emulsions into really small ones. This makes the droplets smaller, forming nano-sized emulsions. Ultrasonication works by shaking things up to make the droplets smaller, making it the best choice for making SNEDDS.

Spontaneous emulsification method

Spontaneous emulsification is a common way to prepare self-emulsifying drug delivery systems (SEDDS), which help make poorly water-soluble drugs more easily absorbed by the body. In this method, nature is allowed to do its work, which happens when the oily part of the medicinal mixture meets the

water and forms small droplets without additional energy. The preparation of these emulsions takes place in several steps, starting with the selection of the right oils and surfactants to match the properties of the drug.

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In this process, the oil part usually contains oils or special fats, such as medium-chain triglycerides, soybean oil or ethyl oleate. They are chosen based on how well they mix with the drug and their ability to make stable mixtures. Surfactants are then added. These can be different, such as Tween, sodium lauryl sulfate, or cetyltrimethylammonium bromide. They prevent small drops of mixture from sticking, so the mixture stays smooth for a while.

The lipid phase, which contains the medication as well as fats and surfactants, is blended with water first. To distribute this mixture uniformly, we might add other ingredients that combine nicely with water. We utilize delicate mixing methods, such as stirring with a magnet or spinning, to break things apart and form minute droplets. The hydrophilic-lipophilic balance (HLB), or balance of surfactant, water, and oil, is critical. If the surfactant contains more water, fewer droplets form and the mixture remains stable for longer.

When the oil mixture comes into contact with water, the tension between the oils and water diminishes, causing minute droplets to form. These droplets resemble little bubbles of oil surrounded by water. Surfactant molecules adhere to the outside of these droplets, generating a thin coating that prevents them from clumping together. This stabilizes the mixture, resulting in many little oil droplets floating in the water. We employ this combination to create a medicine delivery system that is ready to be administered to someone.

To summarize, the spontaneous emulsification method is a simple and effective way to make SEDDS that improves drug dissolution, stability, and efficacy in the body. It produces small emulsion droplets with no expensive technology or a lot of energy. This technology has the potential to develop novel ways to administer water-insoluble medicines, resulting in better therapeutic outcomes in a variety of applications.

Phase inversion method

The phase release method is a flexible way to prepare self-emulsifying drug delivery systems (SEDDS) that improve drug dissolution and absorption into the body. It works by replacing a mixture that is mostly oil with a little water, with a mixture that is mostly water with a little oil, or sometimes a mixture of both. This change is made by adjusting what is in the mix and how it is put together.

First, we make a stable mixture of medicine, fats and substances to help mix them with water. We choose fats based on how well they mix with the medicine, and mixing agents based on how well they keep everything mixed and stable. Then we mix the mixture completely with a machine or with the help of sound waves, so that the fats fall into small droplets in the water.

After making the initial mixture, we start the phase inversion by changing something in the mixture, such as adding certain substances, changing the temperature or adjusting the pH level. These changes shake things up at the surface where the oil and water meet, making the initial mixture less stable. This results in a clutch where the mixture is either mostly water and some oil, or a mixture of both. During this change, the substances in the soil adapt to the new structure, which helps make the mixture more stable. This whole process leads to a better dissolution of the medicine and the formation of smaller droplets, which helps the medicine to be better absorbed after taking.

Basically, the phase inversion method is a convenient way to do SEDDS. This allows us to closely monitor how the mixture looks and works, helping to get the right amount of medicine into it. By playing with different parts of the mixture, we can make a customized drug delivery system that works well for water-insoluble drugs. This helps to improve treatment for different needs.

Invitro Digestion Models OF SNEDDS:

The invitro digestion models are of,

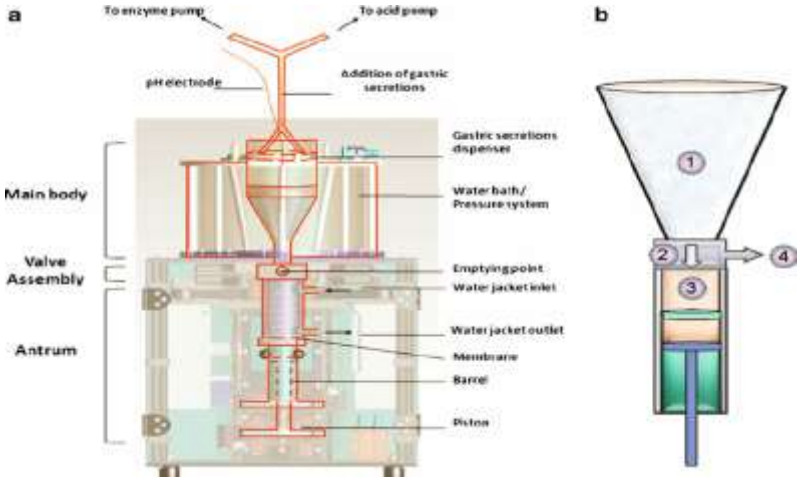
1. Dynamic Digestion Model
2. Static Digestion Model
3. Invitro Lipolysis Model
4. pH Stat Method

DYNAMIC DIGESTION MODEL

The Dynamic Digestive Model is like a high-tech system that can mimic our body's digestion. It is really advanced and can restore things like mixing in the stomach, the release of stomach acid over time and the absorption of nutrients. Unlike simpler models, it is very accurate and closely resembles what happens in our bodies. However, it is not easy to obtain because it is time-consuming, complicated, and requires expensive substances such as enzymes to work.

This model has proved extremely beneficial for researching digestion in detail, including protein conversion, lipids, and nutrient release. It has also been used to evaluate novel techniques of packaging food and medications. This type comes in two kinds: single-chamber and multi-chamber. Single-chamber models simulate the stomach by adding gastric fluid slowly and modeling gastric motions.

One great example is the Human Gastric Simulator (HGS). It has a main chamber made of flexible material that regulates its pH and slowly increases gastric juice. With a large volume of 7 liters, it is more like a real human stomach compared to smaller models. These stomach models use all sorts of tricks to behave like the real thing, helping us understand digestion and how it affects how our bodies absorb food and medicine.



Static digestion model

The static digestion model is the simplest model for simulating the digestion process. First, the food is added to the reaction vessel (beaker, Erlenmeyer flask or test tube). Digestive fluid and enzymes are then added at each stage of digestion (mouth, stomach and intestines). The pH can be left unchecked or kept constant using the pH statistics system. Briefly, for example, 1 g of sample is added to a test tube and mixed with 1 ml of simulated saliva at pH 7 for 2 min at 37 °C. Two milliliters of simulated gastric fluid and pepsin are then added to the same test tube and the pH is adjusted to 3.0 with HCl to obtain a total volume of the gastric phase of 4 ml and a pepsin activity of 2000 U/ml. After 120 min of incubation, the pH is adjusted to 7 with NaOH, then 4 mL of simulated intestinal fluid containing pancreatin and bile salts to simulate the intestinal phase is added and incubated for 120 min. The final volume of the intestinal phase is 8 ml and the trypsin activity is 100 U/ml.

The basic model for simulating the digestion process is the static digestion model. First, the food is placed in a reaction vessel, which can be a test tube, an Erlenmeyer flask, or a beaker. After that, phase-specific digestive fluid and enzymes (from the mouth, stomach and intestines) are added. pH statistics can be used to maintain a constant pH or change it out of control. For example, 1 g of sample is placed in a test tube and mixed for 2 minutes at 37 °C with 1 ml of simulated saliva with a pH of 7. The same test tube is then filled with 2 ml of simulated gastric fluid and pepsin. The pH is then raised to 3.0 with HCl so that the total volume of the gas phase is four milliliters.

Invitro lipolysis model

In vitro lipolysis models are important to accelerate and improve self-emulsifying drug delivery systems (SEDDS) that reproduce the complex lipid cleavage process observed in the gastrointestinal tract. These models provide important information about how SEDDS formulations behave under physiological conditions and help researchers predict their efficacy in living organisms.

A typical in vitro lipolysis model involves three main steps: gastric digestion, intestinal digestion and absorption. During gastric digestion, the SEDDS formula is exposed to simulated gastric fluid (SGF), which contains pepsin and a low pH level that reflects the acidic environment of the stomach. This step initiates the breakdown of lipids into smaller droplets and promotes emulsion.

The emulsified formulation is then mixed in Simulated Intestinal Fluid (SIF), reproducing the conditions observed in the small intestine. SIF contains bile salts, phospholipids, and pancreatic lipases, which further break down lipids into free fatty acids and other digestive byproducts. Bile acid salts promote the dissolution of lipids and the formation of mixed micelles, which are important for the absorption of lipophilic drugs. During lipolysis, parameters such as droplet size distribution, release of free fatty acids and changes in drug solubility are affected. is closely monitored. These parameters provide valuable information about the stability and performance of SEDDS formulations, including their ability to maintain emulsion and drug release under physiological conditions.

In addition, in vitro lipolysis models allow the evaluation of formulation variables such as lipid type and surfactant concentration. and medication burden on SEDDS performance. By systematically adjusting these parameters, researchers can optimize SEDDS.

pH stat method

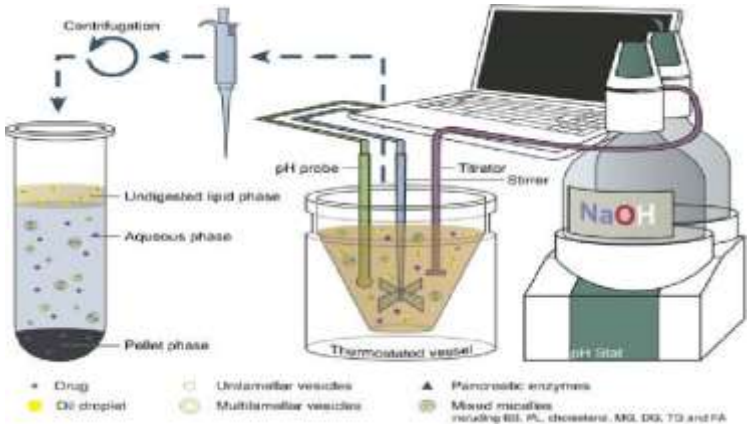
The statistical method of pH is a fundamental method used in pharmaceutical research to study the interstitial kinetics of lipids, especially in self-emulsifying drug delivery systems (SEDDS). This method allows continuous monitoring and quantification of the release of fatty acids during the

enzymatic hydrolysis of lipids, which gives an important picture of the digestion process and the functioning of lipid-based preparations under physiological conditions.

Ph-stat method, an emulsion is prepared with surfactants containing lipids and a pH-sensitive indicator, and a suitable lipase enzyme, usually pancreatic lipase. This emulsion acts as a substrate for enzymatic hydrolysis and simulates the process of lipid breakdown in the digestive tract. A pH-sensitive indicator changes color as the pH fluctuates, allowing continuous monitoring of the reaction.

The Ph-stat device keeps the pH of the reaction mixture constant by titrating it with a base, usually sodium hydroxide (NaOH), to neutralize the fatty acids released. during lipid hydrolysis. When lipase breaks ester bonds in lipid molecules, fatty acids are released into the aqueous phase, which leads to an increase in the concentration of free fatty acids and a subsequent decrease in pH. The pH statistics system automatically adds NaOH to maintain a given pH, making it easy to calculate the rate of fatty acid release based on the amount of NaOH needed.

Estimating the rate and extent of fatty acid release over time, the pH statistics method. provides important kinetic information on lipid degradation, including parameters such as initial hydrolysis rate, total lipid digestion and enzyme activity. These data will help optimize SEDDS formulations by guiding the selection of appropriate lipids and surfactants and predicting their efficacy in vivo. Overall, the pH statistical method is an invaluable tool for understanding and characterizing lipid-based drug delivery systems, ultimately contributing to the development of effective oral delivery strategies for poorly water-soluble drugs.



Potential therapeutic applications of SEEDS :

Self-emulsifying drug delivery systems (SEDDS) hold considerable promise for a variety of therapeutic applications spanning a wide range of diseases. In oncology, SEDDS offers the opportunity to improve the delivery of poorly soluble chemotherapeutic agents that can enhance drug absorption and target tumor sites while minimizing systemic toxicity. SEDDS may also facilitate effective delivery of antimicrobial agents in infectious diseases, resulting in improved bioavailability and effective targeting to sites of infection.

In chronic inflammatory conditions such as rheumatoid arthritis or inflammatory bowel disease, SEDDS formulations may allow controlled release of anti-inflammatory agents. drugs that improve patient outcomes and reduce systemic side effects. In the treatment of tuberculosis, SEDDS can improve the oral delivery of anti-tuberculosis drugs by improving solubility and bioavailability, which increases treatment efficacy.

In viral infections, SEDDS can play an important role in the oral delivery of antiviral drugs, leading to more good drugs absorption and distribution throughout the body, which may result in increased antiviral activity and decreased viral load. Similarly, for bacterial infections, SEDDS offers a promising platform for oral delivery of antibiotics that can overcome the challenges of poor solubility and absorption and improve treatment outcomes.

By optimizing drug delivery and targeting specific pathogens, SEDDS can transform therapy. for the treatment of infectious diseases, which offers better efficacy, lower dose frequency and better patient comfort. In addition, SEDDS may facilitate the passage of neuroprotective agents across the blood-brain barrier in neurodegenerative diseases such as Alzheimer's disease, opening new avenues for disease management and therapy.

COMMERCIAL MARKETED PRODUCTS

SEDDS is one of the commercially viable technologies and several products have been registered as New Drug Applications (NDA) and abbreviated as New Drug Application (ANDA). This review describes some of the approved NDAs and ANDAs. Some NDAs, such as Agenerase, Depakene, Rocaltrol, Targretin, Accutane, and Aptivus, are classified as Type 1 subcategories – New Molecular Entity. Other NDAs such as Sandimmune, Neoral, Norvir, Fortovas and Vesanoid are registered as Type 3 - New Formulation. Depakene and Rocaltrol were approved in 1978. Gengraf has been registered as an ANDA and is available as a hard gelatin capsule.

The ease of preparation and excellent physical stability offered by SEDDS has attracted researcher interest in formulations as evidenced by the commercial success of several NDAs and NDAs. ANDA submitted the request last year.

Product Name /drug	USE	BCS class	Strength(mg)	Active ingredients	Dosage form	Manufactured by
cyclosporine	Systemic immunosuppressant	IV	10/25/50/ 100	Cornoil-mono-ditriglycerides, polyoxyl 40 hydrogenated castor oil NF, DL-αtocopherol USP	Soft gelatin capsule	Novartis Pharmaceuticals Corporation
Norvir® (Ritonavir)	Combination with other antiretroviral agents for the treatment of HIV-1 infection	II	100	Butylated hydroxytoluene, ethanol, oleic acid, polyoxyl 35	Soft gelatin capsule	AbbVie Inc
Aptivus® (Tipranavir)	Combination antiretroviral treatment of HIV-1	II	250	Dehydrated alcohol (7% w/w or 0.1 g per capsule), polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid	Soft gelatin capsule	Boehringer Ingelheim Pharmaceuticals, Inc.
Fortovase® (Saquinavir)	Inhibitor of the human immunodeficiency virus (HIV) protease	IV	200	Medium chain mono and diglycerides, povidone, and dl-alpha-tocopherol	Soft gelatin capsule	Roche Laboratories Inc.
Accutane® (Isotretinoin)	Severe recalcitrant nodular acne	II	10/20/40	Beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, a		Roche Laboratories Inc.
Agenerase® (Amprenavir)	Inhibitor of the human immunodeficiency virus (HIV) protease	II	50	d-alpha tocopheryl PEG 1000 succinate (TPGS), PEG 400, and propylene glycol	Soft gelatin capsule	GlaxoSmithKline
Depakene® (Valproic acid)	Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures	II	250	Cornoil, glycerin, methylparaben,and propylparaben	Soft gelatin capsule	AbbVie Inc
Rocaltrol® (Calcitriol)	Management of secondary hyperparathyroidism and management of hypocalcemia	II	0.25/0.5	Triglyceride of coconut oil	Soft gelatin capsule	Roche Products Limited
Targretin® (Bexarotene)	Treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy	II	75	Polyethylene glycol 400, NF, Polysorbate 20, NF, povidone, USP, and butylated hydroxyanisole, NF	Soft gelatin capsule	Ligand Pharmaceuticals/ Eisai Ltd.

CHALLENGES FOR COMMERCIALISATION OF SEDDS PRODUCTS:

Despite their potential to improve drug solubility, stability, and bioavailability, the commercialization of self-emulsifying drug delivery systems (SEDDS) faces several challenges. Formal approval processes require extensive documentation of formulation safety, efficacy and manufacturing consistency, making market entry difficult. Scaling up production and ensuring cost-effectiveness are logistical obstacles to large-scale production and commercialization.

Another major challenge is to ensure long-term stability and storage of SEDDS formulations under different storage conditions. Lipid-based systems are particularly sensitive to oxidation, hydrolysis, or phase separation over time, necessitating robust stability test protocols. Additionally, differences in patient gastrointestinal conditions create uncertainty regarding the in vivo reproducibility and predictability of SEDDS activity. Extensive preclinical and clinical studies are required for validation and regulatory approval.

Market approval and reimbursement aspects are also challenges, as convincing evidence of therapeutic benefit and cost-effectiveness compared to traditional formulations is required. Overcoming these barriers requires interdisciplinary collaboration, innovative formulation strategies, robust manufacturing processes and strategic partnerships with regulatory agencies and pharmaceutical stakeholders.

CONCLUSION

In vitro digestion models are invaluable tools for analyzing the behavior of self-emulsifying drug delivery systems (SEDDS) under simulated gastrointestinal conditions. These models provide researchers with a controlled environment to study various aspects of SEDDS formulations, such as their response to lipid degradation, drug release patterns, and micelle dissolution. These models accurately represent physiological conditions such as pH level, enzyme activity, and bile salt concentration, and provide valuable insight into the complex processes that affect drug absorption and bioavailability. In addition, in vitro digestion models allow the stability of the formulation to be evaluated. and compatibility. and efficiency, which are critical to optimizing the design and performance of SEDDS to improve oral drug delivery. As pharmaceutical research progresses, the refinement and validation of these models will continue to be critical to the development of SEDDS formulations with improved therapeutic outcomes and clinical relevance.

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