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REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUE SPECIAL EMPHASIS ON SELF EMULSIFYING DRUG DELIVERY SYSTEM AND LIQUISOLID TECHNOLOGY

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ABSTRACT

It is common for solubility, a critical feature that governs the bioavailability and therapeutic efficiency of pharmacological compounds, to be a barrier to the creation of new drugs. As a result of their low solubility, pharmaceutical researchers have a great deal of difficulty when attempting to develop medications that are both more soluble and more sustained (BCS class II). There are issues with the solubility of medications that fall within BCS Class II and Class IV. When it comes to the world of pharmaceutical research, solubility enhancement is of great significance because its primary objective is to improve the solubility and bioavailability of medications that have a poor solubility by increasing their solubility. Because of their propensity to exhibit inadequate absorption, bioavailability, and therapeutic efficacy, medicines that are poorly soluble present a significant problem in the process of drug development. There are a few different approaches that may be taken in order to improve the bioavailability as well as the solubility of drugs that are already poorly soluble. In this review, we will be discussing two of the most essential techniques, which are the Liquisolid technique and the Self Emulsifying Drug Delivery System (SEDDS).

Keywords: SEDDS, Liquisolid technique, BCS Class II and IV, Dissolution, Bio availability.

INTRODUCTION

A drug's or new chemical entity's (NCE) aqueous-solubility plays a pivotal and deciding role in the formulation process. Before an active drug can cross the gastrointestinal tract and enter the bloodstream after an oral administration, it must dissolve in the stomach and/or the

intestines. As a result, absorption of drugs is usually limited by their dissolution rates when they have poor water solubility, and by their permeation rates when they have poor membrane permeability. As a result, there are two main goals for increasing the active drug's oral bioavailability:

1. Improving the rate of dissolution and solubility of medications that are not very water-soluble.
2. Improving the solubility of medicines with low permeability.[1]

When referring to a solute, the term "solubility" pertains to the largest amount of the solute which will dissolve in a certain quantity of a solvent or a specific quantity of a solution at a specific temperature.[2] Virtually more than ninety percent of medications are taken by mouth. Because of the solubility of the chemical in aqueous media, the drug absorption, bioavailability, and pharmacokinetic profile of drug substances that are delivered orally are greatly reliant on the solubility of the compound. Since 1995, more than ninety percent of the medications that have been approved have low solubility. The water solubility of approximately forty percent of the active novel chemical entities (NCEs) that are discovered through combinatorial screening techniques that are utilized by a number of pharmaceutical companies is believed to be lacking.[3] A component that is capable of dissolving another substance in order to produce a combination that is uniformly dispersed at the molecular level is referred to as a solvent. Solvents are defined as solutions that are composed of major constituents. A solute is defined as a substance that exists in a small amount and has the ability to dissolve in a solvent.[2]

The bioavailability of a drug, and ultimately the solubility of drug molecules, are two factors that determine the therapeutic effectiveness of a medicinal substance. In order to acquire the necessary concentration of the drug in the systemic circulation and consequently demonstrate the pharmacological response, solubility is one of the crucial characteristics that must be considered. Because of its convenience, high patient compliance, improved stability, exact dosing, and ease of production, oral medication delivery is the most straightforward and straightforward method of providing pharmaceuticals. The greatest concentration of the medication that may be dissolved in the solvent under a given set of conditions: temperature, pH, and pressure is referred to as the drug's solubility coefficient. Due to the limited absorption and bioavailability of poorly soluble medications, it becomes crucial to enhance their solubility or dissolution rate. This is because these drugs have a slower rate of dissolution. Given that solubility is a significant factor in drug liberation, it is not surprising that it plays a significant part in the drug's bioavailability. The presence of an aqueous solution at the site of absorption is necessary for the absorption of any medicine that is intended to be absorbed.[4]

SOLUBILITY DESCRIPTION TABLE[5]

Definition	**Parts of solvent required for one part of solute**
Very soluble	Less than 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Insoluble or partially insoluble	More than 10000

BCS CLASSIFICATION[4,6,7]

The Biopharmaceutics Classification System (BCS) was developed by the Food and Drug Administration (FDA) of the United States of America. This classification system divides medications into four distinct categories based on the solubility and permeability characteristics of the substances. In Classes II and IV of the system, where the dissolving phase of the medicine absorption process is the rate-limiting phase, low solubility results in the formation of a soluble impediment. The Biopharmaceutical Classification System (BCS) classifies the medications in accordance with the intestinal permeability and intrinsic solubility of the pharmaceuticals. The high bioavailability of a medicine is helped along by its intestinal permeability and its propensity to dissolve in water. In the case of medications that have low solubility and permeability, the bioavailability of these drugs is reliant on the solubility and permeability of the drugs, respectively. The bulk of drugs that are now being manufactured by the pharmaceutical industry have a low solubility. There have been a variety of solubility enhancement techniques that have been successful in addressing the issue of poor solubility.[6]

S. No	BCS class	Solubility	Permeability	Example
1	Class I	High	High	Benzapril
2	Class II	Low	High	Nimesulide
3	Class III	High	Low	Gabapentine
4	Class IV	Low	Low	Meloxicam

SOLUBILITY ENHANCEMENT TECHNIQUES

Various techniques have been used in attempt to improve solubility and dissolution rates of poorly water-soluble drugs which include as following:

a) Particle Size Reduction
b) Nanonization
c) Co-solvency
d) Hydrotropy
e) pH Adjustment
f) Sono crystallization
g) Supercritical Fluid (SCF) Process
h) Solid Dispersion

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system.[8]

(a) Particle Size Reduction[9]

In many cases, the dissolvability of a medication is inextricably linked to the estimation of the molecule of the sedative; as the size of a molecule decreases, the ratio of the surface area to the volume increases. The larger surface area offers the opportunity for a more significant contact with the dissolvable, which ultimately results in an increase in the insolubility. Comminution and shower drying are two examples of routine procedures for molecule measure reduction. These strategies rely on mechanical stretch to disaggregate the dynamic chemical. Molecule estimate reduction is made possible in this manner, which enables an increase in dissolvability that is not only productive but also replicable and financially advantageous. On the other hand, the mechanical powers that are inherent to comminution, such as processing and crushing, sometimes impart significant amounts of physical force upon the sedate item, which might lead to the initiation of corruption.

The elevated stretch that may occur during the process of comminution and splash drying is another worry that one must take into consideration while creating thermo-sensitive or unstable dynamic chemicals. When it comes to medications that are insoluble, using standard methods might not be able to improve the dissolvability to the degree that is desired.

(b) Nanonization[10]

In recent years, a variety of nanonization techniques have emerged with the purpose of enhancing the disintegration rates and bioavailability of a wide range of medications that are not effectively soluble in water. Nanonization is a general term that refers to the process of thinking about and making use of materials and structures at the nanoscale level, which is around 100 nanometers or less. The process of nanonization has the potential to enhance the solubility and pharmacokinetics of drugs, and it may also reduce the degree of systemic side effects.

There is a wide variety of approaches that are employed for the nanonization of the counting of medications. Pear processing, homogenization, emulsification-solvent dissipation approach, shower drying, and other similar techniques are examples of damp processing. In the realm of nanotechnology, there are various examples of medication nanonization.

(c) Cosolvency[11]

It is possible to increase the dissolvability of pharmaceuticals that are not easily soluble in water by combining the drug with a few water miscible dissolvables in which the medication is immediately soluble. Cosolvency is the name given to this preparation, and the dissolvable element that is used in conjunction with it is also referred to as cosolvent. By lowering the interfacial pressure that exists between the watery arrangement and the hydrophobic solute, the cosolvent framework is able to perform its function.

The term "dissolvable mixing" is another common name for this phenomenon. As a result of the expansion of natural co-solvent into the water, there is a change in the emotional state of the medications that are being solved. The co-solvents are characterized by the presence of hydrogen acceptor or giver groups that are located in a small hydrocarbon region. In most cases, the hydrophobic hydrocarbon region interferes with the hydrogen holding organization of water, which in turn reduces the intermolecular attraction of water. On the other hand, the hydrophilic hydrogen bonds ensure that water is able to dissolve.

(d) Hydrotropy[12]

It is possible that hydrotropy is a method of solubilization that is utilized to increase the degree to which hydrophobic chemicals may be dissolved in fluid arrangements. Within the framework of this technique is the employment of a substantial quantity of a water-soluble molecule, which is referred to as a hydrotrope. This hydrotrope has the ability to dissolve the hydrophobic compound by forming a complex with it. Hydrotropes are typically very small atoms that contain both hydrophilic and hydrophobic molecules in their structures. There are hydrophilic groups that are related with water atoms, and there are hydrophobic groups that are associated with the hydrophobic substance. This allows the hydrophobic compound to break down within the fluid arrangement.

The instrument of hydrotropism consists of the arrangement of a micellar arrangement, in which the hydrophobic chemical is encircled by the hydrotrope particles that are contained within the watery arrangement. Micelles are formed around the hydrophobic chemical by the hydrotrope atoms, which increases the compound's propensity to dissolve. Urea, sodium cumene sulfonate, sodium xylene sulfonate, and sodium benzoate are all components that are necessary for the production of hydrotropes. The technology of hydrotropy can be applied in a variety of industries, including the pharmaceutical industry, the cosmetics industry, and the agrochemical industry, in order to improve the bioavailability and solubility of hydrophobic compounds.

When compared to alternative methods of solubilization, hydrotropy benefits from a few key advantages. It is possible that this method is not only basic and economical, but it also does not require the utilization of potentially hazardous solvents. Moreover, hydrotropy is an environmentally friendly innovation because it is naturally appealing and reduces the amount of waste that is produced.

(e) PH Adjustment[13]

Water that is in short supply through the application of a pH change, a dissolvable medication has the potential to decompose in water. Solubilized excipients that raise the natural pH within the dose form to a degree that is more than the pKa of acidic pharmaceuticals on a weekly basis are able to increase the stability of that medication. Similarly, excipients that function as alkalizing agents have the potential to increase the stability of fundamental drugs on a weekly basis.

(f) Sonocrystallization[14]

Recrystallization of materials that are not easily dissolved through the use of fluid solvents and antisolvents has also been utilized successfully in order to reduce the amount of molecules involved. Sono crystallization is a unique strategy that utilizes ultrasound to reduce the amount of molecular estimates. This approach is based on the idea of crystallization itself. For the purpose of actuating crystallization, sono crystallization makes use of ultrasonic control that is characterized by a recurrence extend of from 20 to 100 kHz. In a sense, it is not so much as increasing the nucleation rate as it is a demanding means of reducing the estimate and managing the measure dispersion of the dynamic pharmaceutical fixings. The majority of applications make use of ultrasonic frequencies ranging from 20 kHz to 5 MHz.

(g) Supercritical Fluid Process (SCF)[15]

In addition, there has been a rapid increase in the number of applications and advancements, one of which is the utilization of supercritical liquids. Carbon dioxide is the most widely used supercritical liquid, and it has been known for more than a century that supercritical liquids (SCFs) have the ability to break up non-volatile solvents. Additionally, carbon dioxide is the most widely used supercritical liquid. It is safe, naturally neighbourly, and prudent all at the same time.[16] SCFs are intriguing for medicinal research because of the favourable working conditions, which include temperature and weight alterations. From the perspective of its fundamental temperature (Tc) and pressure (Pc), a SCF is a single stage that exists. Because they have properties that are halfway between those of a gas and a liquid, SCFs have properties that are beneficial to the handling of items. These properties include a thickness similar to that of a liquid, a compressibility and consistency similar to that of a gas, and a higher diffusivity than fluids. In addition, the thickness, transport qualities (such as consistency and diffusivity), and other physical properties (such as dielectric constant and extremity) move by a large amount with relatively minor changes in the working temperature, weight, or both around the fundamental foci.[17,18]

Because of this, it is possible to fine-tune a particular combination of features that are necessary for a certain application that is desired. These specialized handling qualities of SCFs, which have been identified and related within the food sector for a long time, have recently been adapted to pharmaceutical applications. The following substances are examples of supercritical solvents that are frequently used: carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, smelling salts, and water for example. Following the process of solubilization of the medicament particles within SCF, it is possible for them to be recrystallized at drastically reduced molecule sizes. The micronization of sedate particles within limit ranges of molecular measure is made possible by the adaptability and accuracy that are offered by SCF forms. This micronization typically occurs at sub-micron levels. The currently available SCF forms have demonstrated the capability to produce nano-suspensions of particles with a width of between 5 and 2,000 nanometers. A few pharmaceutical

companies, such as Nektar Therapeutics and Lavipharm, are specializing in the construction of molecules by the utilization of SCF innovations for the purpose of reducing the size of molecules and improving their dissolvability. Precipitation with compressed antisolvents handle (PCA), Fast Development of Supercritical Arrangements, Gas Antisolvent Recrystallization, Precipitation with Compressed Liquid Antisolvent, Impregnation or implantation of polymers with bioactive materials, arrangement improved scattering by supercritical liquid, arrangement upgraded scattering by SCF, supercritical antisolvents forms (SAS), and vaporized supercritical extraction framework are some of the strategies that have been developed to address individual perspectives of these deficiencies.[19,20] These are some of the strategies that have been developed to address the shortcomings that have been identified.

(h) Solid Dispersion[13]

Around the early 1960s, Sekiguchi and Obi investigated the period and disintegration execution of eutectic dissolves of a sulfonamide sedate and a water-soluble carrier. It was around this time that the concept of strong scatterings was initially proposed. Strong scatterings are indicative of a worthwhile pharmaceutical method that can be used to enhance the disintegration, assimilation, and beneficial viability of medications in dose shapes. When we talk about strong scattering, we are referring to a collection of strong objects that are made up of at least two unique components. These components are typically a hydrophilic network and a hydrophobic medication. It is important to note that polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), and Plasdone-S630 are the hydrophilic carriers that are most frequently used for powerful scatterings. Surfactants like Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulfate (SLS) moreover discover a put within the details of severe scattering. The dissolvability of celecoxib, halofantrine, and ritonavir can be improved with the utilization of appropriate hydrophilic carriers, such as celecoxib with povidone (PVP) and ritonavir with gelucire. This can be accomplished through the utilization of strong scattering.

In this review, we will be discussing two of the most essential techniques, which are the Liquisolid technique and the Self Emulsifying Drug Delivery System (SEDDS).

SELF EMULSIFYING DRUG DELIVERY SYSTEM

SEDDS, or self-emulsifying drug delivery systems, are a modern technology development based on lipids that has great potential for increasing the oral bioavailability of medications. Medications can be more effectively absorbed from the gastrointestinal tract when they are in this form because these formulations speed up the solubilized phase formation, enhance the drug's conveyance through the intestinal lymphatic system, and avoid the P-gp efflux.[21,22] These self-emulsifying formulations have been observed to facilitate the transportation of medication via the gastrointestinal mucosa towards the systemic circulation through lymphatic routes, as shown in Figure 1. Such lipid-based formulations have been reported in patent and published literature on a global scale at an alarming rate as of late.[23-28] Just by looking at these reports, you can see that the innovative technology behind these solutions is quite successful and very adaptable.

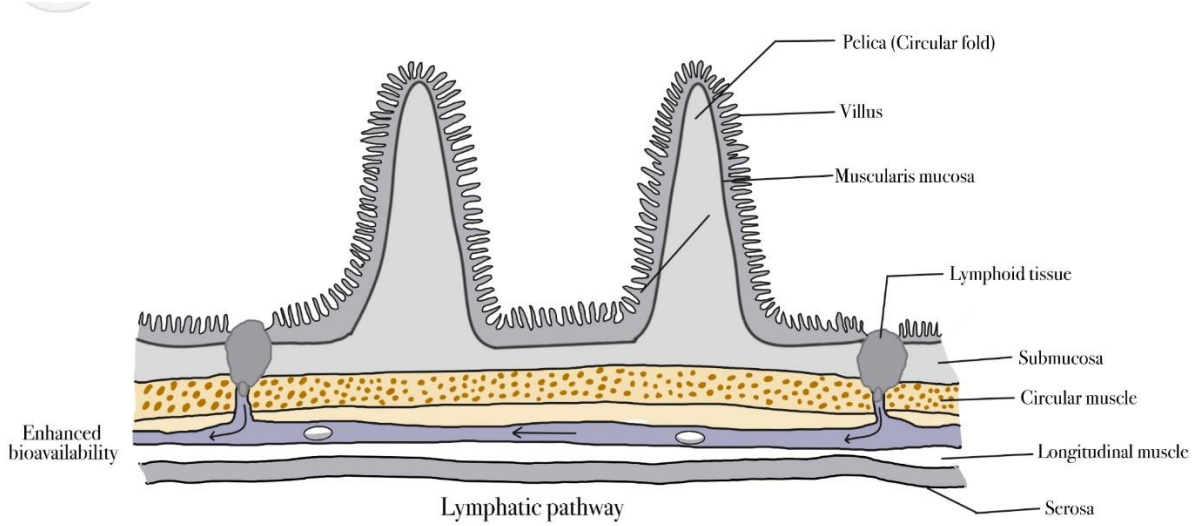

Figure 1 – Transportation of drug through GI mucosa towards systemic circulation through lymphatic route

Isotropic combinations of medication, lipids (oils, either natural or synthetic), and emulsifiers (solid or liquid) typically with at least one hydrophilic co-solvent or co-emulsifier make up self-emulsifying formulations.[29] SEDDS is an umbrella word for emulsions whose droplet sizes vary from microns to a few nanometres. Concentrated microemulsions, nano-emulsions, or pre-concentrates[30] are the terms used to describe these emulsions, which vary in terms of globule size. Formulations that create transparent microemulsions with oil droplet sizes between 100 and 250 nm are known as self-micro emulsified drug delivery systems (SMEDDS). Formulations with globule diameters smaller than 100 nm are now referred to by a more modern abbreviation, "self-nano emulsified drug delivery system" (SNEDDS). While there have been multiple reviews on the subject in the past [31-35], it is necessary to do an updated evaluation due to the enormous increase in the variety of SEDDS and the number of medications enclosed within these carriers.

FORMULATION ASPECTS OF SEDDS

In the gastrointestinal tract, the SEDDS formulation instantly disperses into a clear liquid that does not change with dilution.[36] Depending on the globule size of the SEDDS formulation, these dispersions can be micro or nano emulsions. The active ingredient in a standard SEDDS formulation is a combination of lipidic and emulsifying excipients that have the capacity to dissolve the medicine. The hydrophobic agent must stay soluble for at least the time period that is significant during gastrointestinal absorption when a drug molecule is released from SEDDS in the GI tract. That is why, along with the necessary lipid and emulsifier, a co-emulsifier is also present in a standard SEDDS formulation.[37] Figure 2 shows the typical steps in the approach for making SEDDS formulations and how the micro/nano-emulsions come to be once they are diluted. These SEDDS must be made as an oral solution in soft gelatin capsules or as a solid dosage form in hard gelatin capsules, depending on the ultimate physical nature of the system, which can be either liquid or semisolid/solid.

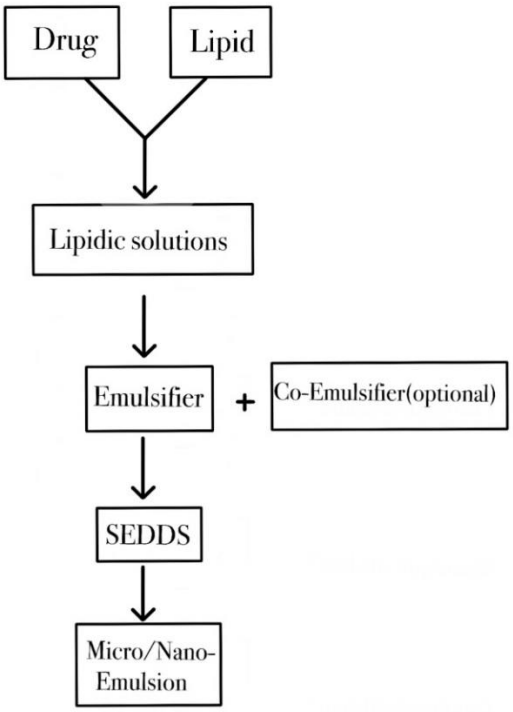

Figure 2 – Formulation approach of SEDDS

Types I, II, IIIA, IIIB, and IV SEDDS are classified according to the amounts of lipidic triglycerides, water-soluble or water-insoluble surfactant emulsifiers, and hydrophobic co-emulsifiers or co-solvents. This categorization is based on the composition of the SEDDS. In general, the production of nanometer-sized globules is the result of all SEDDS formulations, with the exception of Type I, which is made up solely of lipidic components and does not contain any surfactants or co-surfactants. All of the other categories have different proportions of surfactants and co-surfactants, with the exception of Type I, which does not include any of these components.

CHARACTERIZATION OF SEDDS

Assessment of self emulsification[38,39]

The efficiency of self-emulsification was assessed using standard US pharmacopoeia XXIII dissolution apparatus type II. One gm of formulation was added drop wise to 200 ml of buffer at 37ºC. Gentle agitation was provided by a standard stainless steel dissolution paddle at 60 rpm. The in-vitro performance of the formulation was visually assessed using the following grading system.

Grade A: Rapidly forming emulsion having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 minutes.

Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify longer than 2 minutes.

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Emulsification time[40]

The emulsification time of SEDDS was determined according to USP XXIII, dissolution apparatus II. 0.5 g of the SEDDS formulation was introduced into 250 ml of 0.1N HCl in 500 ml conical flask under action of magnetic stirrer rotating at constant speed (50 rpm).

Droplet size analysis[41]

Droplet size determines the rate and extent of drug release as well as the stability of the emulsion. Formation of SEDDS, which are stable, isotropic and clear o/w dispersions, takes place on reduction of the globule size. SEDDS formulations was diluted to 100 ml with distilled water in a flask and is mixed gently by inverting the flask. The droplet size was determined by Dynamic Light Scattering (DLS) technique

Measurement of Zeta potential[42,43]

The emulsion stability is directly related to the magnitude of the surface charge. The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. If all the particles have a large negative or positive zeta potential, they will repel each other and there is dispersion stability. The SEDDS were diluted with a ratio of 1:20 v/v with distilled water and mixed for 1 min using a magnetic stirrer.

Transmission Electron Microscopy[44,45]

SEDDS formulation was diluted with distilled water 1:30 and mixed by gentle shaking. Copper grids are allowed to stand on for 60 seconds on which one drop of sample obtained after dilution was deposited. Filter paper is used to remove excess fluid and then the grid was stained in 1% phosphotungstic acid solution for 30 seconds.

Determination of viscosity[46,47]

Viscosity study is necessary for SEDDS to characterize the system physically and to control its stability. The viscosity of the SEDDS is crucial in determining its ability to be filled in hard or soft gelatin capsules. If the system has very low viscosity, it may enhance the probability of leakage from the capsule and the system with very high viscosity may create problem in pourability. SEDDS formulation of drug around 1ml was diluted with the distilled water in a beaker with constant stirring on magnetic stirrer. Viscosity of the resultant emulsion and initial SEDDS was measured using Brookfield viscometer.

Drug content[48]

The drug content of SEDDS formulation was measured using UV spectroscopic method. The drug content uniformity was determined by preparing 10 µg/ml of aliquot of SEDDS sample using methanol as solvent. The samples were suitably diluted and the absorbance of the solutions was measured at 240 nm using UV-Visible spectrophotometer against methanol as a blank. The amount of drug present was estimated by using standard calibration curve of the drug.

Advantages of SEDDS[49]

- The profile of controlled medication conveyance is overseen by it.
- It prevents the medicine from being damaged by the harsh environment in the digestive system.
- Their medicine payload is higher.
- It improves the drug's bioavailability.
- Reducing the frequency of dosage recurrence.

Disadvantages of SEDDS[50]

- The cost of production is higher.
- The instability of the material that drugs contain.
- The in vitro models of SNEDDS require additional investigation and approval before they can be evaluated for their intensity.
- The incongruence and solidity of the medication are reduced.
- There is a possibility of medical substances leaking out and precipitation

Table -1: Applications of Self Emulsifying Drug Delivery System (SEDDS)

Study	Excipients	Result	Reference
Formulation and characterization of	Oleic acid, Ethanol, PEG-400, Tween –	Azilsartan loaded SEDDS shows super	Naina Dubey et.al 2024.[51]

Azilsartan loaded self-emulsifying drug delivery system.	80	disintegration rate that would additionally help in upgrading oral bio availability.	
Biopharmaceutical justification of the creation of self-emulsifying drug delivery systems with **Simvastatin.**	Castor oil, PEG-40, Tween-80, Glycerol monostearate, PEG-100, Ethanol.	The SEDDS method of medication formulation makes simvastatin more soluble and speeds up the drug's release into the stomach environment, even though simvastatin is not very water-soluble.	Liubov Bodnar et.al 2023.[52]
Formulation studies of solid Self-Emulsifying Drug Delivery system of **Ivermectin.**	Soyabean oil, Tween 80, Span 80, Methanol, Di Methyl Formamide (DMF).	Solid SEDDS formulation of Ivermectin results in improved oral bioavailability.	Vipul P. Patel et.al 2018.[53]
Formulation and evaluation of Self Micro Emulsifying Drug Delivery system for **Efavirenz.**	Polyethylene glycerol triricinoleate-35 castor oil (Cremophor EL), Caprylocaproyl Macrogoglycerides (Acconon MC-8 EP), PEG-400, Mannitol.	The weakly water-soluble medication Efavirenz's oral absorption is improved by SEDDS.	Ardad Rameshwar Madhukar et.al 2012.[54]
Formulation of **ciprofloxacin** loaded oral Self Emulsifying Drug Delivery System to improve the pharmacokinetic and anti-bacterial activity.	Oleic acid, Silicone oil, Olive oil, Castor oil, Sunflower oil, Myglol oil, Polysorbate-80, Polysorbate-20, PEO-200, PEO-400, PEO-600 and Propylene glycol.	This study reveals that SEDDS formulation of ciprofloxacin shows increased aqueous solubility and oral bio availability.	Asghar Ali Asghar et.al 2022.[55]
Formulation and evaluation of Self-Emulsifying Drug Delivery System of **Bosentan.**	Gelucire 44/14, Cremophor EL, PEG-400, Tween-80, Tween-20.	SEDDS of bosentan shows increased solubility, increased in vitro dissolution efficiencies and increased bio availability.	Sailaja Gunnam et.al 2018.[56]
Formulation and characterization of	Oleic acid, PEG-400, Tween-80.	SEDDS of losartan shows improved bio	Karnita Singh Jatt et.al 2022.[57]

Losartan loaded Self-Emulsifying Drug Delivery System.		availability.	

LIQUISOLID TECHNIQUES [58-61]

One exciting new approach that has the potential to alter the rate of drug disintegration is liquid solid innovation. It was employed to enhance the rate of disintegration of poorly water-soluble drugs. Oral absorption rates for class IV and weakly soluble class II medicines are often controlled by their rates of dissolution in the gastrointestinal system. Powders suitable for tableting or injection can be created using the new "Liquisolid" technology, which transforms fluid drugs (such as mixtures of smooth fluid medications and water-insoluble powerful medications) into solid forms that can be transported in a non-unpredictable manner. Reason being, fluid pills contain a reasonable amount of medicine in a soluble form.

FORMULATION ASPECTS OF LIQUISOLID TECHNIQUES

The liquisolid method is a simple way to make a powder that can absorb liquid, like cellulose or silica, from a liquid active pharmaceutical ingredient (API) or a weakly soluble API in a non-volatile hydrophilic solvent. The final product is a powder that is dry and flowable enough for the desired application. The powdered solution, which resembled soft gelatin capsules, facilitated the rapid release of the API, which was poorly soluble in water. The API's presence in the solution made this feasible.

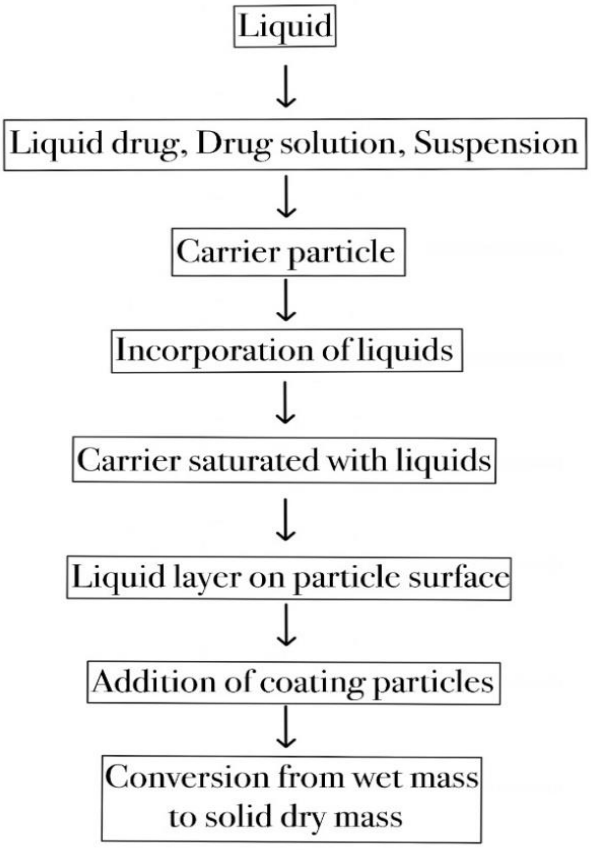

Figure 3 – Formulation approach of Liquisolid technique

When powdered solutions were compressed, there was a certain percentage of active pharmaceutical ingredient (API) lost due to the phenomena of liquid "squeezing out" and

poor compressibility, rendering this idea unusable in industrial settings. Although studies have shown that powdered solutions of APIs with low water solubility can improve their dissolving capabilities, this idea has not yet found a commercial application. Therefore, it was necessary to think about compression and flowability properties at the same time while developing liquisolid (LS) systems as a subsequent technology.[62]

Mixtures of liquid and powder that seem dry yet have good flowability and compression characteristics are called liquisolid systems. Liquid pharmaceuticals, or medications, are solutions or suspensions of lipophilic active pharmaceutical ingredients (APIs) in a non-volatile solvent that is water miscible but poorly soluble. Powdered liquisolid systems are made from a porous carrier material that can soak in liquid through its pores and soak up any excess liquid that falls on the particles' surfaces. In order to remove any surplus liquid from the surface of the carrier particles that contain the liquid medicine, a coating substance containing very adsorptive, small particles is utilized. Liquisolid powder and other components, such as lubricant, binder, and disintegrant, may be combined to form LS compacts, which may be taken in the form of tablets or capsules. Both immediate and sustained release formulations are available in these compacts. This idea was backed by a patent that aimed to ensure its scalability by pointing out that there is a finite amount of liquid that can be held by a particular carrier and coating material combination while still having good compression and flow characteristics.[62]

A formula for liquisolid systems has been created by Spireas and Bolton[62] using mathematics. Quantifying the connection between the quantities of carrier (Q) and coating (q) materials is the carrier to coating ratio (R), a crucial quantity. By applying the "liquisolid flowability test" to a given R value, one may get the "flowable liquid load factor" (ΦLf). The maximum allowable loading of liquids with respect to flowability is this factor.

The liquid load factor (L_f) is the ratio of the mass (in grams) of the liquid (W) to the amount of the carrier (Q). In the past, the flowability of the "powdered solution technology" was assessed using the "angle of slide" method, with a maximum value of 33°. However, in the case of liquisolid systems, flowability is often assessed by measuring the rate at which the powder flows. Powder in a liquisolid system should have a flow that is both consistent and unobstructed. The requirements of the particular processing equipment, such as a tableting and capsule filling machine, should inform the calculation of the maximum practical powder flow rate.

CHARACTERIZATION OF LIQUISOLID TECHNIQUES

Solubility studies[63]

Solubility studies drug was carried out in PG, PEG 400, and Tween 80 to select the best non-volatile solvent for dissolving of drug in a liquid vehicle. Saturated solutions were prepared by adding an excess of drug to the vehicles and shaking using an isothermal shaker water bath at 25 ± 0.5 ^{0}C for 72 hr with constant vibration. Then, the samples were centrifuged at 3000 rpm for 20 min, followed by the collection of the supernatant layer of each sample that was subsequently filtered using a filter membrane (0.45 μm). After filtration, the samples diluted with methanol, and the solubility determined at specific λ max by using UV- visible spectrophotometer in a triplicate measurement, and mean reading is taken.

Drug content[64]

250 mg of prepared Liquisolid system was weighed and triturated with 5 ml of ethanol and finally the volume was made up to 100ml with phosphate buffer 6.8. the solution was filtered through a millipore membrane filter (0.45 μm). The filtrate was used to determine the drug content using UV spectrophotometer at 318nm. Each sample was analysed in triplicate. Theoretically, each 250 mg of Liquisolid system should contain 25 mg of drug content.

Particle size analysis[64]

Particle size of different Liquisolid systems was determined using the sieving method. A set of sieves (710-250 μm) was used. The prepared liquisolid system was placed on the top sieve (710 μm) and placed into the sieve shaker and shaking was performed for 10 mins. The amount retained on each sieve was weighed. Then the percentage of weight fraction retained on each sieve was calculated. The results were plotted as histograms to show the particle size distribution of each formula under investigation.

Flowability studies[65]

In order to ensure the flow properties of the LSS that will be selected to be compressed into tablets, angle of repose measurements (fixed height cone method), Carr's index, and Hausner ratio were adopted. In the bulk density measurement, fixed weight of each of the prepared liquisolid powder formulae was placed in graduated cylinder and the volume (V_0) occupied was measured and the initial bulk density (D_0) was calculated. The graduated cylinder was then tapped at a constant velocity till a constant volume is obtained when the powder is considered to reach the most stable arrangement; the volume of the powder was then recorded as the final bulk volume (V_f), and then the final bulk density (D_f) was calculated.

Carr's compressibility index was calculated according to the following equation:

$$\text{Carr}'\text{s index} = \frac{D_f - D_0}{D_f \times 100}$$

In addition, Hausner ratio was calculated from the following equation:

$$\text{Hausner}'\text{s ratio} = \frac{D_f}{D_0}$$

Advantages of Liquisolid technique[66]

- It is suited for controlled drug delivery systems
- It does not include any process approaches, such as nanonization or micronization procedures
- It is appropriate for both powder and liquid forms of oral medication.
- Through the use of this method, the bioavailability of medications that are not very water-soluble is increased.
- It is an appropriate method for dealing with solid medications and liquids that are almost completely insoluble.
- The medication is generated in the shape of a tablet or an encapsulated dosage form, and it is stored in a liquid state that has been solubilized. This gives the medication developed or enhanced drug wetting qualities, which ultimately results in improved drug dissolution profiles.

Disadvantages of Liquisolid technique[66]

- For the purpose of preserving an adequate level of flowability and compatibility, it is necessary to use a greater quantity of carrier and coating ingredients.
- The medicine must have a high solubility in non-volatile liquid carriers in order for the liquid-solid system to work.
- When it comes to water-insoluble medications, the liquid-solid method is the most prevalent.
- The liquid-solid method is not appropriate for the formulation of lipophilic medicines that have a large dosage capacity and are water insoluble.
- Additionally, modest drug loading capabilities are required for liquid-solid systems.

Table -2: Application of Liqui Solid techniques

Study	Excipients	Results	Reference
Enhancement of dissolution rate of **Indomethacin** using	Micro Crystalline Cellulose (Avicel PH101), PEG-200,	It was discovered that tablets of indomethacin with	Majid Saeedi et.al 2011.[67]

liquisolid compacts	Glycerin, Starch, Potassium hydrogen phosphate, sodium hydroxide, magnesium stearate.	quick release had better dissolving rates and increased oral bioavailability.	
A novel approach to enhance solubility of **Olmesartan medoxomil** by liquid compact technique.	Propylene glycol, PEG-400, Tween-80, Micro Crystalline Cellulose (Avicel-102), Sodium Starch Glycolate, Aerosil-200, Magnesium Stearate, Talc, Magnesium Aluminometasilicate (Neusilin).	Olmesartan medoxomil tablets made of liquisolid technique show increased dissolution rates and bioavailability	Ayesha Sultana et.al 2022.[68]
Liquisolid technique: An approach to enhance the dissolution rate of **Olanzapine.**	PEG-200, Avicel PH-102, Starch, Tween-80, Aerosil-200.	Liquisolid tablets prepared by Direct Compression Technique show increased rate of dissolution and also increases the bio availability.	Korni Ramadevi et.al 2018.[69]
Enhancement of **Ketoconazole** dissolution rate by the liquisolid technique.	Avicel PH-101, Amorphous silicon dioxide, Sodium starch glycolate, Tween-80, Propylene glycol, PEG-200, PEG-400, Glycerin, Corn starch, Monohydrate lactose, Sorbitol, Sodium chloride, HPMC K4M, PVP K25.	The dissolving profile of liquidsolid pills improved when PVP was added to the liquid medicine during preparation.	Karim Osouli et.al 2018.[70]
Formulation and evaluation of **Lumefantrine** capsule prepared by using liquisolid technique.	Aerosil 200, Avicel PH102, Tween-80, Propylene glycol, PEG-400.	The poor water-soluble drug of lumefantrine made into capsule by liquisolid technique enhances the solubility and results in increased bio avaialability.	Ameer khan et.al 2018.[71]
Solubility enhancement of **Labetalol Hydro Chloride** by using liquisolid technique	Propylene glycol, Avicel PH102, Aerosil PH 200, Sodium Starch Glycolate, Talc, PVP K30.	Liquisolid tablet of Labetalol hydrochloride prepared by direct compression	Vinayak Mastiholimath et.al 2022.[72]

for management of hypertension.		technique show increased rate of dissolution.	
Enhancement of **Loperamide** dissolution rate by liquisolid compact technique.	Micro Crystalline Cellulose PH102, Aerosil, Sodium Starch Glycolate, Imodium.	Liquisolid tablet formulation of loperamide show increased dissolution rate.	Kambham Venkateswarlu et.al 2016.[73]

DISCUSSION

In this comprehensive investigation, we assessed the solubility enhancement techniques of the Self Emulsifying Drug Delivery System (SEDDS), as well as the Liquisolid technology, which performs vital tasks in overcoming the obstacles that are faced by medicines that are restricted in their ability to dissolves in water. By utilizing these tactics, it is feasible to increase the solubility of drugs that fall within the BCS Class II and IV categories, which eventually leads to an improvement in the dissolving rate of the drug as well as its bioavailability. As an additional benefit, these methods make it possible for researchers to manufacture medications that have very little solubility in water into whatever type of dosage form they choose.

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