A COMPREHENSIVE REVIEW ON SUPERSATURABLE SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Lipid-based drug delivery systems are extensively reported in the literature for enhancing drug solubility, permeability, and bioavailability. Self-nanoemulsifying drug delivery systems (SNEDDS) are a superior strategy for enhancing solubility and bioavailability of poorly water-soluble compounds and the most prevailing and commercially viable oil-based approach for drugs that exhibit low dissolution rate and inadequate absorption. However, these formulations have few limitations that include in vivo drug precipitation, inferior in vitro in vivo correlation owing to unavailability of in vitro tests, handling issues of liquid formulation, and physicochemical instability of drugs. These limitations are overcome by potential systems such as supersaturable SNEDDS (S-SNEDDS) which are prepared by addition of precipitation inhibitors into formulated SNEDDS to maintain drug supersaturation post dispersion in gastrointestinal tract. These systems improve drug bioavailability and reduce the inconsistency of exposure. In addition, these formulations also help to overcome the drawbacks of liquid and capsule dosage forms. The S-SNEDDS provides an effective approach for improving the dissolution and bioavailability of anti-cancer agents. In this article, an attempt was made to present an overview of SNEDDS, S-SNEDDS, their mechanism, formulation excipients, recent advancements, advantages, and disadvantages of SNEDDS formulations. The article also focuses on reviewing the application of S-SNEDDS in enhancing the solubility and bioavailability of anti-cancer drugs in cancer therapy.

Keywords: Solubility, Supersaturable self-nanoemulsifying drug delivery systems, Nanotechnology, Precipitation inhibitors, Cancer.

INTRODUCTION

Oral route for drug delivery represents more than 70% of total dosage forms utilized by humans, and this can be related to its convenient and acceptability as a mean for the administration of drug molecules to patients since it associates with a high rate of patient compliance in one hand and economic and flexible dosage design in others [1,2]. One of the most important requisite requirements of drug molecules to be available for systemic absorption is aqueous solubility since that is the nature of GIT fluid. Then, when the drug molecules become solubilized, it has to pass the biological membrane to reach the systemic circulation [3].

Food and Drug Administration (FDA) classifies drug molecules to belong to one of four categories based on their aqueous solubility and ability to pass through the biological membrane, termed as permeability. This classification system is called the Biopharmaceutical Classification System (BCS) [4,5].

Drug molecules that belong to Class II have a problem in bioavailability mainly due to low aqueous solubility. In this class, the rate-limiting step is dissolution process and so choosing of suitable drug delivery, and appropriate additives are crucial to overcome this major obstacle and improve the fraction that will reach the systemic circulation [6].

Many approaches were developed to overcome this issue with a variable degree of success, from these approaches solid self-emulsifying drug delivery system (SEDDS) is extensively tried.

SEDDS out of various strategies available to date, SEDDS belonging to lipid-based technique were proved to upsurge drug dissolution rate and assisted the formations of soluble drug phase. These formulations are filled into soft and hard gelatin capsules easily [7,8]. The self-emulsifying formulation is an isotropic blend of drug, lipids, surfactants, and co-solvent that generate superfine emulsion on agitation in the gastro intestinal (GI) tract [9]. The SEDDS are categorized into two types, namely, SEDDS, and Self-nanoemulsifying drug delivery systems (SNEDDS), based on globule sizes formed on dispersion [10]. SEDDS are formulations that produce a transparent microemulsion of oil-in-water or water-in-oil with a globule diameter <250 nm. SEDDS possess a droplet size of 20–200 nm that is transparent [11]. SNEDDS is a competent, well-designed, and patient compliant technique for sparingly soluble drugs, as it enhances the solubility, dissolution patterns in the GI tract, increases permeability, and enhances absorption [12-14].

SNEDDS MECHANISM OF ACTION

The SNEDDS on administration, followed by gentle agitation arising from gastric movements, forms oil-in-water nanoemulsion immediately and impulsively with particles of nanometric range (<200 nm). These nanoparticles comprising the drug that is previously dissolved in the oil phase provides a superior interfacial surface to facilitate dispersion into GI fluids [15]. This increased interfacial area enhances drug solubility and permeability by altering transport property [16]. Nanosize droplets experience rapid digestion followed by quicker absorption of the drug into the GI tract. SNEDDS dosages range between 25 mg and 2 g [17]. These are effectively encapsulated as single dosage forms which provide greater stability, palatability, and patient acceptance [18-21]. They also possess higher drug loading capacity when compared to other lipid-based formulations.

SELECTION OF APPROPRIATE DRUG CANDIDATES FOR SNEDDS FORMULATION

The challenges faced by a formulator during the formulation of an oral dosage form are to solubilize the drug in the GI tract. SNEDDS improve the rate and scope of drug absorption. SNEDDS approach is applied for BCS Class II drugs that suffer from inferior water solubility and bioavailability [22]. Administration of these drugs in form of lipids enhances their bioavailability by bypassing the absorptive barrier of
reduced water solubility and illustrate dissolution in GI by transferring to the bile-salt mixed micellar phase, through which absorption happens readily [23]. Properties of the drug, including water solubility, log P are not adequate to identify the suitability of lipid-based formulation, as they do not predict the in vivo effects [24]. In SNEDDS formulation, the free energy required for the formation of an emulsion is either little or positive or negative. Hence, emulsification happens impulsively. It is essential for the interfacial structure to illustrate no confrontation against surface shearing such that emulsification takes place. The ease of emulsification may be due to the simplicity of water penetration into a variety of liquid crystalline or gel phases on the droplet surface [25-29].

EXCIPIENTS USED IN SNEDDS FORMULATION

Oils
The oil is used in SNEDDS formulation for solubilizing the lipophilic drug and ease self-emulsification, to augment the amount of drug passing through the intestinal lymphatic system, thus, enhancing absorption. The long and medium-chain triglycerides (LCT and MCT) with varying saturations are employed. The edible oils are not chosen for SNEDDS formulation due to their inability to solubilize larger drug concentrations. Hydrolyzed vegetable oils are used due to the formation of superior emulsification systems with more surfactants accepted for oral administration. They put forward formulation and physiological recompense. New semi-synthetic medium chain compounds, known as amphiphilic compounds that possess surfactant characteristics, are substituting the oils in SNEDDS [30-34].

Surfactants
The orally acceptable surfactants are non-ionic that possess higher hydrophilic-lipophilic balance (HLB). Frequently employed emulsifiers, include ethoxylated polyglycolyzed glycerides and polyoxyethylene oleate. Natural emulsifiers are considered safer than synthetic versions but surfactants possess the incomplete self-emulsifying ability. Non-ionic surfactants have lesser toxicity compared to ionic surfactants and direct to enhance permeability through the intestinal lumen [30-34].

Co-surfactant
The SNEDDS formulations require relatively higher concentrations (>30%w/w) of surfactants, which can be condensed by the addition of co-surfactant. These along with surfactants lower the interfacial tension to –ve value, where it expands to form fine droplets that are consequently adsorbed larger quantities of surfactant and surfactant/co T surfactant till the interfacial tension turns + ve. This process is called “spontaneous emulsification.” The addition of co-surfactants into SNEDDS is not obligatory for most non-ionic surfactants [41]. In SNEDDS, the co-surfactants with HLB values ranging between 10 and 14 are used. Hydrophilic co-surfactant is alcohol with medium-chain lengths, including hexanol, pentanol, and octanol that reduce interface between oil and water that facilitate impulsive microemulsion formation [42-45].

ADVANCEMENTS IN SNEDDS

Supersaturated SNEDDS (S-SNEDDS)
The extent of drug solubility in excipients used for SNEDDS formulation determines the dosage of drug loading. The solubilizing ability of SNEDDS is reduced due to a reduction in lipid content that leads to drug precipitation. Drugs that are highly soluble in surfactants or co-surfactant than lipophilic phase precipitate easily as the solubent ability of these excipients reduces with dilution. Hence, the majority of SNEDDS formulations contain drugs lower than equilibrium solubility. In one, the presence of large amounts of hydrophobic surfactants also facilitates drug precipitation. To overcome this drawback, S-SNEDDS comprising hydrophilic precipitation inhibitors (PIs) were studied [46,47]. These S-SNEDDS reduce precipitation of drugs in the GI tract by attaining a metastable saturated state. This mechanism involves the assimilation of polymeric PIs (PPiS) that are water-soluble, resulting in prolonged precipitation time in comparison to mean absorption time. Polyvinyl pyrrolidone, hydroxypropyl methylcellulose (MC), sodium carboxymethyl cellulose, and MC polymers are some commonly used PPIs. Few drugs precipitate in an amorphous state and demonstrate prominently fast dissolution post precipitation when evaluated in vitro. This indicates that the precipitation of such drugs enhances the bioavailability. Few S-SNEDDS were prepared without the use of PPIs by subjecting the formulations to an alternate “heating and cooling cycle” [48,49]. S-SNEDDS enhance the stability, concentration versus time profile, drug release rate, the scope of absorption, drug bioavailability, half-life, and fate of hydrophobic and less lipophilic drugs [50,51]. Recently S-SNEDDS for simvastatin ezetimibe, silymarin halofantrine, tran-zeravatrol, hydrocortisone, and paclitaxel, were reported to exhibit comparatively higher bioavailability [52-58].

ADVANTAGES OF SNEDDS [59-66]
• SNEDDS enhance the bioavailability of the drug, thus, reducing dosage frequency
• SNEDDS enable selective drug targeting toward precise absorption window in GI tract
• They possess higher drug payload
• SNEDDS manage controlled drug delivery profile
• SNEDDS are highly stable formulation and uncomplicated manufacture techniques
• SNEDDS facilitate a larger surface interfacial area for drug partitioning among oil and water
• SNEDDS facilitate wider drug distribution in the stomach and GI tract, thus, reducing the irritation caused by extensive contact among drug and gut walls
• SNEDDS protect the drug from the aggressive environment in the GI tract
• SNEDDS improve the rate and extent of absorption.

DISADVANTAGES OF SNEDDS [67,68]
• The conventional dissolution techniques cannot be applied for SNEDDS as they are dependent on digestion former to dissolution
• The in vitro models of SNEDDS need further research and validation for strength evaluation
• The in vitro in vivo correlations of SNEDDS must be studied further
• The chemical instability of drugs
• Higher amounts of surfactant used for formulation (30-60%)
• Higher production cost
• Lower drug incompatibility and stability
• Possibility of drug leakage and precipitation.

NANO SCIENCE FOR CANCER TREATMENT
Cancer treatment has observed major advancements in past 30 years due to better understanding of the carcinogenesis process, biology of cancer cells and the tumor micro-environment. The targeted drug delivery has enhanced the prognosis of cancer patients. Most promising way for increasing the survival rate of cancer patients is the use of nanocarriers. Nanoscience is defined by Yang et al as a “discipline that studies the phenomena and manipulation of materials at atomic, molecular and macromolecular level, where the properties differ significantly from those on a larger scale.”

The major drawbacks of systemic chemotherapy include lower drug concentrations in tumor, rapid drug clearance from circulation and toxic side effect on non-cancerous cells. Nanoparticles for anticancer drug delivery comprises nanocarrier and drug. For both nonspecific and specific targeting and delivery, better safety and bioavailability and superior pharmacokinetics.

Nanomaterials size range between 1 and 100 nm with larger surface area to volume ratios. The nanomaterial ideally used for drug delivery must be non-toxic, biocompatible, blood stable, non-immunogenic, non-thrombogenic, and biodegradable. Tumor-targeted nanodrugs enhance the anti-cancer effects and help in overcoming the toxicity of chemotherapy [69-76].
The anti-cancer drug delivery is largely associated with toxicity toward healthy body tissues. The nano transporters used as carriers for anti-cancer drugs enhance the drug therapeutic index, amend the pharmacokinetic profile for improved drug delivery and reduced drug concentration in healthy tissue. The administration of these drugs to tumor sites will overcome the side effect toward healthy tissues and enhance efficiency of the treatment by higher doses of drug to tumor site.

Nanotechnology is a potential delivery system for sparingly soluble antihypertensive agents by enhancing their solubility and bioavailability. These also lead to the progress of novel hydrophobic entities. The biocompatibility, colloidal size, drug targeting, lowered dose size, reduced toxicity, and patient compliance are some important advantages of nanosystems. SNEDDS provide larger interfacial areas for drug partitioning and bioavailability enhancement, which donors need for higher-energy emulsification, in turn, reducing manufacturing cost [77-86].

**S-SNEDDS APPLIED FOR ENHANCEMENT OF SOLUBILITY AND BIOAVAILABILITY OF ANTI-CANCER DRUGS**

The current review emphasizes on the model drugs entrectinib and pemigatinib belonging to BCS Class II (low solubility/high permeability), poses a challenge in achievement of optimal dissolution kinetics from the dosage form. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. Hence, formulation into S-SNEDDS might enhance dissolution characteristics of the model drugs by increasing its release and solubility through S-SNEDDS technique.

Entrectinib is an anti-cancer medication used to treat ROS1-positive non-small cell lung cancer and NTRK fusion-positive solid tumors. It is a selective tyrosine kinase inhibitor, of the tropomyosin receptor kinases (TRK) A, B and C, c-ros oncogene 1 (ROS1), and anaplastic lymphoma kinase (ALK) [87-95].

Pemigatinib is a medication for the treatment of adults with previously treated, unresectable locally advanced or metastatic bile duct cancer (cholangiocarcinoma) with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test. Pemigatinib works by blocking FGFR2 in tumor cells to prevent them from growing and spreading. Pemigatinib belongs to a group of medicines called protein kinase inhibitors. It works by blocking enzymes known as protein kinases; particularly those that are part of receptors (targets) called FGFRs. FGFRs are found on the surface of cancer cells and are involved in the growth and spread of the cancer cells. By blocking the tyrosine kinases in FGFRs, pemigatinib is expected to reduce the growth and spread of the cancer. Both Entrectinib and Pemigatinib are a good choice for the development of SNEDDS formulation for the improvement of solubility and oral bioavailability. Few approved anti-cancer nano-formulations are listed below in Table 1 [96-99].

**CONCLUSION AND PERSPECTIVE**

Supersaturable-SNEDDS are a promising approach for the formulation of poorly water-soluble drugs to enhance their bioavailability through the induction and stabilization by PIs of a supersaturated drug state in the GI fluid. This approach overcomes the main limitations associated with conventional solubilized SNEDDS. To use supersaturable-SNEDDS for a target drug, it is important to understand the in-depth mechanism of precipitation through the supersaturation of the drug. From this, it may be possible to inhibit this precipitation and prolong supersaturation by considering the various factors that influence precipitation, based on this mechanism. More insightful understanding of the mechanisms that control the supersaturation and absorption of poorly water-soluble drugs will be achieved by continuing to explore and develop innovatively improved supersaturable-SNEDDS technology, as well as advancing the current characterization and assessment methodologies. This will enhance the therapeutic potential of a wide range of challenging poorly water-soluble drugs that are yet to be discovered. We hope this review will help develop a desired supersaturable-SNEDDS for a model drug.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest, financial, or otherwise.

**AUTHOR CONTRIBUTIONS**

All authors are contributed equally.

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