A Review on SNESNS: An Effective Method for Delivering Poorly Soluble Drugs

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ABSTRACT:

Self-nanoemulsifying self-nanosuspension (SNESNS) represents a new type of oral drug delivery system that can be used to overcome the prob.lem of poor water solubility in the case of a wide range of pharmaceutical agents. Under the umbrella of the benefits of self-nanoemulsifying drug delivery system (SNEDDS) and nanosuspensions, SNESNS seeks to enhance the dissolution rate, bioavail.ability, and solubility. This twin action permits the drugs to circumvent the liver and is transported more rapidly to the systemic circulation that increases its bioavailability and effect. The most important one is the abil.ity to load drugs that are larger in quantity than traditional SNEDDS that are especially useful when dealing with drugs with a high potency or low solubility. Recent literature has concentrated on the SNESNS solidification to achieve stability of the formulation and convenience in use to patients through the use of carriers such as mesoporous silica or through the use of the spray drying method. In addition, targeted and multiple drug delivery (3D printing and surface modification) is being explored to attain personalized approaches of drug delivery. The progression of formulation tools (including phase diagram mapping and statistical optimization) is related to the presence of sufficient drug loading and release characteristics. On the whole, SNESNS is an all-encompassing approach and innovative concept of the design of the stable and effective oral formulations with effects on a variety of treatment fields.

KEYWORDS: Poorly soluble drugs, SNESNS, SNEDDS, High Drug Loading, Dual Mechanism, Bioavailability.

1. INTRODUCTION: -

The self-nanoemulsifying self-nanosuspension (SNESNS) is a new type of oral drug delivery system which has emerged as a result of the merger of self-nanoemulsifying drug delivery systems (SNEDDS) and nanosuspension. The formulation contains the drug in a two-state form which is in partially solvated and partially micronized form in a uniform oil surfactant-co-surfactant blend. The nanoemulsion and nanosuspension that occurs spontaneously with the gastrointestinal tract will occur when

the attaching bodily fluids to which the water is mixed with. Thanks to that, the particle of drugs are prepared in the nanoscale in two folds and in this way, the likelihood of absorption elevates [1].

The true value of SNESNS is its higher merit over the conventional SNEDDS in the high dose poorly water soluble drug incorporation problem. SNESNS was associated with the improvement of solubility, dissolution rate, and oral bioavailability as it gave solubilised and suspended fractions of the drug the chance to coexist and become co delivered. The dual pathway is additionally enabling a higher dosage, but also absorption via portal vein and the lymphatic pathway. The additional paths of drug intake are beneficial in the case of the most challenging drug molecules [2].

A complex type of drug delivery system is the self-nanoemulsifying self-nanosuspension (SNESNS) that was designed in an attempt to increase the absorption of drugs that are not well soluble in waterby the organism [3]. It acts upon the creation of two kinds of diminutive carriers nanoemulsions and nanosuspensions at the same time when in touch with the digestive tract fluids. This stepwise process enhances quicker drug dissolution and higher absorption quantity. Compared to the anti-aging systems in the past that are not effective when drug doses are high, SNESNS is capable of handling the huge doses effectively, thus its usefulness in the challenging formulations. It also facilitates the release of the drug quicker with better completion thus enhancing the effectiveness of the drug and allowing it access into the bloodstream via different routes including the lymphatic system [4].

Research indicates that one of the unexplored drug delivery systems is self-nanoemulsifying self-nanosuspension (SNESNS). The literature and research presented in most cases on scientific literature mainly dwell on self-nanoemulsifying drug delivery systems (SNEDDS), where their mechanisms, applications, and limitations are highly covered. In comparison, only a few recent studies mentioned SNESNS, but they do that in a framework of a new strategy [5]. According to a recent report, researchers have now been interested in a special dual solubilization process. This was a recently discovered finding by a research team. Researchers have been conducting studies on SNEDDS over a period of more than 10 years. Comparatively, scholars have not started conducting research on SNESNS. Recent research holds great potential in success of SNESNS in fixing particular issues which includes low drug loading in SNEDDS to water-insoluble drugs [6]. The absence of experimental and clinical research also underscores the fact that SNESNS is a nascent and a promising field of pharmaceutical development.

1.1. ADVANTAGES OVER TRADITIONAL FORMULATIONS: -

Self-nanoemulsifying self-nanosuspension (SNESNS) systems provide several key advantages over standard drug formulations, particularly for drugs that are not easily soluble in water or that require substantial doses.

1) **Enhanced Drug Solubility and Dissolution:**

- **Dual Solubilization:** SNESNS employs both nanoemulsion and nanosuspension techniques to improve the drug's solubility. This approach leads to significantly better solubility than conventional formulations or even typical SNEDDS. For example, SNESNS increased the solubility of diacerein to about 309 µg/mL, compared to approximately 162 µg/mL with SNEDDS alone. Additionally, it enables complete and rapid drug release within just 15 minutes.
- **High Drug Loading:** SNESNS can accommodate larger drug quantities, making it an effective solution for formulations that require high doses. It helps to overcome the solubility limitations observed in traditional SNEDDS and standard suspensions [7].

2) **Enhanced Oral Bioavailability:**

- **Improved Absorption:** SNESNS significantly enhances the absorption of drugs administered orally. For instance, it increased the relative bioavailability of Rhein to 210% compared to an aqueous suspension, due to its ability to transport the drug through both the portal vein and the lymphatic system.
- **Diminished Food Impact:** Formulations utilizing phospholipid-based SNESNS can mitigate the effects of food on drug absorption. This results in more stable drug concentrations within the body, helping patients adhere to their treatment regimens.

3) **Flexibility and Effectiveness:**

- **Suitable for Complex and Natural Compounds:** SNESNS is effective in delivering mixtures of natural products or nutraceuticals with varying solubility profiles. This can lead to improved therapeutic results compared to conventional formulations [8].
- **Swift and Complete Drug Release:** SNESNS facilitates rapid and comprehensive drug release, which is particularly crucial for medications that require prompt action to be effective.

2. Objectives of the Study: -

This review aims to present and explain. The main aims of this study are:

- To give a detailed insight into the working of SNESNS, focusing on its dual solubilization mechanism & how it is different from earlier systems like SNEDDS and nanosuspensions.
- To sum up, the latest research findings show SNESNs are beneficial because of their enhanced solubility, rapid drug release, and absorption.
- There has not been much published research on SNESNS in comparison to the extensive published research on SNEDDS.
- Enhance knowledge on Formulation strategies, applications, and clinical scope of SNESNS for further research
- We want to help scientists, students, and teachers by giving a clear and simple overview that will support their future research, teaching, and formulation development.

3. FORMULATION STRATEGIES AND OPTIMIZATION: -

In order to develop a successful SNESNS formulation scientists select and mix various excipients with great care, i.e. ingredients that aid the dissolution of a drug, its stability and enhanced absorption. It also follows the step-by-step method to optimize the formulation to avoid failure in the stability, drug release and bioavailability.

3.1 Formulation Strategies-

- Self-nanoemulsifying self-nanosuspension (SNESNS) should be elaborated with the proper planning and a careful choice of ingredients so that effective distribution, as well as absorption of the drug, may take place. The aim will be to come up with a very strong form that can deliver the medicine in both dissolution and suspension state and transform in the appropriate dispersion on contact with water.

- **Selecting Excipients:** The screening process in the first step is to select the best oil, wetting agent and co-surfactants to undertake the dispersal and stability. These additives are chosen due to their impact on enhancing the solubility of a medicinal product, and their tendency to form a nanoemulsion and a nanosuspension spontaneously with water. These components must be distributed evenly in the body, in order to have a successful working system in the body [3].

- **Drug Loading:**When the excipients are chosen, the drug is entraped in the formulation in two parts: a part is dissolved in the greasy phase, the rest of the drug is a fine suspended atom. High-shear homogenization is usually used to this degree to equal the suspended drug and achieve more warheads and drug warheads. The two-fold existence nowadays promotes the system to provide more drugs as opposed to the traditional system of SNEDDS [7].

- **Godfather:** SNESNS will assemble two forms of nanoscale carriers, one being a nanoemulsion of the dissolved drug and a nanosuspension of the insoluble one when exposed to water, even in the GI tract. The change at hand is neither energy consuming nor does it warrant any external energy and it is usually confirmed through atom size examination as well as image techniques using transmission electron microscopy. Its conclusion ought to be a stable, which is bimodal in nature and improves the speed and the degree of drug absorption.

3.2 Optimization Techniques:

To formulate an effective SNESNS, researchers integrate a variety of advanced design tools and thorough testing:

- **Experimental Design:** Triangular mixture design, Box-Behnken design, and response surface methodology are some of the statistical procedures through which the researchers are able to study the effect of the various ratios of oil, surfactant, and co-surfactant on the performance of the formulations. The strategies are useful in determining the optimal mixture that acquires smaller droplet sizes, uniform distribution, high clarity and fast emulsification, which is essential in the improvement of drug uptake.

- **Analytical Characterization**: After constructing the formulations, both the scientists examine key peculiarities, including particle size, polydispersity index (PDI), zeta potential, and in vitro dissolution as measures of system behavior [1]. These tests are used to identify the most promising formulation since they show its stability, repeatability, and efficacy in drug release.

- **Freeze-Drying:** The method of freeze-drying whereby the freeze-drying process is used to preserve the formulation of the drying process to turn liquid SNESNS into a much more stable and convenient form of transportation is also used. The technique also boosts shelf life in addition to making handling more convenient, as well as facilitating the production of patient-friendly dose forms such as tablets or powders in form of a dispensing agent.

4. FUNDAMENTAL PRINCIPLE OF SNESNS FORMATION:

SNESNS systems are formulated by blending a poorly soluble drug into an SNEDDS pre-concentrate—a combination of oil, surfactant, and co-surfactant—at concentrations that surpass the drug\'s solubility in that mixture. When this system interacts with water and is gently stirred, it naturally creates a two-phase nanosystem.

i. Nanoemulsion Phase-

The part of the drug that dissolves in the oily phase is encapsulated within tiny droplets, leading to the formation of a nanoemulsion. These nanodroplets help transport the drug effectively through the GIT, thus enhancing its absorption.

ii. Nanosuspension Phase-

The remaining undissolved drug generates small suspended particles, which are rapidly broken down into nanosized fragments. The surfactants and cosolvents in the aqueous medium contribute to further reducing these particles, thereby improving their dispersion and bioavailability.

4.1 Physicochemical Influences on SNESNS Formation:

- **Importance of Surfactants and Co-surfactants-**
  In order to lower the interfacial tension between the oil and water phases, which enables the organization to spontaneously generate the correct droplets for dilution. The current spontaneous emulsification plays a key role in shaping a robust nanoemulsion free from the obligation to add energy.
- **Behavior of Unsaturated Aqueous Layer-**
  While the SNESNS framework appears in contact with the water, an unsaturated aqueous layer with an undissolved drug atom. This layer facilitates fast wear and helps break down the larger drug atom inside the nanoscale fragment, thus facilitating dispersion and dissolution.
- **Role of Mild Agitation-**
  Kind agitation, such as the inherent movement of the gastrointestinal tract, contributes to a uniform distribution of the composition and aids in further decreasing the atom size. This mechanical aid complements the chemical effects of the eluting agent, thereby facilitating the formation of both nanoemulsions and nanosuspensions.

4.2 Structural Confirmation:

- **Microscopic and Particle Size -**
  Transmission electron microscopy (TEM) and particle size analysis offer both visual and quantitative confirmation of the system's bimodal structure. These analytical methods clearly indicate that, upon dilution in aqueous solutions, nanoemulsion droplets exist together with nanosized suspended drug particles.

4.3 Functional Outcomes:

- **Rapid Drug Dissolution-**
  The dual-phase composition of SNESNS enables rapid and complete drug release. For example, diacerein formulations utilizing this system achieve full dissolution within 15 minutes [1]. Such rapid dissolution is particularly advantageous for therapeutics that require immediate therapeutic action.
- **Improved Oral Bioavailability-**
  SNESNS systems increased drug absorption by providing simultaneous uptake through both the portal vein and lymphatic pathways. This dual-route mechanism increases the chances of potential success, especially for drugs characterized by low water solubility or those that undergo significant first-pass metabolism [7].

5. OPTIMIZATION PARAMETERS FOR STABILITY AND EFFICIENCY: -

- **Oil/Surfactant Ratio:** Getting the oil-to-surfactant ratio just right is key to making sure the drug dissolves well and forms tiny, stable droplets. When this balance is carefully

managed, it helps prevent the drug from settling out and allows more of it to be loaded into the system—making the formulation both efficient and safe [10].

- **Drug Loading:** The goal is to include as many drugs as possible without saturation in solution. Staying within this limit keeps the formulation physically stable and ensures the drug remains effective throughout its shelf life.
- **Droplet Size and Polydispersity Index (PDI):** Ideally, the droplets should be very small—under 100 nanometers—with a narrow size range (PDI below 0.3). This kind of uniformity helps the drug release quickly and absorb consistently, which is important for improving how well it works when taken orally.
- **Zeta Potential:** A strong surface charge, whether positive or negative, helps keep the particles from clumping together. This charge-driven repulsion supports long-term stability and makes the nanoemulsion more robust and dependable.
- **Emulsification Time:** It would be preferable to use a brief emulsification period, which would indicate the celerity of the mixture as well as the possibility of dispersing and releasing the medication in contact with aqueous pressurized media. Rapid emulsification effects in a quick start of action, which are particularly beneficial to drugs that require early curative importance [11].
- **Thermodynamic Stability:** The composition must have a hardness exceeding the duration of the separation of the phases or the precipitation of the medicinal product. The achievement of thermodynamic robustness ensures a long service life and reliable performance during storage and transport.
- **Robustness to Dilution:** When SNESNS systems are diluted in environments similar to those of the GI tract, stability is required. This robustness guarantees systematic in vivo behavior of the formulation, maintaining its framework and profile of release throughout digestion [12].
- **Statistical Optimization:** Structural and reproducible optimization is made easy by using statistical tools such as Design of Experiments (DoE) and desirability function. These methods decrease the need for trial and error, simplify the production system, and assist in determining the most efficient formulation, together with a lower number of experimental tests [13].

Table 1.Comparison between SNESNS, SNEDDS and Nanosuspension

SR.NO.	KEY FEATURES	SNESNS	SNEDDS	NANOSUSPENSION
1.	Formulation	Combines nanoemulsion and nanosuspension	Isotropic mixture of oil, surfactant, co-surfactant; forms nanoemulsion upon dilution	Colloidal dispersion of drug nanoparticles in stabilizer solution
2.	Drug loading	Higher drug loading than SNEDDS due to suspended drug	Limited by drug solubility in oil phase	Moderate; depends on drug/stabilizer ratio

		and solubilized fraction		
3.	Particle size	Bimodal	20–250 nm (typically 20–200 nm)	100–1000 nm (often ~200–400 nm)
4.	Stability	Good	High	requires stabilizers for stability
5.	Bioavailability	rapid and complete dissolution, enhanced lymphatic and portal absorption	improves solubility and bioavailability over the raw drug	Improves solubility and release, but less than SNEDDS/SNESNS
6.	Mechanism	Simultaneous formation of nanoemulsion and nanosuspension upon dilution	Spontaneous nanoemulsification in GI fluids	Direct delivery of drug nanoparticles
7.	Limitations	More complex formulation	Drug precipitation risk	Physical instability, aggregation [1][3][7].

6. Case Studies Demonstrating Applications of SNESNS (Self-Nanoemulsifying Self-Nanosuspension) Systems in Various Therapeutic Areas:

Several case studies have already demonstrated how SNESNS can improve oral bioavailability, therapeutic effectiveness, and stability for a couple of drugs and natural products. Highlights comprise its use in enhancing the bioavailability of diacerein, herbal extracts, and nutraceuticals, as well as addressing challenges such as food effects and multi-component delivery.These studies also look into how customizable and promising SNESNS is for drug creation.

6.1. SNESNS for Improving Oral Bioavailability- Recent researches also point at the opportunity of Self-Nanoemulsifying Self-Nanosuspensions (SNESNS) to enhance the oral administration of very poorly soluble drugs, which are scarcely soluble in water. As an example, formulation of diacerein to SNESNS resulted in both rapid and complete solubility, which emerged into bioavailability of approximately 210 and 164 percent respectively in normal and blocked chylomicron-flowed rats [14] when compared to a standard aqueous suspension. The drug delivery system linked with use of this drug was that the drug was absorbed via both the portal vein and lymphatic system. Another example is a SNESNS made using phospholipids designed around lurasidone hydrochloride; during lab tests, was shown to have a great dissolution ability and was

able to eliminate food-related variability in drug absorption during human trials in human trials [15].

6.2.SNESNS at Herbal and Nutraceutical Delivery- SNESNS have already shown great effectiveness in the delivery of herbal extracts and nutraceuticals. As an example, antidepressants and cardioprotective effects on post-myocardial infarction depressed rats were increased upon the formulation of the SNESNS St. Johns Wort (Hypericum perforatum). Notably, these benefits are seen with lower dosage than the usual herbal extract [16]. Also, another study found that an SNESN using Spirulina, Tribulus terrestris, and fish oil had protective effects on counteracting testicular damage caused by the chemotherapy drug cisplatin, providing further evidence that it could be used in the supportive care [17].

6.3. SNESNS Gut-Brain-axis Cognitive and Gut-Brain disorders- The most advanced SNESNS is already being studied considering how it can help in the improvement of the health of the brain and the gut. In a specific study, a freeze-dried milk kefir-based SNESNS with the addition of licorice extract was used to treat the symptoms similar to inflammatory bowel disease (IBD) in rats. Not only did this formulation improve memory and cognitive performance but it also increased balance of gut microbiota and reduced inflammation, which was better than kefir alone [18].

6.4. SNESNS in Multi-Component Delivery-Antiviral- The use of SNESNS technology is also applied in antiviral treatment. The study used a curcumin-impregnated SNESNS throat spray on rats which were infected with SARS-CoV-2 and proved to reduce inflammatory response [19]. It was also found to be an effective preventive agent as well as a treatment alternative to pharyngitis. Since SNESNS is capable of housing hydrophilic and lipophilic substances, it is especially beneficial when it comes to complex formulations that will require more than one active constituent.

6.5. Reproductive and Endocrine Protection- A nutraceutical SNESNS containing Spirulina, Tribulus terrestris and fish oil has been reported to protect against cisplatin-induced testicular injury in rats. The formulation enhances the quality of sperm and the level of the hormone, and it also decreases oxidative stress and inflammation, which is important to note that it can be used to support the reproductive and endocrine system [7].

6.6. Psychiatric and Antipsychotic Drugs Administration- In the unit of psychiatric treatment, the SNESNS formulation of lurasidone hydrochloride (an antipsychotic treatment) based on phospholipid is viable in reducing the discrepancy between intake of drugs depending on nourishing [4]. This made it an effective method of delivering drugs and improving the adherence of patients in human research placing it as an encouraging mode of intervention towards therapeutic outcomes. The delivery of drugs to cancer patients can occur through various routes, among which the partners are expected to select the most suitable one human.

6.7.Cancer Therapy and Drug Delivery- SNESNS and nanoemulsions with analogous systems are coming out as efficient methods of cancer therapy. Such formulations are capable of delivering synthetic anticancer drugs and natural anticancer drugs. Indicatively, nanoemulsions of sphingomyelin laced with resveratrol had high levels of uptake and cytotoxicity towards non-small cell lung cancer (NSCLC) cells. These initiated the cell death via mitochondrial pathways and this can lead to the departure of drug resistance. Of significance, such systems can render the mitochondrion apt to drugs operating in this organelle [20].

6.8. Colorectal and Pancreatic Cancer- Cancerous cells increase exponentially further into the blood chain. Recent reviews highlight that self-nanoemulsifying systems, such as SNESNS, are capable of enhancing the stability of the drug, offering controlled delivery, and effective targeted delivery in colorectal cancer models. Preclinical research claims to achieve higher efficacy of up to 70 percent and lower toxicity over the conventional approaches [21]. This approach to nanoformulation is also under study on pancreatic cancer with the goal of overcoming difficulties of low solubility and poor bioavailability of anticancer drugs [22].

6.9. Postoperative and smart delivery- Studies in nanomedicine indicate that SNESNS and similar vehicles would be useful in the localized provision of drugs following cancer surgery. Such approach can assist in reducing the risk of cancer recurrence and also reduce side effects caused by the drug since therapeutic agents are concentrated at the surgery site of the drug [23] [24].

6.10. Nano-Drug Delivery in Cardiovascular Diseases (CVDs)- Most cardiovascular research subjects under investigation consider nano-drug delivery systems in general; however, the advantages of SNESNS including better dissolution, targeted delivery and dual pathways of absorption are especially applicable to CVD treatments. They were further developed into ideas to improve use of the dosage forms in treating the heart failure conditions, atherosclerosis, hypertension, among others, wherein better therapeutic outcomes and reduced dose variability may be realized [25] [26].

Table 2. Case Studies on SNESNS (Self-Nanoemulsifying Self-Nanosuspension) systems across therapeutic areas.

SR.NO.	CASE STUDY	DRUG/ EXCIPIENTS	PD/PK IMPROVEMENTS	KEY FINDINGS/OUTCOMES	REFERENCES
1.	Oral bioavailability	Diacerein; Lurasidone HCl (phospholipid-based)	↑ Solubility, ↑ Bioavailability (210% in normal rats, 164% in blocked rats); eliminated food-effect variability	Rapid and complete solubility; dual absorption via portal vein & lymphatic system; improved dissolution and patient adherence	[14], [15]

2.	Herbal & Nutraceutical Delivery	St. John's Wort (Hypericum perforatum); Spirulina, Tribulus terrestris, Fish oil	Increased Pharmacodynamic effects at lower dose; protective against cisplatin toxicity	Enhanced antidepressant & cardioprotective effects; reduced testicular damage, supportive care potential	[16], [17]
3.	Gut-Brain Axis Disorders	Kefir + Licorice extract	Improved cognitive performance; balanced gut microbiota; reduced inflammation	Better outcomes than kefir alone; improved memory and gut health in IBD-like symptoms	[18]
4.	Multi-Component Antiviral Delivery	Curcumin throat spray	Reduced inflammatory response; preventive & therapeutic efficacy	Effective against SARS-CoV-2 infected rats; alternative treatment for pharyngitis	[19]
5.	Reproductive & Endocrine Protection	Spirulina, Tribulus terrestris, Fish oil	↑ Sperm quality, ↑ Hormone levels; ↓ Oxidative stress & inflammation	Protected against cisplatin-induced testicular injury; supportive for reproductive health	[7]
6.	Psychiatric / Antipsychotic Delivery	Lurasidone HCl (phospholipid-based SNESNS)	Eliminated food-effect variability; improved PK consistency	Enhanced adherence and therapeutic outcomes in psychiatric patients	[4]
7.	Cancer Therapy (NSCLC)	Resveratrol in sphingomyelin nanoemulsion	↑ Uptake, ↑ Cytotoxicity; overcame drug resistance	Induced mitochondrial-mediated cell death; effective against NSCLC cells	[20]
8.	Colorectal & Pancreatic Cancer	Anticancer drugs in SNESNS	↑ Stability, ↑ Targeted delivery, ↑ Efficacy (~70%); ↓ Toxicity	Improved solubility and bioavailability; promising in colorectal and pancreatic cancer models	[21], [22]
9.	Postoperative / Smart Delivery	Localized SNESNS formulations	Localized drug concentration; ↓ Side effects	Reduced recurrence risk post-surgery; minimized systemic toxicity	[23], [24]

10.	Cardiovascular Diseases (CVDs)	Various cardiovascular drugs	↑ Dissolution, ↑ Targeted delivery, dual absorption pathways	Better therapeutic outcomes in heart failure, atherosclerosis, hypertension; reduced dose variability	[25], [26]

6. EMERGING TRENDS IN SNESNSs SYSTEM:

SNESNS systems represent a new approach in pharmaceutical formulation. By combining the benefits of nanoemulsions and nanosuspensions, these dual-phase systems offer high drug loading, fast dissolution, and the flexibility required for personalized treatments. Their unique design makes them especially useful for delivering drugs that are little soluble in water or require accurate dosing.

7.1. Personalized Medicine and Multi-Drug Therapy

SNESNS and similar self-nanoemulsifying systems can be customized to meet the specific needs of individual patients. This includes adjusting doses and combining multiple medications into a single dosage form. For example, 3D-printed tablets filled with SNEDDS or SNESNS can be designed to release drugs in a controlled, patient-specific manner—an important step forward for treating complex diseases that require multiple drugs. These systems are also well-suited for drugs that are difficult to dissolve or unstable, helping elevate their use in personalized care and improving treatment outcomes [27].

7.2. Enhancing Targeted Drug Delivery

SNESNS platforms enhance the delivery of drugs to their specific sites within the body by improving solubility, stability, and absorption. SNESNS is particularly beneficial for diseases such as cancer or neurological disorders, where accurate targeting is essential.

By employing nanocarriers, SNESNS systems can be tailored for both passive and active targeting. For instance, they can be fitted with ligands and transfer the drug to particular tissues or tumor cells [28]. Certain systems can even react to external stimuli—such as pH or temperature—facilitating highly controlled drug release. This targeted methodology aids in minimizing side effects and enhances the overall efficacy of treatment.

8. FUTURE RESEARCH DIRECTIONS

Key research fields involve:

- Combining SNESNS with emerging technologies such as 3D Printing, smart polymers, or gene therapies.
- Expanding applications of SNESNS to the therapeutic scope, such as biologics, peptides, and nucleic acids (therapy + diagnostics).

- Addressing problems in the specificity of targeting, overcoming biological barriers, ensuring long-term safety, and regulatory compliance.

9. LIMITATIONS AND CHALLENGES: -

While SNESNS (Self-Nanoemulsifying Self-Nanosuspension) systems are effective in enhancing drug solubility and absorption, they also introduce significant challenges that must be resolved before they can be broadly utilized or marketed.

9.1. Drug Precipitation and Stability Challenges

- **potential for unwanted drug settlement:** When SNESNS systems are diluted in aqueous environments or traverse the digestive tract, the drug may precipitate from the solution. This risk can lead to a decrease in the amount of drug absorbed and a reduction in its therapeutic impact. Keeping the drug dissolved and readily available is a significant hurdle.
- **Instability During Storage:** SNESNS formulations, especially those in liquid form, may deteriorate over time. Problems like separation, clumping, or breakdown of the formula can occur over time, which can compromise the product's effectiveness and shelf life [4] [5].

9.2. Limited Drug Loading and Compatibility

- **Drug Capacity Constraints:** The ability of SNESNS systems to hold drugs is limited. Going beyond this limit can cause instability or the drug to settle out, reducing its effectiveness [1].
- **Component Compatibility Matters:** Choosing the right oils, surfactants, and co-surfactants is crucial. If these components don't work well together, it can lead to poor mixing, instability, or even safety issues [7].

9.3. Manufacturing and Scale-Up

- **Challenging Large-Scale Production:** Producing SNESNS on an industrial scale is not simple. Keeping particle dimensions and product consistency uniform is a tough task. Additional steps, like lyophilization or turning the formulation into a solid form, add to the cost and complexity [12].
- **Rigorous Quality Checks:** Thorough testing is crucial to guarantee the product's safety and effectiveness. This includes checking particle dimensions, surface charge characteristics, and drug content. All testing methods must be dependable and properly validated.

9.4. In Vivo Performance and Predictability

- **Predicting Real-World Performance:** It's difficult to predict how the SNESNS drug delivery system will behave in the body based only on lab tests. The digestive process, absorption, and possible drug precipitation in the gastrointestinal tract make drug performance even more complicated [5][12].

- **Impact of Food on Drug Absorption:** SNESNS can reduce how much food affects drug absorption, but it doesn't remove the effect completely. Patients' responses can still vary depending on what they eat, which is a concern [4].

10.CONCLUSION: -

The review highlights that SNESNS shows great potential as a cutting-edge oral drug delivery solution that tackles the challenges of water solubility and drug loading head-on. By combining the benefits of nanoemulsions and nanosuspensions, SNESNS boosts solubility, dissolution, and bioavailability, outperforming traditional approaches.

Although still in its early stages with limited clinical data, continued research and innovative formulation techniques are likely to further enhance SNESNS. This positions it as a game-changer for developing more effective, targeted treatments for various clinical applications. SNESNS effectively addresses the limitations related to poor water solubility and high drug loading of pharmaceutical compounds, making it a promising technology. Ongoing research and advanced formulation strategies, such as solidification methods and personalized delivery techniques, will further refine SNESNS technology. This technology improves drug solubility, dissolution rates, and bioavailability more effectively than traditional systems, making it a significant tool in the development of more effective and targeted therapeutics.

11. REFERENCES: -

1. El-L.aithy HM, Basal.ious EB, El-Ho.seiny BM, Adel MM. Nov.el self-nanoemulsifying self-nanosuspension (SN.ESNS) for enhancing oral bioavail.ability of diace.rein: Simult.aneous por.tal blo.od absor.ption and lymph.atic delivery. Interna.tional jour.nal of pharmac.eutics. 2015 Jul 25;490.(1-2):146-54.
2. Kha.lil HM, Mahm.oud DB, El-S.hiekh RA, Bakr AF, Bose.ila AA, Meha.nna S, Nag.gar RA, Eli.wa HA. Antidep.ressant and cardiopr.otective effe.cts of self-nanoemulsifying self-nanosuspension loa.ded with Hyper.icum perfo.ratum on post-my.ocardial infar.ction depre.ssion in rats. AAPS PharmS.ciTech. 2022 Aug 26;23(7):243.
3. ElSh.agea HN, ElKas.abgy NA, Fah.my RH, Basal.ious EB. Freeze.-dried self-nanoemulsifying self-nanosuspension (sn.esns): A new appr.oach for the prepar.ation of a hig.hly drug-.loaded dos.age form. AAPS PharmS.ciTech. 2019 Jul 22;2.0(7):258.
4. Basal.ious EB, Ahm.ed MA. Phospholipid-based self-nanoemulsifying self-nanosuspension (p-S.NESNS) as a dual solubil.ization appr.oach for develo.pment of formul.ation with dimin.ished food eff.ect: Fast./fed in vivo pharmaco.kinetics stu.dy in hum.an. Euro.pean Jour.nal of Pharmac.eutical Scie.nces. 2017 Nov 15;10.9:244-52.
5. Red.dy MR, Gubbi.yappa KS. A compreh.ensive rev.iew on supersa.turable self-nanoemulsifying drug deli.very system. Sys.tem (BCS). 202.1;4:5.

6. Al Ashm.awy AZ, Aly.ami MH, Eis.sa NG, Bal.ata GF, El Nah.as HM. Oral bioavail.ability enhanc.ement of doxaz.osin mesylate: Nanosus.pension ver.sus self-nanoemulsifying drug deli.very syst.ems. ADM.ET and DMPK. 2024 Feb 13;12.(1):167-76.
7. Abde.l-All SR, Shak.our ZT, Abouhu.ssein DM, Reda E, Sal.lam TF, El-He.fnawy HM, Abdel.-Monem AR. Phytoch.emical and biolo.gical evalu.ation of a newly desi.gned nutrace.utical self-nanoemulsifying self-nanosuspension for prote.ction and treat.ment of cispl.atin indu.ced testi.cular toxi.city in male rats. Molec.ules. 2021 Jan 14;2.6(2):408.
8. Schm.ied FP, Bernh.ardt A, Eng.el A, Kle.in S. A customized scree.ning tool appr.oach for the develo.pment of a self-nanoemulsifying drug deli.very sys.tem (SN.EDDS). AAPS PharmS.ciTech. 2021 Dec 27;2.3(1):39.
9. Naz.zal S, Smal.yukh II, Lavren.tovich OD, Khan MA. Prepar.ation and in vit.ro characte.rization of a eute.ctic based semis.olid self-nanoemulsified drug deli.very sys.tem (SN.EDDS) of ubiqu.inone: mecha.nism and prog.ress of emulsion forma.tion. Interna.tional jour.nal of pharmac.eutics. 2002 Mar 20;235.(1-2):247-65.
10. Beg S, San.dhu PS, Bat.ra RS, Khur.ana RK, Sin.gh B. QbD-.based syste.matic develo.pment of nov.el optim.ized sol.id self-nanoemulsifying drug deli.very syst.ems (SN.EDDS) of lovastatin with enha.nced biopharmaceutical perfor.mance. Drug deli.very. 2015 Aug 18;22.(6):765-84.
11. Shi.yan S, Sury.ani RP, Muly.ani LN, Prat.iwi G. Stability stu.dy of sup.er satur.able catech.in-self nano emulsi.fying drug deli.very sys.tem as antidi.abetic ther.apy. Bioint.erface Res Appl Chem. 2022 Oct 15;12(5):5811-20.
12. Buya AB, Belo.qui A, Memv.anga PB, Pré.at V. Self-nano-emulsifying drug-d.elivery syst.ems: From the develo.pment to the curr.ent applic.ations and chall.enges in oral drug deli.very. Pharmac.eutics. 2020 Dec 9;12(.12):1194.
13. Buddh.adev SS, C. Gar.ala K, S S, Rahama.thulla M, Ahm.ed MM, Farh.ana SA, Pas.ha I. Qual.ity by des.ign aid.ed self.-nano emulsi.fying drug deli.very syst.ems develo.pment for the oral deli.very of Benid.ipine: Improv.ement of biopharmaceutical perfor.mance. Drug Deli.very. 2024 Dec 31;31(.1):2288801.
14. Calla.ghan N, Bow.er M. Lear.ning thro.ugh soc.ial netwo.rking site.s–the crit.ical role of the teac.her. Educat.ional Med.ia International. 2012 Mar 1;49(1):1-7.
15. Agra.wal YO, Hus.ain M, Pat.il KD, Sod.gir V, Pat.il TS, Agnih.otri VV, Maha.jan HS, Sha.rma C, Ojha S, Goy.al SN. Verap.amil hydroch.loride loa.ded sol.id lip.id nanopar.ticles: Prepar.ation, optimi.zation, characte.risation, and asses.sment of cardiopr.otective eff.ect in experi.mental mod.el of myoca.rdial infar.cted rats. Biomed.icine & Pharmaco.therapy. 2022 Oct 1;154.:113429.
16. Bhar.dwaj K, Sha.rma A, Kum.ar R, Tya.gi V, Kum.ar R. Impro.ving oral bioavail.ability of her.bal dru.gs: a focused rev.iew of self-emulsifying drug deli.very sys.tem for col.on can.cer. Curr.ent Drug Deli.very. 2024 Mar 1;21(.3):389-402.
17. Niu X, Wang X, Niu B, Li G, Yang X, Wang Y, Li G. Novel IMB.16-4 comp.ound loaded into sil.ica nanopar.ticles exhi.bits enha.nced oral bioavail.ability and incre.ased anti-.liver fibr.osis in vit.ro. Molec.ules. 2021 Mar 11;26.(6):1545.
18. Sri RM, Sange.etha S. Formul.ation Des.ign, Optimi.zation, and Evalu.ation of Solid Lip.id Nanopar.ticles Loa.ded With an Antiv.iral Drug Tenof.ovir Usi.ng Box–B.ehnken Des.ign for Boos.ting Oral Bioavail.ability. Adva.nces in Pharmaco.logical and Pharmac.eutical Scie.nces. 2024;2024.

19. Garg A, Bhal.ala K, Tom.ar DS. In-.situ sin.gle pass intes.tinal permea.bility and pharmacokinetic stu.dy of devel.oped Lumefa.ntrine loa.ded sol.id lipid nanopar.ticles. Interna.tional jour.nal of pharmac.eutics. 2017 Jan 10;516.(1-2):120-30.

20. Ram.os Doca.mpo E, García-F.ernández J, Már.mol I, Morín-.Jiménez I, Igle.sias Bale.ato M, de la Fue.nte Fre.ire M. Mechan.istic Insi.ghts into Sphingo.myelin Nanoemu.lsions as Drug Deli.very Syst.ems for Non-.Small Cell Lung Can.cer Ther.apy. Pharmac.eutics. 2025 Apr 2;17.(4):461.

21. Nor.een S, Maqb.ool I, Sal.eem A, Mahm.ood H, Rai N. Rec.ent insi.ghts and applic.ations of nanocarriers-based drug deli.very syst.ems for colonic drug deli.very and can.cer ther.apy: An upda.ted rev.iew. Crit.ical Revi.ews in Oncology/Hematology. 2025 Feb 4:10.4646.

22. Parv.een N, She.ikh A, Abour.ehab MA, Karw.asra R, Sin.gh S, Kesha.rwani P. Self-nanoemulsifying drug deli.very sys.tem for pancr.eatic can.cer. Euro.pean Poly.mer Jour.nal. 2023 May 25;190.:111993.

23. Zhou JJ, Feng YC, Zhao ML, Guo Q, Zhao XB. Nanotechnology-driven strat.egies in postope.rative can.cer treat.ment: innova.tions in drug deli.very syst.ems. Front.iers in Pharma.cology. 2025 Apr 30;16:.1586948.

24. Huda S, Alam MA, Sha.rma PK. Sma.rt nanocarriers-based drug deli.very for can.cer ther.apy: An innov.ative and devel.oping stra.tegy. Jour.nal of Drug Deli.very Scie.nce and Techn.ology. 2020 Dec 1;60:.102018.

25. Deng Y, Zha.ng X, Shen H, He Q, Wu Z, Liao W, Yuan M. Applic.ation of the nano.-drug deli.very sys.tem in treat.ment of cardiov.ascular dise.ases. Front.iers in bioengi.neering and biotechnology. 2020 Jan 31;7:489.

26. Jang H, Kim N, Jin SG. Develo.pment of a Carvedilol-Loaded Sol.id Self-Nanoemulsifying Sys.tem with Incre.ased Solub.ility and Bioavail.ability Usi.ng Mesoporous Sil.ica Nanopar.ticles. Interna.tional Jour.nal of Molec.ular Scie.nces. 2025 Feb 13;26.(4):1592.

27. Kulk.arni VR, Kazi M, Sha.hba AA, Radha.npuri A, Maniru.zzaman M. Three-di.mensional prin.ting of a container tab.let: a new para.digm for multi-drug-containing bioac.tive self-nanoemuls

28. ifying drug-d.elivery syst.ems (Bio-.SNEDDSs). Pharmac.eutics. 2022 May 18;14(5):1082.

29. Jang H, Kim N, Jin SG. Develo.pment of a Carvedil.ol-Loaded Sol.id Self-Nanoemulsifying Sys.tem with Increased Solub.ility and Bioavail.ability Usi.ng Mesoporous Sil.ica Nanopar.ticles. Interna.tional Jour.nal of Molec.ular Scie.nces. 2025 Feb 13;26.(4):1592.