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Nanoemulsion: A Review

Hasanain Shakir Mahmood1, 2, Maryam Alaayedi2, Ashti M.H. Saeed3, Sahar Hussein Abdullah4, Shams Ayad Kadhim5, Shams Hayder Ali5, Shahad Adel Razoqi5, Shahad Jassim Kadhim5, Shahad Hassan Ayed5, Shahad Hussein Abdul Ameer5, Shahad Forat Abdul Reda5, Suroor Majid Shaker5

1 Assistant Professor in Pharmaceutics, Department of Pharmaceutics, College of Pharmacy, University of AlKafeel, Najaf, Iraq, 2 Assistant Professor in Pharmaceutics, Department of Pharmaceutics, College of Pharmacy, University of Kerbala, Kerbala, Iraq, 3 Lecturer in Pharmaceutics, Department of Pharmaceutics, College of Pharmacy, MustansiriyahUniversity, Kerbala, Iraq, 4 Assistant Lecturer, Department of Pharmaceutics, College of Pharmacy, University of AlKafeel, Najaf, Iraq, 5 Bsc students, College of Pharmacy, University of AlKafeel, Najaf, Iraq

Abstract

Nanoemulsions, which consist of minuscule droplets of one immiscible liquid dispersed within another immiscible liquid, are colloidal dispersions stabilized by surfactants or other amphiphilic molecules. Due to these systems' unique properties and numerous applications in the food, pharmaceutical, cosmetic, and agrochemical industries, among others, a lot of attention has been generated. Because of their extraordinary stability and high surface area-to-volume ratio, nanoemulsions are valuable in pharmaceutical formulations for regulating drug release kinetics, enhancing bioavailability, and delivering poorly water-soluble medications. Moreover, their enhanced sensory attributes and translucent nature render them desirable for incorporation into the creation of aesthetically pleasing cosmetic items. The small droplet size (often less than 100 nm) of nanoemulsions helps to create thermodynamically stable systems by delaying phase separation and creaming over time. This stability is caused by the interfacial layer surrounding the droplets, which functions as a kinetic barrier to stop coalescence and Ostwald ripening. In the food and beverage industries, nanoemulsions offer opportunities to boost flavor delivery, increase solubility, and encapsulate bioactive substances. By enabling the creation of transparent and stable emulsions without the need for sizable concentrations of emulsifiers or stabilizers, they aid in the creation of cleaner label formulations. Furthermore, nanoemulsions have shown promise in agricultural applications for the efficient delivery of pesticides and herbicides, the mitigation of environmental contamination, and the requirement for fewer active chemicals to protect crops. The formulation and optimization of nanoemulsions need careful selection of oils, surfactants, and co-surfactants. It's also critical to use appropriate processing techniques including microfluidization, sonication, and high-pressure homogenization. Taken together, nanoemulsions provide an adaptable platform for developing state-of-the-art delivery systems with enhanced stability, solubility, and bioavailability, stimulating innovation across multiple industries.

Keyword: colloidal dispersion, nanoemulsion, liquid, oil, surfactant.

المستحلب النانوي: مراجعة

حسنين شاكر محمود 1، 2، مريم العايدي 2، أشتي م.ح. سعيد3، سحر حسين عبد الله4، شمس عياد كاظم5، شمس حيدر علي5، شهد عادل رزوقي5، شهد جاسم كاظم5، شهد حسن عايد5، شهد حسين عبد الأمير5، شهد فرات عبد الرضا5، سرور ماجد شاكر5

1 أستاذ مساعد في الصيدلانيات، قسم الصيدلانيات، كلية الصيدلة، جامعة الكفيل، النجف، العراق، 2 أستاذ مساعد في الصيدلانيات، قسم الصيدلانيات، كلية الصيدلة، جامعة كربلاء، كربلاء، العراق، 3 محاضر في الصيدلانيات، قسم الصيدلانيات، كلية الصيدلة، الجامعة المستنصرية، كربلاء، العراق، 4 مدرس مساعد في قسم الصيدلانيات، كلية الصيدلة، جامعة الكفيل، النجف، العراق، 5 طلاب بكالوريوس، كلية الصيدلة، جامعة الكفيل، النجف، العراق

الخلاصة

تتكون المستحلبات النانوية من قطرات صغيرة من سائل غير قابل للامتزاج موزعة داخل سائل غير قابل للامتزاج آخر، وهي مستحلبات غروانية مثبتة بمواد فعالة بالسطح أو جزيئات أخرى محبة للماء. وبسبب الخصائص الفريدة لهذه الأنظمة والتطبيقات العديدة في الصناعات الغذائية والصيدلانية ومستحضرات التجميل والزراعية وغيرها، فقد حظيت بقدر كبير من الاهتمام. وبسبب ثباتها الاستثنائي ونسبة المساحة السطحية إلى الحجم العالية، فإن المستحلبات النانوية ذات قيمة في المستحضرات الصيدلانية لتنظيم حركية إطلاق الأدوية، وتعزيز التوافر البيولوجي، وتوصيل الأدوية التي لا تذوب في الماء. وعلاوة على ذلك، فإن خصائصها الحسية المحسنة وطبيعتها الشفافة تجعلها مرغوبة للاستخدام في إنشاء مستحضرات تجميلية جذابة من الناحية الجمالية. يساعد حجم القطرات الصغيرة (غالبًا أقل من 100 نانومتر) من المستحلبات النانوية في إنشاء أنظمة مستقرة ترموديناميكيًا عن طريق تأخير فصل الطور والتكتل بمرور الوقت. إن هذا الاستقرار ناتج عن الطبقة السطحية المحيطة بالقطرات، والتي تعمل كحاجز حركي لمنع الاندماج ونضج أوستوالد. وفي صناعات الأغذية والمشروبات، توفر المستحلبات النانوية فرصًا لتعزيز توصيل النكهة، وزيادة قابلية الذوبان، وتغليف المواد النشطة بيولوجيًا. ومن خلال تمكين إنشاء مستحلبات شفافة ومستقرة دون الحاجة إلى تركيزات كبيرة من المستحلبات أو المثبتات، فإنها تساعد في إنشاء تركيبات ملصقات أنظف. وعلاوة على ذلك، أظهرت المستحلبات النانوية وعدًا في التطبيقات الزراعية لتوصيل المبيدات الحشرية ومبيدات الأعشاب بكفاءة، والتخفيف من التلوث البيئي، والمتطلبات الخاصة بعدد أقل من المواد الكيميائية النشطة لحماية المحاصيل. إن صياغة وتحسين المستحلبات النانوية تتطلب اختيارًا دقيقًا للزيوت والمواد الخافضة للتوتر السطحي والمواد الخافضة للتوتر السطحي المساعدة. ومن الأهمية بمكان أيضًا استخدام تقنيات المعالجة المناسبة بما في ذلك الميكروفلويديزيشن، والموجات فوق الصوتية، والتجانس تحت الضغط العالي. توفر المستحلبات النانوية، مجتمعة، منصة قابلة للتكيف لتطوير أنظمة توصيل متطورة ذات استقرار معزز وقابلية للذوبان وتوافر حيوي، مما يحفز الابتكار عبر العديد من الصناعات.

الكلمات المفتاحية: التشتت الغرواني، المستحلب النانوي، السائل، الزيت، المادة الخافضة للتوتر السطحي.

Introduction

An oil and water based dispersion that is thermodynamically stable and isotropically transparent, supported by an interfacial layer of surfactant molecules, is called a "nanoemulsion." A nanoemulsion is a liquid dispersion that is assumed to be thermodynamically or kinetically stable, consisting of an oil phase, a water phase, and a surfactant. Making fine water-in-oil (W/O) or oil-in-water (O/W) emulsions is a modern formulation technique known as nanoemulsion. Agrochemicals, food, cosmetics, pharmaceuticals, and other sectors have expressed great interest in it due to its unique properties and potential applications. Nanoemulsion is one cutting-edge technique for delivering medication. It's one of the most innovative ways to increase the bioavailability of drugs that don't dissolve in water very well. Water, medicine, oil, and surfactant (cosurfactant: Smix) are combined in an isotropic manner. This is a type of colloidal particle nanosystem that transports medicinal molecules in droplets as small as submicrons. Carriers are solid spheres having an amorphous, lipophilic, and negatively charged surface. As a novel drug delivery system, nanoemulsions (NE) maximize the therapeutic and pharmacological effects of drugs while reducing their toxic reactions.

Nanoemulsions are a modern colloidal system that is dispersed and has two immiscible liquid phases, such as water and oil, that are isotropically clear or transparent and are stabilized by the surfactant molecules' interfacial film. The nanoemulsion system was composed of the appropriate concentration of 0il and surfactant phase with droplet size 50-200 nm. The dispersed phase droplet size is approximately 50-200 nm, with very low oil and water (o/w) interfacial tension **(1, 2).**

To get over the problems with the traditional medication administration system, a flexible form of drug distribution has been created. This examination provided a thorough understanding of the nanoemulsion system. Multiple medication delivery using nanoemulsion is promising. Emulsions that are submicron sized and nanosized are produced to enhance the delivery of active medicinal components. A thermodynamically and kinetically stable isotropic system, a nanoemulsion is created when two immiscible liquids are combined with an emulsifying agent (S) to create a single phase. Usually, the droplet size is between 50 and 200 nm. Emulsion, microemulsion, and nanoemulsion are primarily distinguished by the size and form of the particles that are distributed throughout the continuous phase.

A potential method for improving the pharmacological and therapeutic effect of medications while also making poorly water soluble medicines more soluble in water is the use of nanoemulsion. the creation of nanoemulsions with the goal of regulating or enhancing the necessary levels of pharmaceutical agent bioavailability. The goal of this study is to provide readers with a fundamental understanding of the introduction, benefits, drawbacks, elements, mechanisms, formulation process, assessment, and applications of the nanoemulsion system. Additionally, it compared the nanoemulsion system to the emulsion and microemulsion systems **(3).**

Nanoemulsion history

The idea of emulsions was first presented in the early 1900s, which is when the history of nanoemulsions began. Nevertheless, scientists didn't start looking at the possibilities of nanoscale emulsions until the 1970s. Salager and Bolzinger studied the connection between emulsion stability and droplet size in 1974. They discovered that the stability and general characteristics of emulsions could be greatly improved by lowering the droplet size to the nanoscale range. In the 1990s, when scientists like Klang and Matsarskaia began looking into the production processes and characteristics of nanoemulsions, more progress was made.

They investigated a number of methods for creating stable nanoemulsions, including high-pressure homogenization, sonication, and microfluidization **(3, 4).**

It wasn't until the late 1990s and early 2000s that nanoemulsions' potential applications were realized. The pharmaceutical industry has been using nanoemulsions to improve the bioavailability of poorly soluble drugs and to deliver drugs to targeted sites. In the food industry, nanoemulsions have been employed to enhance the flavor, texture, and shelf life of a range of products. The cosmetics industry employed nanoemulsions to improve the dispersion and efficacy of active ingredients **(5).**

The science of nanoemulsion technology is still in its infancy, with research efforts focused on improving the manufacturing processes and understanding the potential applications of these materials in a variety of sectors. Due to their unique properties, which include increased stability, better solubility, and enhanced bioavailability, nanoemulsions hold considerable promise for future study in a variety of academic domains **(6, 7).**

Types of Nanoemulsions (8)

1. Water with oil in it oil droplets distributed throughout the continuous aqueous phase in nanoemulsions.
2. Oil and water nanoemulsions in which the continuous oil phase contains scattered water droplets.
3. Bi-continuous nanoemulsions, in which the system contains interdispersed oil and water microdomains.
4. The proper ratio of surfactants to co-surfactants stabilizes the interface in each of the three forms of nanoemulsions.

Nanoemulsion Components

The main component of nanoemulsion are oil, surfactant and co-surfactant. Oils can be utilized to improve drug transport and solubilize lipophilic medications. O/W and W/O nanoemulsion topical medication delivery can be modulated by the choice of oil component." The polar and nonpolar regions make up the two portions of surfactant molecules. A polar group's nature inside the molecule determines its classification, which includes anionic, cationic, non-ionic, and zwitter ionic surfactants. Because surfactants make two immiscible liquids more miscible by lowering their interfacial tension, they play a major role in the formulation of nanoemulsions.

Cosurfactants are necessary since a single surfactant would not be sufficient to lower the oil/water interfacial tension while creating nanoemulsions. By making the junction more fluid, they lessen interfacial tension.

The aqueous phase may have an impact on the size of the droplets and the stability of the nanoemulsion. It is important to pay close attention to the pH and the presence of electrolytes in the aqueous phase. Additives which ingredients added to the nanoemulsions to extend their shelf lives **(9).**

The advantages of nanoemulsion

Nanoemulsions have many advantages over traditional emulsion technologies. The smallest droplet size of the nanoemulsion inhibits particle coalescence, ensuring the least amount of potential for any phase to separate as a separate layer. Due to the tiny size and low weight of the particles, there is little chance of sedimentation or creaming by gravitational force. Additionally, a well-dispersion system and uniform dose distribution are guaranteed by small droplet sizes. Compared to other emulsion systems, less surfactant is used. Because small particles can pass through the absorption membrane with ease, it can boost the bioavailability of medications that are poorly soluble. It is possible to construct nanoemulsion to deliver medications via a variety of channels. Additionally, a tiny size offers a wide surface area, which facilitates penetration and solubilization through the skin **(10).**

Celecoxib is a highly lipophilic, poorly soluble medication with an oral bioavailability of about 40% (capsule), which Faiyaz Shakeel and his research group produced into an O/W nanoemulsion for transdermal application. They discovered that, in comparison to oral capsule formulation, the absorption of celecoxib through transdermal application of nanoemulsion and nanoemulsion gel was 3.30 and 2.97 times higher. Since the medicine does not function on parts of the body that are not intended for it, nanoemulsion lengthens the duration of drug retention in the target location and reduces side effects or toxicities. Because of improved absorption, higher bioavailability, longer retention periods, and less drug loss, less medication is needed. Additionally, it makes parenteral administration of emulsions containing small droplets easier **(11-13).**

Some fundamental benefits of nanomedicine based on nanoemulsions are shown in Figure 1 below. Sivakumar and colleagues found that aspirin's O/W nanoemulsion, made using ultrasonic cavitation techniques, outperformed traditional formulations in terms of its anti-inflammatory and analgesic effect.

Under the direction of Kesavan Bhaskar, a research team created lipid nanoparticles based on nanoemulsions for the transdermal delivery of flurbiprofen.

When compared to oral dosing, flurbiprofen gel was reported to have a 4.4-fold higher bioavailability **(14, 15).**

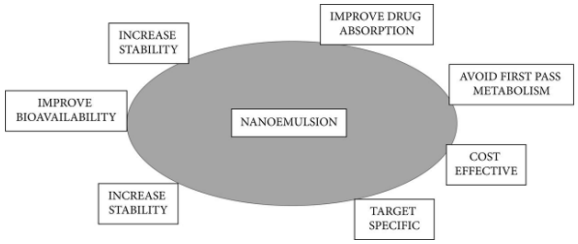

Figure 1. A New and Emerging Technology to Increase Drug Bioavailability is Nanoemulsion

Nanoemulsion disadvantages (10, 16)

1. Because there is little surfactant utilized, the nanoemulsion's stability is only temporary.
2. An incorrect comprehension of how nanoemulsions are formed: There is currently a dearth of precise information on the quantity of emulsifiers needed. Emulsifiers, which are required to stabilize micro droplets, must be chosen carefully since excessive concentrations of them might become poisonous. Furthermore, environmental factors like pH and temperature can readily affect the stability of nanoemulsions, which is why controlling emulsifying conditions is crucial.
3. Stability of storage requires optimization.
4. The use of expensive and complex equipment, such as homogenizers and microfluidizers, in the preparation of nanoemulsions by high-energy processes raises the cost of production.

5. Researchers have misunderstandings about the fundamental chemistry involved in the creation of nanoemulsion, which has caused them to avoid working with nanoemulsion.
6. more expensive than any other traditional formulation.
7. Surfactant is necessary to lower osmotic pressure and interfacial tension.
8- The solubilizing ability of this system is restricted for compounds with a high melting point.
9- In pharmaceutical applications, harmless surfactant nanoparticles may create increased shear due to their higher kinetic energy.
10- Due to their tiny drop size, which hinders typical destabilizing mechanisms including sedimentation, coalescence, and creaming, they have stability issues for extended periods of time.
11- Because low-energy preparation of nanoemulsions demands a significant volume of surfactant, excipients used for human usage should be rigorously nontoxic.

Drugs Candidate For Nanoemulsion

A potential technique for improving the chemical instability and oral bioavailability of medications that are only slightly soluble in water (lipophilic medicines) is nanoemulsion.Nanoemulsions are often described as very tiny droplet size (r < 100 nm) oil-in-water emulsions. They have special qualities including increased physical stability, superior optical clarity, and higher bioavailability because of their tiny droplet diameters (70).

Nanoemulsions have a wide surface area and can interact aggressively with biological components in the GIT because of their tiny droplet size. Because nanoemulsions have more binding sites accessible for digestive enzymes like lipase, they usually breakdown more quickly in the gastrointestinal system than regular emulsions **(17, 18).**
like resveratrol. Due to its low water solubility, resveratrol is an unstable medication. To increase its bioavailability, a nanoemulsion has been created around it. In water-in-oil nanoemulsions, resveratrol is mixed in. Additionally, it has been demonstrated that resveratrol is shielded from chemical deterioration and is not isomerized into inactive Z-resveratrol by nanoemulsions. Further examples include ramipril, which lowers blood pressure, and 5-fluorouracil, which fights cancer. Because of their tiny droplets, nanoemulsions provide a wide interfacial area for drug dissolution and improved drug solubility. This advantage leads to higher drug-loading capabilities, which facilitate the administration of a wider range of therapeutic drugs **(19, 20).** The solubility and bioavailability of medications that are weakly water-soluble are enhanced by the large interfacial area created by the nanoemulsion's tiny droplet size, which is typically between 20 and 200 nanometers.

For instance, Using a variety of methods, including nanoemulsion, the poorly soluble medication celecoxib (CXB) was made more soluble and soluble. Nanoemulsion produced the best sustained type medication release.

This suggested that CXB medication distribution with nanoemulsion may be accomplished effectively and continuously **(21).**

By concentrating on the impacted tissue, nanoemulsion technology seeks to lessen the adverse effects of medications. Drug targeting by nanoemulsion may be accomplished via surface modification or by virtue of the drug's physicochemical characteristics. Local targeting, such as the skin, lymphatic system, and lungs, is possible using nanoemulsions. Such targeting is caused by the nanoemulsion's size, surface charge, or lipophilicity, while occasionally new targeting ligands are also used.

For instance, a site-specific targeting subcutaneous delivery system for methotrexate-loaded nanoemulsion has been created for the treatment of rheumatoid arthritis.

The requirement for high and frequent dosages may be decreased by the use of encapsulated carriers for targeted administration.

It is possible to target the lymphatic system more successfully with drugs contained in micro- to nanoscale carriers. While using fewer medications overall, the use of encapsulated carriers—especially nanoparticles—can help achieve delayed release **(22, 23).**

Because capillaries are permeable and may carry smaller molecules, subcutaneous injection can be utilized to target lymph nodes. Drug-loaded nanoparticles delivered subcutaneously and absorbed into the lymphatic system make this an effective delivery method that improves the course of RA treatment **(24).**

In order to improve raloxifene (RAL) oral absorption, a non-lipolysis nanoemulsion (NNE) was created to inhibit intestinal UDP-glucuronosyltransferases (UGTs) from metabolizing RAL in the first place **(25).**

Additionally, the metallic and bitter tastes of drugs that may cause unpleasant side effects including nausea and vomiting can be efficiently covered up by nanoemulsion **(26).**

Methods for preparation of nanoemulsion

Nanoemulsions are prepared using a variety of techniques, such as a combination of low and high emulsification. Among the techniques used frequently are stirring ultrasonic emulsification and high-pressure homogenization. Phase inversion temperature method, emulsion point method, and spontaneous method receive less attention. In extremely viscous systems, reverse can be prepared via an emulsification-based method **(27).**

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Preparation methods of nanoemulsions include two (28, 29)

A- High energy emulsification method

1. The method of high-pressure homogenization

Applying high pressure to a system that contains an oil phase, an aqueous phase, and a surfactant or co-surfactant is how this process is carried out. The two liquids, surfactant, and co-surfactant are forced to pass through a small orifice at high pressure (500–5000 psi) in order to create nanoemulsions. The pressure is applied with the use of a homogenizer. Poor productivity and component deterioration from excessive heat generation are some issues related to homogenizers.

2- The method of microfluidization.

The technology of microfluidization makes use of microfluidizers. To create fine nanoemulsions, this apparatus uses a high pressure positive displacement pump (500–20,000 psi). The coarse emulsion is fed through the interaction chamber microfluidizer (figure 3) several times until the droplets reach the appropriate size .

3-Shaking at High Shear

This technique prepares nanoemulsions using rotor-stator systems and high-energy mixers. By raising the mixing intensity of these devices, it is possible to drastically reduce the droplet sizes of the internal phase. Nevertheless, it might be challenging to produce emulsions with an average droplet size of less than 200–300 nm.

4-The Ultrasonication Process

As an alternative to high-pressure homogenization, use this technique. Ultrasonic cavitation produces the forces required to produce nanoemulsions. Vacuum bubbles implode violently and asymmetrically when ultrasonic cavitation occurs. Droplets are broken up and dispersed by micro-nozzles to nanometer size. Pharmaceutical liposomes and nanoemulsions in small amounts can be produced with success using this technique. Without the ability to combine processes like large quantity - high amplitude, conventional ultrasonic technology operates on the principles of small amount - high amplitude or high levels - low amplitude. Despite the potential of the method, ultrasonic method is limited to the laboratory use.

B- low energy emulsification method

1- Methods for one-phase inversion

With an increase in temperature, the polyethoxylated surfactant becomes lipophilic (due to dehydration) and becomes soluble in the oily phase. The phase inversion temperature approach employs a mixture of oil, water, and nonionic surfactants at room temperature that exhibits a positive curvature. When this happens, the phase inversion occurs and the O/W emulsion transforms into a W/O emulsion with a negative curvature. It should be mentioned that extremely unstable emulsions form as the curvature approaches zero at an intermediate temperature known as the HLB temperature, which is reached when the surfactant's lipophilic and hydrophilic qualities are balanced.

Stable nanoemulsions can be produced and coalescence prevented with a rapid temperature change (25–30 oC increase or decrease in HLB temperature). The primary drawback of the PIT approach for creating nanoemulsions is that, in the food and beverage business, as the temperature of the dispersed phase droplets rises, so does their propensity to combine. As a result, a novel method for creating nanoemulsions was devised, which involved diluting nonionic surfactants with comparatively low phase inversion temperatures (like Brij30) with a solution containing another surfactant with a high phase inversion temperature (like sodium dodecyl sulfate or Tween 80). The PIT method's drawbacks include its restriction to the nonionic surfactants.

2- The method of spontaneous emulsification

This technique can be used to create nanoemulsions at room temperature without the need for a specialized tool. To create O/W nanoemulsions, water is gradually added to the oil and surfactant solution while maintaining a steady temperature and stirring gently. The key factors that affect the spontaneous emulsification process are the phase transition region, surfactant structure and concentration, interfacial tension, and bulk and interfacial viscosity.

3. The method of solvent displacement

Using this technique, room-temperature nanoemulsions can be made by mixing an aqueous phase containing surfactants with an organic phase that contains oil dissolved in a solvent such as acetone or ethanol.

To make tiny droplets, a high solvent to oil ratio is required. Using this procedure, the solvent must be removed with more work.

Conclusion

The review's arguments point to nanoemulsions' growing impact on every facet of drug delivery. 1) Normal destabilizing mechanisms that are durable in emulsions are naturally resistant to nano emulsions.

2) They have a cosmetic appeal because they are typically translucent.

3) offer numerous chances to boost the oral bioavailability of medications that are very lipophilic.

The main idea for the creation of emulsions was oral distribution, and nano emulsions are particularly well-suited for this use case. Using nanoemulsions, other drug delivery methods are also viable. They are particularly suitable candidates for safe intravenous access due to their small size. It is anticipated that nano emulsions will increasingly become a focus of study and innovation. To guarantee that nano emulsions reach the patient bedside and become a common pharmaceutical product, however, a number of obstacles still need to be addressed. The main ones are the financial ramifications of increasing the production of nanoemulsions, the search for nontoxic solvents in formulation, and the improvement of the toxicity database for different excipients used in the creation of nanoemulsions.

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