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A Systematic Review on "Self- Micro Emulsifying Drug Delivery Systems (SMEDDS) for Herbal and Plant-Based Drugs: Enhancing Solubility and Bioavailability"

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KEYWORDS

Poorly water-soluble drugs, Biopharmaceutical classification system (BCS), Self-micro-emulsifying drug delivery system (SMEDDS), Solid Self-micro-emulsifying drug delivery system (S-SMEDDS), Liquid micro-emulsifying drug delivery system (L-SMEDDS).

ABSTRACT:
The rise of modern drug discovery has led to the identification of numerous lipophilic drug candidates with poor water solubility, posing challenges in achieving optimal oral bioavailability. Micro- and nano-based drug delivery systems, particularly Self-Emulsifying Drug Delivery Systems (SMEDDS), have emerged as effective solutions to enhance solubility and absorption.This brief review highlights key concepts of SMEDDS and their application in herbal and plant-based drug formulations. It outlines formulation strategies, compares phytopharmaceuticals with synthetic drugs in SMEDDS platforms, and discusses challenges such as variability, poor stability, and regulatory issues in the development of herbal drugs. Literature reports demonstrate improved solubility and bioavailability of herbal actives using SMEDDS.The paper also summarises current research, marketed formulations, and future directions aimed at overcoming limitations and optimising the delivery of both herbal and synthetic drugs using SMEDDS.

INTRODUCTION

Herbal medication products have been utilized for centuries as a primary form of healthcare in many cultures worldwide. Derived from plants and plant-derived materials, these products offer a rich source of bioactive compounds with potential therapeutic benefits. The use of herbal medicines spans diverse traditional systems, such as traditional Chinese medicine (TCM), Ayurveda, and indigenous healing practices.[1] In recent years a substantial fraction of phytoconstituents is reported to have poor aqueous solubility that often leads to the challenges like low oral bioavailability, high intra and inter subject variability and lack of dose proportion Advances in In- vitro screening methods like combinatorial chemistry are leading to the emergence of many potential chemical components with marked therapeutic activity. [2][3]In recent years, the formulation of poorly water-soluble compounds

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presents interesting challenges for formulation scientists in the pharmaceutical industry.[4][5] According to the World Health Organisation, 80% of people in developing countries depend on traditional medicinal practices to meet and/or supplement their basic health needs. Although the advancement of a new approach to drug discovery has led to many compounds in clinical development being upregulated, nearly 42% of compounds accepted in the market and approximately 92% of compounds under discovery are less water-soluble, have inadequate intestinal absorption, and will suffer from low oral bioavailability.[6] In this review, we briefly describe the basic concept of self-emulsifying drug delivery systems, mainly the application of SEDDS in plant and herbal drugs and Literature updates on various reports of Solubility /Bioavailability enhancement using herbal drugs self-emulsifying delivery system formulations**.**

Fundamentals of Self-Emulsifying Drug Delivery Systems (SEDDS) [7]

Mechanism of Action:

Explanation of how SEDDS form oil-in-water emulsions when exposed to aqueous environments (e.g. gastrointestinal fluids) Self Self-emulsifying processes are related to the free energy, 5894. According to Reiss 95 (1975),[8] the theory of Formation of microemulsion shows that emulsification occurs when the entropy change that favours dispersion is greater than the energy required to increase the surface area of the dispersion, and the free energy (ΔG) is negative. The free energy in the micro-emulsion formation is directly proportional to the energy required to create a new surface between the two phases and can be described by the equation [9][10]

$\Delta G = \Sigma N \pi r2 \sigma$ ……. (1)[11]

Where, ΔG is the free energy associated with the process, N is the number of droplets of radius r, and σ represents the interfacial energy after a certain time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. To stabilise emulsions, emulsifying agents are added which reduces the interfacial energy, as well as provide a barrier to prevent coalescence. [12]

Methods for Discovery[13]

Discovering and creating therapeutics from natural substances found in plants is an intricate and diverse journey that encompasses several essential stages, each of which has a vital part in transforming the potential of botanical chemicals into successful medications. Below is a thorough analysis of these fundamental techniques for exploration (Fig. 1)

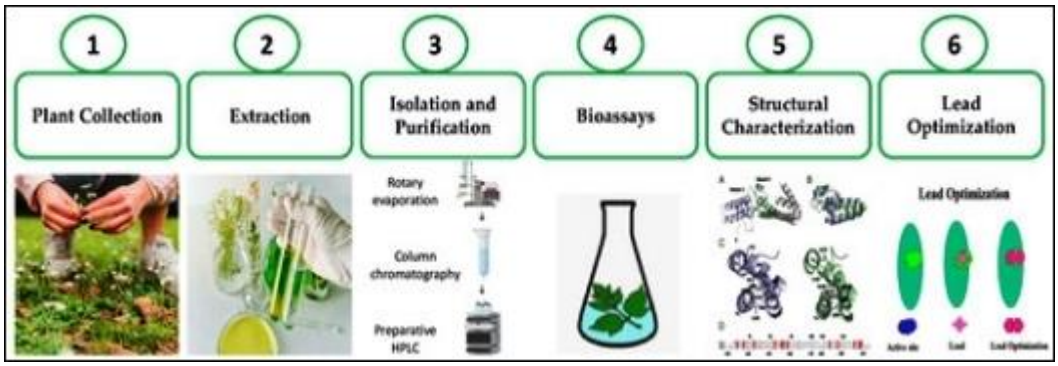

Figure 1. Various stages of the drug discovery process from natural products (1-Plant collection, 2-Extraction,3-Isolation and purification, 4-Bioassays, 5-Structural characterization, 6-Lead Optimization).[14]

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Formulation Strategies for Herbal and Plant-Based Drugs Using SEDDS [15]

Formulating Self-Emulsifying Drug Delivery Systems (SEDDS) for herbal and plant-based drugs requires careful selection of components and optimisation of the formulation to enhance the solubility, bioavailability, and therapeutic efficacy of the active ingredients. These drugs often have poor solubility, low absorption rates, and variable bioavailability when taken orally. SEDDS can overcome these challenges by solubilising hydrophobic compounds, promoting absorption, and providing targeted delivery.

1. **Selection of Lipid Components**: Use of oils, triglycerides, and phospholipids for various herbal drug formulations.
2. **Surfactant and Co-Surfactant Selection**: The choice of surfactants (e.g., polysorbates, lecithins) to optimise emulsification and stability.

Optimisation Techniques:

I. **Pseudo-Ternary Phase Diagrams**: To determine the optimal ratio of lipid, surfactant, and co-surfactant.

II. **Characterisation Methods**: Techniques like dynamic light scattering (DLS), transmission electron microscopy (TEM), and scanning electron microscopy (SEM) to analyse particle size, morphology, and emulsion stability.

Herbal and Plant-Based Active Compounds Delivered by SEDDS

1. **Curcumin**: A lipophilic compound found in turmeric with well-documented benefits in anti-inflammatory and anticancer therapy. SEDDS formulations have significantly improved their solubility and bioavailability.[16][17]
2. **Resveratrol**: A polyphenol from grape skins and berries known for its antioxidant effects. SEDDS formulations enhance their pharmacokinetics.[18][19]
3. **Quercetin**: A flavonoid with anti-inflammatory and antioxidant properties. SEDDS increases its solubility and bioavailability for better therapeutic outcomes. [20][21][22]
4. **Camptothecin**: An alkaloid with anticancer properties. SEDDS has been used to improve its stability and bioavailability. [23][24]
5. **Berberine**: A plant alkaloid with antimicrobial, anti-inflammatory, and metabolic benefits. SEDDS improves its bioavailability and therapeutic efficacy.[25][26][27]
6. **Ginseng and Ginsenosides**: SEDDS formulations improve the solubility of ginsenosides, the active components in ginseng, enhancing their therapeutic potential.[25]

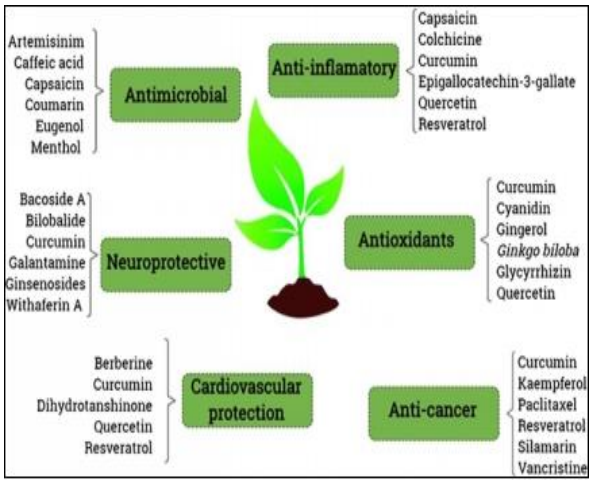

Fig.2. Examples of natural compounds extracted from higher plants used in nanomedicine aiming at different approaches. Some of these extracts are already being marketed, others are in clinical trials, and others are being extensively studied by the scientific community[28]

Components of SEDDS:[29][30]

1. Lipid phase
2. Surfactants
3. Co-surfactants

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Table 1: Example of Surfactants, Co-Surfactants and Co-Solvents Used in Commercial Formulations.[31][32][33][34][35][36][37]

Surfactants/ Co-surfactants	Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), Sorbitan monooleate (Span 80), Polyoxy-40-hydrogenated castor oil (Cremophor RH40), Polyoxyethylated glycerides (Labrafil M 2125 Cs), Polyoxyethlated oleic glycerides (Labrafil M1944 Cs).
Co-solvents	Ethanol, Glycerin, Polypylene glycol, Polyethylene glycol
Lipid ingredients	Corn oil, Mono, di, tri-glycerides, DL-alpha-Tocopherol, Fractionated triglyceride of palm seed oil (medium-chain triglyceride), Medium chain mono-and di-glycerides, Corn oil, Olive oil, Oleic acid, Soyabean oil, Peanut oil, Beeswax, Hydrogenated vegetable oils.

Table 2: Comparative Advantages and Disadvantages of Phytopharmaceuticals and Synthetic Drugs in SMEDDS[38][39]

Sr. No	Criteria	Phytopharmaceuticals (Herbal Drugs)	Synthetic Drugs
1.	**Source & Composition**	Natural origin, complex mixture of bioactive compounds[40]	Chemically synthesized, single, well-defined molecules
2.	**Solubility Issues**	Most are poorly water-soluble, benefiting greatly from SMEDDS	Many are poorly soluble (especially BCS Class II & IV), and also benefit
3.	**Bioavailability Enhancement**	SMEDDS significantly enhances the bioavailability of hydrophobic plant compounds	SMEDDS improves oral bioavailability and onset of action
4.	**Safety Profile**	Generally safer, but may contain unknown or toxic constituents if unpurified	Safety profile well-established through clinical studies
5.	**Standardization Difficulty**	High: batch-to-batch variation, multiple active components	Low: consistent purity and potency of APIs
6.	**6. Regulatory Approval**	Slower due to a lack of global harmonization and quality control issues	Faster, with well-defined regulatory pathways
7.	**Targeted Delivery via SMEDDS**	Possible, but harder to control due to multi-component nature	Easier due to known pharmacokinetics and physicochemical properties

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8.	**Cost of Development**	Lower initial cost but higher complexity in formulation standardization	Higher R&D cost, but scalable and predictable
9.	**Therapeutic Action**	Often multi-targeted with synergistic effects	Usually specific to a particular target or mechanism
10.	**Compatibility with SMEDDS**	Can be challenging due to instability, large molecular size, or complexity	High compatibility; synthetic drugs can be optimized for SMEDDS

Role of SEDDS in Herbal and Plant-Based Drug Delivery

The role of Self-Emulsifying Drug Delivery Systems (SEDDS) in herbal and plant-based drug delivery is significant because it addresses some of the major challenges that these types of drugs face, such as poor solubility, low bioavailability, and instability in the gastrointestinal tract. Many herbal and plant-derived compounds are lipophilic (fat-soluble) and exhibit poor water solubility, which limits their absorption and, consequently, their therapeutic efficacy. SEDDS provides an innovative solution to these problems, enhancing the bioavailability of such compounds and enabling more effective drug delivery.

Herbal/Plant-Based Drug Characteristics: [41]

Low solubility, high molecular weight, and variable Pharmacokinetics of many plant-based compounds.

Challenges: Inconsistent bioavailability and gastrointestinal stability, which hinder their therapeutic efficacy.

SEDDS Applications:

1. **Improvement of Solubility**: SEDDS can increase the solubility of hydrophobic herbal compounds by solubilising them in lipdic formulations.
2. **Enhanced Absorption**: SEDDS can promote lymphatic drug absorption, reducing the first-pass metabolism and improving the bioavailability of herbal drugs.
3. **Targeted Drug Delivery**: The potential for targeted delivery to specific sites in the GI tract or systemic circulation.[42][40][43]

Table 3. Literature updates on various reports of Solubility /Bioavailability enhancement using herbal drugs self-emulsifying delivery system formulations.

Sr. No	Published Year	Title of Research Article	Author Name	Publication/Journal Name	Findings
1	2022	Optimization of supercritical carbon dioxide fluid extraction of seized cannabis and self-emulsifying drug delivery system for enhancing the dissolution of cannabis extract	*Montoon, Chaowalit Chankana, Nataw*	The Journal of Supercritical Fluids 179(2022)105423	**SEDDS Formulation**: Cannabis extract was formulated into a self-emulsifying drug delivery system (SEDDS) to improve dissolution. **Outcome**: The optimised SEDDS significantly enhanced the dissolution of SFE-derived cannabis extract.[44]

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2	2022	SEDDS-loaded mucoadhesive fiber patches for advanced oromucosal delivery of poorly soluble drugs	*Julian David Friedl, Marcel Walther* et al.	Journal of Controlled Release 348 (2022) 692–705	**Patch Development**: Electrospun patches combining mucoadhesive fibres and SEDDS were developed. **Enhanced Residence**: Thiolated fibers extended buccal residence time by 200-fold. **Efficacy & Safety**: Curcumin-loaded patches showed biocompatibility and enhanced therapeutic effects on human keratinocytes and fibroblasts.[45]
3	2021	Enhanced oral bioavailability of rutin by a self-emulsifying drug delivery system of an extract of calyces from Physalisperuviana	*María I. Cardonaa, Gina P. Dominguez* et al.	Journal of Drug Delivery Science and Technology 2021	**Formulation Optimisation**: Used Box-Behnken design; optimal SEDDS included 10% Labrafac, 45% Solutol HS 15, 32% propylene glycol, and 13% PDMSHEPMS, with 45% extract loading. **Bioavailability Boost**: Pharmacokinetics revealed a 6-fold increase in oral bioavailability of rutin versus the unformulated extract. [21]
4	2021	Formulation optimization of solid self micro emulsifying pellets for enhanced oral bioavailability of curcumin	*Kang Sha, Qianfang Ma* et al.	Pharmaceutical Development and Technology 2021	**Optimal SMEDDS Composition**: 10% ethyl oleate, 57.82% Cremophor RH 40, and 32.18% Transcutol P. **Solidification**: Curcumin S-SMEDDS pellets were produced via extrusion–spheronization. **Pharmacokinetics**: In rabbits, $AUC_{0-\infty}$ of S-SMEDDS was 5.91 ± 0.28 mg·h/mL vs. 2.05 ± 0.04 mg·h/mL for suspension, with 289.3% relative bioavailability [15]
5	2021	Hydroalcoholic Extract of Myrciabella Loaded into a Microemulsion System: A Study of Antifungal and Mutagenic Potential	*Gabriel Davi Marena, Luiza Girott* et al.	Bibliography Planta Med 2021	**Antifungal Activity**: *M. bella*-loaded micro-emulsion was tested against *Candida* spp. using the microdilution method for MIC determination. **Safety & Efficacy**: Ames test confirmed safety; *M. bella*, both free and incorporated, showed significant antifungal activity across all tested strains.[46]
6	2021	Preparation of Microemulsion from an Alkyl Polyglycoside Surfactant and Tea Tree Oil	*Thuy-Vi V , Ya-Yen Chou* et al.	Molecules 2021, 26, 1971	**Formulation**: Microemulsions were developed using plant-derived alkyl polyglycoside (APG) surfactant and *Melaleuca alternifolia* (tea tree) essential oil. **Stability**: A stable microemulsion (1% TTO, 9% Triton CG-110/PPG at 1.8:1 w/w) remained unaffected by time and temperature.[47]

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7	2021	Drug Delivery and Pharmaceutical Technology Improvement of Oral Bioavailability and Anti-Tumor Effect of Zingerone Self-Microemulsion Drug Delivery System	*Xia Cao , Qin Zhu* et al.	Journal of Pharmaceutical Sciences 110 (2021) 2718-2727	**Formulation Purpose**: Developed a zingerone-loaded self-micro emulsifying drug delivery system (Z-SMEDDS) to enhance oral bioavailability and anti-tumor activity. **Improved Release & Bioavailability**: Z-SMEDDS showed significantly higher in vitro release and 7.63-fold greater oral bioavailability than free zingerone. **Conclusion**: Results support the potential clinical application of Z-SMEDDS.[48]
8	2020	A butanolic fraction from the standardized stem extract of Cassia occidentalis L delivered by a self-emulsifying drug delivery system protects rats from glucocorticoid-induced osteopenia and muscle atrophy	*Subhashis pal, naresh Mittapelly* et al.	Scientific Reports 2020	**Enhanced Bioavailability**: BuF increased circulating levels of five osteogenic compounds versus CSE-Bu. **Bone Regeneration**: CSE-BuF (50 mg/kg) enhanced bone healing at the osteotomy site and prevented Mp-induced bone loss via osteogenic and anti-resorptive actions.[49]
9	2020	Curcumin-Loaded Self-Microemulsifying Gel for Enhancing Wound Closure	*Jiun Wen Guo , Chi-Ming Pu* et al.	Skin Pharmacology and Physiology 2020	**Improved Skin Delivery**: Curcumin-loaded self-micro-emulsifying gel showed superior skin flux, cumulative amount, and permeability compared to commercial gels, along with enhanced wound healing. **Study Method**: Ex vivo skin permeation was assessed using BALB/c mouse skin and a diffusion cell system.[50]
10	2020	Enhanced oral bioavailability of Bisdemethoxy curcumin-loaded self-microemulsifying drug delivery system: Formulation design, in vitro and in vivo evaluation	*Jian Liua, Qilong Wang* et al.	InternationalJournalofPharmaceutics590(2020)119887	**Goal**: Address poor solubility and bioavailability of bismethoxy curcumin (BDMC) by developing a BDMC-loaded self-micro-emulsifying drug delivery system (BDMC-SMEDDS). **Potential**: BDMC-SMEDDS improved BDMC solubility and bioavailability, supporting clinical application.[51]
11	2019	Anti-inflammatory effect of self-emulsifying delivery system containing Sonchusoleraceus Linn extract on streptozotocin-induced diabetic rats	*Lei Chena, Xiujun Lina, Xiaowei Xua* et al.	Food and Chemical Toxicology, Elsevier 2019	**Study Findings**: SSEDDS showed anti-inflammatory effects in streptozotocin-induced diabetic rats, which exhibited elevated plasma glucose and decreased insulin levels.[52]
12	2019	Novel oral dosage regimen based on self-nanoemulsifying drug delivery systems for	*Majed Alwadei, Mohsi*	Saudi Pharmaceutical Journal 27(2019)866-	**Formulation**: Developed curcumin and thymoquinone SNEDDS, solidified using Syloid and Neusilin adsorbents. **Outcome**: Successfully created liquid and solid

		codelivery of phytochemicals – Curcumin and thymoquinone	*n Kazi* et al.	876	curcumin-thymoquinone SNEDDS with enhanced drug loading and dissolution, promising for anti-inflammatory and anti-cancer therapies.
13	2019	Development and in vitro characterization of an oral self-emulsifying delivery system (SEDDS) for rutin fatty ester with high mucus permeating propertie.	*Maria I. Cardona, Nguyet-Minh Nguyen Le* et al.	International Journal of Pharmaceutics S0378-5173(19)30222-4	**Objective**: Evaluated a SEDDS for oral delivery of rutin fatty ester with enhanced mucus permeation by adding PDMSHEPMS polymer. **Conclusion**: SEDDS with PDMSHEPMS shows promise for improving rutin's oral bioavailability [21]
14	2018	Development of self-nanoemulsifying drug delivery systems for oil extracts of Citrus aurantium L. blossoms and Rose damascena and evaluation of anticancer propertie.	*R. Nazari-Vanani, N. Azarpira, H. Heli* et al.	Journal of Drug Delivery Science and Technology 2018	**Development**: SNEDDS formulated to enhance the efficacy of *Citrus aurantium* and *Rose damascena* oil extracts. **Efficacy**: Cytotoxicity assays on MCF7 and PANC1 cells showed increased toxicity of extracts via SNEDDS, suggesting a promising oral delivery method.[53]
15	2018	Self-emulsifying drug deliverysystem improves preventive effect of curcuminoids on CHF in rats.	*Jiang, Y.* et al	Saudi Pharmaceutical Journal (2018),	**Objective**: Investigated if SEDDS improves the preventive effect of curcuminoids on chronic heart failure (CHF) in rats (model via coronary artery ligation). **Findings**: Curcuminoid SEDDS showed significantly better therapeutic effects than curcuminoid suspension.[54]
16	2018	Pharmacodynamic evaluation of self-micro-emulsifying formulation of standardised extract of Lagerstroemia speciosa for antidiabetic activity.	*Vipin Kumar Agarwal* et al.	Journal of Ayurveda and Integrative Medicine 9(2018) 38-44	**Goal**: Developed a self-microemulsifying formulation (SME) of standardised *SEL* leaf extract for antidiabetic activity. **Results**: SME formulation showed greater blood glucose reduction than non-SME *SEL*, with significant effects at 100 mg/kg by day 15. **Conclusion**: SME formulation enhanced *SEL*'s pharmacodynamic effect by about twofold.[55]
17	2018	Development and characterisation of clove oil nanoemulsions and self-microemulsifying drug delivery systems	*Kantaporn Kheawfu, Surachai Pikulk*	Journal of Drug Delivery Science and Technology S1773-2247(18)30016-9	**Objective**: Developed ethanol-reduced/no-ethanol clove oil nanoformulations to improve aqueous miscibility for fish anaesthesia. **Results**: Anaesthesia induction times in goldfish were shorter for C-NE (4.0 ± 0.6 min) and C-SMEDDS (3.8 ± 0.9 min) compared to ethanolic clove oil (5.0 ± 0.9 min); recovery times were

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18	2018	Enhanced anticancer effect of Bruceajavanica oil by solidified self-microemulsifying drug delivery system	*Wenli Huang a, Huanp eng Su* et al.	Journal of Drug Delivery Science and Technology 48 (2018) 266–273	**Formulation**: Developed solid self-microemulsifying drug delivery system (S-SMEDDS) of BJO. **Efficacy**: Demonstrated promising antitumor effects on A549 (lung) and DU145 (prostate) cancer cell lines, suggesting potential for improved cancer treatment.
19	2018	Self-nanoemulsifying drug delivery systems (SNEDDS)and self-microemulsifying drug delivery systems (SMEDDS) as lipid nanocarriers for improving dissolution rate and bioavailability of poorly soluble drugs	*Marko Krstic, Đorđe Medar evic* et al.	Chapter 12 Lipid Nanocarriers for Drug Targeting. DOI: http://dx.doi.org /10.1016/B978-0-12-813687-4.00012-8 © 2018 Elsevier Inc. All rights reserved	Lipid-based drug delivery systems effectively enhance the bioavailability of poorly soluble drugs through mechanisms distinct from other delivery methods.[57]
20	2017	Overview of solidification techniques for self-emulsifying drug delivery systems from industrial perspective	*Mandi ć, J. , Zvonar Pobirk* et al.	International Journal of Pharmaceutics S0378-5173(17)30448-9	Various industrial solidification techniques and excipients enable transforming liquid SEDDS into solid dosage forms with high yield and scalability for large-scale production.[58]
21	2017	Production, properties, and applications of solid self-emulsifying delivery systems (S-SEDS) in the food and pharmaceutical industries	*Antóni a Gonça lves , Nooshi n Nikma ram* et al.	Colloids and Surfaces A: Physicochem. Eng. Aspects S0927-7757(17)30976-7	**Overview**: Review covers lipid-based carriers for encapsulating nutraceuticals and pharmaceuticals, detailing their structure, components, production, and applications. **Challenges**: Discusses potential issues of using S-SMEDDS and S-SNEDDS in food and pharmaceutical industries[59].
22	2015	Curcumin–piperine mixtures In self-microemulsifying drug Delivery system for ulcerative Colitis therapy	*Li,Q.* et al	International Journal of Pharmaceutics. 2015	**Formulation**: Encapsulated two hydrophobic compounds, curcumin (CUR) and piperine (PIP), in SMEDDS. **Efficacy**: CUR-PIP-SMEDDS showed clear anti-colitis effects in a DSS-induced colitis model via retention enema targeting inflammatory colon tissue.[16]

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23	2015	Stability and performance study of newly developed emulsion prepared with polymeric rubber emulsifier and using the emulsion for nicotine extraction	*Zhifeng Guo ,Jingjing Dong* et al.	Separation and Purification Technology xxx (2015) xxx–xxx	**Emulsion Preparation**: Stable W/O emulsion made using polymeric rubber additives (PBSR or PBR) as emulsifiers instead of Span 80, with kerosene as the organic phase. **Findings**: Rubber emulsifiers functioned like surfactants; nicotine transfer to the strip phase reached over 99% efficiency within 2 minutes.[60]
24	2013	Liquid and solid self-microemulsifying drug delivery systems for improving the oral bioavailability of andrographolide from a crude extract of Andrographispaniculata	*Namfa Sermkaew, Wichan Ketjinda* et al.	European Journal of Pharmaceutical Sciences 2013	**Formulation:** SMEDDS composed of *A. paniculata* extract (11.1%), Capryol 90 (40%), Cremophor RH 40 (40%), and Labrasol (8.9%). **Effectiveness**: Both liquid and solid SMEDDS improved dissolution and oral bioavailability of *A. paniculata* extract. **Benefit**: Enhanced bioavailability may allow dose reduction of the poorly soluble extract.[61]
25	2012	Enhancement of anti-cholinesterase activity of Zingiber cassumunar essential oil using a microemulsion technique	*Siriporn Okonogi, Wantida Chaiyana* et al.	Drug Discoveries & Therapeutics. 2012; 6(5):249-255.	**Objective**: Enhanced cholinesterase inhibitory activity of *Zingiber cassumunar* (ZC) oil via microemulsion (ME) formulation. **Potential**: ZC oil ME is promising for further characterisation and in vivo Alzheimer's disease studies.[62]
26	2011	Enhanced Oral Bioavailability of Curcumin via a Solid Lipid-Based Self Emulsifying Drug Delivery System Using a Spray-Drying Technique	*Yi-Dong YAN, Jung Ae KIM* et al.	Regular Articles 2011 Pharmaceutical Society of Japan.	**Formulation**: Curcumin-loaded SEDDS developed into solid form via spray drying using Aerosil 200. **Pharmacokinetics**: Oral administration in rats showed significant absorption improvement; Cmax and AUC increased 4.6- and 7.6-fold, respectively, when the dose rose from 25 to 100 mg/kg.[63]
27	2011	Self-nanoemulsifying drug delivery system of persimmon leaf extract: Optimization and bioavailability studies	*Wanwen Li, Shaoling Yi, Zhouhua Wang* et al.	International Journal Of Pharmaceutics 420 (2011) 161–171	**Formulation**: Developed SNEDDS of persimmon (Diospyros kaki) leaf extract (PLE) and compared with commercial Naoxinqing tablets. **Bioavailability**: Oral administration of PLE-SNEDDS in fasting beagle dogs increased AUC of quercetin and kaempferol by 1.5-fold and 1.6-fold, respectively. **Conclusion**: SNEDDS is a promising system to enhance oral bioavailability of PLE[64].
28	2011	Pharmaceutical Nanotechnology Self-double-emulsifying drug delivery system (SDEDDS): A new	*Xiaole Qi, Lishuang*	International Journal of Pharmaceutics 409 (2011)	**Mechanism**: SDEDDS forms w/o/w double emulsions in the gastrointestinal environment, encapsulating drugs in the internal water phase. **Safety**: Histopathology confirmed no serious

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		way for oral delivery of drugs with high solubility and low permeability	*Wang* et al.	245–251	local damage, showing SDEDDS as a safe and effective delivery system for peptides and peptidomimetics [65]
29	2010	Self-nanoemulsifying drug delivery system (SNEDDS) for oral delivery of Zedoary essential oil: Formulation and bioavailability studies	*Yi Zhaoa, Chang guang Wanga* et al.	International Journal of Pharmaceutics 383 (2010) 170–177	**Formulation**: Developed SNEDDS for oral delivery of Zedoary turmeric oil (ZTO) from *Curcuma zedoaria* rhizome. **Bioavailability**: Oral administration in rats increased AUC and Cmax of germacrone (GM) by 1.7-fold and 2.5-fold, respectively, compared to unformulated ZTO.
30	2009	Formulation Development and Bioavailability Evaluation of a Self-Nanoemulsified Drug Delivery System of Oleanolic Acid	*Jia Xi, Qi Chang* et al.	AAPS Pharm SciTech, Vol. 10, No. 1, March 2009	**Formulation**: SNEDDS for OA (20 mg/g) was prepared with Sefsol 218 (oil), Cremophor EL, Labrasol (surfactants), and Transcutol P (co-surfactant). **Purpose**: Demonstrates SNEDDS' potential to enhance dissolution and oral bioavailability of poorly water-soluble triterpenoids like OA.[66]
31	2008	Extraction Technologies for Medicinal and Aromatic Plants	*Sukhdev Swami 'Hand a Suman 'Preet Singh* et al.	International Centre For Science And High Technology Trieste, 2008	This book provides techniques for extract production, aimed at helping emerging and developing countries create economical, high-quality, and globally competitive extracts.[41]
32	2005	Rapid communication In vitro evaluation of drug release from self micro-emulsifying drug delivery systems using a biodegradable homolipid from Capra hircus.	*Anthony A. Attama, Megg O* et al.	International Journal of Pharmaceutics 304 (2005) 4–10	**Formulation**: SMEDDS were developed using biodegradable homolipid from *Capra hircus*, Tween 65, and contained piroxicam (lipophilic), chlorpheniramine maleate (hydrophilic), and metronidazole (Hydrolipophilic). **Release Studies**: Conducted in simulated gastric fluid (SGF). **Conclusion**: This approach could be a versatile and reliable alternative to conventional drug delivery methods.[67]

Herbal drug development faces various problems and challenges, despite the long history of herbal medicine use.

1. Lack of Standardisation: One major challenge is the lack of standardisation in the preparation of herbal medicines. Different plants can vary in their chemical composition depending on factors like geographic location, growing conditions, and harvesting methods. This variability can lead to inconsistent effects in herbal remedies.[68]

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2. Quality Control Issues: Ensuring the quality and purity of herbal products is a significant concern. There is no universally accepted method for testing the identity, purity, and strength of herbal ingredients, leading to potential contamination and adulteration. This is particularly problematic for consumers' safety.[69]

3. Limited Scientific Evidence: While herbal medicines have been used for centuries, there is still a lack of extensive clinical trials and scientific research proving the efficacy and safety of many herbal medicines. In modern medicine, rigorous scientific evaluation is crucial, and herbal medicine sometimes lacks this level of evidence.[70]

4. Regulatory and Legal Issues: - Herbal drugs are not always subjected to the same regulatory oversight as conventional pharmaceuticals. In many countries, herbal products may be categorized as dietary supplements, which means they are less rigorously tested and regulated. This creates gaps in consumer protection.

5. Cultural and Knowledge Gaps:- Traditional herbal knowledge, often passed down through generations, is difficult to document and sometimes lost in modern contexts. There is also a gap in understanding between traditional healers and modern medical researchers, which limits the integration of traditional knowledge with modern drug development.

6. Sustainability and Environmental Impact: - The demand for medicinal plants has increased, leading to concerns about the sustainability of plant harvesting. Over-harvesting and habitat destruction threaten the availability of some plant species, which can reduce biodiversity and undermine the future supply of medicinal plants.

7. Public Perception and Education: There is still a lack of education around the proper use of herbal remedies. While they are generally perceived as safer than synthetic drugs, herbal medicines can still have side effects or interact negatively with other medications. Public awareness campaigns are often needed to educate consumers about the benefits and risks.

8. Economic and Market Challenges: - Despite the potential economic benefits, the market for herbal medicines is often fragmented, with insufficient infrastructure to support large-scale commercial production. Supply chains may be underdeveloped, and profitability can be inconsistent due to the variability in quality and demand.[71]

Solutions and Recommendations

- **Research and Development**: More scientific research, especially clinical trials, should be conducted to validate the efficacy and safety of herbal drugs.[71]
- **Standardisation and Quality Control**: Developing and implementing standardised methods for testing herbal drugs can help ensure quality and safety.[1][72]
- **Regulation and Legislation**: Governments need to establish clear regulations for herbal medicine, ensuring that products meet safety standards while allowing for innovation.[25][71]
- **Sustainable Practices**: Encouraging sustainable harvesting practices and promoting the cultivation of medicinal plants can help preserve biodiversity and ensure a steady supply.[14][41]

Challenges and Limitations [69][73][74][59][75][76][77][6]

1. **Stability Issues**: While SEDDS improve solubility, they can face stability issues over time, including phase separation or degradation of the active ingredient.
2. **Regulatory Challenges**: The approval process for herbal-based SEDDS formulations can be more complex compared to synthetic drugs.

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3. **Scalability and Cost**: Large-scale production of SEDDS can be expensive and technically challenging.

4. **Potential Toxicity**: Excessive use of surfactants or co-surfactants may lead to toxicity or gastrointestinal irritation.

Table 4. Marketed SMEDDS Preparation: Phytopharmaceuticals vs. Synthetic Drug

Drug Type	Drug Name	Brand/Marketed Name	Company	Purpose / Indication	SMEDDS Benefit
Synthetic	Cyclosporine A	Sandimmun Neoral®	Novartis	Immunosuppressant (post-transplant)	Enhanced absorption & consistent bioavailability [78][79]
Synthetic	Ritonavir	Norvir®	AbbVie	Antiretroviral (HIV)	Improved solubility and oral bioavailability [80][81]
Synthetic	Saquinavir	Fortovase®	Hoffmann-La Roche	Antiretroviral (HIV)	Enhanced solubility and GI absorption[82] [80][81]
Synthetic	Simvastatin	Zocor® (SMEDDS formulation in studies)	Merck	Lipid-lowering agent (hyperlipidemia)	1.5x increase in oral bioavailability [83][84][85][86][87]
Phytopharmaceutical	Curcumin	Not yet fully commercialized (researched)	-	Anti-inflammatory, antioxidant	Greatly enhanced solubility and bioavailability [88][50][89]
Phytopharmaceutical	Silymarin	Research-based SMEDDS	-	Hepatoprotective (liver disorders)	Improved systemic absorption [90][91][92]
Phytopharmaceutical	Berberine	Experimental SMEDDS	-	Antidiabetic, antimicrobial	Enhanced oral bioavailability [93][94][68][28]

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Phytopharmaceutical	Mangiferin	Research-based SMEDDS	-	Antioxidant, anti-diabetic	Enhanced solubility and GI absorption [15][95][40][13]

Future Directions

1. **Nanotechnology Integration**: Incorporating nanocarriers like solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) with SEDDS for improved targeting and stability.[77]
2. **Personalised Medicine**: Development of personalised SEDDS formulations based on individual patient needs.[75]
3. **Regulatory Acceptance**: More robust clinical evidence and regulatory pathways for herbal-based SEDDS formulations.[96][1][6]
4. **Sustainable and Green Chemistry Approaches**: Exploration of natural, biocompatible surfactants and co-surfactants in SEDDS.[35][97][98][99]

Conclusion:

Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) offer a promising strategy to overcome the poor solubility and limited bioavailability commonly associated with herbal and plant-based drugs. By forming fine oil-in-water emulsions upon mild agitation in gastrointestinal fluids, SMEDDS significantly enhance drug dissolution, absorption, and therapeutic efficacy. This delivery system thus represents a valuable advancement in maximising the clinical potential of phytoconstituents, paving the way for more effective and reliable herbal therapeutics.

Abbreviations: -

SMEDDS: Self-micro-emulsifying drug delivery system
BCS: Biopharmaceutical Classification System
S-SMEDDS: Solid Self-micro-emulsifying drug delivery system
L-SMEDDS: Liquid Self-micro-emulsifying drug delivery system
TCM: Traditional Chinese Medicine
SEDDS: Self-Emulsifying Drug Delivery Systems
DLS: Dynamic Light Scattering
SEM: Scanning Electron Microscopy
APIs: Active pharmaceutical ingredients
HIV: Human Immunodeficiency Virus
SLNs: Solid Lipid Nanoparticles

Declarations: -

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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