Fast track on the surface active agents involved in nanoemulsion for drug delivery

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Abstract:

Nanoemulsions (NEs) are colloidal dispersion systems made of two immiscible liquids combined with co-surfactants and surfactants (emulsifying agents), to form a thermodynamically stable. Numerous synthetic and natural compounds with the aim of enhancing bioactivity, delivery, and stability have been developed utilizing these delivery systems.

This review focuses on the use of surface active agents (SAAs) in the formulation of NE in different drug delivery systems including intranasal, ophthalmic, buccal, dermal and vaginal, including how the type and concentration of SAAs influence the drug delivery system that is used for the NE and the type of NE that is formed (w/o or o/w).

Key words: nanoemulsion, surfactant, co-surfactant, drug delivery system.

لمحة سريعة على فعالية العوامل الاستحلابية المستخدمة في المستحلبات النانوية في انظمة نقل الدواء الموضعية

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الخلاصة:

المستحلبات النانوية هي انظمة تشتت غروية تجمع بين سائلين غير قابلين للامتزاج مع عوامل استحلاب (مواد خافضة للتوتر السطحي) لإنتاج مركب ممتزج مستقر ديناميكيا. انها توفر العديد من الخيارات لتوصيل الادوية خلال الحواجز المحبة للدهون. العديد من المركبات الطبيعية والمصنعة تم انتاجها باستخدام هذا النوع من انظمة التوصيل بهدف تحسين فعاليتها الحيوية، نقلها واستقراريتها. هذا البحث يركز على دور عوامل الاستحلاب في تركيب المستحلبات النانوية بمختلف انظمة النقل الدوائية والذي يتضمن تأثير نوع وتركيز عوامل الاستحلاب نوع المستحلب النانوي ونظام النقل الدوائي

الكلمات المفتاحية: مستحلب نانوي، عامل استحلاب، عامل استحلاب مساعد، نظام نقل دواء موضعي

Introduction

Due to their local action at the point of application by drug permeation into the underlying skin or mucous membrane, topical medicines are utilized [1]. Nanoemulsions (NEs), also known as ultrafine emulsions, mini-emulsions, and submicron emulsions, exhibit heterogeneity,

wherein nanoscale droplets of a distributed phase liquid are scattered throughout a continuous phase liquid [2]. These are o/w, w/o emulsions that are thermodynamically stable and have droplet diameters between 20 and 200 nm. A layer of cosurfactants and surfactants can stabilize them [3].

Advantages of nanoemulsion

In comparison to other dosage forms, nanoemulsions have a number of benefits, including [4] : Increased absorption rate for example in the preparation of ibuprofen nanoemulsion [5]. Less variance in absorption like in letrozole nanoemulsion [6]. Defense against oxidation and hydrolysis such as the bioactive ingredients like co enzyme Q10 [7].After solubilization, lipophilic medicines are administered such as vitamin D3 nanoemulsion and curcumin nanoemulsion [8]. Aqueous dose form for medications that are not water-soluble for example Diflunisal and Niflumic Acid nanoemulsion [9]. Improved bioavailability for numerous medications such as quercetin nanoemulsion [10]. Capability of incorporating both hydrophilic such as doxorubicin nanoemulsion [11] and isoconazole nanoemulsion [12] and hydrophilic medicines such as propranolol nanoemulsion [13] Control of medication release through a liquid layer that can be precisely controlled in terms of its hydrophilicity or lipophilicity and thickness adjusted. Regulating drug release by passing it through a liquid film with precisely controllable thickness, lipophilicity, and hydrophilicity. As non-irritating and non-toxic carriers for distribution to the skin and mucous membranes such as tacrolimus nanoemulsion which used for the treatment of psoriasis [14] . Alternative methods of delivery to increase effectiveness while lowering the overall dose and negative effects such as Disulfiram nose to brain nanoemulsion [15] .

Despite of the advantages of nanoemulsions they also have disadvantages [16]:

Due to the difficulty of reducing droplet size and the need for specialized equipment and manufacturing techniques, creating nanoemulsion formulations is an expensive procedure. For instance, the configuration of the homogenizer (a necessary tool for the creation of nanoemulsions) is an expensive procedure. Again, the manufacturing processes of microfludization and ultrasonication demand substantial financial support. Nanoemulsion stability is poses a significant challenge when a formulation is kept in storage for an extended period of time. The fundamental cause of the unacceptability of nanoemulsion formulations is ostwald ripening. This is because small droplets have a higher rate of curvature than larger drops, which have a lower curvature radius, and hence have better stability.

Applications of nanoemulsion

1-Intranasal drug delivery : Ondansetron HCl nasal nanoemulsion in situ gel is an example of an intranasal drug delivery method that increases the drug's bioavailability and increases patient compliance [17] and lomustine nose to brain nanoemulsion [18].

2-Ophthalmic drug delivery : For instance, nanoemulsion of rifampicin for the treatment of ocular tuberculosis increases the preparation's effectiveness by prolonging its stay in contact with the eye [19], ketoconazole nanoemulsion [20] and ophthalmic dexamethasone nanoemulsion [21].

3- Buccal drug delivery :For instance, atorvastatin calcium nanoemulsion-based buccal films that improve the solubility and bioavailability of the drug, compared to the control film, to increase its hypolipidemic effects [22], penciclovir nanoemulsion [23] and estradiol nanoemulsion [24].

4- Dermal drug delivery: Such as topical nanoemulsion-enriched hydrogel containing econazole nitrate, which improves the drug's solubility and permeability [25], curcumin

nanoemulsion [26] and terbinafine nanoemulsion [27].

5- Vaginal drug delivery :As an illustration, progesterone nanoemulsion vaginal suppositories have a lower progesterone bioavailability than oral preparations [28] clotrimazole vaginal nanoemulsion [29] and nystatin vaginal nanoemulsion [30].

Surface active agents (SAA)

Nanoemulsion may contain cosurfactant or cosolvent in addition to the surfactant as well as the oil phase and the water phase. The choice of them is depend on the solubility of the drug in them. It can be prepared by several techniques like microfluidization, high pressure homogenization, low energy emulsification and solvent evaporation method. First, a simple emulsion is prepared spontaneously then it converted to nanoemulsion by one the previously mentioned methods , so the nanoemulsion is not a spontaneous and need energy to be prepared [31].Surfactants are amphiphilic substances that have a hydrophobic tail and an ionic or non-ionic hydrophilic head group. Surfactants can be categorized as non-ionic (having no charge), anionic (having a negative charge), cationic (having a positive charge), or zwitterionic (having the ability to possess one or more charges) based on the polarity of their head group [32].

By separating the hydrophilic component into the aqueous phase and the hydrophobic component into solid surfaces and the fluid component that is hydrophobic during the second phase, they can adsorb to charges that are both positive and negative. As a result, SAAs can function as lubricants, emulsifiers, foaming and anti-foaming agents, dispersing and wetting agents [33].

A crucial element of a nanoemulsion is surfactants. They are utilized in nanoemulsion for the stabilization of the emulsion system by maintaining globule sizes in the nano range; otherwise, globules would combine to grow in size, which would cause phase separation. The surfactant type and concentration that utilized determine the stability of the system [34].

It should be able to emulsify while still being chemically stable enough to function with the product, nontoxic, tasteless, and odorless. An emulgent should be able to [35]:

(1) Bring the surface tension down to under 10 dynes/cm.

(2) Swiftly create a comprehensive film that is consistent with the dispersed phase globules.

(3) Support the system's ability to establish an appropriate zeta potential and viscosity.

(4) Operate at comparatively low concentrations.

Co-surfactants (Co-SAA) are typically composed of tiny molecules, such as short glycols and alcohols with low molecular weight (C2-C10 long). By being absorbed into the interfacial cover and nanoemulsions, the small size of Co-SAA molecules allows them to penetrate the SAA film, reducing fluidity while imparting enough flexibility to the film to allow the curvature needed for the generation of fine, transparent films [36].

While consuming less of each SAA, combining SAAs or utilizing a co-surfactant helps the system's ultimate HLB get closer to the level needed for full oil emulsion. Stable emulsions require surfactants or mixtures of surfactants with HLB values near the required HLB value (RHLB) of the oil phase. While span 60 (HLB = 4.7) and span 80 (HLB = 4.3) miglyol 812 (HLB value = 1), and capmul MCM (HLB value = 5) were employed as lipophilic surfactants, tween 60 (HLB = 14.9) and tween 80 (HLB value = 15) triton x100(HLB value = 13.4) and Cremophor RH40 (HLB value = 13.0) are instances of hydrophilic surfactants. Additionally, a SAA's HLB value is crucial for preventing drug entrapment in vesicular systems [37].

Surface active agents in Intranasal nanoemulsion

The nasal septum divides the nasal cavity in half, while the nasal cavity extends posterior to the nasopharynx. The nasal vestibule, olfactory area, and respiratory region are the three primary sections that comprise the nasal cavity. This folded structure is composed of the inferior, median, and superior turbinates. The minor nasal airways' small channels assist the nose in carrying out its main function [38].

The mucin layer that coated the nasal cavity is affected in different ways by various types of surfactants. According to a study on nanoemulsion formulations using various surfactants at various concentrations, adding mucin to cationic and nonionic nanoemulsions results in larger particle size, indicating that a complex was formed between the negative charge of the mucin layer and the positive charge of the cationic surfactants. Additionally, the nonionic surfactant's HLB value affects how it interacts with mucin. The bigger polar groups that these surfactants have result in smaller particle sizes and less complex formation [39].

In order to create a nanoemulsion of rizatriptan benzoate, tween 80 and ethanol were used in a 1:1 ratio (55 percent). The medication is solubilized by the surfactant, resulting in a more stable nanoemulsion. Drug distribution from nose to brain was improved by the packaging of the drug as a nanoemulsion (NE), which shielded the drug from biological and/or chemical deterioration [40].

When bromocriptine and glutathione are prepared as a nanoemulsion in a 4:1 ratio with propylene glycol (as a co-surfactant) at concentrations ranging from 3 to 19 percent, PEG 400 is employed as a surfactant to improve the solubility of low water-soluble medicines and increase drug loading capacity. The research revealed that creating microemulsions by raising the surfactant mixture concentration by more than 20% [41].

Intranasal nanoemulsion can be used for brain targeting for example intranasal nanoemulsion of risperidone which contain tween 80 as surfactant (29.33%, w/w). A mixture of transcutol and propylene glycol (1:1, w/w) was used as co-surfactant (14.66%, w/w) [42]. Also intranasal delivery of Clozapine using nanoemulsion-based in-situ gels prepared by using tween 80 (surfactant) and transcutol p (co surfactant) in a ratio of 1:1 [43].

Surface active agents in ophthalmic drug delivery

Poor ocular medication bioavailability is a result of anatomical and physiological limitations on the eye, including the blood-ocular barrier's high effectiveness and the mechanisms controlling tear dynamics, nasolacrimal drainage, and the corneal epithelial barrier. It is anticipated that only 1percentor less of a topically administered dose will pass through the cornea and enter the eye's anterior region [44]. Because it prolongs drug contact with the eye and eliminates adverse effects, nanoemulsion is regarded as one of the greatest drug delivery techniques [45].

Generally speaking, ionic SAAs' ocular uses had been constrained due to toxicity issues. Nonionic surfactants are crucial and frequently utilized in ophthalmic preparations due to their lower toxicity, improved compatibility, and stability as well as their versatility, which can be applied to a variety of innovative ocular drug delivery platforms [46].

Twenty percent and thirty percent concentrations of Brij35, Cremophor RH40, Labrasol, and Tyloxapol were utilized as surfactants in the development of nanoemulsions containing Brinzolamide. The nanoemulsion's corneal penetration was greater than that of the commercial suspension due to the surfactant and oil's penetration-enhancing properties [47].

In the manufacture of Ketorolac Tromethamine (kt) ophthalmic nanoemulsion, additional types of surfactants were utilized, including: (Span 80, Span 20, tween 80, tween 60, tween 20, labrasol ALF, tween 40, tween EL, labrafil M 2125 CS, labrafil M 1944 CS, and labrafil M 2130 CS). The researchers discovered that these surfactants were nearly non-irritating, with the exception of labrasol, which is irritant at doses greater than 3 percent. Surfactants tween60, cremophor RH40, and tween 20 would be utilized in the creation of NE formulations for ocular KT delivery. Cremophor EL concentrations as high as 30 percent (w/w) have been reported as safe for the eyes [48] .

Utilizing the surfactants Pluronic F127, emulgent CO40, span 60, tween 20, tween 80, and cremophor RH 60(1 or 5 percent v/v), an ocular nanoemulsion of itraconazole was created. The formula (PVA 1%, eumulgin CO40 5%, and PG 5%), the optimal surfactant mixture was determined to have the best globule size and PDI (roughly 200 nm and PDI 0.4) [26].

Another examples for application of nanoemulsion in ocular delivery system is acyclovir-Loaded nanoemulsions for ophthalmic delivery prepared by using tween 60 (6.25%) as a surfactant and transcutol p(6.25%) as a cosurfactant [49]. Also, poloxamer 188 and tween® 80 are used as surfactants in the preparation of topical ocular ciprofloxacin nanoemulsion for the management of Bacterial Keratitis [50].

Surface active agents in Buccal nanoemulsions

In order to remove the limitations of oral medication administration via the gastrointestinal (GI) tract, substantial research has been conducted over the past decade on transmucosal oral drug delivery. The former has the advantage of avoiding pre-systemic clearance in the GI tract and first-pass metabolism [51].

The primary drawbacks of this method are that the oral mucosa have a relatively small surface area and the substantial medication loss because of the uncontrolled swallowing and salivary flow[52]. Penciclovir–lavender oil nanoemulsion oral gel was formulated to improve bioavailability and reduce the pain associated with herpes labialis. Surfactants (tween 80, span 80, stereoth 2, stereoth 21, and brij 30) were tested. 40.5% (labrasol: labrafil 1944 6:4) were utilized as surfactants with greater solubility than the rest [23] . A surfactant mixture comprising 40–60 percent (Laureth-21) was used to prepare anomega-3loxoprofen-loadednanoemulsion. This combination was selected from a group of surfactants (MYS25V, laureth21, Sorbeth-20, and Cremophor EL) [53].

In another study, self-nanoemulsifying lyophilized tablets containing zaleplon and lavender oil were developed for fast oral transmucosal administration. Many types of surfactants (Laureth-21, MYS-25V, Cremophor EL, and Sorbeth-20) were utilized, with Sorbeth-20 at a concentration of 0.1% producing the optimal nanoemulsion (35 percent to 65 percent) [54] .

Nystatin-Loaded Nanoemulsion for the Buccal Treatment of Candidosis in which they use Labrasol (35.42%) as a surfactant , Plurol oleique (14.16%) as a cosurfactant [55].

While in the Development of Nanoemulsion-based Buccal Films of Atorvastatin Calcium for Enhancement of Hypolipidemic Effect the surfactant used was tween20 and the co surfactant was ethanol (50% in a ratio of 1:3) [22].

Surface active agents in Dermal nanoemulsion

Due to the stratum corneum SC permeability barrier, the number of effective topical medications remains limited. In order to administer big hydrophilic medicines cutaneously, overcoming this barrier in a safe and reversible manner is one of the greatest

hurdles in dermatologic therapy [56]. Chemical, biochemical, and physical approaches to improving drug delivery can be broadly classified. Chemical strategies have included the creation of chemical enhancers that change the lipid structure of the SC, such as solvents (propylene glycol, DMSO), fatty acid esters (oleic acid), and surfactants (SDS). Chemical enhancers work in a few different ways to increase skin permeability: (1) breaking up the SC lipid structure and allowing it to pass through (this is how many enhancers work, including azone, terpenes, fatty acids, DMSO, and alcohol ; (2) extracting lipids, making the horny layer more permeable through the formation of aqueous channels (DMSO, ethanol); (3) interacting with corneocyte keratin and opening up (for example DMSO, ionic surfactants) [57].

Formulations containing 5 percent (w/w) acyclovir are prepared using surfactants (solutol HS15, S1670, and span 80) that have superior physical and chemical qualities, with a mean droplet size of about 105 nm and PDI values of about 0.07 to prepare acyclovir w/o/w nanoemulsions for dermal delivery [58].

Ketoconazole was loaded with surfactants (capmul PG8, labrasol, tween 80, and poly ethylene glycol) to create a cationic nanoemulsion; capmul PG8 exhibited the highest solubility (74.321.3mg/ml) [59].Next were PG (29.28±1.45mg/ml) and Labrasol (54.53±1.36mg/ml).

The effects of different non-ionic span 80 and between 20, 60, and 80 SAAs at a 15 percent concentration on the creation of nano-emulsions were studied. To determine the optimal surfactant concentration for nanoemulsion preparation, they employed a range of values between 5 and 30 percent. According to the optimization results, the blend of tween 80 and span 80 produces the smallest droplets. Furthermore, it was found that a surfactant composition between 80:span 80 (75:25) was ideal for the spontaneous production of oil droplets [60].

In Olive oil and clove oil-based nanoemulsion for topical delivery of terbinafine hydrochloride tween80 was used as a surfactant and ethanol as a co surfactantin a ratio of 6:4(27). Also in the preparation of Methotrexate Loaded Topical Nanoemulsion Gel for the Treatment of Imiquimod Induced Psoriasis-like Skin Inflammation in an Animal Model tween 80 was used as surfactant and PEG400 as a co surfactant [61].

Surface active agents in vaginal nanoemulsion

Vaginal dosage forms must be developed and evaluated with consideration for the unique properties of the vagina, including secretion, pH, and microbiota. The vaginal membrane is a physical model of a transport barrier. Nanoemulsions possess several desirable characteristics that make them highly suitable for intravaginal drug delivery. These include long-term stability, ease of preparation through spontaneous emulsification, efficient solubilization of drug molecules, optical transparency, protection against enzymatic hydrolysis, enhanced drug release due to the large surface area of the nanosized globules, and improved permeability resulting from surfactant-induced membrane fluidity. One of the main difficulties in creating nanoemulsions is choosing the right oil(s) and surfactant(s) while considering their toxicity and the stability of the resulting system. Non-ionic surfactants are commonly used to create and maintain stable nanoemulsion systems. This is because they have low toxicity, may be used with ionic substances, and remain stable throughout a wide variety of pH levels [62].

Using tween20 and span80 at 1% concentration, a chitosan hydrogel-thickened nanoemulsion containing pelargonium graveolens essential oil is made to treat vaginal candidiasis [63].

A study for the synthesis of syngonanthus nitens (Bong.) nanoemulsion for vaginal medication delivery employs a surfactant composition of 66.7% (brij 58) and 33.3% (FS-epikuron® 200) [64].

In order to enhance the solubility and self-emulsifying capacity of ebselen, an optimal concentration of medium chain triglycerides (MCT; captex 300®) and kolliphor® ELP were utilized as an oil and surfactant, respectively, in the creation of an ebselen-loaded nanoemulsion for vulvovaginal candidiasis [65].

Formulation of oxiconazole nitrate mucoadhesive nanoemulsion based gel for treatment of fungal vaginal infection in which 50% of smix used which were cremophore RH as a surfactant and ethanol as a co surfactant [66]. An other example is the preparation of amphotericin B nanoemulsion-loaded mucoadhesive gel for treatment of vulvovaginal candidiasis in which they use 36% w/w Smix (2:1) which were Cremophor RH 40 as surfactant and Transcutol P as a co surfactant [67].

Important aspects to consider when selecting a phase structure for medication administration include how its physicochemical characteristics relate to the intended application. For example, a topical surfactant system should have a phase structure with enough viscosity to maintain the preparation on the skin surface and disseminate it easily [68]. In contrast, for intravenous system; the surfactant should have a low viscosity to avoid injection pain. Another crucial factor is the aggregate's drug-incorporation capacity where due to low surfactant concentrations, micellar solutions have the lowest drug loading capability, while cubic and other liquid crystalline phases can sustain substantial drug loadings. Recently, it was discovered that a surfactant's toxicity may depend on its aggregate. In vesicular solutions, the same surfactant is far less hazardous than in micellar solutions [69]. It is preferable for the nanoemulsion formulations to have a lower concentration of surfactants due to their potential interaction and toxicity when administered orally or ocularly. However, it is important to carefully assess this matter considering the need for strong thermodynamic stability and efficient emulsification during large-scale preparation [34].

Conclusion

An overview of the application of surface-active agents in drug delivery systems is given in this article. By taking into account SAAs in addition to other formulation ingredients, formulators can select the SAA that is most suitable for the intended application taking in consideration the rout of administration, concentration of surfactant and their type and safety as well as the sensitivity of the tissue to which nanoemulsion applied. The micellization tendencies of surfactant mixtures differ significantly from those of single pure species and the addition of a co-surfactant increases particle flexibility while lowering surfactant concentration.

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