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# Self - Nanoemulsifying Drug Delivery System: A Novel Approach for Anticoagulant Therapy – A Review

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**Abstract:**
Nanotechnology is widely recognized as an essential approach in drug delivery that can influence the therapeutic performance of hydrophobic drugs. Self-Nano emulsifying drug delivery systems (SNEDDS) are a standard technique for increasing the solubility and dissolution rate of poorly water soluble drugs. When diluted with water and gently agitated, SNEDDS are anhydrous homogeneous liquid mixtures of oil, surfactant, co-surfactant, and drugs that spontaneously form o/w nanoemulsions. Patients have been prescribed anticoagulants to prevent deep vein thrombosis or pulmonary embolism. However, due to many factors with anticoagulant therapy, much attention was focused on developing an ideal anticoagulant, and numerous attempts to develop new anticoagulant delivery systems have been made in recent years. In this review, we describe recent advances in SNEDDS for anticoagulant delivery and summarize the current clinical use of anticoagulants and their delivery systems for transporting anticoagulants to their targets in the body, including targeted delivery concepts.

**Keyword:** SNEDDS, Anticoagulants

## INTRODUCTION:

Mostly because of the high level of patient compliance, oral administration is the most convenient and preferred method of drug delivery. However, due to their poor water solubility, more than half of drugs administered orally have limited therapeutic efficacy. [1]To improve oral bioavailability, conventional techniques such as salt formation, micronization and solubilization using cosolvents, permeation enhancers, and complexation, such as cyclodextrin, have been used. Nonetheless, these techniques had limited utility and necessitated the use of a specific drug candidate.

The Biopharmaceutics Classification System (BCS) categorizes drugs into four classes based on their solubility and intestinal permeability, as determined by data from the United States Food and Drug Administration on intestinal drug absorption (US FDA) Drugs with low solubility and high permeability were classified as class II. For these drugs, the rate-limiting step is drug dissolution from formulation and solubility in gastric fluids, not absorption rate. As a result, increasing solubility improves drug bioavailability. [2, 3]

Microemulsions, nanoemulsions, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), polymeric micelles, polymeric nanoparticles, and inorganic nanocarriers are some of the nanoparticle approaches that have been developed. Furthermore, lipid-based drug delivery systems, such as nanoemulsions, have demonstrated successful potential in increasing the solubility of drugs that are poorly water soluble. They have a mechanism to improve drug bioavailability by increasing drug retention time in the stomach, changing the biophysical barrier, improving drug solubility, decreasing drug metabolism, stimulating lymphatic transport, and having less toxicity in vivo. [4-8] as colloidal dispersions, nanoemulsions are the most prominent lipid-based drug delivery systems. They are nanoscopic droplet-sized oil, surfactant, and water systems that are optically isotropic, transparent, thermodynamically unstable, and kinetically stable. For many decades, nanoemulsions have been recognized for their ability to improve the oral bioavailability of poorly water soluble drugs. [9]The water content of nanoemulsions would promote drug hydrolysis and precipitation during storage, reducing their utility in oral delivery. To overcome the limitations of nanoemulsions, the approach of spontaneous self-Nano emulsification for oral drug delivery was developed. [10]

## TYPE OF (SNEDDS)

1. SNEDDS of water in oil (W/O) in which a water bead is dispersed in Continuous Phase oil
2. Oil in water (O/W) snedds in which an oil bead is dispersed in Continuous Phase Water
3. Bi-continuous snedds in which the surfactant is soluble in both oils as if they were water and the bead is scattered in both oils as if they were water.

## ADVANTAGE OF SNEDDS [11]

1. The ease of production and scale-up.
2. Protection of sensitive drug substances from antagonistic conditions in the gut by providing a large interfacial region for drug distribution between oil and water.
3. Medication(s) are selectively focused on the way to an explicit absorption window in the GIT.
4. Improved oral bioavailability by increasing dissolvability and lowering the dose, thereby advancing productive drug transport.
5. The activity gets off to a quick start.
6. SNEDDS has a significantly larger surface area and free vitality than smaller scale emulsions (SMEDDS).
7. Reduction in the subject's and intra-changeability subject's and nutrient effects.

**DISADVANTAGE OF SNEDDS**

1. Capability to deliver peptides that are increasingly susceptible to enzymatic hydrolysis within the GIT. • Has no effect on lipid digestion activity, unlike other lipid-based drug delivery systems.
2. More dependable drug retention profiles in the short term.
3. Management of delivery profiles.
4. When the polymer is incorporated into a SNEDDS arrangement, it delays the arrival of medication.
5. Fine oil beads would pass quickly and advance comprehensive conveyance of medication all through the gastrointestinal tract, thereby limiting aggravations experienced during expanded contact of mass medication substance and the gut wall.
6. The ease of converting SNEDDS to solid-SNEDDS allows for the advancement into a strong measurement structure. • It is used as an Ayurveda scheme and a Unani scheme.
7. 1.4 Snedds' Disadvantages [12]
8. SNEDDS are not appropriate for medications that are controlled at extremely high concentrations. • SNEDDS are difficult to direct for medications that have limited solubility in water and lipids.
9. The ability of SNEDDS to keep medication in a solubilized state is greatly influenced by the medication's solubility in an oily stage.
10. If a surfactant or co-surfactant is added to a greater extent for medicate solubilization, the risk of precipitation increases.
11. Temperature and pH have an impact on the security of SNEDDS. [13]

**COMPOSITION OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS:**

The self-emulsifying process is based on: -
Concentration of surfactant.

1. Nature of surfactant
2. oil phase combination
3. The temperature at which selfemulsification process occurs [14]

**1. Drug/active pharmaceutical ingredient**

The Biopharmaceutical classification system (BCS) divides drugs into four classes based on solubility (the ability of a salute to dissolve in a solvent) and permeability (contact between a solute and solvent to form a solution) [15]. SEDDs are typically used to improve absorption due to the poor permeability and/or solubility of Biopharmaceutical Classification System (BCS) class II to IV drugs. Such systems, however, can be used for the four classes. [16]

**2. Oils**

It is the most important component because it improves GIT absorption by facilitating self-emulsification and increasing the lipophilic drug fraction transported through the intestinal lymphatic system [17]. For the production of self-emulsifying systems, both long and medium chain triglyceride (LCT and MCT) oils with variable saturation degrees have been used. Semi-synthetic MCTs, which are amphiphilic compounds with surfactant properties, are increasingly replacing common medium-chain triglyceride oils. [18]

**Table 1: List of surfactants used in snedds.**

| Class | Example | Commercial name | Application | Reference |
|---|---|---|---|---|
| Phospholipids | Soybean lecithin | | All Routes | [24] |
| POE Castor oil<br>POE hydrogenated castor oil | POE 35 Castor oil,<br>POE 40 Castor oil | Cremophore EL,<br>Etocas 35 HV<br>Cremophore RH 40,<br>HCO40, | P/O/T/Oc/M | [25] |
| POE-PPO Block copolymers | Poloxamer 188<br>Poloxamer 407 | Pluronic / Lutrol F 68<br>Pluronic / Lutrol F 127 | P/O/T/Oc/M | [26] |
| Sorbitan ester | Sorbitan mono oleate span 80,<br>Sorbitan mono laurate span 20,<br>Sorbitan mono stearate 60, | Crill 4<br>Crill 1<br>Crill 3 | P/O/T/Oc/M | [27] |
| Poly sorbates | POE20 Sorbitan monooleate Tween 80,<br>POE 20 Sorbitan monolaurate Tween 20 | Crillet 4<br>Crillet 1 | P/O/T/Oc/M | [28] |
| Polyglycolyzed glycerides | Linoleoyl macrogol glycerides,<br>Oleoyl macrogol glycerides,<br>Caprylocapro-yl macrogol glycerides | Labrafil 2125 CS,<br>Labrafil 1944 CS,<br>Labrasol | O/<br>T | [29] |
| POE stearate | PEG66012 hydroxy stearate | Solutol HS 15 | P/T/O/Oc/M | [30] |

**Table 2: List of generally used co-surfactant.**

| Class | Example | Application | Reference |
|---|---|---|---|
| Short-chain alcohols | Ethanol, benzyl alcohol, Akoline, MCM, Methanol | P/O/T/Oc/M | [33] |
| Polyethylene glycols | PEG 400, Poloxamer 188 | P/O/T/Oc/M | [34] |
| Glycol ethers | Diethylene glycol monoethyl ether (Transcutol) | O/T | [35] |
| Alkane diols and triols | Propylene glycol 200,Lauroglycol FCC | P/O/T/Oc/M | [36],[37] |
| | Glycerol | P/O/T/Oc/M | [37] |

**3. Surfactants**

The hydrophilic-lipophilic balance (HLB), viscosity, affinity for the oily phase, and concentration of the surfactants all have an effect on the self-Nano emulsification process and droplet size of the nanoemulsions [19][20][21]. Surfactants are typically divided into three types: anionic, cationic, and non-ionic. Non-ionic surfactants with high HLB values are commonly used in the preparation of SNEDDS because they are less toxic than ionic surfactants. Many non-ionic surfactants, such as Cremophor EL, have the ability to improve drug permeability and uptake via P-glycoprotein-mediated efflux. [22][23]

As a result, selecting the appropriate type of surfactant is critical for the preparation of the SNEDDS. Furthermore, the concentration of the selected surfactants should be as low as possible in order to limit the adverse effect caused by the surfactants. Several surfactants, either alone or in combination, can be used to prepare SNEDDS with the desired characteristics for oral delivery.

**CO-SURFACTANT**

The comparative capacity to the surfactant component is referred to as co-surfactant. Co-surfactant is used in conjunction with a surfactant unit or a combination of surfactant components to increase the capacity of a surfactant to improve the water dissolvability of a drug that is insufficiently water soluble. Interfacial Fluidity can be avoided by using a cosurfactant that is a single-chain surfactant unit. Surfactant, oil, and water are used as cosurfactants. It can be isolated using a surfactant particle monomolecular layer. The Surfactant particle's Monomolecular Layer is referred to as the Liquid Crystal Arrangement Layer. The most important application of co-surfactant in SNEDDS is to reduce interfacial tension at the oil-water interface. [31][32]

**FACTORS INFLUENCING THE PREPARATION OF SNEDDS**

The surfactant should not crystallise into a lyotropic liquid.

The system consists of a short chain of alkanes, OH, H2O, and surfactant forming phases that are used in conjunction with the co-surfactant.

The nature or type of medication has a significant impact on the nanoemulsion's readiness. The concentration of surfactant is always optimal because a higher concentration of surfactant can be poisonous.[38]

**SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS)**

SEDDS, a lipid-based technique, was shown to increase drug dissolution rate and aid in the formation of soluble drug phase among the various strategies available to date. These formulations can be easily filled into soft and hard gelatin capsules. The self-emulsifying formulation is an isotropic mixture of drug, lipids, surfactants, and a co-solvent that produces a superfine emulsion when agitated in the gastro intestinal (GI) tract. SEDDS are classified into two types based on the globule sizes formed during dispersion: SMEDDS and SNEDDS. SMEDDS are formulations that produce a transparent microemulsion of oil-in-water or water-in-oil with a globule diameter of 250 nm. SNEDDS has a transparent droplet size of 20 to 200 nm.[9] SNEDDS is a competent, well-designed, and patient-compliant technique for sparingly soluble drugs because it improves solubility, dissolution patterns in the GI tract, permeability, and absorption. [39]

**ANTICOAGULANT**

Therapy Heparins, vitamin K antagonists (VKAs), direct thrombin inhibitors (DTIs), and direct factor “xaban” (Xa) inhibitors are the four main anticoagulant drugs. We divided this section into two parts for clarity: traditional anticoagulant agents (heparins and VKAs) and novel anticoagulant drugs (DTIs and direct factor Xa inhibitors).

**Conventional Anticoagulant Agents**

*Unfractionated Heparin (UFH), Low-Molecular-Weight Heparin (LMWH), and Ultra-Low-Molecular-Weight Heparin (ULMWH)*

Unfractionated heparin (UFH) is one of the most ancient biopolymeric drugs still in use in medicine. It is a highly sulfated glycosaminoglycan (GAG) with the highest negative charge density of any biological macromolecule known to science [40]. The affinity of UFH for a naturally occurring serine protease inhibitor, antithrombin III (ATIII), results in an increase in the ATIII thrombin inhibition rate as well as inhibition of other serine proteases involved in the coagulation process [41]. UFH is approved for the treatment and prevention of a number of conditions, including VTE, a potentially fatal condition that includes deep vein thrombosis (DVT) and pulmonary embolism (PE) [2]. UFH is administered parenterally via intravenous or subcutaneous injection; the latter has a

lower bioavailability. The non-specific binding of UFH to plasma proteins explains why individuals' anticoagulant activity varies, necessitating continuous monitoring. UFH is rapidly cleared from the body via the depolymerization mechanisms of endothelial and macrophage cells, whereas the kidneys are in charge of a slower UFH clearance mechanism. [42]

These controlled reactions allow drugs to have more predictable pharmacokinetic and pharmacodynamic profiles, making them dose-dependent compared to UFH. As a result, LMWHs require less monitoring. [43].

However, because LMWHs are heterogeneous compounds with distinct pharmacological and biochemical properties, they are not clinically interchangeable. [44].

Furthermore, when compared to UFH, LMWHs have fewer side effects and higher bioavailability when administered subcutaneously. However, administering protamine sulphate partially reverses the anticoagulant effect, increasing the risk of bleeding due to overdose. Because LMWHs are eliminated by the kidneys, administration in patients with renal failure extends their half-life. [45]

The theory that sparked interest in ULMWH was that compounds with a high anti-activated factor X (FXa) to anti-activated factor II (FIIa) activity ratio would achieve similar or better efficacy than LMWH products while posing a lower risk of bleeding and thrombocytopenia. [46].

ULMWHs are generated through a more extensive controlled depolymerization reaction that keeps the pentasaccharide active site intact. They have a higher proportion of short chains (Mw 3000 Da), resulting in better efficacy and safety profiles. Fondaparinux was the first synthetic ULMWH, an analogue of the pentasaccharide sequence marketed by Sanofi in 2002 and now marketed by GlaxoSmithKline as Arixtra. [47]

Antagonists of Vitamin K (VKAs) VKAs, such as warfarin, have been the standard anticoagulant therapy for more than 60 years, and they continue to be the most commonly prescribed oral anticoagulants globally [48]. VKAs are used to prevent arterial and venous thromboembolic disorders over time [49]. VKAs inhibit the formation of vitamin K-dependent clotting factors such as factor II (FII), factor VII (FVII), factor IX (FIX), factor X (FX), and proteins C and S by antagonising vitamin K [50].

VKAs are rapidly absorbed from the gastrointestinal tract after oral administration; they have a high bioavailability and reach the plasma concentration peak within a few hours. Furthermore, VKAs have a plasma half-life of 40 hours and are highly bound to plasma proteins during circulation. Different enzymes of the cytochrome P450 system, including CYP2C9, CYP1A2, and CYP34A, are involved in biotransformation and inactivation [51-53] because the excretion of unchanged VKAs is negligible; its elimination is dependent on hepatic metabolism. Furthermore, VKA antidotes are available, and a reversal effect could be achieved by administering vitamin K or infusing clotting factor [54].

**COAGULATION TEST PERFORMANCE OF SELF - NANOEMULSIFYING DRUG DELIVERY SYSTEM**

Kazi M, Al-Swairi M *et al.,* (2019) fabricated the Talinolol (TAL) self-nanoemulsifying drug delivery systems using a variety of oils, non-ionic surfactants, and/or water-soluble co-solvents, and were evaluated visually/by droplet size measurement. To achieve the highest drug loading, the equilibrium solubility of TAL in anhydrous and diluted SNEDDS was studied. The representative formulations were compared to the marketed product Cordanum R 50 mg and raw drug in in vitro dissolution experiments and human red blood cells (RBCs) toxicity test, ex vivo gut permeation studies, and bioavailability of SNEDDS in rats, and it was concluded that Talinolol loaded SNEDDS formulations could be a potential oral pharmaceutical product with high drug-loading capacity, [55].

Qiu XL, Fan ZR*et al.,* (2021) improved heparin absorption after oral administration, a self-nanoemulsifying drug delivery system (SNEDDS) was created, in which heparin was compounded with phospholipids to achieve greater fat solubility in the form of heparin-phospholipid (HEP-Pc) complex. The solvent evaporation approach was used to improve the solubility of heparin in n-octanol, resulting in the HEP-Pc complex. Differential scanning calorimetry (DSC), Fourier-transform infrared (FT-IR) spectroscopy, NMR, and SEM were used to demonstrate the successful synthesis of the HEP-Pc complex. High-pressure homogenization was used to make and characterise a heparin lipid microemulsion (HEP-LM). In mice, HEP-LM can improve heparin absorption following oral administration, dramatically extend activated partial thromboplastin time (APTT) and thrombin time (TT), and decrease fibrinogen (FIB) concentration. All of these findings suggest that HEP-LM has a lot of promise as an oral heparin formulation. [56].

Mohsin K, Alamri R*et al*., (2016) were designed the model anticholesterol drug, fenofibrate, LFCS Type III SNEDDS using various oils, watersoluble surfactants, and/or cosolvents (depending on the polarity of the lipids). The developed SNEDDS were evaluated visually and by measuring droplet size. The maximum drug loading was determined by measuring the equilibrium solubility of fenofibrate in the SNEDDS. Dynamic dispersion studies (1/100 dilution) in water were performed to determine how much drug remained in solution after aqueous dispersion of the formulation. The BA of the SNEDDS formulation was tested in rats. [57].

In another study Soltani Y, Goodarzi N*et al*., (2017) Proper ion paired hydrophobic complexes could be prepared and used for the preparation of SNEDDS using a molar ratio of heparin: CPCD (1: 3). Furthermore, using Design-Expert® software, SNEDDS were statistically optimised using central composite response surface methodology. The optimized nano-droplets were morphologically studied using TEM, and the images revealed spherical globules with no sign of aggregation. In vitro release of heparin from nano-droplets revealed a slow rate of drug release in simulated intestinal fluid. The authors suggest that because larger droplets are prepared,

the EE percent is reduced, and the release rate of heparin from SNEDDS prototypes diluted with SGF is faster, it is preferable to protect the SNEDDS prototypes from gastric fluid by using enteric-coated hard gelatine capsules for oral administration. SNEDDS, as a mucus-penetrating drug delivery system, warrant further investigation. It is still unknown how SNEDDS penetrate the mucus layer of the intestinal epithelium, and the effects of physicochemical properties such as size and zeta potential on mucus permeability of nanodroplets should be investigated. Furthermore, the drug release profile of SNEDDS in the mucus layer should be studied in greater depth. It would also be interesting to see how SNEDDS affects trans epithelial electrical resistance (TEER) on Caco-2 cell monolayers, and how this drug delivery system affects tight junctions in the intestinal epithelium. [58].

## CONCLUSION

Several anticoagulants are available orally, and other routes of administration, such as pulmonary and topical, have been investigated. Given the importance of anticoagulants, more safe and effective delivery systems must be researched and developed on a continuous basis. This review concludes that the Self-Nanoemulsifying drug delivery systems (SNEDDS)-based preparation of anticoagulant drugs provide evidence to reduce blood clotting and, as a result, improve drug bioavailability.

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