Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

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

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Mandana Ohadi[1]
Arash Shahravan[2]
Negar Dehghannoudeh[3]
Touba Eslaminejad[1]
Ibrahim M Banat[4]
Gholamreza Dehghannoudeh[1,5]

[1]Pharmaceutics Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran; [2]Endodontology Research Center, Kerman University of Medical Sciences, Kerman, Iran; [3]Faculty of Arts and Science, University of Toronto, Toronto, Ontario, Canada; [4]Faculty of Life & Health Sciences, University of Ulster, Coleraine BT52 1SA, N. Ireland, UK; [5]Department of Pharmaceutics, Faculty of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran

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 biosource 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

Correspondence: Gholamreza Dehghannoudeh
Tel +98-34-31325015
Fax +98-34-31325003
Email ghr_dehghan@kmu.ac.ir

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/DDDT.S232325

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 pharmaceutics 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 al[24] 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 uptake of siRNA, leading to enhancing the particular knockdown impact.

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

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 Hydrophilic/Hydrophobic linker Safety	- Physicochemical Stability - Alcohol free microemulsion - 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 al[15] who describes a microemulsion technique that was believed to be a promising approach for nanoparticle synthesis. The remaining 18 publications selected in

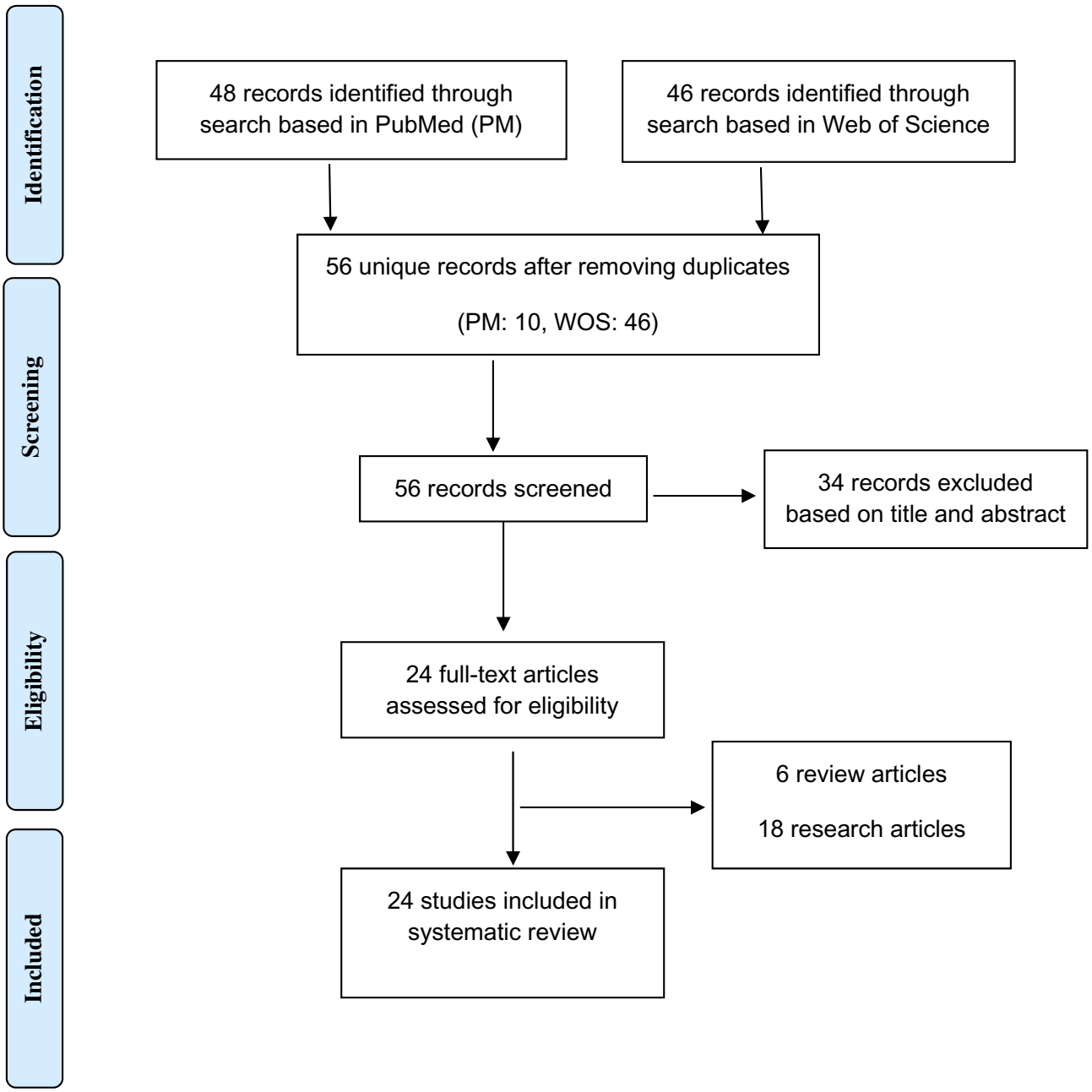

Figure 1 Flowchart of selection criteria/process and included studies.

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 collaborators[33] 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 Sabatini[35] 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]

Table 4 Overview of Microemulsion Formulation by Biosurfactant

Type of Biosurfactant	Research Articles
Mannosylerythritol lipids	3
Rhamnolipids	8
Rhamnolipids and sophorolipids	2
Trehaloselipid	1
Surfactin	4
Total	18

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 al[38] (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

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 5 Functions and Applications of Microbial Surfactant in Different in MDDS

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, Trehaloselipid, 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 collaborators[41] used a reverse micro-emulsion 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 MDDS.

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 biosurfactants 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 collaborators[40] 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.

Acknowledgment

The authors would like to thank Kerman University of Medical Sciences (KMU) for facilitating research into this study.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Rodrigues LR. Microbial surfactants: fundamentals and applicability in the formulation of nano-sized drug delivery vectors. *JCIS*. 2015;449:304–316.
2. Tang B, Cheng G, Gu J-C, Xu C-H. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. *Drug Discov Today*. 2008;13(13–14):606–612. doi:10.1016/j.drudis.2008.04.006
3. Wu Y-S, Ngai S-C, Goh B-H, Chan K-G, Lee L-H, Chuah L-H. Anticancer activities of surfactin and potential application of nanotechnology assisted surfactin delivery. *Front Pharmacol*. 2017;8:761. doi:10.3389/fphar.2017.00761
4. Karasulu HY. Microemulsions as novel drug carriers: the formation, stability, applications and toxicity. *Expert Opin Drug Deliv*. 2008;5 (1):119–135. doi:10.1517/17425247.5.1.119
5. Gibaud S, Attivi D. Microemulsions for oral administration and their therapeutic applications. *Expert Opin Drug Deliv*. 2012;9 (8):937–951. doi:10.1517/17425247.2012.694865
6. Fanun M. Microemulsions as delivery systems. *Curr Opin Colloid Interface Sci*. 2012;17(5):306–313. doi:10.1016/j.cocis.2012.06.001
7. Rodrigues L, Banat IM, Teixeira J, Oliveira R. Biosurfactants: potential applications in medicine. *J Infect Chemother*. 2006;57 (4):609–618. doi:10.1093/jac/dkl024
8. Roy A, Mahata D, Paul D, Korpole S, Franco OL, Mandal SM. Purification, biochemical characterization and self-assembled structure of a fengycin-like antifungal peptide from Bacillus thuringiensis strain SM1. *Front Microbiol*. 2013;4:332. doi:10.3389/fmicb.2013.00332
9. Elshikh M, Funston S, Chebbi A, Ahmed S, Marchant R, Banat IM. Rhamnolipids from non-pathogenic Burkholderia thailandensis E264: physicochemical characterization, antimicrobial and antibiofilm efficacy against oral hygiene related pathogens. *N Biotechnol*. 2017;36:26–36. doi:10.1016/j.nbt.2016.12.009
10. Dey G, Bharti R, Sen R, Mandal M. Microbial amphiphiles: a class of promising new-generation anticancer agents. *Drug Discov Today*. 2015;20(1):136–146. doi:10.1016/j.drudis.2014.09.006
11. Ohadi M, Dehghannoudeh G, Shakibaie M, Banat IM, Pournamdari M, Forootanfar H. Isolation, characterization, and optimization of biosurfactant production by an oil-degrading acinetobacter junii B6 isolated from an Iranian oil excavation site. *Biocatal Agric Biotechnol*. 2017;12:1–9. doi:10.1016/j.bcab.2017.08.007
12. Ohadi M, Forootanfar H, Rahimi HR, et al. Antioxidant potential and wound healing activity of biosurfactant produced by acinetobacter junii B6. *Curr Pharm Biotechnol*. 2017.
13. Gupta S, Raghuwanshi N, Varshney R, et al. Accelerated in vivo wound healing evaluation of microbial glycolipid containing ointment as a transdermal substitute. *Biomed Pharmacother*. 2017;94:1186–1196. doi:10.1016/j.biopha.2017.08.010
14. Ohadi M, Dehghannoudeh G, Forootanfar H, Shakibaie M, Rajaee M. Investigation of the structural, physicochemical properties, and aggregation behavior of lipopeptide biosurfactant produced by acinetobacter junii B6. *Int J Biol Macromol*. 2018;112:712–719. doi:10.1016/j.ijbiomac.2018.01.209
15. Kiran GS, Selvin J, Manilal A, Sujith S. Biosurfactants as green stabilizers for the biological synthesis of nanoparticles. *Crit Rev Biotechnol*. 2011;31(4):354–364. doi:10.3109/07388551.2010.539971
16. Palanisamy P, Raichur AM. Synthesis of spherical NiO nanoparticles through a novel biosurfactant mediated emulsion technique. *Mat Sci Eng C*. 2009;29(1):199–204. doi:10.1016/j.msec.2008.06.008
17. Hazra C, Kundu D, Chaudhari A. Lipopeptide biosurfactant from Bacillus clausii BS02 using sunflower oil soapstock: evaluation of high throughput screening methods, production, purification, characterization and its insecticidal activity. *RSC Adv*. 2015;5 (4):2974–2982. doi:10.1039/C4RA13261K
18. Xie Y, Ye R, Liu H. Synthesis of silver nanoparticles in reverse micelles stabilized by natural biosurfactant. *Colloids Surf a Physicochem Eng Asp*. 2006;279(1–3):175–178. doi:10.1016/j.colsurfa.2005.12.056
19. Kumar CG, Mamidyala SK, Das B, Sridhar B, Devi GS, Karuna MS. Synthesis of biosurfactant-based silver nanoparticles with purified rhamnolipids isolated from Pseudomonas aeruginosa BS-161R. *J Microbiol Biotechnol*. 2010;20(7):1061–1068. doi:10.4014/jmb.1001.01018
20. Gudiña EJ, Rangarajan V, Sen R, Rodrigues LR. Potential therapeutic applications of biosurfactants. *Trends Pharmacol Sci*. 2013;34 (12):667–675. doi:10.1016/j.tips.2013.10.002
21. Fracchia L, Ceresa C, Banat IM. Biosurfactants in cosmetic, biomedical and pharmaceutical industry. In: Banat IM, Rengathavasi T, editors. *Microbial Biosurfactants and Their Environmental and Industrial Applications:*. CRC Press; 2019:258–287.

22. Banat IM, Makkar RS, Cameotra SS. Potential commercial applications of microbial surfactants. *Appl Microbiol Biotechnol*. 2000;53(5):495–508. doi:10.1007/s002530051648
23. Callender SP, Mathews JA, Kobernyk K, Wettig S. Microemulsion utility in pharmaceuticals: implications for multi-drug delivery. *Int J Pharm X*. 2017;526(1–2):425–442. doi:10.1016/j.ijpharm.2017.05.005
24. Shim GY, Kim SH, Han S-E, Kim Y, Oh YJAJPS. Cationic surfactin liposomes for enhanced cellular delivery of siRNA. *Asian J Pharm Sci*. 2009;4:207–214.
25. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264–269. doi:10.7326/0003-4819-151-4-200908180-00135
26. Faivre V, Rosilio V. Interest of glycolipids in drug delivery: from physicochemical properties to drug targeting. *Expert Opin Drug Deliv*. 2010;7(9):1031–1048. doi:10.1517/17425247.2010.511172
27. Nguyen TT, Sabatini DA. Characterization and emulsification properties of rhamnolipid and sophorolipid biosurfactants and their applications. *Int J Mol Sci*. 2011;12(2):1232–1244. doi:10.3390/ijms12021232
28. Worakitkanchanakul W, Imura T, Morita T, et al. Formation of W/O microemulsion based on natural glycolipid biosurfactant, mannosylerythritol Lipid-A. *J Oleo Sci*. 2008;57(1):55–59. doi:10.5650/jos.57.55
29. Fukuoka T, Yanagihara T, Ito S, et al. Reverse vesicle formation from the yeast glycolipid biosurfactant mannosylerythritol lipid-D. *J Oleo Sci*. 2012;61(5):285–289. doi:10.5650/jos.61.285
30. Worakitkanchanakul W, Imura T, Fukuoka T, et al. Aqueous-phase behavior and vesicle formation of natural glycolipid biosurfactant, mannosylerythritol lipid-B. *Colloids Surf B Biointerfaces*. 2008;65(1):106–112. doi:10.1016/j.colsurfb.2008.03.009
31. Xie Y, Ye R, Liu H. Microstructure studies on biosurfactant-rhamnolipid/n-butanol/water/n-heptane microemulsion system. *Colloids Surf a Physicochem Eng Asp*. 2007;292(2–3):189–-195. doi:10.1016/j.colsurfa.2006.06.021
32. Xie Y, Li Y, Ye R. Effect of alcohols on the phase behavior of microemulsions formed by a biosurfactant—rhamnolipid. *J Dispers Sci Technol*. 2005;26(4):455–461. doi:10.1081/DIS-200054576
33. Mendes AN, Filgueiras LA, Pinto JC, Nele M. Physicochemical properties of rhamnolipid biosurfactant from Pseudomonas aeruginosa PA1 to applications in microemulsions. *J Biomater Nanobiotechnol*. 2015;6(01):64. doi:10.4236/jbnb.2015.61007
34. Moya-Ramírez I, García-Román M, Fernández-Arteaga A. Rhamnolipids: highly compatible surfactants for the enzymatic hydrolysis of waste frying oils in microemulsion systems. *ACS Sustain Chem Eng*. 2017;5(8):6768–6775. doi:10.1021/acssuschemeng.7b01008
35. Nguyen TT, Sabatini DA. Formulating alcohol-free microemulsions using rhamnolipid biosurfactant and rhamnolipid mixtures. *J Surfactants Deterg*. 2009;12(2):109–115. doi:10.1007/s11743-008-1098-y
36. Nguyen TT, Edelen A, Neighbors B, Sabatini DA. Biocompatible lecithin-based microemulsions with rhamnolipid and sophorolipid biosurfactants: formulation and potential applications. *J Colloid Interface Sci*. 2010;348(2):498–504. doi:10.1016/j.jcis.2010.04.053
37. Kiran GS, Sabu A, Selvin J. Synthesis of silver nanoparticles by glycolipid biosurfactant produced from marine Brevibacterium casei MSA19. *J Biotechnol*. 2010;148(4):221–225. doi:10.1016/j.jbiotec.2010.06.012
38. Hazra C, Kundu D, Chatterjee A, Chaudhari A, Mishra S. Poly (methyl methacrylate)(core)–biosurfactant (shell) nanoparticles: size controlled sub-100 nm synthesis, characterization, antibacterial activity, cytotoxicity and sustained drug release behavior. *Colloids Surf a Physicochem Eng Asp*. 2014;449:96–113. doi:10.1016/j.colsurfa.2014.02.051
39. Kural FH, Gürsoy RN. Formulation and characterization of surfactin-containing self-microemulsifying drug delivery systems. *Hacettepe Univ Eczacı Fak Derg*. 2010;30:3171–3186.
40. He Z, Zeng W, Zhu X, Zhao H, Lu Y, Lu Z. Influence of surfactin on physical and oxidative stability of microemulsions with docosahexaenoic acid. *Colloids Surf B Biointerfaces*. 2017;151:232–239. doi:10.1016/j.colsurfb.2016.12.026
41. Maity JP, Lin T-J, Cheng -HP-H, et al. Synthesis of brushite particles in reverse microemulsions of the biosurfactant surfactin. *Int J Mol Sci*. 2011;12(6):3821–3830. doi:10.3390/ijms12063821
42. Farias CB, Ferreira Silva A, Diniz Rufino R, Moura Luna J, Gomes Souza JE, Sarubbo LA. Synthesis of silver nanoparticles using a biosurfactant produced in low-cost medium as stabilizing agent. *Electron J Biotechn*. 2014;17(3):122–125. doi:10.1016/j.ejbt.2014.04.003
43. Rodrigues LR. Microbial surfactants: fundamentals and applicability in the formulation of nano-sized drug delivery vectors. *J Colloid Interface Sci*. 2015;449:304–316. doi:10.1016/j.jcis.2015.01.022
44. Eslaminejad T, Nematollahi-Mahani SN, Ansari M. Cationic β-cyclodextrin–Chitosan conjugates as potential carrier for pmcherry-c1 gene delivery. *Mol Biotechnol*. 2016;58(4):287–298. doi:10.1007/s12033-016-9927-0
45. Eslaminejad T, Nematollahi-Mahani SN, Ansari M. Synthesis, characterization, and cytotoxicity of the plasmid EGFP-p53 loaded on pullulan–spermine magnetic nanoparticles. *J Magn Magn Mater*. 2016;402:34–43. doi:10.1016/j.jmmm.2015.11.037
46. Zokaei E, Badoei-dalfrad A, Ansari M, Karami Z, Eslaminejad T, Nematollahi-Mahani SN. Therapeutic potential of DNAzyme loaded on chitosan/cyclodextrin nanoparticle to recovery of chemosensitivity in the mcf-7 cell line. *Appl Biochem Biotechnol*. 2018;1–16.
47. Gangwar M, Singh R, Goel R, Nath G. Recent advances in various emerging vesicular systems: an overview. *Asian Pac J Trop Biomed*. 2012;2(2):S1176–S1188. doi:10.1016/S2221-1691(12)60381-5
48. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. *Adv Drug Deliv Rev*. 2012;64:175–193. doi:10.1016/j.addr.2012.09.018
49. Kitamoto D, Morita T, Fukuoka T, Konishi M-A, Imura T. Self-assembling properties of glycolipid biosurfactants and their potential applications. *Curr Opin Colloid Interface Sci*. 2009;14(5):315–328. doi:10.1016/j.cocis.2009.05.009
50. Fan -L-L, Dong Y-C, Fan Y-F, Zhang J, Chen Q-H. Production and identification of mannosylerythritol lipid-A homologs from the ustilaginomycetous yeast Pseudozyma aphidis ZJUDM34. *Carbohydr Res*. 2014;392:1–6. doi:10.1016/j.carres.2014.04.013
51. Rivera-Rangel RD, González-Muñoz MP, Avila-Rodriguez M, Razo-Lazcano TA, Solans C. Green synthesis of silver nanoparticles in oil-in-water microemulsion and nano-emulsion using geranium leaf aqueous extract as a reducing agent. *Colloids Surf a Physicochem Eng Asp*. 2018;536:60–67. doi:10.1016/j.colsurfa.2017.07.051
52. Raichur AM. Dispersion of colloidal alumina using a rhamnolipid biosurfactant. *J Dispers Sci Technol*. 2007;28(8):1272–1277. doi:10.1080/01932690701528274
53. Han D, Yang H, Zhu C, Wang F. Controlled synthesis of CuO nanoparticles using TritonX-100-based water-in-oil reverse micelles. *Powder Techno*. 2008;185(3):286–290. doi:10.1016/j.powtec.2007.10.018