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A SYSTEMATIC REVIEW ON BERBERINE-LOADED SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEMS: ADVANCES AND FUTURE PERSPECTIVES

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ABSTRACT

The bioactive isoquinoline alkaloid berberine, which is derived from a variety of medicinal plants, has shown promise pharmacologically, with anti-inflammatory, antibacterial, antidiabetic, and anticancer properties. Its significant first-pass metabolism, low oral bioavailability, and poor water solubility, however, restrict its clinical use. In order to improve the solubility, stability, and absorption of berberine, Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) have become a viable approach. With a focus on important formulation elements, production techniques, in vitro and in vivo assessments, and pharmacokinetic improvements, this systematic review critically assesses the most recent developments in the creation of berberine-loaded SNEDDS.[1] The paper also looks at the significance of lipid-based carriers in targeting particular tissues and highlights the mechanistic insights into SNEDDS-mediated absorption enhancement. Concerns about regulations, scalability, and formulation stability are additional difficulties.

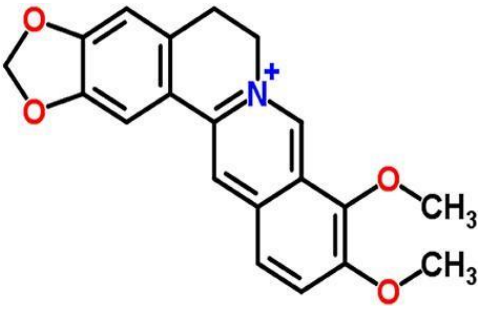
KEYWORDS: Berberine, Self-Nanoemulsifying Drug Delivery System (SNEDDS), Bioavailability enhancement, Lipid-based formulations, Oral drug delivery, Nanotechnology, Phytoconstituents, Pharmacokinetics, Drug solubility, Systematic review, Future perspectives, Herbal drug delivery, Nano Emulsion, Clinical translation, Targeted drug delivery Antihypertensives, Solubility, BCS classification, Excipients.

INTRODUCTION

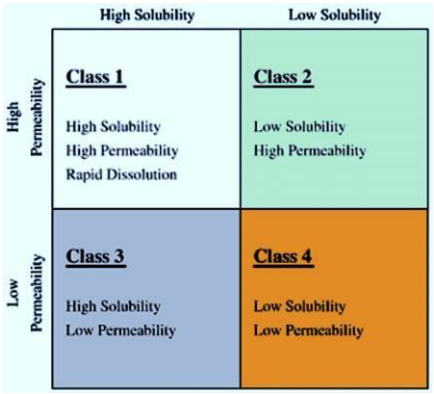
Self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic, thermodynamically stable mixtures composed of oil, surfactant, co-surfactant, and the active pharmaceutical ingredient. These systems are designed to spontaneously emulsify in the aqueous environment of the stomach, resulting in the formation of nanosized oil droplets that solubilize

the drug efficiently. The nanoscale size of these droplets increases the surface area significantly, thereby enhancing drug solubility, dissolution rate, and overall absorption efficiency.[2]

Berberine, a bioactive alkaloid derived primarily from ***Coptis chinensis*** Franch., has been widely used in traditional medicine due to its broad pharmacological effects. It exhibits potent antibacterial, antidiarrheal, antitumor, and hypoglycemic activities. Despite these benefits, berberine's therapeutic potential is limited by its poor water solubility and low oral bioavailability when administered as conventional tablets or capsules.[2]



The objective of this study was to develop a SNEDDS-based oral formulation of berberine to improve its dissolution profile and bioavailability by using the BCS classification **[Fig.1]**. The performance of the formulated SNEDDS was evaluated and compared with that of currently marketed berberine tablets and capsules, with an emphasis on its drug release characteristics.[3]



[Fig.1]: BCS classification.

2. Techniques for Improving Solubility

The first strategy is creating formulations to speed up the initial in-human research without offering a functional connection to these formulations used in clinical trials that may be sold. The second strategy also entails creating formulations.

Fig. 2 lists many methods for improving solubility, most of which entail changing a drug's physical, chemical, or administrative properties.

Scientists have used a variety of methods to change the physical and chemical properties of drugs, such as crystal engineering, drug complexing, reducing the size of drug particles, forming soluble salts of drugs, converting amorphous to crystalline form, supercritical fluid process, use of additives, etc.

To increase medication solubility, formulation techniques such as lipid nanoparticles, liposomes, and SNEDDS were used. The drug's type, absorption location, and dose all play a significant role in the technique choice.[4,5]

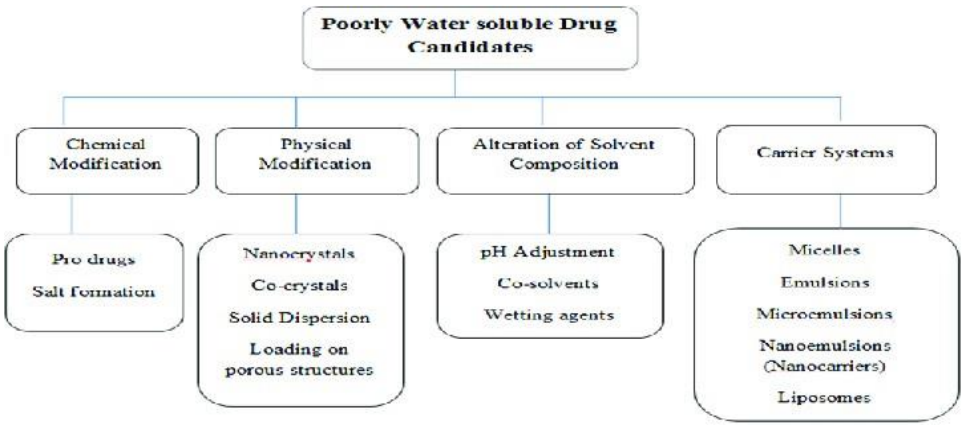


Fig. 2: **Techniques for Improving Solubility.**

3. Challenges with Berberine Delivery.

a. Poor water Solubility. Berberine's extremely low water solubility (less than 1 mg/mL) significantly restricts its ability to dissolve in the gastrointestinal (GI) tract after oral ingestion. It belongs to Class IV medicines (poor solubility and low permeability) in the Biopharmaceutical Classification System (BCS). Even at large oral dosages, this limited solubility leads to inadequate drug levels in the systemic circulation since only dissolved drug molecules may get through the intestinal wall.[6]

b. Extensive First-Pass Metabolism.

Both the intestinal wall and the liver experience substantial first-pass metabolism of berberine following oral delivery, which means that a sizable amount of the medication is metabolically inactivated before to entering the systemic circulation. UDP-glucuronosyltransferases (UGTs) and cytochrome P450 isoenzymes, particularly CYP3A4, are the main players in this metabolic conversion, converting berberine into metabolites like demethyleneberberine, berberrubine, and other conjugated forms that are either pharmacologically less active or quickly removed from the body. Because of this, almost 90% of berberine taken orally is broken down before it has any medicinal effects [7]. The drug's overall bioavailability and peak plasma concentration (C_{max}) are significantly decreased by this thorough pre-systemic clearance. Alternative delivery methods, such Self-Nanoemulsifying Drug Delivery Systems (SNEDDS), have been investigated in order to get around this restriction. By facilitating lymphatic transport and perhaps avoiding hepatic metabolism, SNEDDS can increase the systemic availability of berberine [8]

c. Efflux by P-Glycoprotein (P-gp)

Berberine is recognized as a substrate of P-glycoprotein (P-gp), an ATP-dependent efflux transporter belonging to the ABC (ATP-binding cassette) family, which is abundantly expressed on the apical surface of intestinal epithelial cells. After partial absorption into enterocytes, P-gp actively transports berberine back into the intestinal lumen, thereby reducing its intracellular concentration and limiting its overall absorption. [9] This continuous efflux significantly lowers the effective amount of berberine available for systemic circulation, even if the drug successfully dissolves and initially permeates the intestinal membrane. The presence of this efflux mechanism creates a repetitive cycle of drug uptake followed by expulsion, which makes passive diffusion across the intestinal barrier highly inefficient. Consequently,

innovative drug delivery systems such as Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) have been developed to overcome this challenge by encapsulating berberine within lipid-based nano-sized droplets. These droplets not only protect berberine from recognition and transport by P-gp but may also enhance its intracellular retention and promote absorption via alternative pathways such as lymphatic transport.[10]

d. Low Membrane Permeability

Due mainly to its hydrophilic quaternary ammonium structure, berberine also has low intestinal permeability, which severely restricts its capacity to passively diffuse across the lipophilic membranes of intestinal epithelial cells (enterocytes). Berberine's restricted transcellular transport has been confirmed by experimental research employing models like Caco-2 cell monolayers, which consistently show low apparent permeability coefficients (P_{app}). Further inhibiting the medication's partitioning into and across lipid membranes is the ionic character of berberine, which encourages the creation of a strong hydration shell where water molecules are firmly bonded to the drug. [11] A twofold barrier to effective oral absorption is created by this low permeability and berberine's poor water solubility.

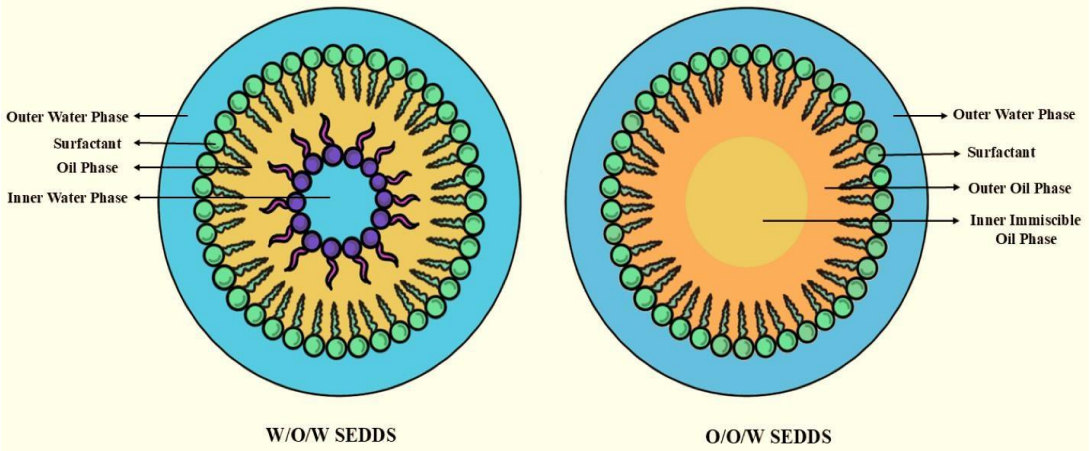
e. Rapid Systemic Elimination

Even when a small fraction of berberine successfully enters systemic circulation, it is rapidly eliminated from the body through metabolic degradation and excretion via the biliary and renal pathways. Pharmacokinetic studies have shown that berberine possesses a relatively short terminal plasma half-life, typically ranging from 1 to 4 hours depending on the administered dose and the formulation used. This rapid elimination is primarily attributed to high hepatic clearance, driven by extensive enzymatic metabolism and active biliary secretion, which collectively lead to a swift decline in plasma drug levels. As a result, maintaining therapeutic concentrations of berberine in the bloodstream often requires frequent administration or higher doses, which not only compromises patient compliance but also increases the risk of gastrointestinal irritation and systemic toxicity. Therefore, developing advanced delivery systems such as Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) becomes essential to prolong berberine's circulation time and improve its overall therapeutic performance [12]

4. Self-Emulsifying Drug Delivery Systems (SEDDS)

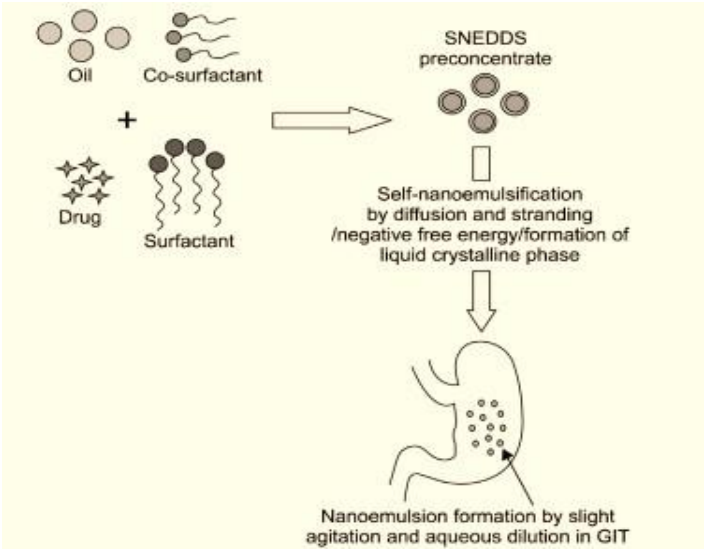
SEDDS, which belong to the lipid-based approach, have been shown to increase the rate of drug dissolution and aid in the development of soluble drug phases out of all the techniques that are now accessible. Gelatin capsules, both soft and hard, are filled with these compositions. An isotropic combination of medication, lipids, surfactants, and a co-solvent, the self-emulsifying formulation produces a fine emulsion when the gastrointestinal (GI) tract is stirred. Based on the diameters of the globules that develop during dispersion, the SEDDS are divided into two types: SMEDDS and SNEDDS [13]

SMEDDS are formulations that result in a clear ***water-in-oil*** or ***oil-in-water*** microemulsion with globules smaller than 250 nm **[Fig.3].** SNEDDS have translucent droplets that range in size from 20 to 200 nm. Because it improves solubility, increases permeability, and improves absorption, SNEDDS is a skilled, well-thought-out, and patient-compliant approach for sparingly soluble medicines.[13,14]



5. SNEDDS Mechanism of Action

After being administered, the SNEDDS causes mild agitation from stomach motions, which instantly and spontaneously creates an oil-in-water nano emulsion with particles of the nanometric range (less than 200 nm). The medicine that has been previously dissolved in the oil phase is present in these nanoparticles, which offer a better interfacial surface to aid in dispersion into GI fluids. The permeability and solubility of drugs are improved by this increased interfacial area, which changes the transport property **(Fig. 4).** Nano size droplets undergo speedy digestion, which is followed by a speedier GI tract absorption of the medication.[15]



(Fig. 4): - SNEDDS Mechanism of Action.

The dose range for SNEDDS is 25 mg to 2 grammes. These are successfully encapsulated in single dose forms, which improve patient acceptability, stability, and palatability. In comparison to other lipid-based formulations, they also have a greater capacity for drug loading.[15]

6. Choosing the Right Drug Candidates for the Formulation of SNEDDS

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. 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. 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. In SNEDDS formulation, the free energy required for the formation of an emulsion is either little or positive or negative. Hence, emulsification happens impulsively.[16,17] 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.[17]

7. Excipients used in SNEDDS Formulation

a. *Oil:* - In SNEDDS formulations, oils are primarily used to dissolve lipophilic drugs and promote self-emulsification, thereby enhancing drug absorption via the intestinal lymphatic pathway. Medium- and long-chain triglycerides (MCTs and LCTs) are commonly used, while regular edible oils are avoided due to their limited solubilizing capacity. Instead, hydrolyzed vegetable oils are preferred as they form better emulsifying systems and are suitable for oral use. Recently, semi- synthetic medium-chain amphiphilic compounds with surfactant-like properties are being used as effective oil substitutes in SNEDDS.[18]

***b. Surfactants:* -** Surfactants used in SNEDDS are typically non-ionic and possess high hydrophilic-lipophilic balance (HLB) values, making them ideal for oral formulations. Common examples include ethoxylated polyglycolyzed glycerides and polyoxyethylene oleate. While natural surfactants are generally considered safer, synthetic non-ionic surfactants offer better emulsification with lower toxicity compared to ionic ones, although their self-emulsifying ability may still be limited.[19]

***c. Co-surfactants:* -** In SNEDDS, co-surfactants are used to reduce the required concentration of surfactants, especially when levels above 30% w/w may cause irritation or instability. When combined with surfactants, co-surfactants lower the interfacial tension to a negative value, allowing spontaneous emulsification into fine droplets, which are stabilized by further adsorption of surfactant or surfactant/co-surfactant combinations until the interfacial tension becomes positive. Although not always necessary with non-ionic surfactants, co-surfactants with hydrophilic-lipophilic balance (HLB) values between 10 and 14 are commonly used. Medium- chain alcohols such as hexanol, pentanol, and octanol serve as effective hydrophilic co-surfactants by reducing the interfacial tension between oil and water phases **[Fig.5].**[19,20]

8. Self-Double Nano Emulsifying Drug Delivery Systems (SDEDDS)

Proteins and the majority of anti-cancer agents cannot be administrated orally as SNEDDS. Studies recommend that SDEDDS that comprises oil-water-oil emulsions are used for the delivery of peptide and protein drugs. SDEDDS are hydrophilic surfactants containing w/o emulsions that produce w/o/w emulsion on dilution with water followed by gentle agitation. SDEDDS preserve peptides and drugs from enzymatic inactivation in gastro intestinal track (GIT), with improved competence and diminished doses.[21]

9. Targeted SNEDDS

Targeted medication distribution can result in increased therapeutic effectiveness and decreased toxicity. Nano emulsions elude mononuclear phagocytes by staying inside the body for extended periods of time. An anionic membrane barrier was the target of cationic droplets. The liver absorbs these formulations, facilitating targeted administration. PEGylation is a process that increases stability by attaching polyethylene glycol (PEG) to a nanodroplet that creates a barrier at the surface where enzymatic degradation is started. Drug retention in the GI tract can also be addressed with HPMC and thiolated chitosan.[22]

Advantages of SNEDDS

a. Enhanced Oral Bioavailability

SNEDDS improve the solubility and dissolution rate of poorly water-soluble drugs, leading to higher absorption and increased bioavailability.

b. Spontaneous Emulsification

Upon contact with gastrointestinal fluids, SNEDDS spontaneously form fine oil-in-water nano emulsions without the need for high shear forces.

c. Improved Lymphatic Transport

Lipid-based nature promotes lymphatic absorption, bypassing the first-pass hepatic metabolism and enhancing systemic availability.

d. Reduced P-gp Efflux

Encapsulation in lipid droplets can reduce drug recognition and efflux by P-glycoprotein (P-gp), enhancing intracellular drug levels.

e. Dose Reduction

Improved absorption may reduce the required dose, minimize side effects and improve patient compliance.

f. Protection of Labile Drugs

The lipid environment protects sensitive drugs from enzymatic degradation in the GI tract.

g. Versatile Formulation

Suitable for both hydrophobic drugs and combination therapies; can be developed in liquid or solid (e.g., solid SNEDDS) dosage forms [23,24]

Disadvantages of SNEDDS

a. Limited Drug Loading

Not suitable for drugs requiring high doses, as the oil and surfactant phases have limited solubilization capacity.

b. Formulation Complexity

Requires careful selection of oil, surfactant, and co-surfactant combinations, and extensive optimization.

c. Stability Issues

Risk of phase separation, drug precipitation, or degradation upon storage or dilution.

d. GI Irritation

High concentrations of surfactants or co-surfactants may cause gastrointestinal side effects like nausea or irritation.

e. Drug Precipitation upon Dilution

If the drug is not sufficiently solubilized or the SNEDDS is not stable, precipitation may occur upon dilution in GI fluids.

f. Scale-up Challenges

Manufacturing at industrial scale can be complex and may require specialized equipment and stringent quality control.[23,24]

10. SNEDDS was used to increase the bioavailability of antihypertensive medications

Hypertension, or high blood pressure, is a serious medical condition that affects around 1.13 billion people globally. Many antihypertensive drugs used to treat it have problems like low bioavailability, short half-life, poor permeability, and unwanted side effects. Therefore, an ideal drug delivery system for such medicines should offer higher bioavailability, lower dosing frequency, better drug targeting, and fewer side effects.[24,26]

In the past, most oral antihypertensive drugs needed to be taken two or three times daily, but newer delivery techniques have helped reduce how often these drugs need to be taken. Technologies like polymer-coated beads, transdermal patches, osmotic pumps, coat-core tablets, sodium alginate beads, Geomatrix systems, and spheroidal oral absorption systems have been used to provide a slow and continuous release of the drug throughout the day to better control blood pressure.[27,28]

However, these sustained-release systems still have some drawbacks. They may cause a delay in the onset of action, inconsistent drug absorption, first-pass metabolism, dose dumping, toxicity, rigid dosing, and high cost.

To overcome these limitations, nanotechnology-based systems have emerged as promising alternatives for poorly soluble antihypertensive drugs. These systems improve solubility, bioavailability, and even allow the development of new hydrophobic drug molecules. They offer benefits such as biocompatibility, small particle size, targeted delivery, lower doses, reduced toxicity, and better patient compliance.

Among these systems, Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) are especially useful. They create a large surface area for drug absorption, improve drug solubility and bioavailability, and require less energy for emulsification, making them cost-effective to manufacture.[29]

11. Future Perspective

The future of SNEDDS lies in its continuous evolution and integration with emerging technologies. Advancements in **solid SNEDDS (S-SNEDDS)** will further improve the stability, portability, and patient convenience of these formulations. The combination of SNEDDS with **targeted delivery strategies**, such as ligand-mediated targeting and pH-responsive systems, is expected to enhance drug selectivity and therapeutic outcomes, especially in diseases like cancer or inflammatory disorders.[30]

Moreover, the use of **machine learning and artificial intelligence (AI)** in formulation design and optimization can accelerate the development process by predicting ideal excipient combinations, droplet size, and absorption profiles. **3D printing** of SNEDDS-based formulations may offer a personalized approach to dosing and release kinetics. Further research into **lymphatic delivery via SNEDDS** can help bypass hepatic metabolism, offering benefits for drugs with high first-pass effect.

Additionally, **regulatory guidance** on SNEDDS needs to evolve to ensure safe and scalable production, particularly for newer excipients and delivery formats. The exploration of SNEDDS for **biologics and peptide drugs** also opens new horizons beyond traditional small molecules.[31]

12. CONCLUSION

Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) represent a promising and versatile approach to overcome the challenges associated with poorly water-soluble and low bioavailability drugs. Their unique ability to form nano-sized emulsions upon mild agitation in gastrointestinal fluids leads to enhanced solubilization, improved absorption, and better therapeutic efficacy. SNEDDS offer significant advantages including reduced dosing frequency, improved patient compliance, and potential for lymphatic transport.

Despite some formulation and scale-up challenges, ongoing advancements in formulation science, nanotechnology, and automation are paving the way for the broader adoption of SNEDDS in pharmaceutical development. As research continues to refine their performance and stability, SNEDDS are poised to play a vital role in the future of oral and targeted drug delivery.[31,32]

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