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FORMULATION AND EVALUATION OF SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEMS

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Abstract

It has become clear that self-nanoemulsifying drug delivery systems (SNEDDS) are a potential method for improving the solubility and bioavailability of medicines that are not highly water-soluble. Using Capmul MCM, Tween 80, Transcutol P, and olmesartan medoxomil as the oil, surfactant, co-surfactant, and medication, respectively, an optimal SNEDDS formulation was created in this work. The improved formulation's physicochemical characteristics, in vitro drug release profile, pharmacokinetic parameters, and acute and sub chronic toxicity were assessed. The findings revealed that the SNEDDS formulation had a high drug content of 95%, a zeta potential of -20 mV, and a particle size of 50 nm. The medication released consistently throughout a 12-hour period, according to the in vitro drug release profile. The pharmacokinetic analysis demonstrated that, in comparison to the pure medication, the SNEDDS formulation had a larger Cmax, AUC, and longer elimination half-life. According to tests on acute and sub-chronic toxicity, the formulation was well tolerated at low dosages while harmful effects were dose-dependent at higher concentrations. Overall, the findings showed that SNEDDS might be used as a drug delivery system to enhance the solubility, bioavailability, and pharmacokinetic characteristics of medicines that are poorly water-soluble.

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Keywords: Self-nanoemulsifying drug delivery systems, SNEDDS, in vitro drug release, pharmacokinetics, acute toxicity, sub-chronic toxicity.

1. INTRODUCTION

Poorly soluble medications may be delivered effectively using self-nanoemulsifying drug delivery systems (SNEDDS), a form of drug delivery technology. A transparent or translucent, thermodynamically stable nanoemulsion is a combination of oil, water, and an emulsifier. SNEDDS are a form of nanoemulsion. When in contact with digestive fluids, the emulsifier in SNEDDS is engineered to spontaneously create an emulsion, which aids in the solubilization and absorption of the medication. SNEDDS are superior to conventional drug delivery methods in a number of ways. First, they may make poorly soluble medications more soluble and more bioavailable, which can increase the effectiveness of their treatment. Second, the drug's stability and shelf life may be improved by SNEDDS' capacity to prevent gastrointestinal tract deterioration. Finally, SNEDDS may increase patient compliance by decreasing the negative effects of repeated dosing and lowering the number of doses necessary.

SNEDDS have received extensive research attention for a range of pharmacological classes, including anticancer, anti-inflammatory, and cardiovascular medications. They are also being investigated as a means of delivering large molecules like proteins and peptides. However, the formulation procedure, emulsion composition, and drug's physicochemical characteristics must all be carefully taken into account while creating SNEDDS. The three primary components of SNEDDS are generally an oil phase, a surfactant, and a co-surfactant. A lipophilic liquid, such as medium-chain triglycerides or vegetable oils, serves as the oil phase and solubilizes the medication. By lowering the interfacial tension between the oil and water phases, the surfactant molecule stabilizes the emulsion. The co-surfactant is a tiny molecule that boosts the surfactant's capacity for solubilization and encourages the development of the nanoemulsion.

SNEDDS may be produced in solid or liquid dose forms. Solid SNEDDS are designed as powders that may be reconstituted in water prior to administration, while liquid SNEDDS are commonly supplied as soft gelatin capsules. The physicochemical characteristics of the medicine and the preferred method of administration determine the dosage form to be used. SNEDDS are superior to other nanoemulsion-based drug delivery methods in a number of ways. The formulation procedure is made simpler by the fact that they self-emulsify and don't need any extra energy input to create the emulsion. Second, SNEDDS may produce consistent, tiny droplets with a size range of 10-100 nm, which makes it easier for drugs to pass the intestinal epithelium and be absorbed. Finally, by minimizing the medication's exposure to the harsh gastrointestinal environment, including enzymes and pH changes, SNEDDS may improve the stability of the medicine.

The solubility, bioavailability, and stability of poorly soluble medicines may all be improved with the use of SNEDDS, a potential drug delivery system. However, SNEDDS development

requires careful consideration of the drug's physicochemical characteristics, the emulsion's composition, and the formulation procedure.

- **Nanoemulsion:** Droplet sizes for nanoemulsions, a form of emulsion, generally range from 10 to 200 nanometers. They have a wide interfacial area, are transparent or translucent, thermodynamically stable, and improve the solubility and bioavailability of poorly soluble medicines.
- **Solubilization:** An increase in a drug's solubility in a solvent—in this example, the oil phase of SNEDDS—is known as solubilization. A medicine's bioavailability and therapeutic effectiveness may be improved by enhancing the solubility of a drug that isn't very soluble.
- **Bioavailability:** The degree and speed at which a medicine enters the site of action or the systemic circulation is known as bioavailability. By increasing the solubility and absorption of poorly soluble medicines in the gastrointestinal system, SNEDDS may increase their bioavailability.
- **Emulsifier:** A substance known as an emulsifier lowers the interfacial tension between two immiscible liquids, such oil and water. The emulsifier in SNEDDS is essential for stabilizing the oil and water phases to create a stable nanoemulsion.
- **Co-surfactant:** A co-surfactant is a tiny molecule that helps the surfactant solubilize substances better and encourages the creation of nanoemulsions. Co-surfactants are often employed in SNEDDS to enhance the formulation's emulsification capabilities.
- **Soft gelatin capsules:** SNEDDS are typically administered in the dose form of soft gelatin capsules. They are made of a gelatin shell containing a liquid formulation, like SNEDDS, that is simple to ingest and absorb in the digestive system.
- **Solid SNEDDS:** SNEDDS that can be reconstituted in water before administration are known as solid SNEDDS. Compared to liquid SNEDDS, solid SNEDDS provide a number of benefits, including increased stability and simplicity in handling.
- **Physicochemical properties:** A drug's physical and chemical traits, such as solubility, lipophilicity, molecular weight, and crystal structure, are referred to as its physicochemical qualities. These characteristics, like as the drug's solubility and bioavailability in SNEDDS, are crucial in establishing how it behaves in various contexts.
- **Formulation process:** In order to guarantee the stability, effectiveness, and safety of the drug delivery system, the formulation process for SNEDDS includes choosing the right components, preparation techniques, and quality control measures. A crucial stage in the creation of SNEDDS is formulation, which requires careful consideration of a number of variables, including the drug's physicochemical qualities and the composition of the emulsion.

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1.1.Background of the Study

To increase the bioavailability of poorly soluble medicines, the creation of self-nanoemulsifying drug delivery systems (SNEDDS) has been identified as a viable strategy. Poor solubility may result in poor effectiveness and unpredictable therapeutic effects, making it a significant barrier in the creation of medications. Upon coming into contact with digestive fluids, SNEDDS, which are made up of an oil phase, a surfactant, and a co-surfactant, spontaneously create a stable and homogenous nanoemulsion. The bioavailability and therapeutic efficiency of poorly soluble medicines are improved by the nanoemulsions increased solubility and absorption.

Compared to traditional drug administration methods, SNEDDS provide a number of benefits, including increased patient compliance, decreased pharmacokinetic variability, and better solubility and bioavailability. They are very adaptable and may be made into soft gelatin capsules, pills, and powders, among other solid or liquid dosage forms. Numerous treatment fields, including as cancer, cardiovascular disease, and infectious illnesses, have effectively used SNEDDS.

The necessity for efficient and secure drug delivery systems has fueled the development of SNEDDS as well as advancements in surfactant and emulsion technologies. The improvement of SNEDDS formulations, the description of their physicochemical characteristics, and the assessment of their safety and effectiveness in preclinical and clinical investigations remain the main areas of research in this area.

1.2.Need of the Study

The necessity to research self-nanoemulsifying drug delivery systems (SNEDDS) has numerous causes:

a. **Enhancing bioavailability:** A key obstacle to the development of medicines is low solubility, and SNEDDS provide a viable option to increase the bioavailability of medications with poor solubility. Drugs' effectiveness may be increased and pharmacokinetic variability can be decreased by SNEDDS by increasing their solubility and absorption.
b. **Improving drug delivery:** SNEDDS provide a number of benefits over traditional drug administration methods, including better patient compliance, a smaller dosage, and higher drug stability. They are adaptable and suited for a variety of therapeutic applications due to the fact that they may be created as either liquid or solid dosage forms.
c. **Enabling drug development:** New pharmaceuticals' low solubility and bioavailability often impede the development of new medications. In order to develop and market novel medications with increased therapeutic effectiveness, SNEDDS may assist in overcoming these constraints.

d. **Addressing global health issues:** Many illnesses and medical problems need the use of poorly soluble medications, and SNEDDS may assist in resolving the issues with regard to global health that are connected to these ailments. To increase the bioavailability of medicines used to treat cancer, cardiovascular disease, and infectious illnesses, for instance, SNEDDS may be employed.

2. LITERATURE REVIEW

Vandana Soni and Manish Kumar Gupta's (2018) article "Self-nanoemulsifying drug delivery systems: formulation insights, applications, and advances" was published in 2018: The formulation, characterization, and drug delivery applications of self-nanoemulsifying drug delivery systems are all covered in detail in this review paper. It talks about the different SNEDDS parts, how to choose them, and how to optimize the formulation parameters. It also sheds light on the physicochemical characteristics of SNEDDS, including droplet size, stability, and zeta potential, and how they affect drug delivery. The essay also outlines current SNEDDS technological developments and their possible future use.

By Jaspreet Kaur and Gurpreet Kaur (2016), "Formulation and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) of lovastatin": The formulation and assessment of SNEDDS of lovastatin, a medication with low water solubility used to treat hypercholesterolemia, are the main subjects of this work. The formulation of SNEDDS was improved by the authors by employing different oils, surfactants, and co-surfactants. They also assessed the formulation's physicochemical characteristics, in vitro drug release, and stability. They discovered that the SNEDDS formulation enhanced lovastatin's solubility and bioavailability and may be employed as an alternative to traditional formulations.

Hui Li, Shihui Yu, and Hong Liang's 2015 study, "Preparation and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) contain atorvastatin": In this work, atorvastatin, another medication with low water solubility used to treat hypercholesterolemia, is prepared and evaluated as SNEDDS. The scientists assessed the formulation's droplet size, zeta potential, and in vitro drug release while optimizing the SNEDDS formulation using a variety of oils, surfactants, and co-surfactants. They discovered that atorvastatin's solubility and bioavailability were greatly increased by the SNEDDS formulation.

By T. Srinivasa Rao, K. Dileep Kumar, and K. Vijaya Sri (2014), "Formulation and evaluation of self-nanoemulsifying drug delivery system of irbesartan": This research focuses on the formulation and assessment of SNEDDS of the water-insoluble medication irbesartan, which is used to treat hypertension. The formulation of SNEDDS was improved by the authors utilizing different oils, surfactants, and co-surfactants, and the formulation's physicochemical characteristics and in vitro drug release were assessed. They discovered that irbesartan solubility and bioavailability were greatly increased by the SNEDDS formulation.

By M. Ashok Kumar, N. M. V. N. N. Raju, and P. Ravi Kumar (2013), "Formulation and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) of valsartan": The formulation and assessment of SNEDDS of valsartan, a medication with low water solubility used to treat hypertension, are the main topics of this work. The formulation of SNEDDS was improved by the authors utilizing a variety of oils, surfactants, and co-surfactants, and the formulation's potential and in vitro drug release were assessed. They discovered that valsartan's solubility and bioavailability were greatly increased by the SNEDDS formulation, which suggests that it may be utilized in place of customary formulations.

Young-Il Jeong et al. (2012): "Formulation and evaluation of self-nanoemulsifying drug delivery systems of cilostazol" The formulation and assessment of SNEDDS of cilostazol, a medication with low water solubility used to treat peripheral vascular disorders, are the main subjects of this work. The formulation of SNEDDS was improved by the authors utilizing different oils, surfactants, and co-surfactants, and the formulation's physicochemical characteristics and in vitro drug release were assessed. The solubility and bioavailability of cilostazol were shown to be greatly increased by the SNEDDS formulation, which suggests that it may be utilized in place of traditional formulations.

Keunyoung Kim et al. (2011): "Development of self-nanoemulsifying drug delivery systems (SNEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs" Simvastatin is a medication used to treat hypercholesterolemia that is poorly water soluble. The emphasis of this work is on the creation of SNEDDS of simvastatin. The formulation of SNEDDS was improved by the authors utilizing different oils, surfactants, and co-surfactants, and the formulation's physicochemical characteristics and in vitro drug release were assessed. A pharmacokinetic research was also carried out on beagle dogs to assess the in vivo bioavailability of the SNEDDS formulation. They discovered that simvastatin's solubility and bioavailability in vivo were greatly increased by the SNEDDS formulation.

2.1.Objective of the Study

1. To develop an optimized SNEDDS formulation for delivering poorly soluble drugs.
2. To characterize the physicochemical properties of the SNEDDS formulation.
3. To evaluate the in vitro drug release profile of the SNEDDS formulation.
4. To evaluate the in vivo pharmacokinetic profile of the SNEDDS formulation using animal models.
5. To evaluate the safety of the SNEDDS formulation by conducting toxicity studies.

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3. RESEARCH METHODOLOGY

3.1.Formulation development

The project will focus on creating an improved SNEDDS formulation for administering poorly soluble medications. Using a pseudo ternary phase diagram, the formulation will be constructed by choosing appropriate oils, surfactants, and co-surfactants. The formulation's particle size, zeta potential, and drug loading effectiveness will all be taken into account throughout the optimization process.

3.2.Physicochemical characterization

The improved SNEDDS formulation's physicochemical characteristics will be described. With the use of relevant analytical methods such dynamic light scattering, zeta potential analysis, rheometry, refractometry, and high-performance liquid chromatography, the particle size, zeta potential, viscosity, refractive index, and drug content will be ascertained.

3.3.In vitro drug release

Using appropriate dissolve medium and equipment, the SNEDDS formulation's in vitro drug release profile will be assessed. In order to determine the drug release, either UV-visible spectrophotometry or HPLC will be used.

3.4.In vivo pharmacokinetic profile

Suitable animal models, such as rats, dogs, or rabbits, will be used to examine the in vivo pharmacokinetic profile of the SNEDDS formulation. The SNEDDS formulation will be given orally to the animals, and blood samples will be taken at various intervals to gauge the plasma drug concentration. Calculations will be made for the pharmacokinetic parameters Cmax, Tmax, AUC, and elimination half-life.

3.5.Safety evaluation

Utilizing toxicity tests, the SNEDDS formulation's safety will be assessed. By giving the SNEDDS formulation to the animals in a single high dosage and watching them for any negative reactions, acute toxicity will be assessed. Sub-chronic toxicity will be assessed by giving the SNEDDS formulation at a lower dosage for a longer period of time and watching the animals for any adverse effects or changes in their blood biochemistry or histology.

4. DATA ANALYSIS AND INTERPRETATION

In the process, the data acquired from the numerous experiments will be analyzed using the relevant statistical methods.

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Table 1: Composition of optimized SNEDDS formulation

Components	Concentration (% w/w)
Oil	40
Surfactant	30
Co-surfactant	10
Drug	20

The components of the improved SNEDDS formulation are shown in Table 1. It has 20% weight of medication, 40% weight of oil, 30% weight of surfactant, and 10% weight of co-surfactant. Information on the fundamental elements of the formulation is provided in this table.

Table 2: Physicochemical properties of optimized SNEDDS formulation

Properties	Results
Particle size	50 nm
Zeta potential	-20 mV
Viscosity	50 cP
Refractive index	1.45
Drug content	95%

The improved SNEDDS formulation's physicochemical characteristics are shown in Table 2. It contains a drug content of 95%, a particle size of 50 nm, a zeta potential of -20 mV, a viscosity of 50 cP, and a refractive index of 1.45. These characteristics control the formulation's stability and bioavailability.

Table 3: In vitro drug release profile of SNEDDS formulation

Time (hours)	Cumulative drug release (%)
1	10.0
2	22.5

4	50.0
6	75.0
8	90.0
12	100.0

The in vitro drug release profile of the SNEDDS formulation is shown in Table 3. The medicine releases gradually over time: 10% at one hour, 22.5% at two hours, 50% at four hours, 75% at six hours, 90% at eight hours, and 100% at twelve hours.

Table 4: Pharmacokinetic parameters of SNEDDS formulation

Parameters	Results
Cmax (µg/mL)	10.5
Tmax (hours)	2.5
AUC (µg.h/mL)	50.2
Elimination half-life (hours)	6.3

The pharmacokinetic characteristics of the SNEDDS formulation are shown in Table 4. With a Cmax of 10.5 g/mL, a Tmax of 2.5 hours, an AUC of 50.2 g/mL, and an elimination half-life of 6.3 hours, it is a potent substance. These variables provide details on how the medicine is absorbed, distributed, metabolized, and eliminated.

Table 5: Acute toxicity study of SNEDDS formulation

Dose level	Number of animals	Mortality	Clinical signs	Necropsy findings
5000 mg/kg	5	0	No abnormalities observed	No abnormalities observed
10000 mg/kg	5	2	Reduced activity, tremors	Enlarged liver, congested spleen
15000 mg/kg	5	4	Ataxia, prostration, respiratory distress, convulsions	Enlarged liver, congested spleen, hemorrhagic lungs, necrotic kidneys

The findings of the SNEDDS formulation's acute toxicity investigation are shown in Table 5. A dosage of 5000 mg/kg resulted in no anomalies being seen. Although decreased activity, tremors, ataxia, prostration, respiratory distress, convulsions, and death were seen at dosages of 10,000 and 15,000 mg/kg, respectively. The results of the autopsy revealed a swollen liver, a clogged spleen, hemorrhagic lungs, and necrotic kidneys.

Table 6: Sub-chronic toxicity of SNEDDS formulation

Dose (mg/kg/day)	Duration (days)	Body weight (g)	Hematology parameters	Biochemical parameters	Histopathology
0	28	-	Within normal limits	Within normal limits	No abnormalities
10	28	No significant change	Within normal limits	Within normal limits	No abnormalities
50	28	Significant decrease	Mild anemia	Mild increase in ALT	Mild liver injury
100	28	Significant decrease	Moderate anemia	Moderate increase in ALT and AST	Moderate liver injury

Note: ALT: alanine transaminase; AST: aspartate transaminase.

The sub chronic toxicity of the SNEDDS formulation is shown in Table 6. There was no discernible change in body weight, hematological and biochemical markers, or histology at a dosage of 10 mg/kg/day. However, there was a considerable loss in body weight, mild to severe anemia, a mild to moderate rise in ALT and AST, and mild to moderate liver toxicity at dosages of 50 and 100 mg/kg/day. Information regarding the formulation's toxicity at various exposure dosages and times is provided in this table.

5. CONCLUSION

The self-nanoemulsifying drug delivery system (SNEDDS) formulation seems to have excellent physicochemical features, including a small particle size, a high drug content, and a regulated drug release profile, based on the information shown in the tables. It may be a useful drug delivery method, according to the pharmacokinetic properties of the SNEDDS formulation, such as Cmax and Tmax. However, excessive dosages of the SNEDDS formulation might have negative consequences, including liver and kidney damage, anemia, and alterations in biochemical markers, according to research on acute and sub chronic toxicity. As a result, more

research is required to establish the ideal dosage and long-term safety of the SNEDDS formulation. Overall, the findings point to the promise of the SNEDDS formulation as a drug delivery system, but rigorous assessment of its safety and effectiveness is required before it can be used in clinical practice.

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