

Article Review

Pharmaceutical Emulsions: Exploring the Potential of Natural Surfactants from Plant Sources

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ABSTRACT

This study highlights the use of plant-derived natural surfactants in formulating pharmaceutical emulsions, addressing concerns with traditional synthetic surfactants. Emulsions are vital for enhancing drug bioavailability, but their formulation often involves environmentally concerning agents. Natural surfactants from plant extracts emerge as eco-friendly alternatives. The review explores diverse plant-derived surfactants, emphasizing their unique structures and surface-active properties. Extraction methods, purification techniques, and their compatibility with pharmaceutical ingredients are evaluated, showcasing their efficacy in stabilizing emulsions. Physicochemical aspects of emulsion stability, including interactions between natural surfactants, co-surfactants, and hydrophobic drugs, are discussed. Case studies demonstrate successful formulations across various pharmaceutical emulsion systems, highlighting their potential in controlled drug delivery. Safety is crucial, especially in pharmaceuticals. The abstract reviews toxicity, irritation, and allergies tied to plant-derived surfactants, confirming their suitability. In conclusion, integrating natural surfactants from plant extracts in pharmaceutical emulsions offers a biocompatible and sustainable approach to enhancing drug delivery. This research emphasizes the need for further studies to optimize formulations, assess long-term stability, and validate their clinical potential.

Keywords: Pharmaceutical emulsions; Natural surfactants; Drug delivery; Biocompatibility; Eco-friendly

1. Introduction

Natural surfactants derived from plant extracts are gaining traction in the pharmaceutical industry due to their unique advantages over synthetic alternatives [1]. These plant-based surfactants are biocompatible, indicating they exhibit low toxicity and are less likely to cause adverse reactions in pharmaceutical formulations. This is especially crucial in drug delivery systems where patient safety is paramount [2]. In addition to their safety profile, natural surfactants are environmentally friendly [3]. Their production processes typically involve fewer harsh chemicals, thus reducing the environmental footprint [4]. This aligns with the growing emphasis on sustainable practices within the pharmaceutical sector. Moreover, these surfactants, due to their natural origin, often present lower risks of skin irritation, allergic reactions, or toxicity, making them ideal for products intended for topical or oral use [5]. Understanding the molecular structures and properties of these surfactants is essential for their effective application. They display amphiphilic behaviour, possessing both hydrophobic and hydrophilic components, which is vital for stabilizing emulsions [6]. These surfactants can form micelles in solution, a property that enhances the solubility and bioavailability of lipophilic drug compounds [7].

To harness the benefits of plant-derived surfactants in pharmaceutical emulsions, efficient extraction and purification processes are necessary. Various methods, such as solvent extraction and foam fractionation, can be employed [8]. Post-extraction, purification techniques like ultrafiltration and chromatography refine these surfactants for their intended pharmaceutical use [9]. It's also crucial to ensure the compatibility of natural surfactants with hydrophobic drug compounds and other surfactants to achieve stable and effective emulsions [10]. Natural surfactants are adaptable, adjusting their hydrophilic-lipophilic balance (HLB) to meet different formulation needs [11]. They have been successfully used in various pharmaceutical emulsion systems, enhancing stability and solubility. For instance, they've been incorporated into lipid-based drug delivery systems and emulsions for oral, topical, and even injectable drug delivery, showcasing their versatility, stability, and low toxicity [12].

Outside of pharmaceuticals, these surfactants are also utilized in the nutraceutical and cosmeceutical sectors, aligning with consumer preferences for safe and sustainable ingredients [13]. However, irrespective of the application, ensuring the safety and biocompatibility of these surfactants remains

a top priority [14]. Comprehensive toxicity assessments, skin and eye irritation tests, and allergenicity studies are conducted to ensure their safety in various products [15].

Natural surfactants derived from plant extracts offer a promising alternative to synthetic surfactants for pharmaceutical emulsion formulation. They have advantages such as biocompatibility, eco-friendliness, and unique surface-active properties that make them suitable for drug delivery systems [16]. However, to use natural surfactants effectively, their molecular structures, compatibility with pharmaceutical ingredients, and safety profiles need to be well understood. Various case studies have shown their efficacy in controlled drug delivery across different pharmaceutical emulsion systems [17]. Future research and optimization are required to fully exploit the potential of these natural surfactants, leading to safer and more sustainable pharmaceutical formulations.

2. Natural Surfactants from Plant Extracts

Surfactants, or surface-active agents, are amphiphilic molecules with a dual affinity for both hydrophilic (water-attracting) and hydrophobic (water-repelling) components. These remarkable compounds play a pivotal role in various industries, ranging from pharmaceuticals to cosmetics and food processing. While synthetic surfactants have dominated these applications for decades, there is a growing interest in exploring natural alternatives derived from plant extracts. This shift towards natural surfactants is driven by their unique structures and surface-active properties, which not only enhance their biocompatibility but also align with the growing demand for sustainable and eco-friendly solutions.

2.1. Unique Structures of Natural Surfactants

One of the distinguishing features of natural surfactants from plant extracts is their diverse and intricate molecular structures. These structures are often complex, with a combination of hydrophilic and hydrophobic moieties that can vary widely among different plant-derived surfactants. This structural diversity is a result of the vast array of compounds produced by plants for various ecological functions, including protection, communication, and defense against environmental stressors [18].

2.2. Phospholipids

Phospholipids are a prominent class of natural surfactants found abundantly in plant cell membranes. These molecules possess a hydrophilic phosphate head group and two hydrophobic fatty acid tails. This unique structure allows phospholipids to spontaneously form lipid bilayers, a fundamental

component of cell membranes [19]. The surface-active properties of phospholipids play a crucial role in cellular processes and have significant implications for pharmaceutical and cosmetic applications.

2.3. Saponins

Saponins are glycosidic compounds found in various plant species, including legumes and oats. They consist of a hydrophobic aglycone (the sapogenin) and one or more hydrophilic sugar moieties [20]. Saponins exhibit surfactant behavior due to their amphiphilic nature, capable of reducing surface tension and forming stable foams and emulsions. In traditional medicine and agriculture, saponin-rich plant extracts have been used as natural surfactants with diverse applications [21].

2.4. Tannins

Tannins are a class of polyphenolic compounds found in plants, particularly in fruits, leaves, and bark. These molecules possess a unique combination of hydrophilic and hydrophobic regions, making them effective natural surfactants [22]. Tannins are known for their ability to form complexes with proteins, an essential property in industries. Moreover, their surfactant properties have potential applications in areas such as emulsification and wastewater treatment [23].

3. Surface-Active Properties of Natural Surfactants

Natural surfactants from plant extracts exhibit a diverse range of surface-active properties, making them valuable in various industrial and scientific applications. These properties are a direct consequence of their unique structures and are often tailored to the plants' ecological roles.

3.1. Emulsification and Dispersion

One of the primary functions of surfactants is to stabilize emulsions, which are colloidal systems of immiscible liquids [24]. Natural surfactants, with their amphiphilic structures, excel in this regard. They can lower the interfacial tension between oil and water, allowing for the formation of stable emulsions. This property is particularly valuable in the food industry for creating products like salad dressings, mayonnaise, and cream liqueurs.

3.2. Foaming and Detergency

Many natural surfactants from plant extracts are proficient at generating and stabilizing foams [25]. Foams find applications in industries such as food processing (e.g., whipped cream), cosmetics (e.g., shampoos), and firefighting (e.g., foam extinguishers). Additionally, the detergent properties of

certain plant-derived surfactants make them suitable for cleaning applications, further expanding their utility [26].

3.3. Biological Compatibility

Natural surfactants are often favored in pharmaceutical and cosmetic formulations due to their biocompatibility and reduced likelihood of causing skin irritation or allergies [5]. Phospholipids, for example, are integral to cell membranes and are well-tolerated by the human body. This biocompatibility extends their use in drug delivery systems and skincare products [23].

3.4. Environmental Friendliness

The shift towards natural surfactants aligns with the growing demand for sustainable and eco-friendly solutions [3]. Many synthetic surfactants have adverse environmental impacts, whereas plant-derived surfactants are often biodegradable and less harmful to ecosystems. This eco-friendliness makes them suitable for applications in agriculture, where minimizing environmental impact is crucial [27].

4. Applications of Natural Surfactants

The distinctive structures and surface-active attributes of natural surfactants have unlocked many possibilities for their utilization. These options extend across various industries and scientific domains, underscoring the adaptability and promise of surfactants derived from plants. In the pharmaceutical realm, natural surfactants assume a crucial role, especially in the formulation of drug delivery systems. [7]. Phospholipids, such as phosphatidylcholine, are used to formulate liposomal drug carriers that enhance the solubility and bioavailability of poorly water-soluble drugs [28]. This article explores the multifaceted applications of these natural surfactants in pharmaceuticals and their pivotal role in improving drug solubility, bioavailability, and formulation stability.

4.1. Natural Surfactants as Solubility Enhancers

One of the fundamental challenges in pharmaceutical development is the formulation of drugs with poor water solubility. Many drug compounds, especially those of hydrophobic nature, exhibit low solubility in the aqueous environment of the human body. This limited solubility often leads to inadequate drug absorption, reduced bioavailability, and ineffective therapeutic outcomes.

Natural surfactants, owing to their amphiphilic nature, have the ability to enhance the solubility of hydrophobic drug compounds [29]. Their unique molecular structures allow them to interact with

both water and lipid phases, effectively dispersing hydrophobic drugs in aqueous solutions. This property is particularly valuable in formulating oral dosage forms, where improved drug solubility translates into better absorption and therapeutic efficacy [28, 29, 30, 32, 36].

4.2. Emulsification and Lipid-Based Drug Delivery

Natural surfactants are essential components in the development of lipid-based drug delivery systems. These systems, such as liposomes, micelles, and nanoemulsions, utilize the self-assembling properties of surfactants to encapsulate and deliver drugs [12]. Advanced drug delivery, using liposomes, micelles, and nanoemulsions, relies on surfactant self-assembly for efficient drug encapsulation and targeted release. Liposomes self-assemble phospholipids into vesicles, forming a bilayer structure for hydrophobic and hydrophilic drugs. Micelles, created by surfactant molecules, organize into nanoscale structures, improving solubility for poorly water-soluble drugs. Nanoemulsions involve surfactant-stabilized oil droplets in water, offering a versatile platform for drug encapsulation. These systems enhance drug solubility and provide precise control over release kinetics, optimizing therapeutic outcomes [31].

In this context, natural surfactants play a pivotal role in stabilizing lipid-based formulations and preventing drug precipitation [12, 31].

4.3. Biocompatibility and Reduced Toxicity

Pharmaceutical formulations must prioritize patient safety and minimize the risk of adverse effects. Natural surfactants derived from plant extracts are generally well-tolerated by the human body, leading to reduced toxicity and fewer side effects compared to synthetic counterparts [32]. This biocompatibility is especially crucial in the development of parenteral drug delivery systems, where any potential toxicity can have severe consequences.

4.3.1. Improved Bioavailability

Enhancing drug bioavailability is a key objective in pharmaceutical research, as it directly impacts the therapeutic effectiveness of a drug. Natural surfactants contribute to improved bioavailability through several mechanisms:

4.3.1. 1. Micellar Solubilization

Natural surfactants have the capacity to form micelles in aqueous solutions, where their hydrophobic tails sequester hydrophobic drug molecules. This solubilization process significantly increases the

apparent solubility of poorly water-soluble drugs [33]. As a result, the drugs can be absorbed more efficiently in the gastrointestinal tract, leading to enhanced bioavailability.

4.3.1.2. Emulsification

Lipid-based drug delivery systems formulated with natural surfactants can increase drug bioavailability by promoting lymphatic transport [12]. This is particularly relevant for drugs that undergo extensive first-pass metabolism in the liver, as it bypasses this route and improves systemic drug exposure.

4.3.1.3. Enhanced Permeability

Some natural surfactants, such as phospholipids, can interact with cell membranes and promote drug permeability [34]. This mechanism is crucial for drugs targeting intracellular compartments or crossing physiological barriers like the blood-brain barrier [34,35].

4.4. Stability of Pharmaceutical Formulations

The stability of pharmaceutical formulations is paramount to ensure that drugs retain their potency and efficacy throughout their shelf life. Natural surfactants contribute significantly to the stability of various drug formulations:

4.4.1. Prevention of Drug Aggregation

Natural surfactants are effective in preventing drug aggregation and precipitation, which can occur due to poor drug solubility [10]. By maintaining drug dispersion in the formulation, they ensure that the drug remains in a usable form until administration [67].

4.4.2. Emulsion Stability

In emulsion-based formulations, such as oral suspensions or parenteral emulsions, natural surfactants play a crucial role in stabilizing the oil-in-water or water-in-oil systems. They reduce interfacial tension and prevent phase separation, ensuring uniform drug distribution and consistent dosing [36].

4.4.3. Long-Term Storage

The inherent stability of natural surfactants renders them well-suited for the prolonged storage of pharmaceutical products [37]. This quality proves especially beneficial for biopharmaceuticals and vaccines, where an extended shelf life is imperative.

4.5. Biodegradability and Environmental Considerations

With increasing awareness of environmental sustainability, pharmaceutical companies are seeking formulations with minimal environmental impact. Natural surfactants, often derived from renewable plant sources, align with these sustainability goals [38]. They are biodegradable and less likely to accumulate in the environment, reducing the ecological footprint of pharmaceutical formulations. As the pharmaceutical industry continues to prioritize patient safety, therapeutic effectiveness, and environmental responsibility, the versatile applications of natural surfactants are poised to play a pivotal role in shaping the future of pharmaceutical formulations [4,17,21,27,32].

5. Natural Surfactants from Plant Extracts: Extraction, Purification, and Pharmaceutical Compatibility

The quest for sustainable and biocompatible alternatives in the pharmaceutical industry has spurred interest in natural surfactants derived from plant extracts. These surfactants, sourced from a diverse range of plant materials including roots, leaves, fruits, and seeds, offer a promising avenue to address the limitations associated with synthetic surfactants. [21, 22,32,39].

5.1. Extraction Methods for Natural Surfactants

The extraction of natural surfactants from plant materials is a critical step in harnessing their surface-active properties for pharmaceutical applications. Various extraction techniques are employed to isolate these surfactants efficiently:

5.1.1. Solvent Extraction

Solvent extraction involves the use of organic solvents, such as ethanol or hexane, to dissolve surfactants from plant materials. This method is particularly useful for extracting lipophilic surfactants found in plant oils [39].

5.1.2. Aqueous Extraction

Aqueous extraction methods use water-based solutions to extract surfactants [40]. These methods are ideal for hydrophilic surfactants present in plant tissues.

5.1.3. Supercritical Fluid Extraction

Supercritical fluid extraction utilizes supercritical carbon dioxide as a solvent to extract surfactants from plant materials. This method offers the advantage of avoiding the use of toxic organic solvents and has gained attention for its green extraction approach [41].

5.1.4. Microwave-Assisted Extraction

Microwave-assisted extraction uses microwave energy to enhance the extraction efficiency of surfactants from plant materials, it reduces extraction time and energy consumption [42].

5.1.5. Ultrasound-Assisted Extraction

Ultrasound-assisted extraction employs high-frequency sound waves to disrupt plant cell walls and facilitate the release of surfactants into the solvent. This method is known for its ability to enhance extraction yields [43].

5.2. Purification Techniques for Natural Surfactants

After extraction, natural surfactants often require purification to isolate the desired compounds and remove impurities. Purification techniques play a crucial role in ensuring the suitability of these surfactants for pharmaceutical applications:

5.2.1. Chromatography

Various chromatographic techniques, such as column chromatography or high-performance liquid chromatography (HPLC), are employed to separate and purify natural surfactants. These methods offer high precision in isolating specific compounds [44].

5.2.2. Filtration

Filtration methods, including ultrafiltration or microfiltration, are used to remove larger impurities and particulate matter from surfactant solutions. They are particularly effective for clarifying plant extracts [45].

5.2.3. Distillation

Distillation techniques can be employed to separate surfactants from solvents used in the extraction process. This is especially relevant when organic solvents are used in the extraction [46].

5.2.4. Precipitation

Precipitation methods involve adding a suitable precipitant to the surfactant solution to induce the formation of surfactant-rich precipitates. These precipitates can then be separated and further purified [47].

5.3. Compatibility with Pharmaceutical Ingredients

The successful integration of natural surfactants into pharmaceutical emulsions necessitates an understanding of their compatibility with hydrophobic drug compounds and co-surfactants. Several factors influence the compatibility of natural surfactants with pharmaceutical ingredients:

5.3.1. Molecular Structure

The molecular structure of natural surfactants plays a pivotal role in their compatibility with pharmaceutical ingredients. Surfactants with tail and head groups that can interact favorably with drug compounds are more likely to form stable emulsions [48].

5.3.2. Hydrophilic-Lipophilic Balance (HLB)

The HLB value of a surfactant determines its affinity for water or oil phases. Matching the HLB of natural surfactants with the specific requirements of the drug compound is crucial for achieving emulsion stability [49].

5.3.3. Drug-Polymer Interactions

In some cases, natural surfactants may interact with pharmaceutical polymers used in drug formulations [10]. Understanding these interactions is essential for optimizing the emulsion's stability and drug release profiles.

5.3.4. Co-Surfactants

The inclusion of co-surfactants in pharmaceutical emulsions can enhance stability. Natural surfactants must be compatible with these co-surfactants to ensure effective emulsion formation and long-term storage [50].

6. Exploration of Application: Natural Surfactants in Pharmaceuticals

Natural surfactants derived from plant extracts have gained prominence in pharmaceutical applications due to their biocompatibility, sustainability, and potential to enhance drug delivery systems. Several case studies highlight the successful utilization of these natural surfactants in pharmaceutical formulations, addressing issues related to solubility, stability, and bioavailability of drugs. This article explores some notable case studies that demonstrate the efficacy of natural surfactants in pharmaceuticals [51, 52, 53, 54,55].

6.1. Nanoemulsions for Enhanced Bioavailability

One of the primary challenges in pharmaceuticals is improving the bioavailability of poorly water-soluble drugs. Natural surfactants have been instrumental in the development of nanoemulsions to address this issue. A study focused on curcumin, a bioactive compound with limited aqueous solubility. By using plant-derived surfactants, they successfully formulated curcumin-loaded nanoemulsions. These nanoemulsions exhibited significantly improved bioavailability compared to

conventional formulations [51]. They concluded that natural surfactants not only stabilized the nanoemulsion but also enhanced the solubility and absorption of curcumin, highlighting their potential for improving the therapeutic efficacy of hydrophobic drugs.

6.2. Herbal Extract Emulsions for Controlled Release

Herbal extracts are widely used in pharmaceuticals due to their therapeutic properties. However, achieving controlled release of bioactive compounds from herbal extracts can be challenging. The case study where they formulated herbal extract emulsions using natural surfactants. These emulsions allowed for the controlled release of bioactive compounds from herbal extracts, ensuring a sustained therapeutic effect. The natural surfactants played a crucial role in stabilizing the emulsion and controlling the release kinetics, making them valuable in herbal-based pharmaceutical formulations [52].

6.3. Essential Oil-Based Emulsions for Aromatherapy

Essential oils have gained recognition for their therapeutic potential in aromatherapy and skin care products. However, their hydrophobic nature poses formulation challenges. One study explored the use of natural surfactants derived from plant extracts to formulate essential oil-based emulsions. These emulsions provided an effective carrier system for essential oils, allowing for their controlled release and improved skin penetration. The natural surfactants not only stabilized the emulsions but also enhanced the delivery of essential oil actives, demonstrating their utility in pharmaceutical and cosmetic applications [53].

6.4. Lipid-Based Drug Delivery Systems

Lipid-based drug delivery systems are widely employed in pharmaceuticals for enhancing the solubility and bioavailability of lipophilic drugs. A case study focused on the development of lipid-based formulations using natural surfactants sourced from plant extracts. These formulations effectively encapsulated lipophilic drugs, ensuring their solubilization and controlled release. The biocompatible nature of natural surfactants made them suitable for lipid-based drug delivery systems, offering a sustainable and safe approach to drug formulation [54].

6.5. Oral Delivery of Phytochemicals

Phytochemicals derived from plants have garnered attention for their potential health benefits. However, their bioavailability through oral administration can be limited. Natural surfactants obtained from plant extracts were utilized to enhance the oral delivery of phytochemicals. The surfactants improved the solubility and absorption of phytochemicals, leading to increased bioavailability. This

approach opens new possibilities for utilizing plant-derived surfactants to unlock the therapeutic potential of phytochemicals in pharmaceutical applications [55].

7. Toxicity, Irritation, and Allergies in Plant-Derived Surfactants: Assessing Suitability for Pharmaceutical Applications

The increasing demand for sustainable and biocompatible pharmaceutical formulations has driven the exploration of plant-derived surfactants as alternatives to synthetic counterparts. While these natural surfactants offer numerous advantages, concerns related to toxicity, irritation, and allergies must be thoroughly evaluated to confirm their suitability for pharmaceutical applications [68].

7.1. Biocompatibility and Safety of Plant-Derived Surfactants

Plant-derived surfactants are inherently biocompatible, making them an attractive choice for pharmaceutical applications. They are sourced from renewable plant materials and are often considered eco-friendly. These surfactants exhibit low toxicity in their native form, as they have evolved within living organisms, where they perform essential functions in cell membranes and metabolic processes [69]. In a recent study, the biocompatibility of plant-derived surfactants was assessed using *in vitro* and *in vivo* models. The study focused on surfactants extracted from quillaja saponin, a natural source. The results demonstrated minimal cytotoxicity and low irritation potential, confirming the biocompatibility of these surfactants. Furthermore, animal studies revealed no adverse effects, supporting their safety profile for pharmaceutical use [56].

7.2. Toxicity Assessment in Plant-Derived Surfactants

While plant-derived surfactants are generally considered safe, toxicity assessments are essential to confirm their suitability for specific pharmaceutical formulations. Researchers have conducted comprehensive toxicity studies to evaluate the potential risks associated with these surfactants. A study investigated the acute and chronic toxicity of plant-derived surfactants extracted from *yucca schidigera*, a desert plant. The acute toxicity assessment showed no adverse effects in rats, even at high doses. In the chronic toxicity study, no observable toxicological effects were reported during a six-month exposure period [57]. These findings highlight the low toxicity of yucca-derived surfactants, supporting their safety for pharmaceutical applications.

7.3. Irritation Potential of Plant-Derived Surfactants

Skin and mucous membrane irritation potential is a crucial consideration when formulating pharmaceutical products. Plant-derived surfactants are known for their mildness, but rigorous assessments are necessary to ensure their compatibility with human tissues [70].

In one study, plant-derived surfactants from aloe vera were evaluated for their potential to cause skin irritation. The surfactants were incorporated into topical formulations. The results showed no significant irritation when applied to human skin, confirming their suitability for dermatological pharmaceuticals [58].

7.4. Allergenicity Evaluation

Allergic reactions are a critical concern in pharmaceutical applications, as they can lead to severe adverse effects in patients. Assessing the allergenic potential of plant-derived surfactants is essential to ensure patient safety [70, 56, 57]. A study focused on allergenicity testing of plant-derived surfactants derived from soybeans. Skin patch tests were conducted on human volunteers to evaluate the potential for allergic reactions. The results indicated no allergic responses, suggesting that soybean-derived surfactants are unlikely to cause allergenic reactions in pharmaceutical formulations [59].

8. Physicochemical Aspects of Emulsion Stability in Pharmaceutical Formulations

Emulsions play a pivotal role in modern pharmaceutical formulations, offering a versatile platform for drug delivery. Among the key factors influencing emulsion stability, physicochemical interactions between natural surfactants, co-surfactants, and hydrophobic drugs are of paramount importance. This article explores recent research and developments in understanding these interactions, shedding light on their significance in pharmaceutical emulsion design [60, 61, 62, 63].

8.1. Interfacial Tension and Emulsion Stability

Interfacial tension at the oil-water interface is a critical factor in emulsion stability. It defines the ability of surfactants and co-surfactants to lower the interfacial tension, preventing the separation of immiscible phases. Natural surfactants, derived from plant extracts, have garnered attention for their unique surface-active properties [60]. These properties allow them to effectively reduce interfacial tension, contributing to stable emulsions. In a recent study, the interfacial tension-lowering capacity of natural surfactants extracted from fenugreek seeds was investigated. The results demonstrated that fenugreek-derived surfactants exhibited a remarkable ability to reduce interfacial tension, promoting emulsion stability [61]. This finding highlights the potential of plant-derived surfactants in enhancing the performance of pharmaceutical emulsions.

8.2. Role of Co-Surfactants

Co-surfactants are often employed in emulsion formulations to synergize with surfactants, further improving emulsion stability. These compounds work in conjunction with surfactants to lower interfacial tension and enhance the formation of micelles or vesicles, contributing to emulsion stability [62]. A study investigated the compatibility of natural surfactants from sunflower lecithin with various co-surfactants commonly used in pharmaceutical emulsions. The research demonstrated that sunflower lecithin-based surfactants exhibited excellent compatibility with a range of co-surfactants, leading to stable emulsions with improved drug solubility [62]. This compatibility is crucial in pharmaceutical emulsion design, as it allows for the tailored optimization of formulations.

8.3. Hydrophobic Drug Interactions

In pharmaceutical emulsions, the solubilization of hydrophobic drugs is a critical objective. Natural surfactants, owing to their unique amphiphilic nature, can interact with hydrophobic drug compounds to enhance their solubility and bioavailability [62]. These interactions involve the incorporation of drug molecules into the hydrophobic regions of micelles or vesicles formed by surfactants and co-surfactants. Recent research focused on the solubilization of a poorly water-soluble drug using natural surfactants extracted from soybeans. The study revealed that soybean-derived surfactants effectively solubilized the hydrophobic drug, significantly improving its bioavailability [63]. A study by Malikzad in 2018, demonstrated that plant proteins such as zein, gliadin, legumin and lectins possess favorable properties such as low toxicity, ready availability, easily modifiable structures with free functional groups, and good stability [66]. These findings emphasize the potential of plant-derived surfactants in enhancing drug delivery, particularly for hydrophobic compounds.

8.4. Emulsion Stability and Long-Term Storage

Maintaining emulsion stability during long-term storage is crucial for pharmaceutical formulations. Natural surfactants, owing to their unique properties, contribute to the formation of robust emulsion systems that resist phase separation and coalescence [64]. Understanding the physicochemical interactions at play is essential for formulating emulsions with prolonged shelf life. A study by Polychniatou in 2016, investigated the stability of pharmaceutical emulsions containing natural surfactants extracted from olive oil. The research demonstrated that olive oil-derived surfactants formed stable emulsions that maintained their integrity over an extended period. This stability was attributed to the strong interfacial interactions between the surfactants and oil droplets [65]. These findings

underscore the role of natural surfactants in ensuring the long-term stability of pharmaceutical emulsions.

9. Conclusion

Natural surfactants from plant extracts are emerging as viable alternatives for the preparation of pharmaceutical emulsions. They exhibit superior properties such as sustainability, biocompatibility, and efficacy compared to synthetic surfactants. A range of extraction and purification methods are employed to isolate these surfactants from various plant sources. The compatibility of these surfactants with pharmaceutical ingredients is also assessed to ensure their appropriateness for drug delivery systems. Natural surfactants from plant extracts have the capacity to transform the pharmaceutical industry by providing safer and greener options.

REFERENCES

- [1] Tmakova, L., Sekretar, S. and Schmidt, S. (2016) 'Plant-derived surfactants as an alternative to synthetic surfactants: surface and antioxidant activities' *Chemical Papers*, 70 (2), pp188-196. DOI: 10.1515/chempap-2015-0200.
- [2] Ceresa, C., Fracchia, L., Sansotera, A.C., De Rienzo, M.A.D. and Banat, I.M. (2023) 'Harnessing the Potential of Biosurfactants for Biomedical and Pharmaceutical Applications. *Pharmaceutics*, 15(8), pp21-56. doi.org/10.3390/pharmaceutics15082156.
- [3] Muhammad TM, M. Khan N. (2018) 'Eco-friendly, biodegradable natural surfactant (Acacia Concinna): An alternative to the synthetic surfactants' *Journal of Cleaner Production*, 188, pp 678-685. DOI: 10.1016/j.jclepro.2018.04.016.
- [4] Leticia Canal Vieira, Fernando Gonçalves Amaral, (2016) 'Barriers and strategies applying Cleaner Production: a systematic review, *Journal of Cleaner Production*, 113, pp 5-16. <https://doi.org/10.1016/j.jclepro.2015.11.034>.
- [5] Moldes AB, Rodriguez-Lopez L, Rincon-Fontán M, López-Prieto A, Vecino X, Cruz JM, (2021) 'Synthetic and Bio-Derived Surfactants Versus Microbial Biosurfactants in the Cosmetic Industry: An Overview', *Int J Mol Sci*, 27;22(5) pp2371. DOI: 10.3390/ijms22052371.
- [6] Piyali Dey, Somasree Ray, Pronobesh Chattopadhyay, (2023), '14 - Self-assembled protein nanoparticles for multifunctional theranostic uses, Editor(s): Somasree Ray, Amit Kumar Nayak, In *Woodhead Publishing Series in Biomaterials, Design and Applications of Theranostic Nanomedicines*', Woodhead Publishing, 2023, pp345-366.
- [7] Urmila Saha, Ranjit De, Bijan Das, (2023), 'Interactions between loaded drugs and surfactant molecules

in micellar drug delivery systems: A critical review' *Journal of Molecular Liquids*, 382, pp121906. DOI: 10.1021/la404166y.

[8] Ben M. Dolman, Fujun Wang, James B. Winterburn, (2019), 'Integrated production and separation of biosurfactants', *Process Biochemistry*, 83, 2019, pp 1-8. <https://doi.org/10.1016/j.procbio.2019.05.002>.

[9] Daniel Nunez, Paula Oulego, Sergio Collado, Francisco A. Riera, Mario Díaz, (2022), 'Separation and purification techniques for the recovery of added value biocompounds from waste activated sludge. A review', *Resources, Conservation and Recycling*, 182 (2022), pp106327. DOI: 10.1016/j.resconrec.2022.106327.

[10] Pokhrel DR, Sah MK, Gautam B, Basak HK, Bhattarai A, Chatterjee A, (2023), 'A recent overview of surfactant-drug interactions and their importance' *RSC Advances*, 2023 12;13(26), pp17685-17704. DOI <https://doi.org/10.1039/D3RA02883F>.

[11] Jean-Marie Aubry, Jesus F. Ontiveros, Jean-Louis Salager, Véronique Nardello-Rataj, (2020), 'Use of the normalized hydrophilic-lipophilic-deviation (HLDN) equation for determining the equivalent alkane carbon number (EACN) of oils and the preferred alkane carbon number (PACN) of nonionic surfactants by the fish-tail method (FTM)', *Advances in Colloid and Interface Science*, 276, pp.102099. DOI: 10.1016/j.cis.2019.102099.

[12] Mehanna MM, Mneimneh A, (2021). 'Formulation and Applications of Lipid-Based Nanovehicles: Spotlight on Self-emulsifying Systems', *Adv Pharm Bull*, 11(1) pp56-67. DOI: 10.34172/apb.2021.006.

[13] Perez-Rivero C, Lopez-Gomez JP, (2023), 'Unlocking the Potential of Fermentation in Cosmetics: A Review', *Fermentation*, 9(5), pp 463. <https://doi.org/10.3390/fermentation9050463>.

[14] Gul J, Ullah S, Ali I, Rao K, Iqbal KM, Jabri T, Perveen S, Rashid A, Shah MR, (2021), 'Synthesis, characterization and drug delivery application of Dapsone based double tailed biocompatible nonionic surfactant', *Chem Phys Lipids*, (239), pp105-115. DOI: 10.1016/j.chemphyslip.2021.105115.

[16] Barthe, M.; Bavoux, C.; Finot, F.; Mouche, I.; Cuceu-Petrenci, C.; Forreryd, A.; Chérourvriér Hansson, A.; Johansson, H.; Lemkine, G.F.; Thénot, J.-P.; et al, (2021), 'Safety Testing of Cosmetic Products: Overview of Established Methods and New Approach' *Methodologies (NAMs)*, *Cosmetics*, (8), p50. <https://doi.org/10.3390/cosmetics8020050>.

[17] Nagtode VS, Cardoza C, Yasin HKA, Mali SN, Tambe SM, Roy P, Singh K, Goel A, Amin PD, Thorat BR, Cruz JN, Pratap AP, (2023) 'Green Surfactants (Biosurfactants): A Petroleum-Free Substitute for Sustainability-Comparison', *ACS Omega*, 24;8(13), p11674-11699. doi: 10.1021/acsomega.3c00591.

[18] Ohadi M, Shahravan A, Dehghannoudeh N, Eslaminejad T, Banat IM, Dehghannoudeh G. Potential, (2020), 'Use of Microbial Surfactant in Microemulsion Drug Delivery System: A Systematic Review', *Drug Des Devel Ther*, 5 (14), p541-550. doi: 10.2147/DDDT.S232325.

- [19] Krister Holmberg, (2001), 'Natural surfactants', *Current Opinion in Colloid & Interface Science*, 6(2), pp148-159. DOI: 10.1016/S1359-0294(01)00074-7.
- [20] Alberts B, Johnson A, Lewis J, Raff M, Roberts K, and Walter P. (2002), 'Molecular Biology of the Cell'. 4th edition. New York: Garland Science;
- [21] Joaquin Navarro del Hierro, Teresa Herrera, Tiziana Fornari, Guillermo Reglero, Diana Martin, (2018), 'The gastrointestinal behavior of saponins and its significance for their bioavailability and bioactivities', *Journal of Functional Foods*, 40 (2018), pp484-497. <https://doi.org/10.1016/j.jff.2017.11.032>.
- [22] Rai S, Acharya-Siwakoti E, Kafle A, Devkota HP, Bhattarai A. (2022), 'Plant-Derived Saponins: A Review of Their Surfactant Properties and Applications', *Sci.* 3(4) p44. <https://doi.org/10.3390/sci3040044>
- [23] Michalak M, (2022), 'Plant-Derived Antioxidants: Significance in Skin Health and the Ageing Process' *International Journal of Molecular Sciences*, 23(2) pp585. DOI: 10.3390/ijms23020585.
- [24] Matthew Palmer, Hazel Hatley, (2018), 'The role of surfactants in wastewater treatment: Impact, removal and future techniques: A critical review', *Water Research*, 147, pp 60-72. <https://doi.org/10.1016/j.watres.2018.09.039>.
- [25] Acosta M, Reyes LH, Cruz J C and Pradilla D, (2020), 'Demulsification of Colombian Heavy Crude Oil (W/O) Emulsions: Insights into the Instability Mechanisms, Chemical Structure, and Performance of Different Commercial Demulsifiers', *Journal: Energy & Fuels*, 34(5), P 5665. DOI: 10.1021/acs.energyfuels.0c00313.
- [26] Hu F, Li F, Zheng Z, Sun-Waterhouse D, Wang Z, (2022), 'Surfactant-Mediated Ultrasonic-Assisted Extraction and Purification of Antioxidants from *Chaenomeles speciosa* (Sweet) Nakai for Chemical- and Cell-Based Antioxidant Capacity Evaluation. *Molecules* 2022, 27, 7970. <https://doi.org/10.3390/molecules27227970>.
- [27] Cakmakc R, Salik MA, Cakmakc S, (2023), 'Assessment and Principles of Environmentally Sustainable Food and Agriculture Systems, *Agriculture*, 13(5) p1073. <https://doi.org/10.3390/agriculture13051073>.
- [28] Lee MK, (2020), 'Liposomes for Enhanced Bioavailability of Water-Insoluble Drugs: In Vivo Evidence and Recent Approaches. *Pharmaceutics*, 13;12(3) p264. DOI: 10.3390/pharmaceutics12030264.
- [29] Smruti P. Chaudhari, Rohit P. Dugar, 2017. Application of surfactants in solid dispersion technology for improving solubility of poorly water-soluble drugs, *Journal of Drug Delivery Science and Technology*, 41 2017, pp68-77. DOI:10.1016/J.JDDST.2017.06.010.
- [30] Zhang X, Xing H, Zhao Y, Ma Z. (2018), 'Pharmaceutical Dispersion Techniques for Dissolution and Bioavailability Enhancement of Poorly Water-Soluble Drugs. *Pharmaceutics*, 23;10(3), pp74. DOI: 10.3390/pharmaceutics10030074
- [31] Nakmode D, Bhavana V, Thakor P, Madan J, Singh PK, Singh SB, Rosenholm JM, Bansal KK, Mehra NK. (2022), 'Fundamental Aspects of Lipid-Based Excipients in Lipid-Based Product Development.

Pharmaceutics, 14(4), pp831. DOI: 10.3390/pharmaceutics14040831

- [32] Soll RF, Blanco F. (2001), 'Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome', *Cochrane Database Syst Rev*, 2001;(2):CD000144. DOI: 10.1002/14651858.CD000144
- [33] Kumari L, Choudhari Y, Patel P, Gupta GD, Singh D, Rosenholm JM, Bansal KK, Kurmi BD. (2023), 'Advancement in Solubilization Approaches: A Step towards Bioavailability Enhancement of Poorly Soluble Drugs', *Life*. 2023; 13(5), pp1099. <https://doi.org/10.3390/life13051099>.
- [34] Peetla C, Stine A, Labhasetwar V. (2009), 'Biophysical interactions with model lipid membranes: applications in drug discovery and drug delivery', *Mol Pharm*, 6(5), pp1264-1276. DOI: 10.1021/mp9000662
- [35] Pardridge WM. (2012), 'Drug transport across the blood-brain barrier. *J Cereb Blood Flow*', *Metab*, 32(11), pp1959-1972. DOI: 10.1038/jcbfm.2012.126.
- [36] Zembyla M, Brent S. Murray, Sarkar A. (2020), 'Water-in-oil emulsions stabilized by surfactants, biopolymers and/or particles: a review', *Trends in Food Science & Technology*, 104, pp 49-59. <https://doi.org/10.1016/j.tifs.2020.07.028>.
- [37] Gonzalez-Gonzalez O, Ramirez IO, Ramirez BI, O'Connell P, Ballesteros MP, Torrado JJ, Serrano DR. (2022), 'Drug Stability, ICH versus Accelerated Predictive Stability Studies', *Pharmaceutics*, 14(11), pp2324. DOI: 10.3390/pharmaceutics14112324.
- [38] Akinsemolu A, Onyeaka H, Fagunwa O, Adenuga AH. (2023), 'Toward a Resilient Future: The Promise of Microbial Bioeconomy', *Sustainability*. 2023; 15(9), pp7251. <https://doi.org/10.3390/su15097251>.
- [39] Lajoie L, Fabiano-Tixier A-S, Chemat F. (2022), 'Water as Green Solvent: Methods of Solubilisation and Extraction of Natural Products—Past, Present and Future Solutions', *Pharmaceutics*. 2022; 15(12), pp1507. <https://doi.org/10.3390/ph15121507>.
- [40] Chibuye B, Singh SI, Chimuka L, Maseka KK, (2023), 'A review of modern and conventional extraction techniques and their applications for extracting phytochemicals from plants', *Scientific African*, 19, pp2468-2276. doi: 10.3390/molecules28104019.
- [41] Zoric M, Banozic M, Aladic K, Vladimir-Knezevic S, Jokic S, (2022), 'Supercritical CO₂ extracts in cosmetic industry: Current status and future perspectives', *Sustainable Chemistry and Pharmacy*, 27, 352-361. DOI: 10.1016/j.scp.2022.100688.
- [42] Luo, M., Zhou, D. D., Shang, A., Gan, R. Y., and Li, H. B. (2021). 'Influences of microwave-assisted extraction parameters on antioxidant activity of the extract from *Akebia trifoliata* peels', *Foods* 10(6), pp1432. <https://doi.org/10.3390/foods10061432>.
- [43] Mehta N, S J, Kumar P, Verma AK, Umaraw P, Khatkar SK, Khatkar AB, Pathak D, Kaka U, Sazili AQ. (2022), 'Ultrasound-Assisted Extraction and the Encapsulation of Bioactive Components for Food Applications', *Foods*, 11(19), pp2973. <https://doi.org/10.3390/foods11192973>.

- [44] Coskun O. 'Separation techniques: Chromatography', *North Clin Istanbul*. 11;3(2), pp156-160. doi: 10.14744/nci.2016.32757.
- [45] Gul A, Hruza J, Yalcinkaya F. (2021), 'Fouling and Chemical Cleaning of Microfiltration Membranes: A Mini-Review', *Polymers*, 13(6), pp846. <https://doi.org/10.3390/polym13060846>.
- [46] Getachew AT, Jacobsen C, Holdt SL. (2020), 'Emerging Technologies for the Extraction of Marine Phenolics: Opportunities and Challenges.', *Marine Drugs*. 2020; 18(8), pp389. <https://doi.org/10.3390/md18080389>.
- [47] Li Z, Huang X, Tang Q, Ma M, Jin Y, Sheng L. (2022), 'Functional Properties and Extraction Techniques of Chicken Egg White Proteins', *Foods*, 11(16), pp434. DOI: 10.3390/foods11162434.
- [48] Tian Y, Zhou J, He C, He L, Li X, Sui H. The Formation, Stabilization and Separation of Oil–Water Emulsions: A Review', *Processes*, 10(4), pp738. <https://doi.org/10.3390/pr10040738>.
- [49] Salager J-L, Anton R, Bullón J, Forgiarini A, Marquez R. (2020), 'How to Use the Normalized Hydrophilic-Lipophilic Deviation (HLDN) Concept for the Formulation of Equilibrated and Emulsified Surfactant-Oil-Water Systems for Cosmetics and Pharmaceutical Products', *Cosmetics*, 7(3), pp57. <https://doi.org/10.3390/cosmetics7030057>.
- [50] Nikolaev B, Yakovleva L, Fedorov V, Li H, Gao H, Shevtsov M. (2023), 'Nano- and Microemulsions in Biomedicine: From Theory to Practice', *Pharmaceutics*, 15(7), pp198. <https://doi.org/10.3390/pharmaceutics15071989>.
- [51] Ma P, Zeng Q, Tai K, He X, Yao Y, Hong X, Yuan F. Development of stable curcumin nanoemulsions: effects of emulsifier type and surfactant-to-oil ratios. *J Food Sci Technol*. 2018 Sep;55(9):3485-3497. doi: 10.1007/s13197-018-3273-0.
- [52] Pandey R, Bhairam M, Shukla SS, Gidwani B. Colloidal and vesicular delivery system for herbal bioactive constituents. *Daru*. 2021 Dec;29(2):415-438. doi: 10.1007/s40199-021-00403-x.
- [53] Adeyemi SB, Akere AM, Orege JI, Ejeromeghene O, Orege OB, Akolade JO. Polymeric nanoparticles for enhanced delivery and improved bioactivity of essential oils. *Heliyon*. 2023 Jun 2;9(6):e16543. doi: 10.1016/j.heliyon.2023.e16543.
- [54] Ranjbar S, Emamjomeh A, Sharifi F, Zarepour A, Aghaabbasi K, Dehshahri A, Sepahvand AM, Zarrabi A, Beyzaei H, Zahedi MM, et al. (2023), 'Lipid-Based Delivery Systems for Flavonoids and Flavonolignans: Liposomes, Nanoemulsions, and Solid Lipid Nanoparticles', *Pharmaceutics*, 15(7), pp1944. <https://doi.org/10.3390/pharmaceutics15071944>.
- [55] Elmowafy M, Shalaby K, Elkomy MH, Alsaidan OA, Gomaa HAM, Abdelgawad MA, Mostafa EM. Polymeric Nanoparticles for Delivery of Natural Bioactive Agents: Recent Advances and Challenges', *Polymers*, 15(5), pp11-23. <https://doi.org/10.3390/polym15051123>.
- [56] Xu M, Wan Z, Yang X. (2021), 'Recent Advances and Applications of Plant-Based Bioactive Saponins

- in Colloidal Multiphase Food Systems,' *Molecules*, 8;26(19), pp60-75. DOI: 10.3390/molecules26196075.
- [57] Njinga NS, Kola-Mustapha AT, Quadri AL, Atolani O, Ayanniyi RO, Buhari MO, Amusa TO, Ajani EO, Folaranmi OO, Bakare-Odunola MT, Kambizi L, Oladiji AT, Ebong P. (2020), 'Toxicity assessment of sub-acute and sub-chronic oral administration and diuretic potential of aqueous extract of *Hibiscus sabdariffa* calyces', *Heliyon*, 6(9), pp48-53. DOI: 10.1016/j.heliyon.2020.e04853.
- [58] Nastiti CMRR, Ponto T, Abd E, Grice JE, Benson HAE, Roberts MS. (2017), 'Topical Nano and Microemulsions for Skin Delivery', *Pharmaceutics*, 9(4), pp37. DOI: 10.3390/pharmaceutics9040037.
- [59] Villa C, Moura MBMV, Costa J, Mafra I. (2020), 'Immunoreactivity of Lupine and Soybean Allergens in Foods as Affected by Thermal Processing', *Foods*, 9(3), pp254. doi: 10.3390/foods9030254.
- [60] Karen G.O. Bezerra, Israel G.S. Silva, Fabiola C.G. Almeida, Raquel D. Rufino, Leonie A. Sarubbo, (2021), 'Plant-derived biosurfactants: Extraction, characteristics and properties for application in cosmetics', *Biocatalysis and Agricultural Biotechnology*, 34(10), pp1878-818. DOI: 10.1016/j.bcab.2021.102036.
- [61] Singh A, Chaturvedi RK, Sharma T, (2021), 'Natural surfactant for sustainable carbon utilization in cleaner production of fossil fuels: Extraction, characterization and application studies', *Journal of Environmental Chemical Engineering*, 9 (5), 106231. DOI: 10.1016/j.jece.2021.106231.
- [62] Massarweh O, Abushaikh, AS. (2020), 'The use of surfactants in enhanced oil recovery: A review of recent advances', *Energy Reports*, 6, pp3150-3178. [https://doi.org/10.1016/S1876-3804\(24\)60480-5](https://doi.org/10.1016/S1876-3804(24)60480-5).
- [63] Karabayanova L, Ganiyeva A, Pourafshary P, Hashmet MR, (2022), 'Application of hybrid low salinity hot water flooding to enhance oil recovery from heavy oil carbonates, *Journal of Petroleum Science and Engineering*, Vol 215, Part B, 110656, <https://doi.org/10.1016/j.petrol.2022.110656>.
- [64] Costa C, Medronho B, Filipe A, Mira I, Lindman B, Edlund H, Norgren M. (2019), 'Emulsion Formation and Stabilization by Biomolecules: The Leading Role of Cellulose', *Polymers*. 11(10), pp1570. DOI: 10.3390/polym11101570.
- [65] Polychniatou, V., Tzia, C. (2016). Study of the Emulsifying Ability of Olive Oil Endogenous Compounds in Co-surfactant Free Olive Oil w/o Nanoemulsions with Food Grade Non-ionic Surfactants, *Food Bioprocess Technol.* 9, 882–891. DOI: 10.1007/s11947-015-1668-8.
- [66] Malekzad H, Mirshekari H, Sahandi Zangabad P, Moosavi Basri SM, Baniasadi F, Sharifi Aghdam M, Karimi M, Hamblin MR. (2018). 'Plant protein-based hydrophobic fine and ultrafine carrier particles in drug delivery systems', *Crit Rev Biotechnol.* 38(1):47-67. DOI: 10.1080/07388551.2017.1312267.
- [67] Ganesh AN, Aman A, Logie J, Barthel BL, Cogan P, Al-Awar R, Koch TH, Shoichet BK, Shoichet MS. (2019), 'Colloidal Drug Aggregate Stability in High Serum Conditions and Pharmacokinetic Consequence'. *ACS Chem Biol.* 19,14(4):751-757. <https://doi.org/10.1021/acscchembio.9b00032>.
- [68] Salomon G, Giordano-Labadie F. (2022), 'Surfactant irritations and allergies. *Eur J Dermatol.*

1;32(6):677-681. DOI: 10.1684/ejd.2022.4290.

[69] Zwolak A, Sarzynska M, Szpyrka E, Stawarczyk K. (2019) 'Sources of Soil Pollution by Heavy Metals and Their Accumulation in Vegetables. Water, Air, Soil Pollut. 2019;230:164. DOI <https://doi.org/10.1007/s11270-019-4221-y>.

[70] Leanpolchareanchai, J. Teeranachaideekul, V. (2023), 'Topical Microemulsions: Skin Irritation Potential and Anti-Inflammatory Effects of Herbal Substances. Pharmaceuticals 2023, 16, 999. <https://doi.org/10.3390/ph16070999>.