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SELF-EMULSIFYING DRUG DELIVERY SYSTEMS FOR HERBAL BIOACTIVES: FORMULATION CHALLENGES AND OPPORTUNITIES A DETAILED REVIEW

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ABSTRACT

Self-emulsifying drug delivery system (SEDDS) technology has been developed as a novel lipophilic solution to the current issue of phytochemicals in herbal medicines having restricted bioavailability and low water solubility. BCS classes II and IV include around 60% of commonly used herbal medications and almost 40% of newly discovered bioactive compounds. These medications present a problem for the creation of pharmaceutical formulations. When combined with water and stirred, the homogenous mixture of oils, surfactants, and co-solvents in the SEDDS easily forms an oil-water emulsion.

In this article, a thorough description of fundamental concepts of SEDDS technology, properties of the complex plant extract, and methods for designing these formulations is proposed. The method involves designing the tests, characterizing the formulations, making the pseudoternary phase diagram, and choosing the appropriate components. The mechanisms of action of contemporary SEDDS techniques, such as solidified SEDDS (solid SE-DDS) and supersaturated SEDDS (s-SEDDS), will be taken into consideration. There will be examples of how this technology is used in a number of medications, such as silymarin, curcumin, quercetin, and resveratrol.

Keywords: Herbal bioactives, phytopharmaceuticals, oral bioavailability, lipid-based drug delivery, curcumin, quercetin, supersaturated SEDDS, solid SEDDS, and self-emulsifying drug delivery systems

1. INTRODUCTION

Herbal medicine constitutes a substantial component of health care delivery systems globally. As per WHO, 80% of the world population utilize traditional plant-based medicinal system as the primary health care system **[1].** Over the last two decades, the advancements in phytochemistry and pharmacology have facilitated the isolation and characterization of various bioactive phytochemical constituents found in medicinal plants like flavonoids, terpenoids, alkaloids, and glycosides. These substances exhibit a broad range of biological actions, from anti-inflammatory and antioxidant properties to neuroprotective and antineoplastic effects.

Despite the promising potential of numerous herbal bioactives as medicines, their clinical efficacy remains hindered due to undesirable biopharmaceutical characteristics. Drugs are categorized by the Biopharmaceutics Classification System (BCS) according to their intestinal permeability and water solubility **[2]**. Curcumin, quercetin, resveratrol, silymarin, berberine, and piperine are among the phytochemical elements that fall into either BCS Class II (Low Solubility/High Permeability) or Class IV (Low Solubility/Low Permeability). Consequently, oral bioavailability of such compounds is usually below 5%, thereby, making it difficult to predict their effect on human subjects and dosage requirements.

Several approaches offered by formulation science to overcome issues associated with solubility and permeability include cyclodextrin complex formation, nanoparticulates, solid dispersions, phospholipid complexes (phytosomes), and LBDDS. Due to their capacity to keep the bioactive in its solubilized state throughout the gastrointestinal system, avoid the first-pass impact by using lymphatic routes, and be relatively easy to make, SEDDS have garnered a lot of interest **[3, 4]**.

The preparation of SEDDS based on herbal bioactives poses several challenges, however. Unlike pure chemical substances, herbal extracts contain many components, making the phytochemical content variable. The profile of phytochemicals in any given herbal extract may differ according to factors such as origin, cultivation practices, extraction process, and storage conditions. In contrast, synthetic compounds have a fixed chemical formula, ensuring consistent performance across batches. Furthermore, numerous phytochemicals are unstable under conditions of light, air, moisture, or enzymes, and require the selection of proper excipients and process optimization **[5, 6]**.

The purpose of this review It is crucial to remember that the goal of this review is to give a thorough analysis of the SEDDS technology used with herbal bioactives. It will include various aspects such as the

pharmaceutical importance of SEDDS, methods of formulations, selection of compounds, analysis methods, and complex drug delivery systems.

2. Biopharmaceutical Challenges of Herbal Bioactives

2.1 Aqueous Solubility and Dissolution

As far as compounds transported through the intestine membrane by passive diffusion, the capacity to dissolve in water would be the main determinant of their absorbability into the bloodstream. Polyphenolic phytochemicals usually feature large aromatic structures and numerous hydroxyl groups. While the former facilitates the antioxidative properties of such chemicals and their ability to bind to receptors, the latter contribute to the formation of crystals and reduce their water solubility. The solubility of curcumin in water amounts to merely 11 ng/mL under physiological conditions, whereas the same parameter of quercetin equals 7.7 μg/mL **[7]**. In either case, the results fall well below the threshold necessary for optimal absorption into the bloodstream.

2.2 Gastrointestinal Permeability

The size of molecules, lipophilicity, ability to establish hydrogen bonds, and sensitivity to efflux via P-glycoproteins (P-gp) and Multidrug Resistance-associated proteins (MRP) are some of the factors that affect the permeability across the enterocytic membrane. For example, quercetin and epigallocatechin gallate are known substrates for P-gp-mediated efflux mechanism. This means that these drugs are actively secreted from the cell back into the intestinal lumen, hence lowering the amount of the drugs absorbed **[8]**. Encapsulation of drugs within liposomes helps overcome efflux problem by saturation of the transporters.

2.3 First-Pass Metabolism

The existence of sufficient metabolic pathways before the systemic action of medications is another significant issue related to this element. Curcumin, on the other hand, is extensively metabolized by glucuronide and sulfate conjugates, which renders it ineffective because of the first-pass action upon oral drug administration **[9]**. The two important metabolic processes responsible for the ineffective nature of resveratrol include sulfation and glucuronidation. However, the enterohepatic cycle of silymarin is well established. It should be mentioned that one of the major benefits of formulating SEDDS involves the ability to utilize the lymphatic pathway.

2.4 Complexity of Herbal Extracts

The production of a functional pharmaceutical formulation using the herbal extract is quite a difficult task due to the heterogeneous nature of the chemical compounds found in the plant extracts. The standardization of the extract of turmeric may involve the use of different curcuminoids

(curcumin, bisdemethoxycurcumin, etc.) in different amounts, as well as other components like essential oils, polysaccharides, and proteins in different amounts. In addition, the presence of multiple flavonolignans in the extract of milk thistle (also referred to as silymarin) poses a problem to the formulation of SEDD because of different chemical properties of the molecules (different log P values, different molecular weights, and polarity) **[10]**.

Table 1:

Compound	MW (g/mol)	log P	Solubility	BCS Class	Key Challenge
Curcumin	368.4	3.29	~11 ng/mL	Class II/IV	Rapid metabolism, photodegradation
Quercetin	302.2	1.54	7.7 µg/mL	Class II/IV	P-gp efflux, low solubility
Resveratrol	228.2	3.10	3 mg/L	Class II	Rapid glucuronidation
Silymarin	482.4	1.90	<50 mg/L	Class II/IV	Multi-component extract
Berberine	336.4	-1.3	~0.7 mg/mL	Class III/IV	P-gp efflux, membrane retention
Piperine	285.3	3.26	40 mg/mL	Class II	Rapid hepatic metabolism

3. Fundamental Principles of SEDDS

3.1 Definition and Classification

A homogenous mixture of lipids, surfactants, and co-surfactants/co-solvents that, when combined and/or physically shaken with an aqueous media, automatically forms an emulsion is known as a SEDDS. The most used classification scheme for lipid-based formulations is the Lipid Formulation Classification System (LFCS). Lipid-based formulations are divided into four groups by LFCS according to their physicochemical properties and constituent parts **[42]**.

TG-only/glycerol-based oily formulations (TG = Triglycerides) are oily formulations without any surfactant and belong to type I and are formulated using bile-mediated emulsification. Type II SEDDS are formulated using lipid (triglyceride) and hydrophilic surfactants (HLB < 12) and generate coarse emulsions upon mixing with the aqueous phase. Type III formulations are developed using lipid (triglycerides) and water-miscible surfactants (HLB > 12) along with co-solvents to generate fine emulsions/microemulsions. Surfactants and co-solvents are combined in type IV formulations, which do not have an oil phase. Nevertheless, self-emulsification can still occur in the absence of an oil phase **[3, 11]**. Type III and type IV formulations that produce droplets smaller than 100 nm and with the least amount of turbidity make up SMEDDS (Self-Micro Emulsifying Drug Delivery Systems).

3.2 Mechanism of Self-Emulsification

From the perspective of thermodynamics, another important factor that has been of significance in spontaneous emulsification

is the nature of the process involved. According to the idea, which is based on the literature currently available on the subject, spontaneous emulsification happens when there is a brief negative interfacial tension between water and oil, which is equal to zero and results in the formation of interface and droplets **[12]**. At the interface between oil and water, amphiphilic surfactants help reduce the energy involved in the formation of droplets; therefore, such an emulsion created becomes stable and is resistant to coalescence and Ostwald ripening.

SEDDS underwent gradual dilution in water due to its interaction with the aqueous environment (stomach and small intestine). Gradual dilution of SEDDS due to peristaltic movement in the digestive tract led to the formation of an emulsion of SEDDS. The smaller droplets provided 10,000 times more surface area compared to larger-sized coarse emulsions (droplets). This made it possible for the medications to dissolve quickly in the solvent and made it easier for them to interact with the intestinal mucosa **[4]**. Additionally, the presence of lipids in the colloidal dispersion enhances the production of phospholipids and bile acids, which further stabilize the suspension and micellarly solubilize the hydrophobic molecules.

3.3 Lymphatic Absorption and Bypass of First-Pass Metabolism

An additional natural advantage that SEDDS offer is the pharmacokinetics of drug transportation within the body by enabling the passage of drugs in the gut through the lymphatics. As noted above, if a person ingests long chain fatty acids (C14-C22) through food, then they will be converted into chylomicrons before they are transported to the 49 25 40 lymphatics **[13]**. Consequently, if medications are given along with long-chain fatty acids, they will enter the bloodstream straight from the lymphatics without going through the liver's first-pass action. This is due to the fact that some herbs, such as curcumin (first pass effect = 99%), suffer significantly from these phenomena in traditional or aqueous preparations.

4. Components of SEDDS and Selection Criteria

4.1 Oils

The oil phase of SEDDS serves as the main solubilizer of lipophilic bioactive compounds. The oil phases can be mainly classified into two groups depending upon their chain lengths and saturation levels: (1) Medium chain triglycerides (MCT), such as Miglyol 812® or Captex 355® (from coconut or palm kernel oil), which are readily hydrolyzed by stomach and pancreatic lipase enzymes, form fine emulsions, and are not highly dependent on bile salt formation during absorption **[14]**. Long chain triglycerides (LCT), such as

soybean oil, corn oil, and olive oil, have relatively poor solubilization properties of lipophilic substances compared to hydrocarbons.

Intermediate glycerols of fatty acids such as Labrafil M1944®, Labrafac PG®, Capryol 90® and Maisine CC®, comprising of one mono/diglyceride and propylene glycol esters, possess both oil solubilizing properties and mild surfactant effect, making them ideal candidates for SEDDS, where both solubility and emulsification become effective at reduced concentrations of surfactants **[15]**.

For determining the oil phase for the bioactive compounds from herbs, solubility tests for the compounds of the candidate oils must be done using equilibrium solubility testing methods. If there is an extraction from multiple compounds from herbs, only the index marker compound in the herb extract, such as curcumin in turmeric extract, will serve as the basis for determining the candidate excipient, together with avoiding negative interactions between herb extract components and the candidate excipient.

4.2 Surfactants

Surfactants work as the driving force for SEDDS by reducing interfacial tension between both phases and by stabilizing emulsion droplets. Ionic surfactants are preferred less than non-ionic pharmaceutical surfactants in oral preparations because non-ionic surfactants have lower toxicity and irritability towards the mucus lining. Cremophor EL® (Polyoxyl 35 castor oil), Tween 80® (Polysorbate 80), Cremophor RH40®, Labrasol ALF®, and Kolliphor HS 15® are a few examples of non-ionic surfactants **[16]**. It is very significant to choose a surfactant with an appropriate HLB (Hydrophilic-Lipophilic Balance) value, as it can dictate the type of emulsion formed and droplet size (10-15 HLB values forming oils-in-water emulsion with smaller droplets).

It is crucial to remember that in order to achieve the desired droplet size and self-emulsification performance, the ideal amount of surfactant must be utilized. However, high amounts of surfactant (>60% w/w) may irritate the stomach, precipitate the drug in case of limited solubility when diluted, and react with the lipid bilayers in the intestine. The minimum amount of surfactant needed to achieve the above specifications will be determined through dilution studies **[42]**.

4.3 Co-solvents and Co-surfactants

There are various Co-solvents and Co-surfactants, including polyethylene glycols (PEG), which have molecular weights of 400 and 600, and Transcutol HP® (diethylene glycol monoethylether), among others, such as ethanol, propylene glycol, and Labrasol ALF®, all serving several purposes, such as decreasing the HLB of the

main surfactant systems to an optimum level, hence minimizing the formulation's viscosity, enabling easy emulsification, enhancing the drug's solubility, and improving the wetting of solid herbal extract particles **[17]**. Furthermore, co-solvents are also used to prevent crystallization of drugs in the state of transient supersaturation created by SEDDS dilution.

5. Formulation Challenges Specific to Herbal Bioactives

5.1 Compositional Variability of Herbal Extracts

The largest hindrance in creating an FDD using single drug lipid formulations is the difficulty in controlling the chemical profile of the extract obtained from plants because there are several parameters that influence the chemical profile. The parameters include genetic makeup of the variety, soil quality, altitude, rainfall, harvesting season, post-harvesting procedures, and extraction technique. The percentage of curcuminoids present in turmeric can vary from 60% to 80% in different preparations **[10, 18]**. This makes it difficult to establish a standard excipient to drug ratio when formulating the drug. Therefore, formulation procedures should allow for such variations.

5.2 Chemical Instability of Phytochemicals

Further, many high-value herbal bioactive agents are characterized by poor chemical stability. Thus, for instance, curcumin is highly unstable owing to fast alkaline hydrolysis and photolytic degradation, hence giving the substance a shelf life of less than 30 minutes under proper formulation and room temperature storage, and limiting its medicinal applications **[7]**. Resveratrol is unstable owing to the occurrence of cis-trans photoisomerization that reduces its biological activity. The volatile and unstable oxidative nature of some compounds such as thymol, eugenol, and carvacrol limits the medicinal application of essential oils. Further, EGCG is prone to oxidative degradation especially within pH neutral to slightly alkaline conditions. Such characteristics greatly dictate the extent of protection offered by the SEDDS formulation to such agents.

5.3 Drug-Excipient Incompatibilities

Commonly present in herbal extracts are functional groups that are chemically reactive (e.g., phenolic hydroxyl groups, Michael acceptors, nucleophilic nitrogen groups). Functional group reactivity can lead to the production of adducts between extract and excipient functional groups. Examples of such interactions include PEGylation (which involves reaction with the glycerol-based excipients using polyethylene glycols) and the production of esters between excipients containing glycerols and also the oxidation processes driven by metal ions present in commercial excipients have all been observed **[19]**.

Therefore, interaction studies should be done at the early stages of the formulation using DSC, FTIR, and HPLC stability-indicating assays.

5.4 Simultaneous Solubilization of Multiple Actives

designing SEDDS using phytochemical extract, such as Ginkgo Biloba Extract EGb 761 (standardized to contain flavonol glycosides and terpenes), requires the formulation to sustain solubility of all the bioactive constituents in solution. Hence, there will be competition amongst lipid phase/solutes concerning solubility, resulting in disparity in the proportion/percentage of each constituent within the formulation. Consequently, the phytochemical profile of the herbal extract will not match that expected to be achieved from the SEDDS delivery system, thus failing to provide for the synergy/additive pharmacology of these bioactive compounds, depending on specific proportions of each component **[20]**. This problem has been encountered during development of silymarin-based SEDDS because of great disparity in the lipid solubility of silibinin (the most active flavonolignan) and iso-silibinin.

5.5 Precipitation upon Dilution

The process of the disintegration of SEDDS in aqueous media in the GIT, commencing from an isotropic medium with a high concentration, diluted 100-1000 times, to attain dispersion. The effectiveness of SEDDS in solubilisation would be compromised during this dilution process because the dilution of the cosolvents would induce supersaturation beyond the drug solubility in SEDDS **[21]**. In cases where the SEDDS is devoid of a suitable precipitant inhibitor, precipitation would be instantaneous, thereby nullifying the benefits achieved from increased solubility of the drug through the use of SEDDS. This process is much more complicated if herbal extracts that contain multiple chemical compounds with different supersaturation and nucleation potentials are used.

6. Formulation Development and Optimization

6.1 Equilibrium Solubility Screening

Formulation development involves the initial step of conducting a systematic solubility test of potential oils, surfactants, and cosolvents. In conducting the solubility tests, the excess quantity of the drug or extract is combined with individual excipient solutions; the mixtures are left to reach equilibrium in 72 hours at a temperature of 37°C with intermittent stirring; and the supernatants are quantitatively analyzed through HPLC **[22]**. Excipients that show maximum capacity to dissolve the marker compound(s) are considered first for inclusion in the formulation. Solubility testing will provide data for a preliminary list of excipients that

may be included in the formulation, while at the same time estimating the likely concentrations of those excipients.

6.2 Diagrams of Pseudo-Ternary Phases

Studying the system's phase behavior using a pseudoternary phase diagram is crucial to developing SEDDS. The triangle's three vertices are water or simulated gastric/intestinal fluid, oil, and an efficient mixture of surfactants and/or co-surfactants (Smix). Water is used to create a variety of formulations with different compositions, which are then assessed visually or with instruments according to the self-emulsifying quality requirements (such as clear, semiclear, or muddy) **[23]**. The phase diagram's data indicates the self-emulsification region, which helps determine the ideal oil:Smix ratio.

The proportion of Smix with surfactant or co-surfactant (Surfactants to Co-surfactants) is the key factor to obtain an optimum output of the self-emulsification region.

6.3 Design of Experiments Approaches

Using the phase diagram mapping, it is feasible to select an appropriate area in which to formulate the SEDDS using the composition method In terms of the DoE method's real application, optimization can be carried out using response parameters such droplet size (Z-average diameter), polydispersity index (PDI), emulsification duration, percentage drug release, and zeta potential **[24]**. DoE can be carried out using the response surface methodology (RSM) and desirability function optimization. In this method, the simultaneous optimization of the response parameters is conducted to provide an optimized formulation. ANNs and GAs are the recent methodologies used to optimize the SEDDS that contain at least four components.

7. Characterization Methods

7.1 Zeta Potential and Droplet Size Analysis

DLS is the primary technique used to ascertain the hydrodynamic size distribution of the SEDDS when it is diluted with water. After correct formulation, the z-average values should fall between 50 and 200 nm for SMEDDS and between 200 and 5 μm for SEDDS. Since the zeta potential indicates the amount of electric charge that the droplet or droplets possess, it will be appropriate to measure it. This will allow one to determine the stability of the droplet based on the physical stability obtained through measurement, which in this case should be of ± 30 mV and above **[25]**. Zeta potential measurement is greatly reduced when dealing with steric stabilized SEDDS with non-ionic surfactants, making all other stability measurement methods highly relevant.

7.2 Self-Emulsification Efficiency Assessment

The grading scale method created by Craig *et al*. and later developed by others consists

of visual grading scales with a specified dilution of 5X, 10X, 100X, 1000X in three solvents (water, 6.8 pH phosphate buffer, 0.1 M HCL) **[26]**.

Grading makes it possible to provide different grades (A to E) based on the time needed to create an emulsion, types of emulsion: clear-blue or coarse emulsions, and precipitation of the drug(s). The highest grade (grade A) will show the self-emulsification and clarity of emulsification in one minute. There are two other methods for testing such emulsification: Turbiscan® and Spectrophotometric Transmission tests.

7.3 Drug Release in Vitro

The Type II dissolution apparatus (paddle method) is used to measure the drug release from SEDDS utilizing biorelevant dissolution media such as fed state simulated intestinal fluid (FeSSIF) and fasted state simulated intestinal fluid (FaSSIF) at a rotation speed of 75 rotations per minute. Simulated intestinal fluids in the fed and fasted states contain phospholipids and bile salts, which more closely resemble the physiochemical conditions seen in the body than merely an aqueous medium. When creating formulations including lipids, fasted state and fed state dissolving media are essential because variations in bile salt concentrations might result in significant differences in micellar solubilization and stabilization of emulsion droplets. As a consequence, SEDDS must keep the bioactive compound in dissolved (supersaturated) form without forming any precipitation **[27]**.

7.4 Testing for Thermodynamic Stability

A number of techniques, such as heating/cooling (at 4°C and 45°C for six runs each), freezing/thawing (-21°C and +25°C for three times each), and centrifugation (3,500 rpm for thirty minutes), can be used to examine the stability of the thermodynamics of SEDDS. Phase separation, drug crystallization, and any changes that may occur in terms of the material's properties, such as viscosity, will all be used to identify thermodynamic instability **[42]**. The ICH recommends certain parameters for extended stability tests, such as 25°C and 60% relative humidity (RH) and 40°C and 75% RH, among others.

8. Advanced SEDDS Formulation Strategies

8.1 Supersaturated SEDDS (s-SEDDS)

One of the unique characteristics of the Self Emulsifying Drug Delivery System of Supersaturated, commonly called "SEDDS," is its capability of utilizing the "spring and parachute effect" theory that helps increase the absorption potential of supersaturated drugs. Spring effect is attained where the drug formulation attains a concentration beyond the equilibrium solubility of SEDDS; this can be done through the use of amorphous and/or

nanocrystalline drug formulations. The parachute effect is achieved through precipitation inhibition using hydrophilic polymers, e.g., HPMC, PVP, and Soluplus® **[21, 28]**.

It is also important to note that the fast crystallization of the super saturated solution of herbs such as quercetin and apigenin happens naturally, which means that the right precipitating agent needs to be selected. It should also be noted that the utilization of s SEDDS has been responsible for doubling the time taken for retention of the drug within the super saturated solution. This was achieved through 2-4 times increased duration when compared to that of regular SEDDS of curcumin and resveratrol **[29]**. HPMC can also be utilized with curcumin because of hydrogen bonding.

8.2 Solid SEDDS (S-SEDDS)

Some difficulties associated with liquid and semi-solid SEDDS for pharmaceutical applications include dose uniformity, container compatibility, stability, and compliance. Tabletting, encapsulating, and granulation of SEDDS, apart from solving these problems, ensures that the self-emulsification feature remains intact. There are four methods available for solid SEDDS product manufacturing. Spray drying of the SEDDS formulation onto solid carriers such as Aerosil 200®, Neusilin US2® or Sylysia 320® is one of the methods of SEDDS formulation manufacturing **[30]**. Melt extrusion, using polymers such as Kollidon® VA64 or Soluplus® as matrix polymers is another method of manufacturing solid SEDDS formulations.

The third method of SEDDS production is adsorption of the liquid or semi-solid SEDDS formulation to silica or calcium silicateIt should be emphasized that the most crucial. The S-SEDDS's solid matrix's capacity to hold the greatest amount of liquid SEDDS while preserving its and tablettability independent of how gastrointestinal fluid affects the drug's release from the solid matrix **[31]**. Oil adsorption capacity (oil retention index) can be considered as one of the key characteristics for assessment of solid carriers. It should be stressed that the oil adsorption capacity of mesoporous silica (such as Neusilin US2®) is much higher than adsorption capacity of conventional silicasBecause of their enormous specific surface area and pore size management, mesoporous silica materials can carry significantly more oil (up to 1.5–2.0 g/g) than other silica materials. This is one of its main advantages.

8.3 Nanostructured and Nanoemulsion-Based Systems

Nanoemulsions are incredibly small, thermodynamically or kinetically stable emulsions with droplet sizes smaller than 100 nm. Higher surface area for active ingredients, optical clarity, increased drug

load capacity, and possibility for improved mucosal penetration is some of their distinctive features as compared to standard SEDDS formulations **[32]**. When creating these nanoemulsions from plant extracts, high energy methods like homogenization/microfluidization and low energy methods like spontaneous emulsification and phase inversion can be used, enabling the creation of such formulations for a variety of lipophilic herbal products. Nanostructured Lipid Carriers (NLCs) are structures made of a combination of liquid and solid lipids that have a higher drug loading capacity and some of the special characteristics of solid lipid nanoparticles.

9. Applications to Specific Herbal Bioactives

9.1 Curcumin

One of the advantages that the efficacy of curcumin (diferuloylmethane) has is the fact that it has been the most researched phytochemical for usage in SEDDS formulation, while it also has good pharmacological properties but poor bioavailability. The average bioavailability of curcumin when used orally in its natural state by the human body is less than 1% **[7, 9]**. Several SEDDS/SMEDDS preparations for curcumin have been found to consistently increase bioavailability between five times and forty times when compared with regular curcumin, both in animal and human trials. One such formulation includes combining curcumin SEDDS with a phospholipid complex known as phyto-some which results in increased solubility and/or partitioning through the intestinal barrier. In an experiment involving Longvida and Meriva curcumin, a marked increase in blood plasma concentration was seen.

9.2 Quercetin

Onions, apples, and several other medicinal plants like Sophora japonica contain quercetin, an active flavonoid molecule with a number of pharmacologically beneficial qualities, including anti-inflammatory, antioxidant, and anticancer activities. However, research has shown that humans' oral bioavailability of quercetin varies greatly, ranging from 0 to 50%. Furthermore, quercetin-based solid self-emulsifying drug delivery systems (SEDDS) with Transcutol HP® as the co-solvent, Cremophor EL® as the surfactant, and Capryol 90® as the oil produced 85–120 nm mean droplet sizes and nearly full release in biorelevant media in 45 minutes, resulting in a 3.5-fold increase in relative oral bioavailability in rats compared to quercetin suspension **[8]**.

9.3 Resveratrol

Due to its potential cardiovascular, neuroprotective, and anti-aging effects through activation of SIRT1 and modulation of the NF-κB pathway, resveratrol (3,5,4'-

trihydroxystilbene), a polyphenol found in a number of fruits, including berries and grapes, as well as in the roots of the plant Polygonum cuspidatum, has garnered significant attention. Because of its quick metabolism in Phase II, resveratrol's high passive permeability (Papp ~20-30 $\times 10^{-2}$ cm/s) leads to poor oral bioavailability. As a result, conjugates that are mostly sulfated and glucuronidated develop in plasma **[33]**. SEDDS containing PEG 400, Captex 355®, and Labrasol® as a surfactant (which can inhibit P-gp) significantly decreased resveratrol sulfation and raised resveratrol plasma levels by 2.5 times.

9.4 Silymarin

Silymarin (which is an active substance derived from Silybum marianum plant or Milk Thistle containing four distinct flavonoids namely: silibinin, iso-silibinin, silicristin, and silidianin), is a widely used herbal drug due to its hepatoprotective properties. Because of the poor solubility and bioavailability (20-50%) of silymarin, the need to continue formulating it persists **[34]**. The formulation of SEDDS of silymarin is further made complicated because the four bioactive compounds exhibit different degrees of lipophilicity (silicristin having log P of ~1.9 and silibinin ~2.4). SEDDS formulations of silymarin employing soybean oil, Tween 80®, and polyethylene glycol 400 can boost solubilization and bioavailability two to three times higher than that of the commercial medicine Legalon®.

10. Stability Considerations

10.1 Physical Stability

The following four points are stated to be the factors that lead to the instability of drug products developed by SEDDS technology based on the physical instability of the drug. Phase separation or phase break down, creaming or puddling, flocculation or particle clustering, and lastly, Oswald ripening in the emulsion following dilution. In addition to the four SEDDS formulation-related physical characteristics listed above that could affect the drug product's stability during production, there are other pre-concentrate-related physical characteristics that could affect the concentrate's stability during manufacturing. These include the presence of moisture in the air leading to poor visibility and low viscosity of the concentrate, changes in temperature leading to phase inversion and changes in fats, and migration of the plasticizer from the capsule shell to the SEDDS concentrate. Although hard gel capsules tend to be more resistant to moisture content compared to soft gel capsules, hard capsules containing high surfactant concentrations tend to become brittle and therefore unable to hold all the ingredients in a viscosified form **[35]**.

10.2 Chemical Stability

However, it is important to acknowledge that the chemical stability of the active

components of herbal medicine within SEDDS formulation depends on four essential elements. These include moisture content, which is usually expressed in terms of water activity, oxygen content in the formulation, pH, and presence of metals. Antioxidants that are normally used to prevent oxidation reactions of drugs include butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA). Examples of other antioxidants include ascorbyl and tocopheryl palmitate **[36]**.

Ethylenediaminetetraacetic acid (EDTA) is one type of chelating agent that can be added to the medication formulation during production to guarantee that no free metal ions are present. Because nitrogen gas is used in the inerting process, the drug's oxidative shelf life will rise during processing. When a drug's formulation is photostable, such as when it contains curcumin and resveratrol, amber bottles or photostable polymers must be used for packaging.

11. Regulatory Perspectives

However, regulations and policies on herbal medications prepared using SEDDS are not uniform from one nation to another. They even vary depending on whether the medication falls under the category of drugs-based formulation or botanical formulation, nutraceuticals. When it comes to policies applicable to the classification of botanic drugs in the US, FDA – Botanical Drug Guidance is used. This implies that in order to qualify for recognition, the quality of herbal formulations must be consistent **[37]**.

The quality guidelines for the preparation of standardized extracts of herbal substances for SEDDS formulation have been derived from EMA Guidelines for Pharmaceutical Development of Medicines for Paediatric Use, and other quality guidelines provided by the HMPC for assessing the quality of a drug product in Europe. Quality control of SEDDS formulations produced using herbal ingredients will involve evaluating not only the analytical properties of the standardized herbal extracts, but also the drug delivery system's effectiveness. It is essential that the standardized extract (defined marker compound concentrations and fingerprint profiles, based on HPLC-DAD and/or HPLC MS analysis) be used for obtaining consistent results for different batches. Furthermore, in order to account for the impact of matrix, it is essential to validate analytical techniques for determining the concentrations of the herbal active in the lipid matrix in accordance with the ICH Q2(R1) standards **[38]**.

According to toxicology, every component of SEDDS must be either generally regarded as safe (GRAS) or have an acceptable daily intake (ADI) that is appropriate for the dosage and period of application. High surfactant concentrations may cause mucosal permeability, hence safety testing is

necessary before using them in clinical settings.

12. Future Directions

There are several directions for development of research in the area of SEDDS based on herbs that should be undertaken on a short-term basis. For example, QbD-based approach in the formulation of SEDDS is the first direction; the objective here is to identify and characterize CQA, CPP, and to build up the design space via conducting systematic experiments – all these tasks constitute the major opportunity for the development of a new generation of SEDDS of plants that will be easier to regulate; coupling this technology with IVPBPK could contribute to minimizing the necessity for in vitro animal studies **[39]**.

The second direction of research into SEDDS relates to their targeted delivery to specific organs of the body. Specifically, several techniques to attach adhesion mucosal protein such as chitosan to the surface of particles and receptor targeting ligands have been identified and considered attractive, although further development effort needs to be made **[40]**.

Thirdly, there is the issue of growing use of green chemistry strategies in the creation of emulsifier modifications known as SEDDS excipients, which consist of saponins, lecithin, and glycolipids found in plants because of their environmental advantages as well as the fact that they are not regulated. Finally, advancements in machine learning and high throughput screening systems will play an important role in developing herbal SEDDS **[41]**.

13. CONCLUSION

One of the most adaptable and practical ways to increase the oral bioavailability of the natural substances included in herbals is through the use of SEDDS. The technique has strong physical chemistry foundations, has been proven effective across many phytochemical classes, and offers promising possibilities for clinical applications in many human pharmacokinetic trials.

Herbal matrices pose particular difficulties, such as variations in composition, instability, the need to dissolve multiple components, and the risk of interactions between the active compound and the excipients. A specialized approach that will extend beyond conventional drug formulation methods for single-molecule synthetics is required to overcome these difficulties. The combination of screening for solubility, optimization using Design of Experiments techniques, in vitro tests based on biological relevance, and comprehensive stability testing represents an effective methodological solution.

Super-SAT SEDDS as well as solid SEDDS are some of the other advanced platforms that expand the scope of this delivery system to cater to the needs of difficult compounds. The development of regulatory guidelines

with respect to botanical medications along with the rising need for clinically evaluated herbal medications provides a conducive ground for investing in this area.

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