

Potential Use of Microbial Surfactant in Microemulsion Drug Delivery System: A Systematic Review

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Background: Microemulsions drug delivery systems (MDDS) have been known to increase the bioavailability of hydrophobic drugs. The main challenge of the MDDS is the development of an effective and safe system for drug carriage and delivery. Biosurfactants are preferred surface-active molecules because of their lower toxicity and safe characteristics when compared to synthetic surfactants. Glycolipid and lipopeptide are the most common biosurfactants that were tested for MDDS. The main goal of the present systematic review was to estimate the available evidence on the role of biosurfactant in the development of MDDS.

Search Strategy: Literature searches involved the main scientific databases and were focused on the period from 2005 until 2017. The Search filter composed of two items: “Biosurfactant” and/or “Microemulsion.”

Inclusion Criteria: Twenty-four studies evaluating the use of biosurfactant in MDDS were eligible for inclusion. Among these 14 were related to the use of glycolipid biosurfactants in the MDDS formulations, while four reported using lipopeptide biosurfactants and six other related review articles.

Results: According to the output study parameters, biosurfactants acted as active stabilizers, hydrophilic or hydrophobic linkers and safety carriers in MDDS, and among them glycolipid biosurfactants had the most application in MDDS formulations.

Conclusion: Synthetic surfactants could be replaced by biosurfactants as an effective bio-source for MDDS due to their excellent self-assembling and emulsifying activity properties.

Keywords: microemulsion, drug delivery systems, biosurfactant, systematic review glycolipid, lipopeptide

Introduction

A major challenge in the pharmaceutical sciences is the development of drug delivery systems (DDS) for the improvement of oral bioavailability of a great number of drugs that exhibit poor aqueous solubility.¹ Some strategies such as MDDS have been pursued towards the development of delivery systems that are able to overcome this challenge. MDDS are usually used to improve the oral bioavailability of hydrophobic drugs.^{1,2} MDDS contain lipids, surfactants, co-surfactants and/or co-solvents.³ MDDS are being formulated to be used through diverse routes of delivery eg, oral, nasal, ocular, topical and intravenous. They are usually small size, globular shaped and can solubilize hydrophobic drugs.⁴ Despite the popularity of MDDS, there have been numerous challenges during

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their formulation, stability and packaging. The shortcomings related to the formulation of MDDS include inadequate solubility in lipidic constituents, lower drug loading ability and higher risks of gastrointestinal irritation (GI) due to the presence of high quantities of surfactants (30–60% w/w).⁵ Hence, increased efforts are applied in the search for acceptable excipients for use in the design of safer MDDS, specifically for oral or parental routes.⁵ The major constituents used for the production of MDDS are surfactants or emulsifiers.

The self-aggregates characteristics of the surfactant can form different structures, which are able to encapsulate and solubilize the hydrophobic or hydrophilic drugs in the presence of a dispersed phase [oil for oil-in-water (O/W) or water for water-in-oil (W/O) microemulsion] within their structural core.⁶ Using biosurfactants in formulating microemulsion instead of surfactants, increases the safety and minimizes toxicity and gastric irritation typically associated with or caused by using a surfactant.¹ Biosurfactants comprise a wide variety of structurally distinct amphipathic molecules with potential applications in a wide range of biomedical fields, such as gene delivery,⁷ antimicrobial,^{8,9} anticancer,¹⁰ and wound healing activities.^{11–13} According to chemical structures, biosurfactants are categorized into two main groups; the lipopeptides and the glycolipids.¹⁴ In nature, microemulsions formed using biosurfactant are thermodynamically stable and their isotropic systems are considered to be very promising in the development for DDS.^{1,7} The production of nanoparticles with different physical structures and high monodispersity is another challenge in the targeted DDS.¹⁵ The available techniques in industrial pharmaceuticals are very expensive, time-consuming and often produce hazardous wastes.¹⁶ Therefore, clean, non-toxic, size-controlled and environmentally acceptable techniques are vital.¹⁵ Microemulsion techniques using an oil-water biosurfactant mixture are useful in the production of the stable and uniform nanoparticles.¹⁷ For instance, glycolipid biosurfactants were used as a bioemulsifier in the synthesis of the silver nanoparticles by reverse microemulsion technique.^{18,19} Therefore, the main goal of the present study was to assess the efficacy and safety of biosurfactant in MDDS formulations.

Phase Behavior and Properties of Biosurfactants in Microemulsion Drug Delivery System

Microemulsions have several specific features that make them appropriate for drug delivery. The identification of

the benefits and drawbacks of microemulsion drug delivery systems, therefore, is crucial in making informed decisions about the delivery of active pharmaceutical ingredients (APIs).¹ The most important benefit of microemulsion systems is solubilizing both hydrophilic and lipophilic APIs. This feature is challenging when considering APIs which do not fall into both categories, such as minerals. APIs, such as iron and calcium follow the same pattern when adding to a microemulsion system, forming a suspension is possible.²⁰ On the other hand, to produce a microemulsion-based colloidal DDS product, emulsifiers like surfactants are needed. Synthetic surfactants, which have not been approved for use in pharmaceutical formulations have been used and have exhibited some toxic effects. However, recently using microbial surfactants to replace synthetic surfactants for formulating approved microemulsion systems pharmaceutically with no toxicity has been considered.¹ Microbial surfactants have different amphipathic molecules and specific chemical design naturally generated via different microorganisms. In contrast to surfactants generated by chemical synthesis and categorized based on the head group, microbial surfactants are commonly classified according to the chemical composition as well as molecular weight, including low (glycolipids and lipopeptides) and high (polysaccharides, proteins, and lipoproteins) molecular weight surfactants. Generally, the amphiphilic and polyphilic polymers have shown to be commonly more beneficial to stabilize emulsions, whereas the microbial surfactants that have lower molecular weights possess simpler designs resulting in appropriate surface-active characteristics.²¹ An acid, peptide cations/anions, and mono/di-polysaccharides commonly form hydrophilic moiety of microbial surfactants, whereas their hydrophobic moiety is mainly the unsaturated/saturated hydrocarbon chains or fatty acid part. They have several advantages compared to chemical surfactants, including biodegradability, moderate generation states, adaptability to the environment, lower toxic effects, high selectivity and effectiveness in environments with high temperature, pH and salinity.²¹ The nature as well as stability of a microemulsion-based DDS cannot be predicted easily; however, it has widely been accepted that prior awareness regarding the features of the system and its elements via an appropriate evaluation of several factors, including surface characteristics and the hydrophilic–lipophilic balance (HLB) can remarkably decrease the complexity of rational element selection resulting in a successful

microemulsion formulation.¹ Adding surfactants into a specific solution can lower its surface tension because of its molecules partitioning at the interface. Many surfactant adsorption as well as self-accumulation or aggregations within aqueous solutions has been reported to produce micelle, lamellar and crystalline structures.²⁰ The stability of the emulsion can be affected by HLB and shows the moderate effect of the surfactant's hydrophilic and lipophilic groups. Low HLB grades (3 to 6) lead to the formation of W/O microemulsions, while high HLB grades (8 to 18) lead to the formation of O/W microemulsions (Table 1).^{22,23}

In contrast to synthetic surfactants, biosurfactants show uncertain demarcations among their hydrophilic and lipophilic groups. Their head groups' complicated nature (amino acids in lipopeptide and saccharides in glycolipids) can result in difficulty in appropriate evaluation of their structure, since they are adoptable to different structures with just a little alteration in the environment. For example, such biosurfactants are possibly anionic at higher pH levels (because of carboxylic groups) and non-ionic at lower pH values. In addition, a transition from micellar toward lamellar structure after adding electrolyte has been shown, which is valuable for tailoring a DDS for a specific API, or for conferring its function in special environmental situations (managed drug release), triggered via pH, temperature or salinity changes.¹ Besides the imperative possibility of using biosurfactants in microemulsion-oriented drug formulations, they are used for triggered as well as targeted drug delivery. Shim et al²⁴ investigated small interfering RNA (siRNA) enhanced delivery of the HeLa cells by cationic surfactin liposomes then surfactin-free liposomes. They have shown that the surfactin with liposomes through their more biocompatibility can increase the given gene silencing process. Accordingly, the more effective delivery system results in a rise in the cellular

Table 1 The Uses of Surfactants with Different HLB Values

| Surfactant HLB Value | Uses Surface |
|----------------------|--------------------------|
| <3 | Surface films |
| 3–6 | Water-in-oil emulsifiers |
| 7–9 | Wetting agent |
| 8–15 | Oil-in-Water emulsifiers |
| 13–15 | Detergents |
| 15–18 | Solubilizes |

uptake of siRNA, leading to enhancing the particular knockdown impact.

Research Question

Could microbial surfactant be effective in MDDS?

Study Objectives

The main goal of the present systematic review was to estimate the available evidence on the role of the biosurfactant in the development of MDDS.

Methods

A comprehensive literature search was carried out using the ISI Web of Science and PubMed search engines. Both databases were selected in order to cover all of the published peer-reviewed literature. A search filter composed of two items, "Biosurfactant" and "Microemulsion," was executed. These topics were combined using the Boolean operators "AND" and "OR" and the search strategy path was shown as following (Table 2).

Eligibility Criteria

The search was limited to publications in English between 2005 and 2017. Outcome parameters were grouped into three different categories (Table 3) and discussed.

Table 2 Search Strategy for Each Database by Topic

| PubMed |
|--|
| (biosurfactant [All Fields] OR (microbial [All Fields] AND ("surface-active agents"[Pharmacological Action] OR "pulmonary surfactants"[Pharmacological Action] OR "surface-active agents"[MeSH Terms] OR ("surface-active"[All Fields] AND "agents"[All Fields]) OR "surface-active agents"[All Fields] OR "surfactant"[All Fields] OR "pulmonary surfactants"[MeSH Terms] OR ("pulmonary"[All Fields] AND "surfactants"[All Fields]) OR "pulmonary surfactants"[All Fields])) AND microemulsion [All Fields]. |
| ISI Web of Science |
| ((biosurfactant) OR (microbial surfactant) AND microemulsion). |

Table 3 Categories of Outcome Parameters

| Outcome Group | Outcome Parameter |
|--------------------------------|---|
| Stable formulation | - Physicochemical Stability |
| Hydrophilic/Hydrophobic linker | - Alcohol free microemulsion |
| Safety | - Nontoxic, biodegradable, and biocompatible MDDS |

Data Collection and Analysis

PRISMA guidelines were followed using the PRISMA 2009 checklist.²⁵

Results

Description of Related Published Literature

24 unique publications were found from PubMed and Web of Science (Figure 1).

Six of 24 papers were review articles that clarify the selection of design is indicated. The publications of Rodrigues et al

and Gudina et al^{1,20} are review articles that discuss the fundamentals and applicability of biosurfactants in the formulation of nano-sized drug delivery vectors. Therefore, they were considered pivotal publications in this area. This was followed by two review articles referring to the self-assembling and emulsification properties of glycolipid biosurfactants and their role in drug delivery.^{26,27} Another important publication was that of Kiran et al¹⁵ who describes a microemulsion technique that was believed to be a promising approach for nanoparticle synthesis. The remaining 18 publications selected in

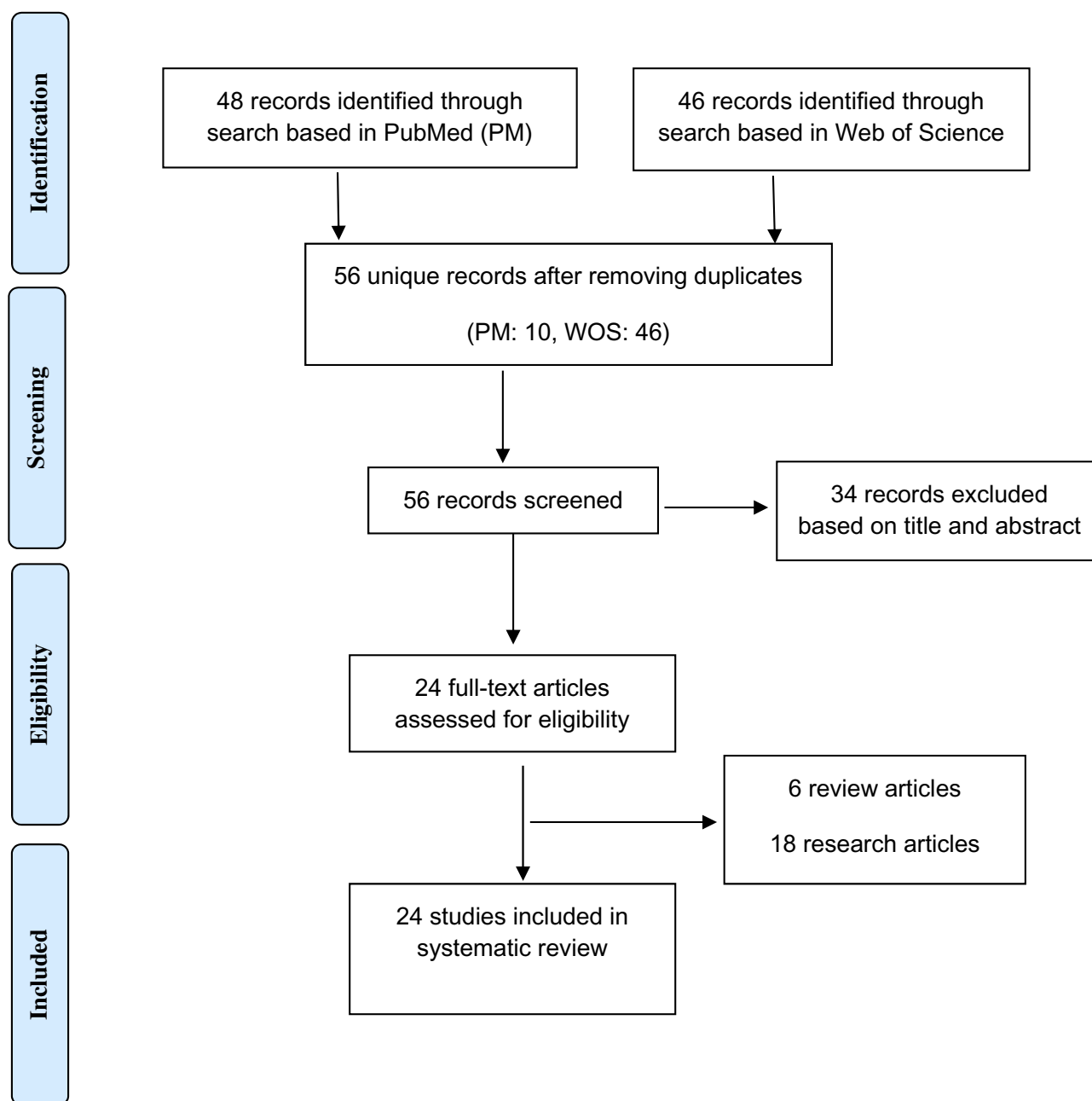


Figure 1 Flowchart of selection criteria/process and included studies.

this study described various biosurfactants such as surfactin, rhamnolipid, sophorolipid, mannosylerythritol lipid (MEL_S) and trehalose lipid used in the formulation of MDDS. The different types of biosurfactants investigated in these articles are presented in Table 4. Due to the heterogeneity of the studies, a meta-analysis could not be carried out.

The study parameters were systematically included in the detailed analysis and the methodological strengths or weaknesses were identified (Table 5).

Glycolipid Biosurfactants as Ingredients for Microemulsion Systems

Mannosylerythritol Lipid

The role of MEL_S biosurfactant as constituents of microemulsion systems was investigated by three research articles (Table 5). MEL-A and MEL-D can be used to prepare stable W/O microemulsions without the addition of a co-surfactant or salt.^{28,29} Another study investigated the aqueous-phase behavior, capability of self-assembling and vesicle-forming activity of MEL-B.³⁰ Overall, it can be concluded that MEL_S has shown distinct emulsifying activity to form stable W/O microemulsions in the absence of co-surfactants or salts.

Rhamnolipids and Sophorolipids

The effects of rhamnolipids and sophorolipids in microemulsion formulation were examined by 10 research articles (Table 5). Rhamnolipids are used in the microemulsion synthesis as co-surfactant. Moreover, the phase behavior and microstructure of these microemulsions were rational to the conformational changes of rhamnolipid molecules at the interface of O/W.^{31,32} The results from Mendes and collaborators³³ suggested that rhamnolipid extracts from *Pseudomonas aeruginosa* PA1 may be used to formulate stable emulsions of methyl methacrylate. Rhamnolipids were used as the stabilizer of a W/O microemulsion, which was used as the medium for an enzymatic reaction.³⁴ Nguyen and Sabatini³⁵ formulated alcohol-free microemulsions using rhamnolipids. In addition, microemulsions of lecithin/

rhamnolipid/sophorolipid biosurfactants using a range of oils have been developed and evaluated. Results showed that the phase behavior of these biocompatible microemulsions did not change significantly with changing temperature and electrolyte concentration.³⁶

Some successful examples have been reported in the literature on the use of microemulsions such as nanoreactor through using glycolipid biosurfactants for the production of stable and uniform nanoparticles.^{16,18,19,37} Purified rhamnolipids from *P. aeruginosa* strain BS-161R were used to synthesize silver nanoparticles which exhibited good antibiotic activity against both Gram-positive and Gram-negative pathogens and *Candida albicans*.¹⁹ Glycolipids were used as a stabilizer for the synthesis of stable and uniform silver nanoparticles.³⁷ Nickel oxide nanoparticles were synthesized by microemulsion technique using rhamnolipids which were fully crystalline and spherical in shape with uniform distribution.¹⁶ Rhamnolipids were used as reverse micelles and shell phase in the silver nanoparticles and polymethyl methacrylate nanoparticles (nPMMA), respectively.¹⁸ The unique biosurfactant-coated nPMMA enabled it to be both a pH-responsive nanocarrier and to possess a tailored release profile.³⁸ Therefore, it can be concluded that rhamnolipids and sophorolipids were successfully used for the synthesis and stabilization of metal-bound nanoparticles and developing stable and alcohol-free microemulsions.

Trehalose Lipid

The role of trehalose lipid in microemulsion formulation was described by Hazra et al³⁸ (Table 5). Trehalose lipid could be successfully used to O/W-modified atomized microemulsion process for the synthesis of novel nPMMA. The amounts of biosurfactant required for the synthesis of the nPMMA were much lower in comparison with those used in a conventional microemulsion polymerization system. Thus, it can be concluded that these nanoparticles were non-toxic and biocompatible.

Lipopeptide Biosurfactant as Ingredients for Microemulsion Systems

Surfactin was successfully used to form microemulsions. Remarkably, the use of surfactin in microemulsion formulations instead of synthetic surfactants has been reported to result in lower toxicity and physicochemical stability of microemulsion formulation.^{39,40} As an example, surfactin has been used to prepare an MDDS of vitamin E and docosahexaenoic acid

Table 4 Overview of Microemulsion Formulation by Biosurfactant

| Type of Biosurfactant | Research Articles |
|--------------------------------|-------------------|
| Mannosylerythritol lipids | 3 |
| Rhamnolipids | 8 |
| Rhamnolipids and sophorolipids | 2 |
| Trehalose lipid | 1 |
| Surfactin | 4 |
| Total | 18 |

Table 5 Functions and Applications of Microbial Surfactant in Different in MDSS

| Microemulsion Formulation | Type of Biosurfactant | Biosurfactant Function | Application of Microemulsion Formulation | References |
|---|---|--|---|---------------|
| Lipopeptide biosurfactants -containing self-microemulsifying system (SMEDDS) with vitamin E | Surfactin | As active stabilizer | -A stable drug delivery system | [39] |
| Lipopeptide biosurfactants-containing SMEDDS with Docosahexaenoic acid | Surfactin | As active stabilizer | -A stable drug delivery system | [40] |
| Mixed lecithin/glycolipid biosurfactants with a range of oils | Rhamnolipid/Sophorolipid | Stabilizer, Hydrophilic/Hydrophobic Linker | -Cosmetic, drug delivery and detergency application | [36] |
| Mixed glycolipid biosurfactants/alcohol/n-heptane/water | Rhamnolipid | Emulsifier, Stabilizer | -Drug delivery | [32] |
| Mixed glycolipid biosurfactants/n-butanol/water/n-heptane | Rhamnolipid | Emulsifier, Stabilizer | -Drug delivery | [31] |
| Mixed glycolipid biosurfactants/oils/water | Rhamnolipid | Hydrophilic/Hydrophobic linker, Emulsifier | -Drug delivery and detergency application | [35] |
| Mixed glycolipid biosurfactants/water/n-decane | Mannosylerythritol Lipid-A | Hydrophilic/Hydrophobic linker, Emulsifier | -Detergency application | [28] |
| Glycolipid biosurfactants – functionalized | Mannosylerythritol lipid-B | Vesicle-forming | -Transdermal delivery systems | [30] |
| Mixed glycolipid biosurfactants/water/various oily solution | Mannosylerythritol Lipid-D | Hydrophilic/Hydrophobic linker, Emulsifier | -Detergency application | [29] |
| Lipopeptide biosurfactants -mediated Brushite nanoparticles | Surfactin | Stabilizer | -Technological applications | [41] |
| Glycolipid biosurfactants -containing SMEDDS | Rhamnolipid | Emulsifier, Stabilizer | -Drug delivery and detergency application -Enzymatic-hydrolysis-enhancer | [33,34] |
| Novel poly(methylmethacrylate) (nPMMA) (core)–biosurfactant (shell) nanoparticle | Rhamnolipid, Trehalose lipid, Surfactin | Stabilizer, Hydrophilic/Hydrophobic linker | -Drug delivery -Anticancer -Antibacterial | [38] |
| Glycolipid biosurfactants -mediated Silver nanoparticles | Rhamnolipid | Stabilizer | -Drug delivery -Anticancer -Antibacterial | [18,19,37,42] |
| Glycolipid biosurfactants -mediated nickel oxide (NiO) particles nanoparticles | Rhamnolipid | Stabilizer | -Drug delivery | [16] |

(DHA) to enhance their pharmaceutical performance.^{39,40} Additionally, Maity and collaborators⁴¹ used a reverse microemulsion technique with surfactin to build up nanocrystalline brushite particles of calcium phosphate. The particle sizes ranged from 16 to 200 nm. Morphological varieties were observed in the synthesized microemulsions, which consisted of nano-spheres and needle-like noncalcinated particles. The calcinated products included nano-spheres, oval and nano-rod particles. Surfactin and rhamnolipid were used in an emulsion polymerization approach to develop a biodegradable core-shell poly (methyl methacrylate)/biosurfactant bionano-composites for protein drug release.³⁸ All of these results

indicated a significant increase in the emulsification efficiency, dissociation rate and consequently oral bioavailability of the therapeutic agent when using surfactin as ingredients for MDSS.

Discussion

Discovering new drugs and developing their best DDS are one of the main challenges in the medical field as it affects efficacies and outcome of several types of diseases and treatments.⁴³ Drug loading capacity and subsequent release are two key characters of an ideal DDS, which cause the increased drug bioavailability, ability to reach

the target and release in a controlled and timely manner.²⁰ Therefore, polymeric, particulate, macromolecular and cellular carriers have been developed as diverse types of drug delivery vectors.^{44–46} Microspheres, nanoparticles, micelles and liposomes are all among colloidal forms of DDS.⁴⁷ Microemulsions have become popular as new DDS that are composed of at least water, oil and surfactants. One of the most important challenges in the optimal formulation is the biocompatibility and the safety of the materials used.⁴ Natural oils and microbial surfactants were used in the formulation of microemulsions. Natural oils are relatively difficult to solubilize in microemulsions while microbial surfactants have emerged as alternatives to their synthetic counterparts.⁴⁸

According to two described biosurfactant types (glycolipid and lipopeptide), it was clear that MDDS containing biosurfactants have been demonstrated to greatly increase the efficacy and safety of microemulsion formulation (Table 5). The evidence has been presented that among biosurfactants, glycolipid biosurfactants, in particular, showed versatile surface-active properties including emulsifying and solubilizing actions (Table 5). MEL glycolipids exhibited excellent self-assembling properties and pharmacological activities. They were able to spontaneously self-assemble into distinctive lyotropic liquid crystals including sponge, bicontinuous cubic and lamellar phases.⁴⁹ Among these molecular assemblies, vesicle constructs were the most studied shapes. MEL-B was able to form giant vesicles with diameters larger than 10 μm due to their efficient molecular orientation and effective balance between the hydrophilic and hydrophobic moieties.³⁰ It is important to mention that the formation of such giant vesicles is not straightforward since the vesicle structure requires strictly balanced hydrophobic and hydrophilic groups for this to occur. On the other hand, MEL-A and MEL-D were the first natural compound to display the formation of the sponge phase by themselves. Although MEL-A and MEL-D have poor solubility in water, they can form a stable W/O microemulsion without the addition of a co-surfactant or salt.⁵⁰

The results of this systematic review provided a strong evidence that rhamnolipids and sophorolipids can act as hydrophilic/hydrophobic linkers (Table 5). For instance, rhamnolipid and sophorolipid can be mixed with lecithins to prepare stable and biocompatible microemulsions without the addition of a co-surfactant.³⁶ Rhamnolipid played an important role as the hydrophilic component due to having two hydrophilic sugar head groups, whereas sophorolipid

were found to be more hydrophobic as a result of the presence of one long tail of an unsaturated fatty acid and acetyl groups in their formulations.³⁶ Among lipopeptide biosurfactants, surfactin, as a harmless biosurfactant, has extremely strong surface activity. The results reported by He and collaborators⁴⁰ confirmed that a small amount of surfactin could enhance the formation of O/W docosahexaenoic acid single cell oil (DHASCO) microemulsion and decrease O/W DHASCO particle to nano-scale, which promotes the physical stability of the microemulsion and significantly reduces the oxidation of DHA in microemulsion during long storage periods.

Another interesting evidence in this study is the application of reverse microemulsion techniques as nanoreactors to synthesize metal-bound nanoparticles using an environmentally friendly technology (Table 5). One of the easiest and lowest-cost process methods for the synthesis of nanoparticles is chemical reduction.⁵¹ The drawbacks of this method are that the nanoparticles are unstable and inclined to aggregate into larger structures. Additionally, the process involves chemicals that are toxic and has associated health risks.¹ However, alternatives to these chemical methods have been developed recently, using reverse microemulsion technique and substituting the common reducing agents with non-toxic biocompatible microbial surfactant.¹⁵ Surfactants and biosurfactant as a stabilization agent adsorb on the particle surface, inhibiting them from aggregating, thus controlling their size and shape or preventing the formation of aggregates.^{15,52} The influence of the molar ratio of water to surfactant on particle size, distribution and monodispersity of the particles was demonstrated.⁵³

Conclusion

The output study parameters indicate that biosurfactants are active stabilizer, hydrophilic or hydrophobic linkers and safety carriers in MDDS. It seems that among biosurfactants glycolipid had the most application in the formulation of microemulsions. It could be concluded therefore that synthetic surfactants could be replaced by biosurfactants as a bio-source due to their excellent self-assembling and emulsifying activity in MDDS. However, detailed studies are required to fully investigate this process possibly on animal models to ensure safety validation.

Challenges and Recommendations for Future Research

This paper provides an overview of the usage of microbial surfactant in MDDS. Due to the heterogeneity of the

included studies, a meta-analysis was not carried out. Congress papers, expert opinions, books, and unpublished papers should be expanded in the literature search. The present challenges in the medical field are developing enhanced bioavailability of new drugs and DDS. MDDS are easy to formulate and have become popular as new DDS. They can be used as oral, nasal, ocular, topical and intravenous devices.⁶ Therefore, increased efforts in the search for acceptable excipients to be used in the design of safer microemulsions for drug delivery applications have been observed lately. Biocompatibility and safety of microemulsion formulations can be enhanced using microbial surfactant as alternatives to their synthetic counterparts. However, limited reports addressing safety issues on the use of biosurfactants as adjuvants and the scarcity of clinical data on the use and validation of such molecules in animal models and human volunteers pose a major challenge in preparing safe microemulsion formulations.

Abbreviations

MDDS, microemulsions drug delivery systems; DDS, drug delivery systems; GI, gastrointestinal irritation; O/W, oil-in-water; W/O, water-in-oil; MEL_S, mannosylerythritol lipid; nPMMA, polymethyl methacrylate nanoparticles; DHA, docosahexaenoic acid; SMEDDS, self-microemulsifying system; NiO, nickel oxide; DHASCO, docosahexaenoic acid single cell oil; WOS, Web of Science; PM, PubMed.

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Disclosure

The authors report no conflicts of interest in this work.

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