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Solubility Enhancement of Poorly Water-Soluble Drugs through Self-Nano Emulsifying Drug Delivery System

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ABSTRACT:
Drug solubility is a key consideration in the creation of any dosage form. To get the desired drug concentration in the absorption site for optimal pharmacological activity, solubility is one of the crucial factors. The main issue with developing novel chemical entities for formulation is their low water solubility. The majority of NCEs (New Chemical Entities) created in the pharmaceutical sector are essentially water-insoluble. Particle size reduction, salt creation, solid dispersion, and formulations based on lipids are only a few of the approaches utilized to improve the solubility of poorly soluble medications.The literature extensively discusses lipid-based drug delivery systems for improving drug solubility, permeability, and bioavailability. A self-nanoemulsifying drug delivery system is an efficient oil-based technique for administering medications with low dissolution rates and insufficient absorption. Researchers' focus has been drawn to the difficulties of developing poorly water-soluble medications due to SNEDDS's success. Enhancing the solubility and bioavailability of lipophilic drugs can be done successfully with SNEDDS. A summary of SNEDDS, their composition, mechanism, method of synthesis, and formulation characterization methods was attempted in this article. Additionally, the SNEDDS formulation of hepatoprotective medications is reviewed in this article.
Keywords: Self-nano emulsifying drug delivery system (SNEDDS), solubility, poor bioavailability, pseudo ternary phase diagram.

I. INTRODUCTION:

Drug Solubility

One of the crucial factors to consider in order to get the required drug concentration in the systemic circulation for the desired pharmacological action is solubility, the phenomenon of the solute dissolving in the solvent to produce a homogenous system. The drugs must be present in solution form at the absorption site. For a poorly water-soluble medicine, drug solubility is the rate-limiting stage of dissolution. Based on the biopharmaceutical classification system (BCS) classification, drugs that belong to classes II and IV have low solubility in water**(Surhery et al., 2020)**. In the pharmaceutical industry, up to 40% of novel chemical entities are discovered that are poorly soluble or lipophilic, which causes limited oral bioavailability, considerable intra- and inter-subject variability, and a lack of dose proportionality. Many efforts are made to improve the solubility and oral bioavailability of water-insoluble drugs to resolve these issues. Drugs are typically modified physically, chemically, physically, or by the administration of solubility improvement procedures. Reduced particle size, salt formation of the drug, drug complexing, and lipid-based formulation techniques like liposomes **(Bahareh Sabeti et al., 2014)**, nano-emulsion **(Rabea Parveen et al., 2011)**, SNEDDS (self-nano emulsifying drug delivery system) **(Aristote B. Buya et al., 2020)**, and nanostructured lipid carriers **(Mishra A et al 2016)**.Lipid-based formulations improve the absorption of poorly water-soluble drugs from the gastrointestinal tract by boosting drug solubilization, enlisting intestinal lymphatic drug transport, and interacting with enterocyte-based transport mechanisms.

SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM:

There are numerous methods for increasing drug solubility, however, SNEDDS, a lipid-based technology, has been shown to increase drug dissolving rates and aid in the creation of the soluble drug phase.

SNEDDS (self-nano emulsifying drug delivery systems) are nanoemulsion preconcentrates or anhydrous forms of nanoemulsions SNEDDS are anhydrous isotropic mixtures of oil, surfactant, active pharmaceutical ingredient, and hydrophilic co-surfactant or solubilizer**(B.Singh et al., 2009)**. The o/w nanoemulsions form quickly and spontaneously

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after being introduced into the aqueous phase and are composed of globules with sizes varying from a few nanometers to less than 200 nm. The o/w nanoemulsions are made up of globules with diameters ranging from a few nanometers to less than 200 nm, and they develop fast and spontaneously after being added to the aqueous phase. A larger interfacial surface area is created for the drug dispersion into a gastrointestinal fluid by the minute droplets of the drug that are dissolved in the oil phase. The increase in the interfacial surface area leads to an increase in both drug solubilization and diffusion. The nanosized SNEDDS allowed for rapid drug absorption and digestion via the gastrointestinal system. Because the medication has already been partially dissolved, SNEDDS can skip the simple rate-limiting phase of dissolution. Consequently, a quick start to action could be accomplished. An increase in the lymphatic uptake of an extremely lipophilic drug would result from the lipid carrier of the SNEDDS and the first-pass metabolism may also be decreased**(S. Gupta et al., 2011)**Triglycerides, cholesterol esters, and long-chain fatty acids are only a few examples of the byproducts of dietary lipid digestion that can be absorbed by the intestinal lymphatic system. In the enterocytes, long-chain fatty acids and monoglycerides are changed into triglycerides. Before leaving the enterocytes, triglycerides are incorporated into chylomicrons. The chylomicrons' huge size prohibits them from passing through blood capillaries, but they can circumvent the hepatic first transit by penetrating lymphatic capillaries instead. This hypothesis has been used to explain the mechanism of lipophilic medication absorption. Through the lymphatic system, they can combine with the chylomicron triglyceride found in enterocytes and move through the systemic bloodstream. Lymphatic drug delivery can be enhanced by lipid-based delivery systems like SNEDDS. The oil phase is a very important component of the SNEDDS composition. It can facilitate the dissolution of a lipophilic substance while also promoting the lymphatic transport of lipophilic drugs that bypass the portal vein of the liver. There would be reduced possibility of hepatic first-pass metabolism as a result. Additionally, eating fatty foods may facilitate the assimilation of the SNEDDS and increase their bioavailability **(Cherniakov I et al., 2015)**.

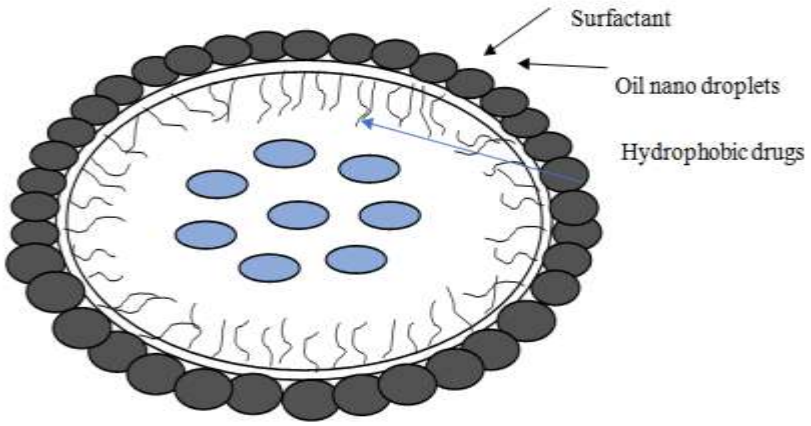

Figure 1. Typical structure of SNEDDS after aqueous dispersion.

ADVANTAGES: (Larsen AT et al., 2013), (Chime S et al., 2014), (Zhao T et al., 2015).

- SNEDDS formulations do not contain water due to this the chemical and physical stability should be increased during long-term storage.
- The aqueous-free formulation known as SNEDDS can be put into capsules made of soft/hard gelatin or HPMC, which are used for single-unit dosages. Less than 25 mg to more than 25 mg of SNEDDS can be administered over 2g. These can guarantee both patient compliance and commercial sustainability.
- By placing the SNEDDS into capsules, the problem with palatability can be solved.
- SNEDDS can be scaled up and produced commercially.
- SNEDDS manage controlled drug delivery profile.
- SNEDDS are highly stable formulations and uncomplicated manufacturing techniques.

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- SNEDDS enable drug partitioning between oil and water at a greater surface interfacial area.
- SNEDDS made it easier for drugs to be distributed more widely throughout the GI tract and stomach, which decreased irritation from prolonged contact between the medication and gut walls.
- SNEDDS shield the medication from the hostile environment in the gastrointestinal tract.
- SNEDDS increase absorption rate and volume.

DISADVANTAGES: (Krishnaiah YS., 2010)

- Drug's chemical instabilities.
- Difficult to prepare.
- Undesirable toxicity.
- The in vitro models of SNEDDS need further research and validation for strength evaluation.
- Because SNEDDS require digestion prior to dissolution, typical dissolution procedures cannot be used.
- The in vitro-in vivo correlations of SNEDDS must be studied further chemical instability of drugs.
- Higher amounts of surfactant used for formulation (30–60%).
- Higher production cost.
- Possibility of drug leakage and precipitation.

APPLICATIONS:

- Increasing the water solubility of drugs with low water solubility -

The Self-Nanoemulsifying Drug Delivery System is crucial for increasing oral bioavailability and improving the water solubility of drugs with low water solubility**(RabeaParveen et al., 2011).**

- Use in the delivery of drugs- SNEDDS have been used in a variety of drug delivery contexts, such as cosmetics, transdermal drug administration, cancer treatment, and vaccine therapy.

Increased oral delivery of weakly soluble drugs, ocular and otic drug delivery systems, intranasal drug delivery, parenteral drug delivery, and pulmonary drug delivery are all possible thanks to cell culture technology and preparation**(Shilpi Rawat et al., 2014).**

- Defence against biodegradation-

SNEDDS, SMEDDS, and SEDDS can transport macromolecules like peptides, hormones, and inhibitors of enzyme substrates, so it's crucial to guard against enzymatic degradation.

METHODS FOR THE PREPARATION OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM:

HIGH ENERGY APPROACH

The formation of a nanoemulsionusing a high-energy approach is based on the mixture composition, which includes oil, surfactant, co-surfactant, and co-solvents. Energy is used to prepare the mixture. The Emulsion is mechanically processed to become a nanoemulsion**(Ashish D et al., 2014).**

1. High-Pressure Homogenization
2. Micro Fluidization
3. Ultrasonication

1. High-Pressure Homogenization

High-pressure homogenizers provide high energy and offer homogeneous flow to produce the smallest particle sizes. Therefore, the most popular tool for creating self-nanoemulsions is the high-pressure homogenizer. High-pressure homogenizers generate intense destructive forces to produce self-nanoemulsions with incredibly small particle sizes(up to 1 nm). The coarse emulsion is then forced under great pressure through a small orifice. (500 to 5,000 psi). Intense turbulence, hydraulic shear, and cavitation are some of the forces that are combined during this process to produce self-nanoemulsions with extremely tiny droplet sizes **(Haritha et al., 2002).**

2. Micro fluidization:

A tool called a microfluidizer is used in the mixing method known as microfluidization. In micro fluidization, high-pressure fluids (500–20,000 psi) are pushed to travel via tiny channels. Microchannels are typically channels of a micron size or less that permit mixing. The water and oil phases of the macroemulsion are combined before being fed through the microfluidizer. Under strong pressure, the macroemulsion is moved via the microchannels and into the interaction chamber. Two streams of macroemulsions collide quickly inside the interaction chamber. This collision generates impact, cavitation, and shearing forces that result in stable self-nanoemulsions**(P K Patelet al., 2014).**

3. Ultrasonication method:

Compared to other high-energy techniques, ultrasonication is superior in terms of cleaning and operation. Ultrasonic waves create cavitation forces during ultrasonic emulsifications,

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which cause the macroemulsion to separate into nanoemulsions. This technique makes use of ultrasonicators, which are just a probe that emits ultrasonic waves. The self-nanoemulsion can be stabilized and have the required particle size by adjusting the ultrasonic energy input and time. The process of acoustic cavitation is primarily responsible for providing physical shear in ultrasonic emulsification. Cavitation, which is brought on by the acoustic wave's pressure variations, is the phenomenon of the development, growth, and eventual collapse of microbubbles. The development of the nano-sized droplet is caused by the strong turbulence that results from the collapse of microbubbles**(Seyed Mohammad Mohsen Modarres Gheisari et al., 2018).**

LOWER ENERGY APPROACH:

Low energy is needed for the creation of nanoemulsion systems using these techniques. Low-energy emulsification techniques use the chemical energy that exists inside the systems and only mild agitation to create self-nanoemulsions, making them more energy-efficient. The phase inversion approach is typically used in low-energy procedures.In this technique, phase transition during emulsification is caused by spontaneous curvature of the surfactant. Temperature, composition, and other variations in factors cause the surfactant's spontaneous curvature to alter.

COMPOSITION OF SELF –NANO EMULSIFYINGDRUG DELIVERY SYSTEM:

- **DRUGS:**

SNEDDs are frequently made for medications with low water solubility. In the majority of cases, BCS class II and class IV drugs are frequently used in the production of SNEDDs. The efficacy of SNEDDS is greatly influenced by the physicochemical characteristics of the drug, including log P, pKa, molecular weight, presence of ionizable groups, and quantity**(RohanG et al., 2017).**

- **OIL:**

The oil-in-water nanoemulsion is primarily linked to the self-nano emulsifying drug delivery system (SNEDDS), in which the choice of oily phase is a crucial factor in the choice of ingredients in nanoemulsion. The choice of oily phases for the formulation of nanoemulsions and the greatest solubilizing ability of chosen drug candidates both depend on the oil. This is the most crucial strategy because it has a large capacity for drug loading. The ability of the solubilized drugs to form the desired characteristics of the nanoemulsions relies on the oily phase selection. Oil is crucial to transport medicines into intracellular compartments with less resistance and to making less water-soluble drugs more water-soluble. The SNEDDS formulation uses a variety of oils, including sesame oil, olive oil, sunflower oil, etc**(BoontidaMorakul., 2020).**

- **SURFACTANT:**

The term "surfactants" refers to molecules and ions that are absorbed at the interface. It is able to give interfacial space and reduce interfacial tension. It plays a significant role in the creation of SNEEDS. It can self-emulsify poorly water-soluble pharmaceuticals by self-nano-emulsifying, self-emulsifying, and self-micro-emulsifying. Surfactants that can be consumed orally are non-ionic and have a higher hydrophilic-lipophilic balance (HLB). Ethoxylated polyglycolide glycerides and polyoxyethylene oleate are two common emulsifiers. Natural emulsifiers are regarded as being less dangerous than synthetic versions, however, surfactants have only partial self-emulsifying capabilities. Intestinal permeability is directly increased by non-ionic surfactants, which are less hazardous than ionic surfactants**(Aristote B.Buya et al., 2020).**Surfactants are categorized as hydrophilic (HLB > 10) or lipophilic (HLB 10) surfactants based on the HLB value. Because they enable spontaneous nano-emulsification with particle sizes smaller than 200 nm following aqueous dispersion, the HLB value > 12 is primarily used in the formulation of SNEDDS. The emulsion particle size is influenced by the surfactant content. Due to the surfactant's ability to lower surface tension at the oil-water interface, which lowers the emulsification process' free energy, an increase in surfactant concentration can result in a reduction in the size of the emulsion particles **(Gursoy et al., 2004).**But in some cases, the increased concentration of surfactant results in higher emulsion particle size due to the excess penetration of water into the lipid droplet which causes massive disruption of the oil-water interfacial and relaxation of polydisperse nanodroplets **(Gupta et al., 2013).**

- **CO-SURFACTANT:**

The SNEDDS formulations need co-surfactants to condense the considerably higher surfactant concentrations that are required. These lower the interfacial tension to a -ve value, where it

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expands to form tiny droplets that are subsequently absorbed by increasing amounts of surfactant and surfactant/co-surfactant until the interfacial tension is restored to a +ve value. These substances work in conjunction with surfactants to do this. This process is known as "spontaneous emulsification." Co-surfactants are not necessarily necessary when using non-ionic surfactants with SNEDDS**(Charman WN et al., 2007)**.The HLB values of the co-surfactants used in SNEDDS range from 10 to 14. Examples of co-surfactants include ethanol and polyethylene glycol. They function by reducing the oil-water contact and encouraging the creation of impulsive nanoemulsions**.**

PREPARATION OF SNEDDS

LIQUID SNEDDS PREPARATION:

The essential procedure for developing self-nano emulsifying drug delivery systems with the surfactant/co-surfactant ratio and oil/surfactant/co-surfactant ratio was chosen using the pseudo ternary phase diagram. Different concentrations of oil, surfactant, and cosurfactant were utilized to process various formulation changes. In an oil and surfactant mixture that had been weighed in the right proportions, the drug was dissolved. After then, the mixture was left at room temperature.**(Ashish D et al., 2014).**

SOLID SNEDDS PREPARATION: The preparation process for the solid Self Nanoemulsifying Drug Delivery System (SNEDDS) is as follows: If required, the drug was melted in a water bath after being added to a precisely calibrated amount of oil in a screw-capped vial. Using a positive displacement pipette, the surfactant and cosurfactant were then added to the oily mixture to produce a homogenous solution. A solid Self Nano Emulsifying Drug Delivery System (SSNEDDS) was produced by adding predetermined liquid SNEDDS dropwise over acceptable novel adsorbents like Neusillin and fully combining them with a glass rod. The remaining moist material was sieved through number 120 and allowed to air dry at room temperature. **(Ashish D et al., 2014).**

CONSTRUCTION OF PSEUDO TERNARY PHASE DIAGRAM:

The phase diagrams for the pseudo-ternary compounds were created using the water titration method. Different oil, surfactant, and co-surfactant ratios were selected to create a phase diagram. For each phase diagram, the different ratios of oil to a particular Smix (O/Smix, 2:8, 3:7, 4:6, 5:5, 6:4, and 7:3) were thoroughly combined in glass vials before the distilled water was gradually added. Using visual observation, the phase boundary was measured **(Nguyen- Thach Tung et al., 2018).**

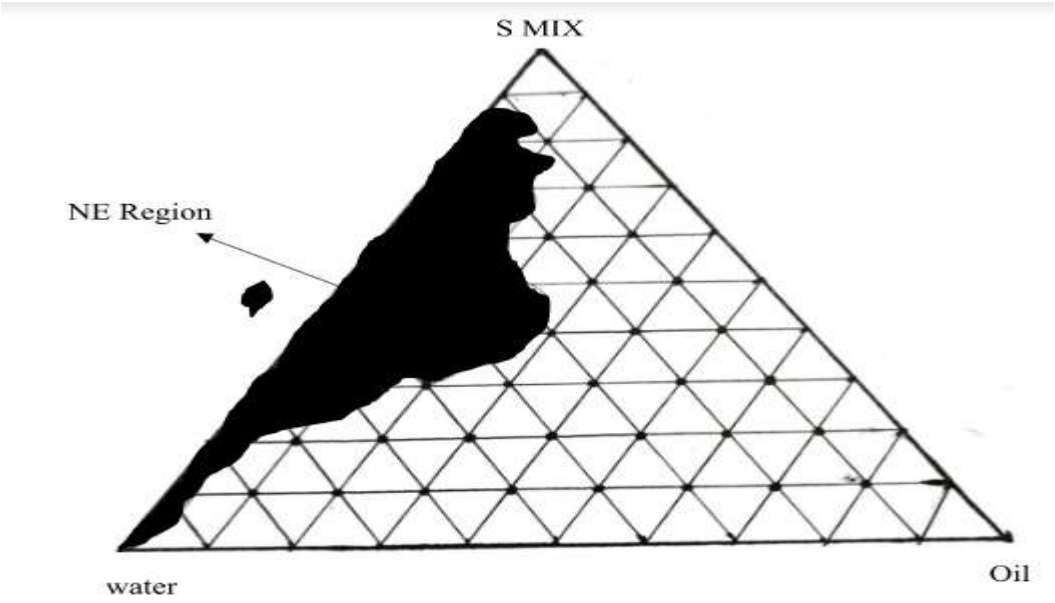

Figure 2.Pseudo Ternary Phase Diagram

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MECHANISM OF EMULSIFICATION

The free energy (G) of a conventional emulsion is a (negative) direct function of the energy required to create a new surface between the two phases (oil and water phase), and the emulsion was stabilized. According to Reiss' theory, emulsification occurs when the entropy changes favor dispersion and are greater than the energy required to increase the dispersion surface. The equation can be used to describe the relationship between G and the free energy of a conventional emulsion **(Harman WN et al., 1997).**

$\Delta G = \sum NNr2\ \sigma$

Where;

G stands for the process's free energy.
N is the total number of droplets.
r is the radius of the droplets.
σ is the Interfacial energy.

EVALUATION OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM:

- Visual observation
- Surface morphology
- Droplet size analysis
- Viscosity determination
- Drug content
- Cloud point measurement
- Thermodynamically stability testing
- In vitro release study

➢ **VISUAL OBSERVATION:**

Visual observation is done to differentiate between macroemulsion and nanoemulsion.

➢ **SURFACE MORPHOLOGY:**

Transmission electron spectroscopy (TEM) was used to examine the surface morphology of SNEDDS. Because an electron's wavelength is significantly shorter than a photon's, TEM can be used to see particles with far higher magnification and resolution than is possible with a light microscope.

➢ **DROPLET SIZE ANALYSIS:**

Droplet size and polydispersity index of nanoemulsion were determined using a zeta sizer. The samples were diluted with a ratio of 1:100 (v/v) with distilled water and repeated in triplicate **(Balakumar et al., 2013).**

➢ **ZETA POTENTIAL ANALYSIS:**

The Zeta potential of the formulations is determined by dynamic light scattering using a particle size analyzer. The samples were diluted with a ratio of 1:100(v/v) with distilled water and repeated in triplicate **(Balakumar et al., 2013).**

➢ **VISCOSITY MEASUREMENT:**

A viscometer, such as a Brookfield cone and plate viscometer, is typically used to measure the viscosity of liquid SNEDDS. Centipoises, which relate to shear rate, are used to express viscosity. To gauge viscosity, an instrument (spindle) is submerged in the oil and rotated at a specific rate. The dynamic viscosity is determined by the force needed to maintain this speed.

➢ **DRUG CONTENT:**

By allowing it to dissolve in a suitable solvent, the drug is extracted from pre-weighed SNEDDS. Utilizing an appropriate analytical technique, the drug content in the solvent extract was compared to a standard drug solvent solution.**(Pathak CV et al., 2013).**

➢ **CLOUD POINT MEASUREMENT:**

The formulation was diluted with distilled water in a ratio of 1:100. The diluted samples were placed in a water bath and their temperature was increased gradually. Cloud point was determined as the temperature at which the cloudiness suddenly appeared**(S Gupta et al., 2011).**

➢ **THERMODYNAMICALLY STABILITY TESTING:**

To remove unstable/metastable SNEDDS, various thermodynamic stability tests on prepared SNEDDS were carried out. The prepared SNEDDS was put through a variety of stress conditions, including centrifugation at 500 rpm for 30 min, three cycles of heating and cooling between 45 and 25°C, and three cycles of freeze-pump-thaw between 25 and 25°C. Following these tests, the physical appearance of the various formulations was scrutinized for any changes. These studies were run to assess the SNEDDS's thermodynamic stability under various stress scenarios. Testing for thermodynamic stability yields qualitative results. If the synthesized SNEDDS were discovered to be thermodynamically stable during various stress conditions, such as centrifugation, heating and cooling cycles, and freeze-pump-thaw cycles, the formulation would have a positive outcome. (**Saad M. Alsahrani et al., 2018**).

➢ **IN – VITRO RELEASE STUDY:**

For every one of the generated formulations, in vitro, diffusion experiments were

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carried out utilizing a dialysis method. The dialyzing solution was a pH 6.8 phosphate buffer. One ml of the self-nano-emulsifying formulation and 0.5 ml of dialyzing medium were added to one end of pre-treated, 7 cm long cellulose dialysis tubing before it was tied off with thread. The other end of the tubing was also threaded shut, then placed in 200 ml of dialyzing media, and allowed to spin freely while being continuously stirred at 100 rpm at 37°C with a magnetic bead on a magnetic plate. At various times, 1 ml aliquots were taken out and further diluted. Each time, the dialyzing medium was changed and a new volume of aliquots was added. Such examples utilizing a UV-visible spectrophotometer were quantitatively examined for drug dialyzed across the membrane at the relevant period.**(Saad M. Alsahrani et al., 2018).**

SNEDDS USED FOR ENHANCEMENT OF SOLUBILITY AND BIOAVAILABILITY OF HEPATOPROTECTIVE DRUGS:

The drugs that are mostly utilized to treat liver illness are hepatoprotective ones. Hepatotoxicity has become the most serious liver disorder, which accounts for about 15% of the world's burden of diseases**(Ramesh Patel et al., 2011).** There are several hepatoprotective medications on the market to treat liver disease, but most of these drugs have poor aqueous solubility and poor bioavailability, making it difficult for them to have the desired therapeutic impact. Therefore, to increase the solubility and bioavailability of medications to enhance their therapeutic effects, researchers have developed several innovative drug delivery systems.

Nanotechnology is widely acknowledged as a vital drug delivery strategy that can affect how well hydrophobic drugs work therapeutically. Self-nanoemulsifying is one of the tested techniques for improving the solubility and bioavailability of poorly water-soluble drugs. A few hepatoprotective medication SNEDDS formulations are listed in the table.

Table :1 lists a few SNEDDS formulations of hepatoprotective drugs.

Formulations	**Composition**	**Purpose**	**References**
Thymoquinone SNEDDS	Capryol 90, Tween 20	Oral bioavailability enhancement and increase the hepatoprotective effect.	Faiyaz Shakeel Et al.,2017
Luteolin SNEDDS	Capryol-PGMC, Tween 80, Transcutol-HP	Improve in vitro dissolution and hepatoprotective effects which results in increased bioavailability.	Shakeel F et al., 2021

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Beta vulgaris l. leaf SNEDDS	Linseed, castor, and sesame oil(oil phase) tween 20 and tween 80, Dimethylsulfoxide (DMSO), propylene glycol (PG).	Improve the hepatoprotective effect of bl extract.	Ahmed Alaa Kasen et al., 2020
Quercetin SNEDDS	Sefsol, linoleic acid, tween 80, polyethylene glycol 400.	To enhance hepatoprotective activity.	Osama A A. Ahmed et al., 2014.

II. CONCLUSION:

Drug solubility is the fundamental prerequisite for the absorption of pharmaceuticals from the gastrointestinal tract (GIT), and drug dissolution is the rate-determining step for oral absorption of weakly water-soluble drugs **(Ketan T et al., 2012)**. The solubility of the pharmaceuticals can be improved by using lipid-based drug delivery systems (SNEDDS). Drug delivery systems that self-nano-emulsify are anhydrous homogenous liquid solutions made up of oil, a surfactant, the drug, a co-surfactant, and a co-solvent. Due to the increased surface area on the dispersion and absorption of drug molecules, SNEDDS improves the ability of the drug to dissolve. SNEDDS frequently enable the oral distribution of lipophilic medicines, which is crucial to increase oral bioavailability. SNEDDS seems to be an original, commercially viable strategy for future development.

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