Chapter 1

Introduction

1.1 Oral Route of Drug Administration

Out of various ways of administering drugs, the oral route provides the benefits of simplicity of use and patient comfort. Drug delivery via the oral route is appropriate for both solid and liquid dose forms. Liquid dosage forms are exceptional owing to the ease of administration, the accuracy of measures, self-medication, unpleasant avoidance, and notably patient compliance [1]. About 40–70% of newly produced active compounds are known to possess low water solubility, leading to a restricted dissolution rate and poor oral bioavailability with significant inter- and intra-subject variability [2].

In spite of the various benefits of the oral route, the physicochemical properties of lipophilic drug compounds and the physiological circumstances of the body are important barriers to the administration of pharmaceuticals. Gastrointestinal contents, pre-systemic metabolism, water solubility, drug permeability, drug extent of dissolution, and efflux pump are some of the intricate elements that impact the effectiveness of medication delivery via the oral route. Upon oral intake, lipophilic medication in dose form is simply taken by patients, traveling via the gastrointestinal tract (GIT) and passing through a fantastically diversified environment. When a drug transits from a severely acidic pH in the gastric to the fundamental condition of the digestive system, it encounters an abrasive adjustment in pH; however, there are also separate stomach-digesting enzymes and microbes. After the stomach-related passage, a modest amount of measures is accessible to the fundamental flow for the execution of the restorative response. According to this perspective, the physicochemical characteristics of drugs and the physiological state of the body offer the primary obstacles to administering them by mouth. [3].

Biopharmaceutical classification system (BCS) is a technique that separates drugs on the basis of solubility and permeability. According to BCS, medications are categorized into four classes. Less bioavailability is frequently connected with the drugs related to BCS II, III, and IV. Traditional approaches for enhancing solubility—solid dispersions,

inclusion complexes, micronization, co-crystals, super saturable systems, and complexation with hydrophilic polymers—are all various types of oral bioavailability; however, these strategies frequently only address the issue of low solubility [4, 5].

1.2 Lipid Formulation Classification System

The most significant challenge to creating new and better pharmaceutical drugs is the fact that over half of the distinct chemical entities listed have poor water solubility. The result of this issue is a variation in dose, an unknown absorption profile, reduced oral bioavailability, considerable intra- and inter-subjective variability, and ultimately poor therapeutic effectiveness [6]. The solubility of drugs has been improved by the use of surfactants, solid dispersions, cyclodextrin inclusion complexes, co-solvents, particle size reduction, prodrug production, and pH adjustment, among other common methods. Still, the best method for increasing the solubility of BCS classes II and IV drugs—those with weak solubility—has been referred to as "lipid formulations" [7].

Lipid-based drug delivery systems (LBDDS) for oral administration demonstrate a lot of variation, ranging from simple oil solutions on the bottom side to complex surfactant, co-surfactant, or co-solubilizer and oil combinations at the top. LBDDS may be modified extensively according to demands by adjusting their components and by altering the amount of these excipients, which makes them feasible for both hydrophilic and hydrophobic medicines [8]. Their efforts to boost bioavailability include longer retention time in the stomach, adjustments in the physical barrier as well as modifications in the biochemical barrier, additional solubilization, reduced drug metabolism, and stimulation of lymphatic transport. Throughout a period of time, these systems have been created up to micro- and nano-sized, leading to their increasing therapeutic potential for BCS class II and IV medicines [9–10].

Among the various multifunctional nanocarriers that have been created in recent years as therapeutic nanocarriers, lipid-based nanocarriers have the benefit of being the least damaging in vivo. Lipid nanocarriers comprise liposomes, solid lipid nanoparticles (SLNs), lipid-polymer hybrid nanoparticles, microemulsions, nanoemulsions, lipid-containing micelles, nanostructured lipid carriers (NLC), and self-microemulsifying

emulsifying drug delivery systems (SMEDDS) and self-nanoemulsifying emulsifying drug delivery systems (SNEDDS) [11–14].

1.3 Self-Emulsifying Drug Delivery Systems

"Self-emulsifying drug delivery systems (SEDDS) are generally described as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or any blend of hydrophilic solvents and co-solvents or surfactants". These systems get emulsified in fine oil-in-water (o/w) micro emulsions or nanoemulsions by moderate agitation induced by digestive motility of the stomach and intestine [15–16]. Micro-emulsified or nano-emulsified oil droplets containing medicine in solubilized form give bigger regions of the surface and hence allow better dissolving rate and bioavailability of poor water-soluble lipophilic medicaments.

Oil is the major functional excipient in these formulations since it can solubilize a considerable quantity of hydrophobic drugs and also assists the absorption of medicine via lymphatic transport, which slows the first-pass metabolism. The solubility of medicine in oil may be enhanced by applying co-surfactants or co-solvents [17].

According to the size of the droplets, the SEDDS may be categorized as Self micro -emulsifying drug delivery systems (SMEDDS) and Self nano -emulsifying drug delivery systems (SNEDDS). The variances between SEDDS, SMEDDS, and SNEDDS are provided in Table 1.1. SMEDDS produces a droplet size of 100–250 nm. Since SNEDDS resulted in a globule size of <100 nm, they are also referred to as nanoemulsions, mini-emulsions, ultrafine emulsions, and submicron emulsions. These SNEDDS are supplied as solid or hard gelatin capsules [18–19].

Oils, surfactants, hydrophilic co-surfactants, and drugs are the major constituents of SEDDS that generate a fine o/w self-emulsion when mixed into the aqueous phase. SNEDDS is an incredibly essential approach that combines the advantages of both nanotechnology and LBDDS.

Features	SEDDS	SMEDDS	SNEDDS
Size	>300 nm	<250 nm	<100 nm
Classification as per LFCs	Type II	Type IIIA	Type IIIB
HLB value of surfactant	<12	>12	>12
Amount of oil	40–80%	<20%	<20%
Amount of surfactant	30–40%	40–80%	40–80%
Appearance	Turbid	Optically clear	Optically clear

Table 1.1: Major distinctions among SEDDS, SMEDDS and SNEDDS

These are becoming more prevalent for boosting the solubility of low-water-soluble drugs in the formulation. SNEDDS can frequently be helpful for improving the speed and amount of assimilation of hydrophobic or lipophilic medicines categorized into BCS classes II and IV (with poor solubility), which display dissolution rate-limited absorption [20]. Several commercial goods based on SNEDDS are described in Table 1.2.

Trade Name	Manufacturer	Drug	SEDDS Use
Targretin	Novartis	Bexarotene	Antineoplastic agent
Agenerase	Galaxo smithkline	Amprenavir	To treat HIV infection
Rocaltrol	Roche	Calcitriol	Calcium regulator
Neoral	Novartis	Cyclosporine A/I	Immuno-suppressant
Vesanoid	Roche	Isotretinoin	For acne
Convulex	Pharmacia	Valproic acid	To treat epilepsy and seizers
Norvir	Abbott Laboratories	Ritonavir	HIV Antiviral
SandimmunNeoral	Novartis	Cyclosporine A	Immunosuppressant
Gengraf	Abbott Laboratories	Cyclosporine A/III	Immuno-suppressant

Table 1.2: Marketed products founded on SNEDDS

1.4 Mechanism of Self-emulsification

The development of new surfaces or the expansion of existing contact surfaces involving water and oil is a process that requires a certain amount of energy Self-

emulsification occurs when the quantity of entropy shift that favors dispersion is larger than the energy that's necessary for extending the surface area of dispersion [21]. The free energy of the emulsion is an indicator of the energy necessary for creating a new interface between the oil and water phases. The amount of free transformation of energy may be described using the following equation:

$$\Delta G = \Sigma N \pi r^2 \sigma \ldots\ldots\ldots\ldots\ldots\ldots \text{ Equation 1.1}$$

Where ΔG is the total free energy associated with the process,

N is the number of droplets of radius r, and σ is the interfacial energy.

In the case of SNEDDS, spontaneous or quick emulsification can arise due to very low, positive, or even negative free energy of formation. In most conditions, a modest amount of energy is essential for the instability of specific interphase zones, their shrinking, and subsequently self-emulsification to occur. With time, emulsion tends to partition into lower interfacial areas and consequently lower the free energy of the system. Emulsifiers stabilize emulsions generated by aqueous dilution by forming a monolayer over the globules, therefore decreasing interfacial energy and providing a barrier for coalescence [22].

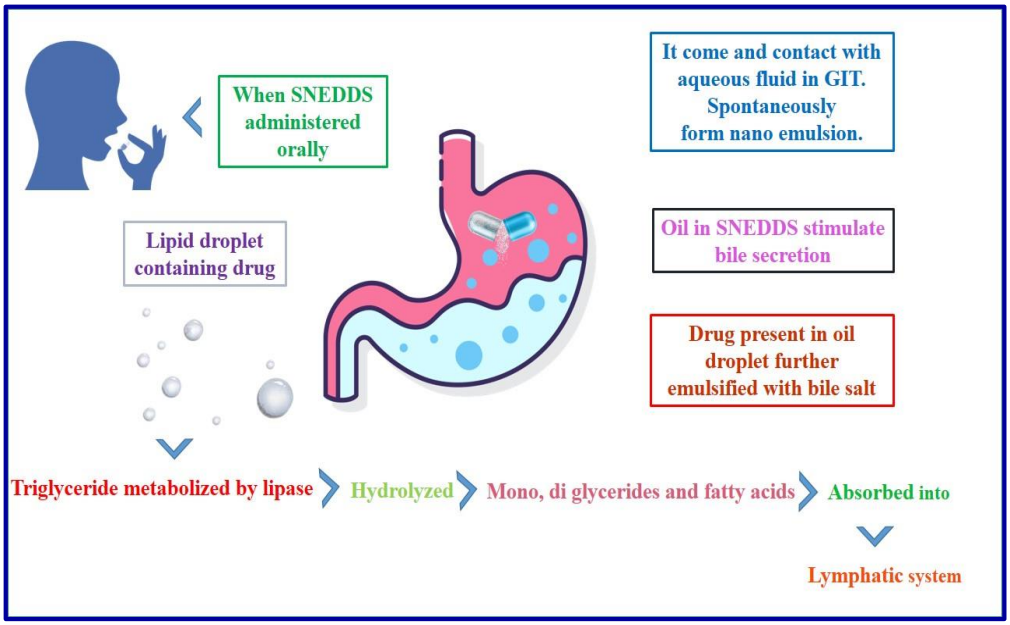


Figure 1.1: Process of Self Emulsification

The ease of emulsification is associated with the ease of water penetration into liquid crystals or gel phases produced on the surface of globules. Incorporation of a binary combination (oil or non-ionic surfactant) into water forms an interface between the oily and aqueous phases, followed by solubilization within the oil phase. This occurs until solubilization reaches the interphase. However, there is constant interchange of components between each phase. Interchanging substances generally happen in two distinct ways, like the amalgamation of tiny droplets followed by the splitting of bigger droplets into little droplets and the fragmentation of droplets, which subsequently coagulate with other droplets [21].

1.5 Composition of SNEDDS

The composition of excipients retains a crucial role in the formulation of SNEDDS. The various excipients often utilized in the formulation of SNEDDS are described below.

1.5.1 Active Pharmaceutical Ingredient (API)

Previously, it had been believed that Class II compounds' relatively small and diverse bioavailability was attributed to their constrained water solubility. The idea behind implementing LBDDS like SNEDDS to increase the bioavailability of Class II drugs was that the co-administration of poorly water-soluble pharmaceuticals with a high-fat meal would improve their bioavailability. BCS class II drug was selected because SNEDDS is used to increase the solubility of low-water-soluble medicines by providing and preserving them in a dissolved condition. Throughout the transit through the GI system, the drugs are delivered via tiny oil droplets at the molecular level.

Drugs that can be administered in extremely large amounts are not appropriate unless they demonstrate unusually remarkable solubility in at least one of the SEDDS components, generally the lipophilic phase. The most problematic drug to distribute using SNEDDS are those with a high melting point and limited solubility in water and lipids, often with log P values of approximately 2. The concentrations of drug as well as its physicochemical features like molecular structure, molecular weight, log P, pKa,

and ionizable group substantially impact the many properties of SNEDDS, such as droplet size and phase behavior [23].

Considering pharmacological acceptance and toxicity challenges, choosing the right kind of excipients is particularly critical. Therefore, there is a considerable constraint to which excipients must be applied. The self-emulsification mechanism is particular to the amount and composition of the oil/surfactant proportion, the surfactant/co-surfactant proportion, and the ambient temperature that occurs when self-emulsification takes place. So, each individual component ought to be taken into consideration when choosing any of the excipients in SNEDDS.

1.5.2 Oil

Oil is crucial for lipophilic medicine solubilization. It improves the drug's availability for rapid absorption through the GI tract via the intestinal lymphatic system. According to the chemical structure of the triglyceride, oils might dissolve a suitable quantity of lipophilic medicines and allow self-emulsification. Interestingly, long-chain triglycerides, in contrast to medium-chain tri-, di-, and mono-glycerides, have demonstrated greater capacity to enhance lymphatic transport of drugs (responsible for preventing first-pass metabolism of drugs), whereas medium-chain mono- and di-glycerides have higher solubilization potential for hydrophobic drugs and permeation-enhancing properties. Hence, it's going to be challenging for a single oily component to contain ideal qualities with reference to nano-emulsification and medication administration. In rare circumstances, a combination of oils may also be employed to meet the ideal qualities of the oily phase. For nanoemulsions and micro emulsions, an equivalent idea has been applied. As an example, a combination of fixed oil and medium-chain triglyceride (MCT) is applied in some cases to provide a favorable balance between drug loading and emulsification [24].

The size of the droplets of a nanoemulsion is precisely determined by the lipophilicity and amount of the oily phase. Additionally, it is crucial to remember that the same oil should solubilize the greatest quantity of medicine. Additionally, it emerged that digested lipids could potentially be able to improve the absorption of drugs with low solubility, in contrast with lipids that are not digestible. Therefore, it is vital to pick the

lipid phase that can solubilize the medication and, at the same time, be able to generate nanoemulsion with the needed qualities.

Novel semi-synthetic MCTs, which are classified as amphiphilic compounds with surfactant properties and are progressively and effectively replacing traditional MCT oils in the SNEDDS, are successfully replacing conventional MCT oils. MCT is more soluble and mobile at the lipid/water interface than long-chain triglyceride (LCT), allowing for more rapid MCT hydrolysis. Modified vegetable oils, digestible or non-digestible oils, and fats including palm oil, olive oil, sesame oil, peanut oil, maize oil, captex®355, capmul® MCM, myritol®318, geleol TM, imwitor®, and the wax of bees are some examples of suitable oil phases.

1.5.3 Surfactant

The surfactant selected is for its capability of reducing interfacial tension to a very low value, facilitating the dispersion process, and offering a flexible film that can effortlessly deform around the droplets, as well as having the correct lipophilic character that generates the correct curvature at the interfacial region.

The surfactants included in these formulations are known to increase bioavailability by numerous mechanisms, including greater medicine solubility, higher intestinal epithelial permeability, enhanced tight junction permeability, and reduced or blocked glycoprotein drug efflux.

Several features of the surfactant, such as affinity for the lipid phase, cloud point, and HLB, are known to impact the droplet size, self-emulsification area, and emulsification process. In contrast to ionic surfactants, non-ionic surfactants are nontoxic. Tween 80 and Pluronic F127 are the most extensively used non-ionic surfactants [25].

The surfactant concentration also plays a key part in the formulation. It has been observed that a surfactant concentration over 25% (w/w) is necessary for the self-emulsification and rapid dispersion of SNEDDS. However, surfactant concentrations of 50–60% (w/w) generate a crystalline gel-like liquid at the boundary of O/W, which might disrupt the development of emulsification.

However, the discomfort potential may be reduced due to the speedy elimination of tiny drops of lipids in the formulation and the extensive diffusion of the formulation throughout the GIT, which decreases the quantity of medication at the localized level. As an outcome, safety is a fundamental issue when selecting a surfactant molecule. Water-soluble surfactants are the most widely employed surfactants in self-emulsifying compositions. Cremophor® RH40, Gelucire®44, and Cremophor® EL are also being utilized today.

1.5.4 Co-surfactant

Co-surfactant reduces the instantaneous negative impact of interfacial tension even more. It affords the interfacial film flexibility so that differing curvatures can easily be obtained for the creation of different nanoemulsion [25]. By adding co-surfactant, greater amounts of surfactant (approximately 30%) may be recreated. The contact expansion at this moment leads to the creation of finely scattered droplets [24]. It will absorb more surfactant or a larger surfactant/co-surfactant ratio until the film is depleted enough to restore positive interfacial tension. A spontaneous emulsion is created as a consequence of this. Co-surfactants are generally made of medium-chain alcohols (C3–C8) [26].

The development of an ideal SNEDDS necessitates surfactants in extremely high quantities (typically more than 30% w/w). The surfactant is designed to decrease the amount of water in the body, even if the interfacial tension is at its minimal negative value. At this step, the interface would grow into finely distributed droplets, allowing them to absorb more of their surfactant and co-surfactant. The bulk situation has deteriorated to the point that the interfacial tension is now positive. This is how it works. In the absence of co-surfactant, an extraordinarily rigid film is produced by the surfactant, which forms nanoemulsion over a very tiny range of concentration.

The inclusion of co-surfactants provides the interfacial layer with the flexibility to take up the numerous curvatures required to perform nanoemulsion over a wide diversity of compositions. Medium-chain length alcohols (C3–C8), which are commonly utilized as co-surfactants, have the impact of significantly reducing the interfacial tension while enhancing the fluidity of the contact, therefore raising the entropy of the

system. Newly developed cosolvents like Transcutol® TM and Glycofuro® TM have significant benefits over regular ones, notably better stability and reduced volatility.

1.5.5 Antioxidants

It is additionally noted that certain medicine compounds are not stable in the lipid system, which requires the addition of antioxidants or chelating agents to enhance their stability. Thus, SNEDDS comprising antioxidants or chelating agents offers formulations enhanced bioavailability along with acceptable stability. Antioxidants that are soluble in fat, such as α-tocopherol, β-carotene, butylated hydroxyl anisole (BHA), or butylated hydroxyl toluene (BHT), are also advantageous for the purpose of avoiding the degradation of excipients, particularly lipids, and increasing their liposolubility alongside their solubility in water, thereby enhancing their therapeutic effectiveness [27].

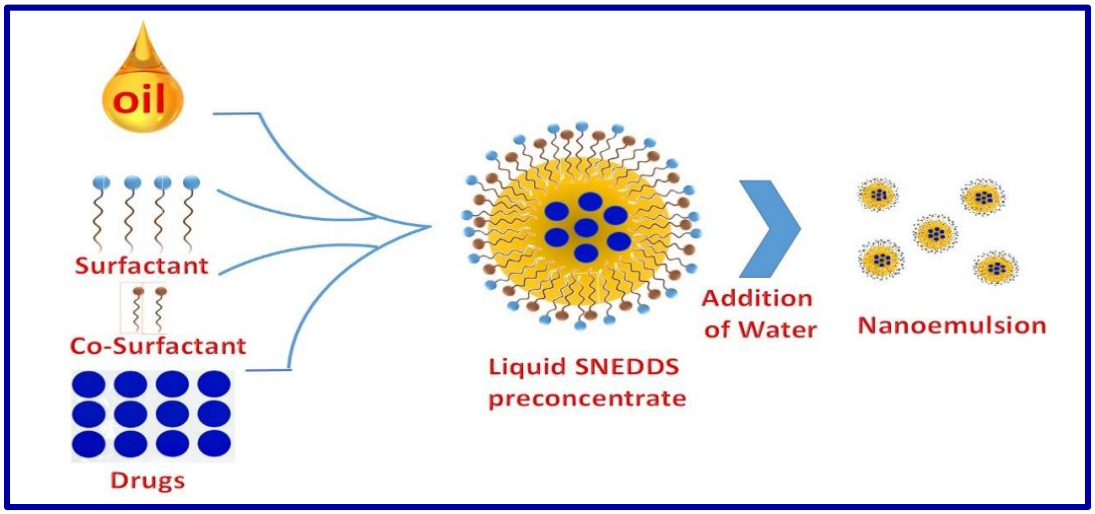


Figure 1.2 Mechanism of self-nano emulsifying drug delivery systems (SNEDDS)

1.5.6 Polymers

In certain cases, the solvent capability of SEDDS is reduced, resulting in drug precipitation. The utilization of supersaturated substances that sustain drug solubilization above the equilibrium phase of solubility and prevent drug precipitation for a long period is an innovative approach to increasing drug absorption. Typically, the precipitation inhibitors are hydrophilic polymers such as polyethylene glycol (PEG) 4000, hydroxypropyl methylcellulose (HPMC), and polyvinyl pyrrolidone

(PVP), which allow the creation of super saturable systems. These chemicals might inhibit the crystallization of pharmaceuticals by absorbing them onto the outer layer of the drugs, preventing precipitation by hydrogen bonding [28]. Polymers, including tragacanth, cetyl alcohol, stearic acid, or beeswax, are sometimes added to the formulation in order to alter consistency and increase the physical stability of SEEDS. For achieving modified release of drugs from SEEDS, inert polymers that do not ionize in physiological pH range, and which can form a matrix, are used in 5%- 40% concentration. HPMC and ethyl cellulose are commonly used.

1.6 Approaches for preparation of Nanoemulsion

Nanoemulsions can be developed using high- and low-energy technologies. In high-energy approaches, mechanical devices deliver needed disruptive forces.

On the other hand, with low-energy techniques, there is no demand for an external force. At the beginning of the study on nanoemulsions, high-energy technologies were the only option, and therefore, high-energy stirring and ultrasonic emulsification were the most extensively employed methods. Currently, low-energy methods are receiving substantial attention since they are 'soft', non-destructive, and cause no damage to contained molecules [28-29].

1.6.1 High-energy approach

During the production of nanoemulsion, a high amount of energy is applied, mostly depending on the selected composition of the mixture and also on the mixture comprising surfactant, cosurfactant, cosolvents, and other useful chemicals [30]. The emulsification undergoes mechanical processing to form nanoemulsion. There are several approaches which work on principles of high energy which are mentioned below.

1.6.1.1 High-Pressure Homogenizer

It is one of the important devices for the detection and preparation of fine emulsions, mainly to produce nanoemulsion. This method is important in that the oil/water surfactant mixture is under very high pressure, and the mixture is pumped by a resistive

valve. The very high shear stress is responsible for the formation of very fine emulsion droplets. The integration of the two hypotheses, turbulence and cavitation, describes the droplet size reduction throughout the process of homogenization. The extremely high velocity of the resultant mixture provides the liquid with tremendous energy in the homogenizer valve and forms intense turbulent waves of exactly the same size as a mean diameter droplet (MDD). Droplets have been separated from Eddie currents, which leads to a reduction in droplet size. Simultaneously, the pressure drops across the valve, cavitation occurs, and further eddies disrupt droplets [31]. Decreasing the gap size ultimately increases the pressure of the droplet and is responsible for a greater degree of cavitation. Emulsion droplets having diameters < 100 nm can be produced using this method if a sufficient amount of surfactant is present to completely cover the oil-water interface and the adsorption kinetics are high, which is important to prevent droplet coalescence.

1.6.1.2 Micro fluidization

It is an important method to detect and prepare nanoemulsion. Micro fluidization is achieved by a device called a micro fluidizer. This type of device is used in high-pressure positive displacement pumps (150 to 650 MPa.), which force the product through the interaction chamber, which consists of small channel droplets called micro channels. The product flows through the micro channels onto the impingement area, which results in very fine particles in the submicron range, i.e., nanoemulsion. The two solutions containing a mixture of aqueous phase and oil phase systems are combined and formed in the inline homogenizer to yield a coarse emulsion [32]. The coarse emulsion is processed by a micro fluidizer, and it undergoes further processing to become a homogeneous, transparent, and stable nanoemulsion.

1.6.1.3 Ultrasonic Emulsification

There are two processes that take part in ultrasonic emulsification. Firstly, an acoustic field creates interfacial waves which allow the oil phase to disperse in the continuous phase as droplets. Secondly, ultrasonography stimulates acoustic cavitation, which enables the production and collapse of micro bubbles correspondingly due to pressure changes in a single sound wave. In this approach, massive volumes of highly localized

turbulence are generated, and this generates micro-implosions that disrupt large droplets into sub-micron size. In this approach, premixed nanoemulsion is agitated by a vibrating solid surface at 29 kHz or higher frequencies. High-power ultrasonic devices, such as focusing horns, and pointed tips cause significant shear and cavitation, leading to the splitting of drops [33].

It has been discovered that in most ultrasonic systems, the generated sound field is uneven. For this reason, in order for all droplets to experience a maximal shear rate, recirculation of the emulsion through the region of high power must be given. Moreover, by conducting this type of recirculation several times, it is possible to generate emulsions with homogeneous droplet sizes at dilute concentrations. Emulsifier type, the quantity of emulsifier, and the viscosity of phases are the most significant elements that affect homogenization efficiency. Thus, adjustment of these parameters is important to prepare nanoemulsion possessing fine droplets. However, there are certain issues associated with sonication procedures owing to the fact that they have the potential to lead to protein denaturation, polysaccharide depolymerization, and lipid oxidation [32].

1.6.2 Low-energy approach

It is additionally known as the condensation technique, requires relatively little energy for the generation of nanoemulsion, and depends upon the phase transformations taking place during the emulsification process. This approach is largely dependent on the modification of interfacial phenomena or phase transitions and the intrinsic physicochemical characteristics of the surfactants, co-surfactants, and oil in order to create nano-sized emulsion droplets. The low-energy approach is fascinating as it brings on the built-up energy of the system to produce smaller droplets. This emulsification might possibly be caused by modifications to variables that may affect the hydrophilic-lipophilic balance (HLB) of the system, such as temperature, composition, etc. The regularly utilized low-energy emulsification techniques are as follows:

1.6.2.1 Phase Inversion Temperature Method

It is an important method for creating nanoemulsions. The technique is primarily dependent on the reaction to temperature. In this kind of method, several physical changes occur, including physicochemical modifications, particle size, and in vivo and in vitro drug release rates [34]. These approaches also take advantage of the shift in spontaneous emulsion formation. The non-ionic surfactant could potentially be produced by altering the ambient temperature of the system. The forces in transition produce O/W nanoemulsion at a low temperature and W/O nanoemulsion at a higher temperature.

1.6.2.2 Solvent displacement method

The solvent displacement methodology employed for the spontaneous production of nanoemulsion has been obtained from the nanoprecipitation method utilized for producing polymeric nanoparticles. In this procedure, the oily phase proceeds with dissolution in water-miscible organic solvents such as acetone, ethanol, and ethyl methyl ketone. The organic component is injected into an aqueous phase containing surfactant, which results in a spontaneous or quickly formed nanoemulsion by the rapid diffusion of organic solvent. The organic solvent is removed from the nanoemulsion using suitable procedures, including vacuum evaporation. [34].

1.6.2.3 Phase Inversion Composition Method

It makes nanoemulsion at room temperature without the use of any kind of organic solvent or heat. Forgirani et al. showed in their experiment that kinetically stable nanoemulsion under a smaller droplet size (~50 nm) may be generated with the consecutive addition of water into a solution of surfactant and oil under moderate stirring while keeping a constant temperature [35]. While the components utilized during the previously mentioned experiment failed to be of pharmaceutical efficacy, it has offered techniques for generating pharmaceutically acceptable nanoemulsions utilizing a similar technology [36].

1.7 Steps for the Design of SNEDDS

The key pathways underlying the creation of SEDDS are briefly detailed below

- Selection of drug
- Screening of a mixture of excipients
- Construction of Ternary Phase Diagrams
- Preparation of SNEDDS
- Optimization Techniques
- Characterization of SNEDDS

1.7.1 Selection of Drugs

When a drug exhibits remarkable solubility in at least any of the components of SNEDDS, notably the lipophilic phase, it will not be practical to employ it with SNEDDS. The medications should not be extremely soluble in water, and SNEDDS has the most difficulty delivering lipids.

The drug's solubility in the oily phase has a substantial influence on SNEDDS's capacity for retaining the molecules in a solubilized form. Dilution of SNEDDS will decrease the solvent capacity of the surfactant or co-surfactant; thus, there may be a chance of precipitation when they contribute further to the solubilization of the drug [37].

1.7.2 Screening of a mixture of excipients

SNEDDS originate as the result of a specific combination of several lipid excipients, encompassing oils, surfactants, and co-surfactants. There are a huge variety of liquid or waxy excipients available that may be employed to make drug-loaded emulsions. However, identification of an acceptable excipient or excipient combination plays a significant part in the formulation that solubilizes the medication dosage in a unit volume suitable for oral consumption.

Generally, excipients' screening research covers drug excipient testing for compatibility, solubility, and stability. Out of them, solubility of medication in excipients is the most notable property and may be conducted using question shaking procedures. An excess quantity of medicine is added to the fixed volume of excipients and subjected to vortexing. Then, the mixture is allowed to shake continuously for 72 hours at ambient room temperature (~25 ºC) and then centrifuged. The supernatant is

collected and filtrated for any apparent impurities, and the drug concentration is quantitatively assessed utilizing an ultraviolet (UV) spectrophotometer.

Since formulation contains numerous components, it is necessary to identify the drug solubility in the entire system instead of depend on drug solubility in individual components. Maximum drug loading, lowest droplet size, self-emulsification duration in the stomach environment, and the protection of the medication against GI degradation or reduction of metabolism are the major focuses on of the selection technique [38].

1.7.3 Construction of Ternary Phase Diagrams

The proper proportion of lipid, surfactant, and co-surfactant may be identified by generating a diagram for the pseudo-ternary phase, which provides a key foundation for the design of emulsion formulations. Development of a ternary phase diagram: this illustration assists in determining the ratio of oils, surfactants, and co-surfactants necessary for creating a nanoemulsion.100% of the specified component is represented by each corner of the diagram. After identification of this area, the next step will be to discover which compositions create nano - or micro emulsions with desirable qualities. To detect this, the pre-concentrate is titrated with water until a shift in the phase is noticed from gels to micro emulsions [35]. All this information, such as the quantity of individual phases necessary for optimum formulation and the amount of water injected, is utilized to generate the diagram utilizing triplot or chemix school software. Figure 1.4 shows a typical ternary phase diagram of the water, surfactant, and oil systems used to generate SNEDDS.

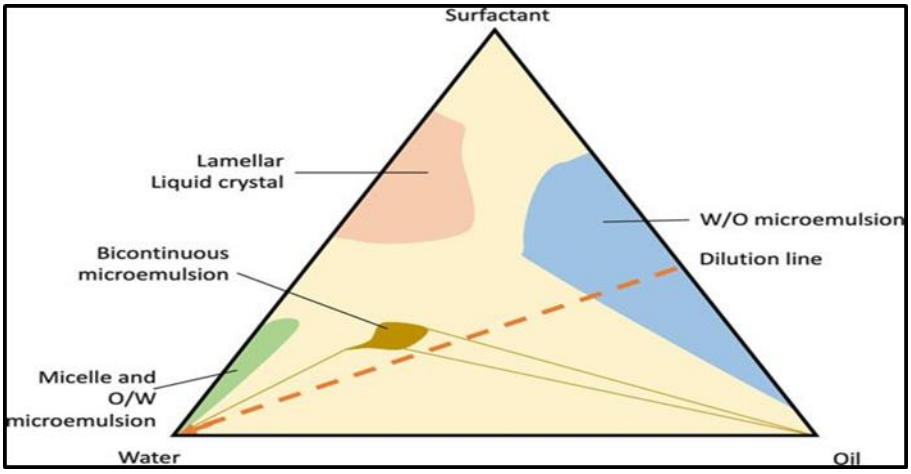


Figure 1.3: Typical ternary phase diagram of oil, surfactant and water system

1.7.4 Solid SNEDDS

1.7.4.1 Difficulties with Liquid SNEDDS

The majority of SNEDDs exist in liquid form, as the primary constituents (oil, surfactants, and co-surfactants) used in SNEDDs typically exist in a liquid state at ambient temperatures. The liquid consistency of SNEDDs restricts the broad potential of this kind of technology in enhancing the oral bioavailability of numerous drugs because of many disadvantages including lack of stability, large dose volume because of relatively low drug loading capacity, irreversible precipitation of drug and migration of volatile ingredients into shell of gelatin capsule [39].

1.7.4.2 Solidification of self-emulsified formulations

Solidification of Liquid SNEDDS is an efficient strategy to overcome the restrictions of liquid SNEDDS and combine the benefits of SNEDDs (enhancement of both solubility and bioavailability) with the advantages of solid dosage forms (ease of handling and portability, higher stability and reproducibility, compact dosage form and better patient compliance). Regarding the advantages of solid dosage forms, S-SNEDDs have been widely considered in the recent few years, as they considered more efficient alternatives to conventional liquid SNEDDs. Solid SNEDDS (S-SNEDDS) have a range of advantages, including regulated drug release, prolonged stomach residence time, and enhanced permeability [40].

Liquid SNEDDS may be transformed into solid SNEDDS to address different restrictions associated with the liquid state of the formulation. Various processes, comprising encapsulation of liquid and semi-solid self-emulsified formulations, spray drying, adsorption, melt granulation, and lyophilization, are being extensively utilized for the creation of S-SNEDDS.

A) Encapsulation of liquid and semi-solid self-emulsified mixtures

This procedure, which contained soft or hard gelatin capsules for oral administration with a semi-solid or liquid self-emulsifying products, is the most extensively used approach for creating solid self-emulsifying formulations owing to its simplicity and outstanding drug loading capability. The compatibility of the formula filled with the capsule shell controls the filling of the capsule. If the formulation contains volatile oils, another approach should be taken because these ingredients have a tendency to penetrate through the capsule shell. The Liquid-OROS technique, which uses osmotic properties—a layer that expands upon contact with aqueous media—is applied to liquid self-emulsification formulations. The layer is pumped into either hard or soft gelatin capsules. The semisolids are heated at a temperature 20 degrees above their melting point for the semi-solid self-emulsifying formulations. They are then put into the capsule body, sealed, and allowed to cool to room temperature [41].

B) Spray drying

This approach includes the addition of the liquid SNEDDs to the solution of a suitable solid carrier that could be either hydrophilic (e.g., dextran) or hydrophobic (e.g., colloidal silica). The resulting solution is then atomized into very tiny droplets in the drying chamber, where the volatile solvent (water and/or organic solvent) evaporates, and producing dry particles at regulated temperature and airflow conditions. The resulting dry emulsion powder can be utilized to manufacture self-emulsifying tablets or capsules to tackle the problems of drug stability and the employment of hazardous organic solvents [42].

C) Adsorption of solid carriers

It is an easy procedure in which the liquid SNEDDs are incorporated into a suitable carrier to form solid SNEDDs. The selected solid carrier has to adsorb a sufficient quantity of

the liquid self-emulsifying formulation, and the resultant freely flowing powder can be put directly into capsules or, alternatively, be compressed into tablets after mixing with appropriate excipients. The resulting powder gives excellent uniformity but has inadequate drug loading capacity [43].

D) Melt granulation

The use of a binder serves in this procedure to induce powder aggregation. At comparatively low temperatures, the binders can be melted or softened. It provides significant benefits over usual wet granulation because it is a single-step approach that prevents the integration of liquid components and subsequent drying procedures. A few aspects to be managed while manufacturing involve mixing time, impeller speed, particle size, and binder viscosity [44].

E) Lyophilization Technique

The lyophilization technique (which is additionally referred to as freeze drying) requires mass and heat transfer from and to the formulation. Such an approach is ideal for drugs that are sensitive to oxygen, air, and temperature. The most significant disadvantage of this approach is its substantial operation cost [45].

1.7.5 Optimization Techniques

There are many methods accessible to improve the formulation. The response surface technique has advantages over other methodologies in terms of the number of trials. The technique mentioned previously could optimize the formulation with the smallest number of trials without compromising the characteristics of the final product. This approach may be used to study the influence of dependent attributes for example the amount of constituents on independent variables such as droplet size, solubility, and self-nanoemulsification time characteristics of SNEDDS. The recommended design was constructed employing these elements and tested statistically. Then the mathematical relationship is established and validated in numerous ways. The confirmed design is utilized to create the formulation with the required features [46].

1.7.6 Characterization of SNEDDS

The final SNEDDS formulation is assessed using multiple in vitro, in vivo, and ex vivo criteria. Various approaches have been utilized to study these characteristics with the purpose to establish the efficiency of the manufacturing process, formulation stability, and in vivo behavior [47].

1.7.6.1 Morphological Study

Morphological research is significant as it gives information on the formulation's exterior appearance, such as color, aroma, consistency, density, and look. The transmission electron microscope (TEM) was successfully used to investigate globules in the SNEDDS.

1.7.6.2 Thermodynamic Stability Studies

The physical stability of a lipid-based formulation is also essential to its performance, which might be impaired by drug precipitation in the excipient matrix. Furthermore, insufficient formulation physical stability could result in excipient phase separation, influencing not only formulation performance but also visual appearance. Additionally, incompatibilities within the formulation and, as a consequence, the gelatin capsule shell might result in brittleness or deformations, prolonged disintegration, or inadequate drug release [48].

Heating and cooling cycle

The researchers looked at three cycles ranging from 4°C (refrigerator) to 45°C (Oven), with storage durations of at least 48 hours at each temperature. Centrifugation tests are carried out only on those mixtures that have proven stable at these temperatures [49].

Centrifugation

Centrifuged thaw cycles between 21°C and +25°C, including storing at each temperature for a minimum of 48 hours are conducted at 3500 rpm for 30 minutes. The freeze-thaw stress test is done on formulations that do not demonstrate any phase separation.

Freeze-thaw cycle

The stability of SNEDDS was tested using freeze-thawing. Three freeze-thaw cycles were conducted on the formulations, with freezing at −21 °C (freeze) for not less than 48 hours and thawing at +25 °C (thaw) for not less than 48 hours. For 5 minutes, centrifugation was done at 3000 RPM. After that, the preparations were examined for phase separation. The products

that passed this test indicated high stability, with a lack of separation, creaming, or breaking [50].

1.7.6.3 Dispersibility Test

A traditional USP XXII dissolving equipment 2 is utilized for assessing the efficiency of self-emulsification of oral nanoemulsion. At 37±0.5 °C, 1 ml of each formulation was mixed into 500 ml of water. Moderate stirring was given by a standard stainless steel dissolving paddle working at 50 rpm. The ensuing grading system has been developed to visually evaluate the formulation's in vitro performance [51].

1.7.6.4 Turbid metric evaluation

The rise in emulsification is assessed by nephelo-turbidimetric analysis. Under constant stirring (50 rpm) on a magnetic plate at room temperature, a rise in turbidity was measured by applying a turbidity meter after a specific amount of the self-emulsifying system had been added to a fixed amount of appropriate medium (0.1N HCL). It might be difficult to measure the rate of change in turbidity when the time required to reach completely emulsification is too quick (rate of emulsification) [52].

Grades	**Appearance**
Grade A	Rapidly developing nanoemulsion (less than 1 minute), having a translucent or bluish appearance.
Grade B	Rapidly forming nanoemulsion, a slightly less clear emulsion that has a blue-white look.
Grade C	A fine, whitish milky emulsion formed within 2 minutes.
Grade D	Dull, grayish-white emulsion, which has a slightly oily appearance, is slow to emulsify (longer than 2 minutes).
Grade E	Formulation, demonstrating either low or minimal emulsification with big oil globules observed on the surface.

Table 1.3: Assessment of the in vitro performance of the formulations

1.7.6.5 Droplet Size Analysis Measurements

Dynamic light scattering (DLS), formerly referred to as photon correlation spectroscopy (PCS), is a method used to investigate the variations in the intensity of scattering by droplets or particles that result from Brownian motion. Nanoemulsion droplet size, polydispersity, and zeta potential are being assessed by PCS utilizing a particle size analyzer. This instrument further calculates the polydispersity index, which serves as a measure of the broadness of the size distribution measured from the cumulative analysis of dynamic light scattering. The polydispersity index assesses the quality or homogeneity of the dispersion. PCS produces the z-average particle diameter. Laser diffraction is another means of evaluating particle size. The basic particle size distribution created by this approach is volume-based and is given in terms of the percentage of volume of similar spheres (DN%) and the weighted mean of the volume distribution (mass mean diameter). As the laser diffraction method is applied for this inquiry, a rough estimate of particle polydispersity could possibly be provided through two elements or values, namely, uniformity (also known as how symmetrical the distribution is around the median point) and breadth (the width of the distribution) [53].

1.7.6.6 Viscosity Determination

The SNEDDS's viscosity has been assessed using Brookfield viscometers. The viscosity of a nanoemulsion is dependent on the amount of the surfactant, water, and oil components and their concentrations. Increasing the water content decreases the viscosity, but reducing the quantity of surfactant and cosurfactant enhances the interfacial tension between water and oil, resulting in higher viscosity. Viscosity is particularly important for stability and effective drug release. Nanoemulsion carrier formulations are fundamentally oil-in-water, and consequently, in addition to being less greasy than water-in-oil formulations, they frequently show lower apparent viscosities.

They are accordingly shown to demonstrate quicker drug release and wash away quickly following application to the skin surface. Assessing viscosity change is a means of monitoring the stability of both liquid and semi-solid preparations, including nanoemulsion mixtures. Liquid SNEDDS formulations are frequently delivered in capsule form. Difficulties of leaking have been associated with low-viscosity formulations, while fluidity issues restrict highly viscous SNEDDSs from being packed into capsules. In general, at 25 °C, a viscosity of 0.1–1.0 Pa suggests that formed SNEDDS may readily be packed into capsules [54].

1.7.6.7 Stability Study

Stability studies are performed as per the ICH specifications for the formulation that is placed in gelatin capsules. According to the ICH recommendation, the stability study of the microspheres was tested for any changes in physical stability, size, shape, drug content, and release profile. Selected formulations were submitted to accurate stability testing at 25 ± 2 °C, 60 ± 5% RH for the 1st and 2nd months, and 40 ± 2 °C, 75 ± 5% RH for the 3rd month. Samples were taken at 1, 2, and 3 months, according to ICH recommendations. If there is no change in any of these characteristics during storage conditions, composition can be decided as a stable composition [55].

1.7.6.8 Refractive Index and Percent Transmittance

The index of refraction and % transmittance demonstrated the transparency of the formulation. The refractometer measures the system's index of refraction by putting a drop of solution on a slide, and it corresponds with the water (1.333). With the assistance of a UV-spectrophotometer and purified water as a blank, the transmittance of the system is determined at a specific wavelength. If the formulation has a transparent nature, then the index of refractive index of the system has a similarity to the index of refraction of water (1.333), and the formulation has a percentage of transmittance >99 percent. The refractive index is essentially reliant on two elements: the amount of the cosurfactant and the size of the globule. Refractive index decreases with an enhancement in cosurfactant concentration, which is ascribed to a reduction in the firmness of the nanoemulsion structure, and it increases with an increase in globule size [56].

1.7.6.9 *Invitro* Diffusion Study

The Franz diffusion cell is employed for assessing the drug release profile of the nanoemulsion formulation in the case of preparations for transdermal application. In vitro drug release can be measured by dispersing an amount of the preparation in the donor compartment of a Franz cell with a membrane as a barrier and monitoring the appearance of the drug that has been encapsulated in the receptor compartment, typically containing phosphate buffered saline (PBS, pH 7.4) and stirring on a magnetic stirrer at 100 rpm at 37 ± 1 °C. Samples (1 ml) of the dispersion are collected from the receptor media and replenished with an equal amount of the medium at predetermined intervals.

The withdrawn sample is subsequently filtrated using a 0.22–50 μm filter (e.g., Millipore, USA), and the drug released is measured using HPLC or UV-Vis spectroscopy at the wavelength of peak absorption of the drugs. A different and standard approach to ex-vivo release investigation is done using diffusion cells. The skin is pulled from the ear or abdomen, and the underlying cartilage and fatty substances are carefully removed. The required piece of skin is sliced and put on the diffusion cell, which was previously filled with receptor solution. Samples of the vesicular preparation are then put on the dorsal surface of the skin, and the instrument commences.

At intervals of up to 24 hours, samples are taken from the receptor media and replaced with similar quantities of the medium, and the withdrawn samples are evaluated for drug penetration using HPLC or UV spectroscopy. Semi-permeable membranes, including regenerated cellulose, can be utilized in place of skin for in vitro release tests [57]. The flow J of the drug over the skin or membrane can be calculated from the formula

$$J = \frac{Ddc}{dx} \text{…….. Equation 1.2}$$

Here D is the diffusion coefficient and is a function of the size, shape and flexibility of the diffusion molecule also as the membrane resistance,
c is the concentration of the diffused species, x is the spatial coordinate

1.7.6.10 Drug Content

The drug can be extracted from pre-weighed SNEDDS by dissolving it in an appropriate solvent. The amount of drug in the solvent extract was checked against a reference drug solvent solution utilizing an acceptable analytical technique [58].

1.7.6.11 Bioavailability Study

Depending on the self-emulsification capacity, size distribution data, and stability of the nanoemulsion, a formulation is selected for bioavailability studies. An in vivo study is carried out to calculate the drug after the administration of the formulation. The pharmacokinetic parameters of the maximum plasma concentration (Cmax), which signifies the corresponding

time of the drug's action (tmax) after oral administration, are calculated. The following estimation provides insight into the relative bioavailability of the SNEDDS formulation in contrast to the conventional tablet [59].

$$\text{Relative bioavailability}(\%) = \frac{\text{AUC test}}{\text{AUC reference}} \times \frac{\text{Dose reference}}{\text{Dose test}} \quad \text{.....Equation 1.3}$$

1.8 Potential of SNEDDS in Bioavailability Enhancement

The SNEDDS formulation encounters a variety of well-defined pathways following oral distribution, corresponding to the behavior of lipid-based formulations. These pathways encompass the digestive, absorptive, and circulatory processes. The process begins with the digesting phase, commencing with gastric lipase, whenever SNEDDS are transported to generate a crude emulsion in the GI (gastrointestinal) tract. Afterward, pancreatic lipase and co-lipase continue to break down the crude emulsion into monoglycerides in the small intestine, leaving and spreading any drugs contained in the SNEDDS.

The presence of exogenous lipids enhances the creation of bile salts, leading to the development of mixed micelles and vesicles. This environment in the stomach enhance the solubilization capability of both the drug and lipid-digested products. Any residual undissolved drug is transported, either in its ionized state through carrier-mediated absorption or by passive diffusion in the aqueous medium.

After finishing the digestion phase, these mixed micelles and vesicles cross the enterocyte membrane by collisional transfer, binding, and endocytosis or absorption into the lymphatic system. The surfactants used in the formulation might also help in the opening of tight junctions between cells, boosting the permeability of high-molecular-weight drugs [60].

Additionally, the drug may be delivered by various pathways, including paracellular and transcellular absorption. Along with enhancing the solubility of poorly soluble drugs, SNEDDS additionally enhances drug bioavailability by a variety of other possible pathways, for example, bypassing the hepatic first-pass effect, inhibiting P-gp efflux, and resisting metabolism by the cytochrome P450 family of enzymes inside the gut and liver.

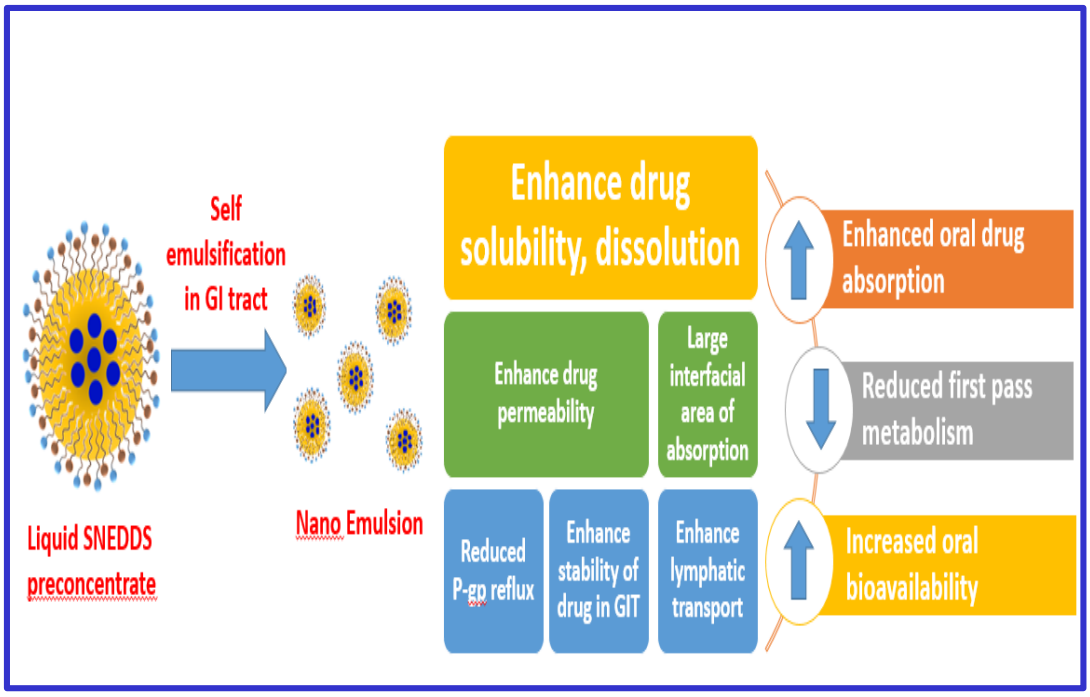


Figure 1.4: Overview of potential mechanism of SNEDDS to enhance bioavailability of drugs

The tiny globule size of SNEDDS, together with their surface activity, facilitates greater drug transport across the intestinal boundary layer and absorptive brush border membranes, finally leading to a more rapid onset and longer duration of therapeutic action. Further, the reduced susceptibility of SNEDDS to stomach emptying delays and lipolysis in the GI tract, as well as their outstanding thermodynamic stability and capacity for resistance to dilution, thereby keeping the drug in a solubilized state throughout the absorption phase, further reduces variation in bioavailability [61].

1.9 Advantages of SNEDDS

On the basis of the composition, SNEDDS gives distinct advantages in comparison to other lipid-based formulations [62]

- A nano-emulsifying drug delivery technique is set forward to boost the water solubility and bioavailability of lipophilic drugs.
- It helps transport drugs that are both hydrophilic and lipophilic.
- Flocculation, aggregation, creaming, and coalescence are not feasible since this system is thermodynamically and kinetically stable.
- It could be administered by a variety of methods, including oral, topical, parenteral, and transdermal.

- The huge surface area of the droplet, which also lowers fluctuation and speeds up absorption.
- Protection of medications that are prone to being broken down or digested by GI tract enzymes, resulting in improved drug bioavailability.
- Generally, fed and fasted states produce different bioavailability for humans, which may be overcome by SNEDDS.
- Reduction in intra- and inter-subject variation and nutritional effects.
- Enhanced absorption of orally taken medicine through numerous pathways and generation of quick commencement of action.
- Tiny droplets generated following the self-emulsification process in the GI tract greatly improve the interfacial surface for drug partition in two phases.
- The SNEDDS formulation employs emulsifying substances such as Tween 80, Span, TPGS (tocopherol polyethylene glycol succinate), and Cremophor EL, which demonstrate efflux transporter inhibitory properties in order to boost the bioavailability of the medication.
- The emulsifying agent with a high HLB value may also be able to loosen the tight connection between cells, which promotes the penetration of medicine.
- It can be preserved easily because of its excellent thermodynamic stability.
- The production and scale-up are simple.
- Improve patient compliance and safety.

1.10 Limitations of SNEDDS

There are several difficulties linked to SNEDDS, as follows [63]:

- The significant quantity of surfactant used in the SNEDDS formulation increases the drug's instability or decomposition, irritating the gastrointestinal tract and having serious side effects.
- Some of the lipids utilized in the generation of SNEDDS are unsaturated in nature, which makes them sensitive to oxidation. A high amount of unsaturation can result in an accelerated process of oxidation of lipids.
- Some conventional SNEDDS formulations include volatile co-solvents (ethanol and propylene glycol), which produce the precipitation of hydrophobic drugs due to the

migration of this co-solvent inside the shell of a hard or soft gelatin capsule.

- The incompatibility of liquid SNEDDS ingredients with capsule shells during long-term storage. Additionally, maintaining liquid SNEDDS at low temperatures remains among the key challenges. The entire problem could possibly be controlled through the creation of solid SNEDDS.
- The SNEDDS cannot be suited for hydrophobic medicines that are vulnerable to being catalyzed at an acidic pH.
- Normally, lymphatic transport of medicines via SNEDDS needs high log P and high triglyceride solubility. However, the amount of drug absorption via the lymphatic system suffers from substantial fluctuation and also relies on the physiological constitution of the individual. Therefore, the lipophilicity and triglyceride solubility of the medicine with regard to lymphatic transport need in-depth research, which necessitates a strong predictive in vitro or in vivo model.
- The dispersion of SNEDDS in physiological or aqueous media is not altered by polymorphism variations. However, it may substantially alter the release of medication if the matrix is sluggish or incapable of erosion in the dissolving medium.
- Traditional dissolve procedures are ineffective because these formulations may be dependent on stomach digestion prior to drug release. Many prototype lipid-based formulations must be derived and validated in vivo in an accepted animal model.
- Validation of formulations with components becomes increasingly complex.

1.11 Challenges in Formulations

The issue of drug precipitation in the GI tract may be solved by constructing supersaturable SNEDDS. This is a thermodynamically stable solution with a reduced quantity of emulsifier and a precipitation inhibitor polymer. Generally, medicines in traditional SNEDDS are precipitated after dilution in the GI milieu owing to disruption in the supersaturated condition. However, supersaturable SNEDDS may be able to avert these problems by establishing and retaining the supersaturated state. Sometimes, pharmaceuticals in the supersaturated formulation may also become crystallized during storage, this can also be prevented by adopting supersaturable formulations. Methyl cellulose, hydroxyl propyl methyl cellulose (HPMC), sodium carboxy methyl, and

cellulose polyvinyl pyrrolidone (PVP) are some of the most commonly utilized polymers to suppress precipitation in SNEEDS [64].

Generally, liquid SNEDDS formulations are filled in a hard or soft gelatin capsule; however, occasionally the shell of the capsule may weaken or become brittle owing to the leaching or interaction of the formulation with the shell. At lower temperatures, medication may also precipitate. To tackle these challenges, liquid SNEDD is turned into solid SNEDD in numerous ways. Thus, solid SNEDDS gives stability and resilience to the liquid formulation with higher patient compliance and also cheaper production costs. Lipid oxidation owing to unsaturation or due to their designs with oxidizable moiety may be decreased by the inclusion of specific antioxidants. In addition, dissolution of lipid by heating the system at a temperature above 20 ºC above the melting point of lipids might avoid the polymorphism of lipid. Moreover, solidification time may be enhanced by utilizing fatty excipients such as macrogol. This technique ensures the minimization and control of polymorphic alteration of the lipid matrix. However, this correction technique might significantly affect formulation handling and the packaging of capsules.

In relation to lymphatic transport, there is an urgent requirement for a good predictive model since the lipid solubility of medicine is not entirely sufficient for prediction. Nowadays, animal models that include intestinal lymphatic duct cannulation are available to predict the distribution of drugs via the lymphatic system. Another important challenge is the absence of a precise in vitro model to estimate the in vivo performance of SEDDS, which hinders the formulations from coming onto the market. To solve this challenge, in vitro lipolysis in addition to a dynamic gastric model (DGM) has been conducted to test lipid-based formulations [65].

1.12 Patent on Self-Nanoemulsifying Drug Delivery Systems

The rise in demand in SNEDDS has been sparked by their potential to improve drugs dissolution rates, especially for drugs under BCS Classes II and IV. SNEDDS offers the potential to increase the treatment of patients and compliance while additionally demonstrating interest in delivering therapeutic peptides and genes. However, the transition from research to market involves complex processes like technology transfer

and patent protection. This process can create a significant time gap between cutting-edge research and market availability.

Despite this challenge, the advantages of SNEDDS are likely to lead to increased patent submissions in the future, contributing to innovative drug delivery systems and advancements in the pharmaceutical field. There are a few listed patents on SNEDDS, as displayed in Table 1.4.

Patent No.	**Agency**	**Year**	**API**	**Lipid/Oil**	**Surfactant**	**Ref.**
US2013/0303495 A1	United State Patent	2013	Testosterone	Castor Oil	CremophorRH40 Imwitor742	66
US8728518B2	United State Patent	2014	Butylpthalide	Castor Oil, Almond Oil, Oleic acid	Cremophor EL, LabrafacCM10, Labrasol M1944, Labrafil M2125CS	67
US2015164851 A1	United State Patent	2015	Diacerein	Miglyol derivatives, Soya oil, Almond oil, Olive oil, Peanut oil	Tween, Labrafil, Labrafac, Labrasol	68
WO2016/179247 A1	World Intellectual Property Organization	2016	Delta-9-tetra hydro cannabinol, Extracts of Cannabis sativa	Polyethylen glycol-fatty acid esters	Triglycerides, Free fatty acid	69
US2018036233 A1	United State Patent	2018	Cyclosporine, Prednisolone, Loteprednol, Dexamethasone	Captex 355, Capmul MCM	CremophorRH40 Polysorbate 80, PEG 400	70
WO2020/212976 A1	World Intellectual Property Organization	2020	Cannabinoid, Cyclosporin, Antimalarial, Antibiotics	Hydrogenated Vegetable oil, Cinnamon oil, Coconut oil	Cremophor RH 40, Labrafil® M1944 CS, Labrafil® M2125 CS	71
EP 3915543A1	European Patent Application	2021	Celecoxib, Eavirenz and Fenofibrate, Paclitaxel, Paracetamol,	Captex® 200, Labrafac™ Witepsol®H35	Poloxamer 407 Polyoxyl-40 stearate, Poloxamer 188	72

Table 1.4: Patent on SNEDDS

1.13 Application of Quality by Design (QBD) in Formulation

Quality by Design (QbD) is an innovative approach to the quality of drugs. The core feature of Quality by Design is the ICH Guidelines. A quality specialist named Joseph Moses Juran established Quality by Design to be applied in production planning. To secure a specific degree of quality in products, every industry applies the quality by design (QbD) approach in developing pharmaceutical processes.

The QbD principles are detailed in the ICH standards Q8 (R1) (pharmaceutical development), Q9 (quality risk management), and Q10 (pharmaceutical quality system). QbD is "a systematic method for creating products that start with" corresponding to the ICH Q8 (R1) standard, producing the quality target product profile (QTPP), assessing the critical quality features (CQAs), critical material characteristics (CMAs), and critical process variables (CPPs), promoting investigating and assessing the risk, optimization, and validation [73].

With the adoption of such guidelines, cooperation in the processes of reviewing, compliance, regulatory filing, inspection, and decision-making becomes simpler, reducing time to the greatest degree and boosting technology implementation. The end result is quicker approval along with greater regulatory connections. QbD is a stringent, scientific, risk-based, comprehensive, and proactive technique that benefits both the industry and the FDA in pharmaceutical development [74, 75].

The optimization process is necessary for the design of pharmaceutical formulations for the following reasons:

- To investigate the effect of independent variables on the selected responses, i.e., a decrease in particle size by differing the temperature and pressure.
- To discover the connection between factors and responses, such as the quantitative variations of a reaction when we change the component and its quantity.
- To minimize the experimental time.
- To pick the most optimal formulation across all.
- It helps pick the best attainable product with a decrease in expenditure of time and

effort and limited expenditures for development, in contrast to traditional methods.

1.13.1 Terminology Utilized in Optimization

Various terms are utilized in optimization, such as factor, response, level, interaction, design space, contour plot, response surface technique, confidence interval, and so on. A few of them are listed below:

Variables: They consist of two kinds: dependent variables and independent variables. Independent variables are not dependent on any other value, for example, temperature, pressure, concentration, etc.

Factor: Factors like temperature, pressure, flow rate, and concentration have been allocated factors. The factor can be either qualitative or quantitative. Quantitative components have quantitative value, such as the concentration (1% and 2%) in a polymeric solution. A qualitative factor describes anything that is not quantitative, such as polymer quality or equipment type.

Level: A level is the value or label allocated to the factor. The value supplied to the factor is low to high, as shown in Table 1.5.

Response: It is the outcome of the experiment that can be operated on by the best factor. Afterwards, the influence has been explored, such as particle size and dissolving investigations. It gives the relationship between components and levels [76].

Factors	**Levels**		
	+1	**0**	**-1**
Temperature	35 ºC	45ºC	55ºC
Pressure	75 bar	85 bar	95 bar

Table 1.5: Factor and level for optimization

Interaction: It reveals the total influence of two or more factors on the response given. It presents a graphical portrayal to demonstrate the influence of the variable on the response.

Such as the combined influence of pressure and temperature on the particle size of the medicine [77].

1.13.2 Types of Designs

There are numerous distinct types of experimental designs to evaluate. Usually, good experimental designs include response surface methods (central composite design and box-benkhen design), screening (Plackett-Burman design), factorial design, fractional factorial design, mixture design, and taguchi design [78]. The various designs and descriptions they have applied throughout the product or the process layout of drug delivery systems are presented in Table 1.6.

1.13.2.1 Response Surface Design: Response surface design includes a set of sophisticated design of experiments (DoE) approaches that help us to better understand and optimize their responses. The response surface design technique is generally employed to enhance models after we have found key characteristics using screening designs or factorial designs, especially if we identify curvature in the response surface.

Design name	Description
Factorial designs	It refers to a design whereby the levels (a) of the mentioned factor (b) combine with each of the levels of every additional variable that is independent in the study, and the overall number of experiments is a^b.
Plackett–Burman designs (PBD)	These are two-level FFDs that are frequently employed in the initial assessment of A. Such as n-1 factors, where n is a multiple of 4. This concept might be performed by utilizing the least amount of runs.
Central composite designs (CCD)	It is typically employed for non-stationary responses employing a second-order model. It includes embedded (2k) FD or (2k-r) FFD, augmented by a collection of stellar points (2k) and a center point. 2k+2k+1 provides the total number of variables that are autonomous.
Box–behnken design	It needs simply three levels for any of the independent variables, such as l, 0, and +1. It is an affordable alternative to central composite design.
Mixture design	This design is useful when the attributes of the finished product generally depend not so much on the quantity of each element existing

	but on their percentages. These are strongly advised in such instances.
Taguchi designs	It is an offline quality control design that provides excellent performance in manufacturing powerful products with "I" pointing to the interior range and "E" as the outer matrix.
Optimal designs	These are non-classic customized designs that have become relevant when the area is irregular.

Table 1.6: Different experimental designs applied for optimization

There are two fundamental kinds of response surface designs:

(A) Central Composite Designs (CCD)

A Box-Wilson central composite design, usually known as central composite design (CCD), is widely used for creating a second-order polynomial representing the response variables in response surface techniques without utilizing a whole full factorial design of testsTo establish the value of the coefficients of a polynomial with quadratic terms, the experimental design must contain at least three levels of each component. They are generally adopted when the design plan involves sequential experimentation, as these designs may integrate knowledge from correctly designed factorial experimentation. A central composite design is the most often employed response surface in a planned experiment. CCD are factorial or fractional factorial designs with center points, expanded with a collection of axial points (often referred to as star points) that assist us estimate curvature. We may apply a central composite design to:

- Successfully predict first- and second-order terms.
- Model a response factor with curvature by incorporating center and axial points to a previously-done factorial design. CCD are particularly beneficial in sequential testing as you can commonly improve on prior factorial tests by integrating axial and center points [79].

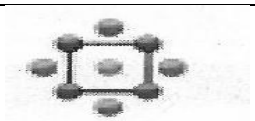
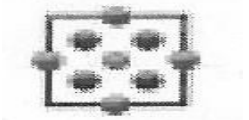
Circumscribed Central CompositeDesign (CCD)	
Faced Central Composite Design(CCF)	
Inscribed Central Composite Design(CCI)	

Figure 1.5: Different types of CCD

Design	**Number of levels**	**Uses point outside high and low variables**	**Accuracy of estimates**
Circumscribed	5	Yes	Excellent across full design space
Inscribed	5	No	Outstanding throughout center portion of the design space
Faced	3	No	Good for entire design space, inadequate for pure quadratic coefficients
Box Behnken	3	No	Excellent over whole design space, more uncertainly toward the limit of the design area

Table 1.7: Different designs with different number of levels with accuracy of estimates

Properties of Central Composite Designs

Rotability: We lack the capability to pick the location of the response surface best; we aim to ensure that the prediction error is the same for any point at the same distance from the center of the design. This attribute is termed rotability.

(B) Box-Behnken designs (BBD):

A Box-Behnken design is a type of response surface design which is devoid of an embedded factorial or fractional factorial design. BBD often have fewer design points than central composite designs; hence, they have the advantage of being affordable to run with an identical number of components. They can correctly forecast the first- and second-order coefficients, but they can't incorporate data from a factorial experiment. BBD generally include three levels per factor, unlike central composite designs, which

may have up to five. Also comparing central composite designs; BBD have never featured ranges where all components are at their maximum levels, such as each of the low values. BBD contains treatment combinations that are at the midpoints of the outermost edges of the experimental space and require a minimum of three consistent components. The following figure represents a three-factor BBD. Points on the figure show the tests and experiments that have been done.

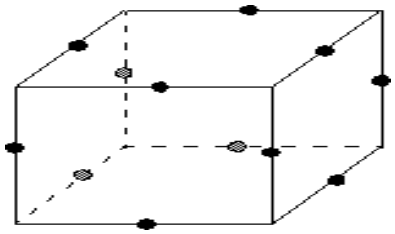


Figure 1.6: Three-factor Box-Behnken design

These designs allow efficient predict of the first- and second-order coefficients. Because BBD generally contain fewer design points, they may be less economical to implement than central composite designs with the same number of components. However, as they lack an in-built factorial design, they are not suitable for sequential research. BBD might also be beneficial, assuming that you understand the safe operating zone for your process. CCD usually involve axial points outside the "cube." These spots may not be in the region of interest or may be impossible to achieve as they are outside safe operating limitations. BBD do not have axial points; hence, we may assure that all design points remain within the safe operating zone. BBD also ensure that every single factor are not configured at their highest values at the exact same time.

After evaluating diverse design techniques, central composite designs (CCD) and box-behnken designs (BBD) were discovered to be acceptable for the present investigation. So, this design was employed to improve the SNEDDS formulation using the stated parameters [80].

1.14 Current status of Hypertension in the world

Cardiovascular disease is a serious health problem. Hypertension is among the most significant modifiable risk factors for cardiovascular disorders. High blood pressure is

responsible for 8.5 million fatalities owing to cardiovascular diseases and renal-associated disorders [81]. Hence, regulating normal blood pressure is vital. Hypertension is a risk factor for cardiovascular disease; uncontrolled hypertension boosts the relative risk from two to four times for coronary disease, stroke, heart failure, peripheral arterial disease, renal insufficiency, atrial fibrillation, and dementia/cognitive impairment. Undoubtedly, people with poorly controlled hypertension have an elevated risk for cardiovascular problems. Late eating, unnecessary time spent on electronic devices, insufficient physical activity, lazy lives, and numerous other factors further precipitate hypertension.

Hypertension has a vital role in producing cardiovascular diseases (CVDs) such myocardial infarction and stroke worldwide. Hypertension is the major risk factor for death and disability in India, according to research published in The Lancet on regional health (South-East Asia), 2022. It adds that less than one-fourth of hypertension patients in India had their blood pressure under control between 2016 and 2020; however, this rate has improved compared to prior years, and major disparities exist across areas. The number of people living with hypertension (blood pressure of ≥140 mmHg systolic or ≥90 mmHg diastolic or on medication) doubled between 1990 and 2019, from 650 million to 1.3 billion. Although hypertension can be prevented and managed, few countries currently do so effectively. Better hypertension control will save lives. Increasing the percentage of people whose hypertension is under control globally to 50% could save 76 million lives between 2023 and 2050. Treating hypertension is one of the most significant interventions to accomplish Sustainable Development Goal (SDG) target 3.4 of a one-third reduction in premature mortality from the primary non communicable diseases [82].

Antihypertensive are a group of medicines that are employed to treat hypertension (high blood pressure). Antihypertensive treatment is designed to prevent the consequences of high blood pressure, such as strokes and myocardial infarction. Research shows that lowering the blood pressure by 5 mmHg could decrease the risk of stroke by 34% and of ischemic heart disease by 21%, while lowering the chance of dementia, heart failure, and death from cardiovascular disease. There are numerous kinds of antihypertensive that reduce blood pressure in various ways. Among the most significant and most often

used medicines are thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACE), angiotensin II receptor antagonists (ARBs), and beta blockers [83].

1.15 Combination therapy for Hypertension treatment

When patients with hypertension fail to obtain appropriate control of their blood pressure, the choices to attempt to reach the required goals for therapy are increasing the dosage of mono therapy or employing pharmaceutical combinations with minimal adverse effects [84].

There is strong evidence to suggest that antihypertensive medications offer protection against complications of hypertension. Fortunately, a selection of drugs are accessible to achieve successful therapy for hypertension problems. While it is common to start treatment with a single prescription, an adequate combination of drugs is occasionally needed to maintain blood pressure successfully. Different studies imply that combination therapy of medicines with a specific mechanism of action assists in the effective and quick management of blood pressure. Combining a number of antihypertensive drugs is one key technique to achieve blood pressure control in most hypertensive people. By combining two medicines with distinct modes of action, an antihypertensive effect two to five times greater than that achieved through mono therapy is achievable. Therefore, the use of combined therapies affords stronger protection to a target organ than increasing the amount of monotherapy [85].

A combination of two pharmacological substances in one pill has been utilized for the management of hypertension since the mid-1960s. Today, various single-pill combinations (SPC) exist and are utilized not only for the treatment of hypertension but also for managing several other chronic conditions characterized by a significant mortality and morbidity risk. Fixed-dose combinations (both drugs in the same pill) deliver further advantages such as enhanced compliance by 24%, simpler indications, and maybe even decreased cost.

Multiple studies have demonstrated that hypertensive people with high cardiovascular risk benefit more when getting combinations of drugs, as well as those who have moderate hypertension and low risk for cardiovascular disease. Combination studies

Calcium channel blockers (CCB) are commonly used in clinical practice, and confirmation from multiple clinical trials suggests that CCBs efficiently and safely decrease BP and reduce long-term CV risk in a broad variety of patient population demographics.

As CCBs have a distinct mechanism of action in comparison to frequently used inhibitors of the renin-angiotensin-aldosterone (RAAS) system (such as ACE inhibitors and ARBs), their combination with these drugs could provide additive or complimentary benefits compared with utilizing two drugs that inhibit the same route. Actually, in patients with recently diagnosed stage 1 or 2 hypertension or in patients with insufficient BP control following conventional low-dose mono therapy, low-dose combination treatment with CCBs and ARBs has been demonstrated to deliver better blood pressure control than either high-dose mono therapy ($p < 0.05$ vs. either mono therapy) [86].

Benidipine and telmisartan are the suggested combinations of calcium channel blockers (CCBs) with angiotensin receptor blockers (ARBs) for the management of hypertension because of their anti-proteinuria effects [87]. Benidipine, a potent and long-acting calcium channel blocker, acts by inhibiting three kinds of calcium channels (L, N, and T) and shows a kidney protective effect. It also displayed a cardio-preventive effect owing to enhanced nitric oxide production along with greater vascular selectivity.

Telmisartan, an azole-class angiotensin II receptor antagonist, behaves by lowering the production of aldosterone by reversibly binding angiotensin II to the AT1 receptor located on vascular smooth muscle and adrenal glands. Thereby, arterial blood pressure decreases by reducing the overall vascular resistance. Telmisartan further demonstrated PPAR-γ agonistic action, which has a beneficial impact on glucose metabolism and antidiabetic properties [88]. Telmisartan is often administered together with additional antihypertensive medicines, such as calcium channel blockers, for the management of hypertension in renal failure conditions.

1.16 SNEDDS applied for Enhancement of Bioavailability of Anti-Hypertensive Drugs

Hypertension, characterized by a rise in blood pressure, normally influences 1.30 billion people all throughout the world and is recognized as one of the primary health diseases. A substantial majority of these drugs involve lower bioavailability, a short half-life, reduced permeability, and undesirable side effects. The effective drug technique for delivery needs to provide less dose frequency, higher bioavailability, enhanced selectivity, and fewer adverse reactions.

Traditional oral drug delivery strategies minimize the dosage frequency of antihypertensive medicines, which were formerly provided twice or thrice a day. The application chemical-dispensing systems that use different methods like a polymer-coated bead, transdermal therapeutic systems, osmotic pumps and coat-cores oral delivery absorption systems, were applied for these agents with the primary goal of decreasing lower blood pressure by constantly drug supply throughout the day long.

Sr.No.	Drug	Excipients	Application	Ref.
1	Irbesartan	Cremophor® EL Carbitol®, and Capryol® 90	About eight times increase in oral bioavailability, improved dissolution	90
2	Telmisartan	Tween® 20 Carbitol®, and Acrysol® EL	7.5 folds increase in oral bioavailability	91
3	Telmisartan	CapmulMCM , Tween 80 and Propylene glycol	1.54 fold increase in the oral bioavailability	92
4	Nitrendipine	Miglyol® 812, Cremophor® RH 40, Tween 80, and Transcutol® P),	1.6-fold greater than the conventional tablets	93
5	Nimodipine	Capryol 90,Kolliphor EL and PEG 400	Better control of hypertension in comparison to nimodipine suspension	94
6	Ramipril	Capmul PG8, Gelucire 44/14, and Transcutol P	Considerable enhancement of the process of dissolution of ramipril	95
7	Valsartan	Capmul MCM, Labrasol, Tween 20	3 folds increase in dissolution rate of the drug owing to enhanced solubility	96
8	Candesartan	Capmul PG-8, Kolliphor EL, and Transcutol P	1-fold increase in dissolution rate from SNEDDS	97

9	Cilnidipine	Ethyl Oleate, CremophoreEL and Transcutol	2.5 folds enhancement of dissolution rate.	98
10	Cilnidipine	Canola oil, Tween 80, and PEG 300	Optimized SEDDS formulation showed more than 98% drug release within 15 min	99

Table 1.8: Potential of SNEDDS for Enhancement of Bioavailability of Anti-Hypertensive Drugs

These sustained- release methods suffer from delay the time of obtaining the pharmacodynamics effect, exhibit spontaneous bioavailability, undergo first-pass metabolism, and experience dosage dumping, persistent toxicity, dose obstinacy, and higher costs.

Nanotechnology is a promising delivery approach to delivering sparingly soluble antihypertensive drugs by improving their stability and bioavailability. These also promote the progress of novel hydrophobic molecules. Biocompatibility, colloidal size, therapeutic targeting, lowering dose size, minimized toxicity, and compliance among patients are some key benefits of nano systems. SNEDDS provides greater interface areas to facilitate the dispersion of drugs and an improvement in bioavailability, thereby eliminating the requirement for higher-energy emulsification and, in turn, lowering manufacturing costs [89]. Table 1.8 addresses a few SNEDDS formulations of drugs that treat hypertension.

1.17 Need and Objective of the work

Need for the study

Recently generated new chemical substances show poor water solubility and represent a big challenge to existing drug development strategies because of their limited bioavailability. Still, various research applications have been working on solubility enhancement strategies. The most significant responsibility of the formulation is to create a secure and efficient pharmaceutical product. Drugs that have low water solubility usually influence their absorption owing to a poor dissolving rate; therefore, restricted drugs enter the systemic circulation as a result of poor therapeutic efficacy.

Those drugs, when administered without modification or formulation, failed to dissolve, resulting in limited bioavailability and low therapeutic effectiveness and compliance from patients. Whereas, intake of drugs with restricted bioavailability has little therapeutic efficacy, which is a significant concern for the drug delivery system. Therefore, it is necessary to develop a strong drug delivery system that permits treatment to have effective performance. However, self-nanoemulsifying drug delivery systems (SNEDDS) have become popular and have gained prominence for the enhancement of water solubility as well as the bioavailability of such hydrophobic drugs.

It is a significant drug delivery technique owing to solubility improvement, absorption uptake via the lymphatic system, and flexibility. Besides, pre-dissolved drugs and nanosized ranges of globules could increase the dissolving rate of drugs, therefore avoiding the absorption rate restriction problem. Drug absorption via the lymphatic system may avoid the hepatic first-pass metabolism, consequently escaping drugs from degradation and improving the drug bioavailability and efficiency of therapy. These vital steps make it a more stable, attractive, and unique drug delivery technology.

The traditional SNEDDS formulations, being in liquid dosage form, have several stability and formulation challenges. The formulation and stability obstacles of liquid SNEDDS formulations may be corrected by conversion into a solid dosage form, which is more stable and convenient. The solidification of liquid SNEDDS formulation is straightforward and has gained relevance with the current investigation.

Benidipine, a dihydropyridine calcium channel inhibitor that blocks L, N, and T-type calcium channels, is used for the treatment of high blood pressure. Benidipine is a BCS class II medication that has limited solubility and high permeability. The half-life of medication is 1 hour after delivery. Benidipine has significant protein binding (~ 98%), and the poor solubility of benidipine is a major issue in developing a novel formulation. Telmisartan is an angiotensin II receptor antagonist utilized for the treatment of hypertension. Generally, angiotensin II receptor blockers bind to angiotensin II type I receptors with high affinity, producing inhibition of the action of angiotensin II on

vascular smooth muscle and finally resulting in a reduction in arterial blood pressure. Telmisartan is a BCS class II drug with limited solubility and high permeability. Telmisartan is almost insoluble in water (0.0035 mg/mL) and exhibits a log P of 6.66 with only 42% oral bioavailability.

Telmisartan is generally taken with additional antihypertensive drugs such as calcium channel blockers for the treatment of hypertension with renal failure circumstances. Thus, the need for the investigation is to address the difficulties related to the administration of drugs with restricted water solubility and bioavailability.

Objective

The objectives of the current study include:

1) To build a self-emulsifying drug delivery system (SNEDDS) for benidipine and benidipine with telmisartan that are suffering low water solubility and bioavailability.
2) To conduct statistical optimization of the self-emulsifying drug delivery system for benidipine and benidipine with telmisartan utilizing factorial design.
3) To apply multiple linear regression analysis (MLRA) to examine the influence of independent factors on dependent variables.
4) To develop a new optimized formulation by employing an optimization approach using a quality-by approach.
5) To carry out in vitro assessments of SNEDDS formulations of benidipine and benidipine with telmisartan.
6) To accomplish the solidification of liquid SNEDDS into solid SNEDDS by physical adsorption onto inert solid material.
7) To examine the solid-state characteristics of solid SNEDDS.
8) To perform accelerated stability testing of the established solid SNEDDS formulation.
9) To compare against market formulation.
10) To evaluate the bioavailability of the generated solid SNEDDS using animal research.

1.18 Plan of work

1) Review of Literature: Related to Drug Delivery Systems and Drug Profiles from Global and National Journals
2) Characterization and identification of the drugs Benidipine and Telmisartan
   a. IR spectra, melting point using the capillary technique, etc.
   b. Determination of λmax of drug and creation of calibration curve of drug by appropriate technique of analysis
   c. Estimation technique development for API
3) Optimization of formulations implementing QbD paradigms
4) Setting the Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs)
5) Preformulation Study (for benidipine and benidipine with telmisartan)
   a. Solubility study (in oil, surfactant, and cosurfactant)
   b. Preparation of a phase diagram for each combination and each ratio
6) Characterization of liquid SNEDDS of Benidipine and Benidipine with Telmisartan
   a. Globule size, polydispersity index, and zeta potential
   b. Emulsification Time and liquification Time
   c. Cloud point determination
   d. Drug Content
   e. Thermodynamic Stability Studies
   f. Scanning electron microscopy
   g. *In vitro* drug release study
   h. Rheological Study
   i. Robustness to dilution and pH change
7) Solidification of the formulation of benidipine and benidipine with telmisartan SNEDDS
   a. Selection of an adsorbent
   b. Selection of the quantity of adsorbent necessary for optimal flow characteristics
   c. Micromeritic characteristics of benidipine and benidipine with telmisartan S-SNEDDS
8) Characterization of Benidipine and Benidipine with Telmisartan S-SNEDDS:

Employing Fourier transform infrared spectroscopy (FTIR) study, differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and particle diffraction with X-ray techniques

9) In vitro drug release examination of the developed formulation S-SNEDDS
10) Determine the kinetics of drug release.
11) Stability studies according to ICH guidelines
12) Comparison with a commercial formulation
13) Determination of bioavailability utilizing animal studies

The antihypertensive effectiveness of an optimized S-SNEDDS was investigated in adult wistar albino rats.

14) Statistical analysis of all the in vitro and in vivo outcomes

It will be conducted using relevant parametric tests like one-way ANOVA with the use of suitable software, such as Graph Pad Prism, Minitab, Kinetica, etc., in order to evaluate the statistical significance of the results.