Review Article

Int J. Pharm. Drug. Anal, Vol: 11, Issue: 4, 2023; 8-13

International Journal of Pharmaceutics and Drug Analysis

Content Available at www.ijpda.com ISSN: 2348:8948

NANOEMULGEL: FOR PROMISING TOPICAL AND SYSTEMIC DELIVERY

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Received: 04 Sept 2023 Revised: 25 Sept 2023 Accepted: 05 Nov 2023

Abstract

A Nanoemulgel is a topical gel that contains a nanoemulsion dispersed within a gel matrix. The nanoemulsion is typically prepared using high shear mixing techniques and contains droplets of oil. The droplets size of nanoemulsion was in range of of 28 to 500nm. The sizes were confirmed by dynamic light scattering method. Nano-emulgel is an emerging drug delivery system intended to enhance the therapeutic profile of lipophilic drugs. Lipophilic formulations have a variety of limitations, which includes poor solubility, unpredictable absorption, and low oral bioavailability. Nano-emulgel, an amalgamated preparation of different systems aims to deal with these limitations. The novel system prepared by the incorporation of nano-emulsion into gel improves stability and enables drug delivery for both immediate and controlled release. Nanoemulgel improves the stability of a nanoemulsion formulation by lowering surface and interfacial tension, which increases the aqueous phase viscosity. Because the system has a higher viscosity than the nanoemulsion system, nanoemulgel is also known as hydrogel-thickened nanoemulsions. Hydrophobic medication delivery using nanoemulgel is extremely effective. Nanoemulgel use has increased in recent years as a result of the preparation's improved acceptability among patients due to its non-greasy, convenient Spread ability, easy application, and good therapeutic and safety profile.

Keywords: Nanoemulgel, nanoemulsion, bioavailability.

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DOI: https://doi.org/10.47957/ijpda.v11i4.561

Produced and Published by

South Asian Academic Publications

Introduction

Nanotechnology is one of the growing technological applications that had been increasingly applied in various demands, especially in cosmetics, biopharmaceutical, and food industries [1]. Nanotechnology containing products show a potential market because of the superior characteristics' properties such as small droplet size with the high interfacial area, enhance the delivery of the active ingredients, and excellent solubilization capacity [2].

Nanolipoidal delivery system belongs to the category of Novel drug delivery system, which is used mostly for different stabilization activities and for enhancing bioavailability. To the following different nanolipoidal delivery system such as- solid lipid nanoparticles (SLNs), liposomes, microemulsions, nanostructured lipid carriers (NLCs), etc [3].

Nanoemulsion is the most effective delivery system for drugs with low bioavailability and lipophilic nature that are administered through different routes along with the topical route. Nanoemulgel, without affecting the skin releases oil droplets from the gel and these oil droplets permeate the subcutaneous layer of the skin and transmit the drug to the desired site [4].

Nanoemulsion-gel seems to have a strong adherence potential and higher solubilization of the drug in the oily phase results in higher concentration gradient towards the skin which ultimately increases the skin permeability of drug. Patient adherence has been significantly enhanced due to increased succor capacity compared with creams and ointments, with minimal stickiness.

Nanoemulsions are the colloidal dispersions that consist of oil, water, and emulsifier, with the range of the droplets size between 20 nm to 500 nm. The emulsifier plays a vital role in creating small-sized droplets as it decreases the interfacial tension between the water phases and the oil phase of the nanoemulsion [5]. Water in oil (W/O) nanoemulsion offers a superior emollient property, but the costumers do not accept them well because of the high content of oil and greasy texture. On the other hand, oil in water nanoemulsion (O/W) is more favored as it enhances the absorption speed, and less oil content in the

formulation caused it to be easily washed from the skin. Nanoemulgels are topical gels contain nanoemulsions. They are commonly used in dermatology for the treatment of skin conditions such as eczema, relief, pscoriasis and acne. They can also be used to deliver medications for pain relief, anti-inflammatory agents, and anti-infective agents [6]. Nanogels are nanoparticles - based hydrogels that have been studied for their potential in drug delivery, tissue engineering and other biomedical applications. They are commonly used due to their biocompatibility, biodegradability and high drug loading capacity [7].

Important Content Nano-Emulgel

A) OILS: The oils utilized in the nanoemulsion are usually oil used as a vehicle for the drug. aperient and numerous fixing oils (cottonseed oil, corn oil, peanut oil) vegetable oil, oil, essential oil, rose oil, clove oil, etc8.

B) liquid PHASE: H2O is usually used because the liquid part is for the preparation of Nanoemulsion and colloidal gel.

C) Surfactant: Surfactants were wont to give emulsions at the time of formulation and to regulate the daily stability throughout the ready nanoemulsion. The general selection of chemical agents depends on the kind of emulsion. (O/W or W/O) E.g. Span eighty (Sorbitanmonooleate), AcrysolK a hundred and forty, Polyethylene-glycol-40-stearate, Acrysol, Labrasol, Stearic acid, PlurolOleique, Tween eighty (Polyoxyethylenesorbitanmonooleate), Labrafil, metal stearate, wherever agents like Transcutol, Captex, Cammul, Migyol, etc. is used as cosurfactant or co-solvents9.

D) Gelling Agent: Polymers essential to present the structural network for the preparation of gels are referred to as gelling agents. E.g. Natural - Agar, Tragacanth, Guar gum, Xanthan Gum, Semisynthetic and artificial Carbapol, Poloxamer, HPMC (cellulose derivatives).

Method of preparation

Step 1: Preparation of nanoemulsion

Nanoemulsions may be made spontaneously by blending the compositions and lowering the interfacial tension between the oil/water interfaces, or by introducing high energy into the heterogeneous mixture. Thus, high-energy and low-energy emulsification processes may be used to develop a thermodynamically stable nanoemulsion10.

High-energy method

Since nanoemulsion droplet sizes usually range from 5 to 500 nm, achieving this size requires a lot of mechanical energy. High-energy input for fabrication can be accomplished using a variety of techniques, including high-pressure homogenizers, ultrasound generators, microfluidizers, and high-speed homogenizer. The use of low emulsifier concentrations is the most important benefit of a high-energy mediated nanoemulsion formulation. The formation of an emulsion by mechanical stirring, with droplet size in the micron range, is the first step in using high-energy techniques. To turn the emulsion into a nanoemulsion, the second step is breaking huge droplets into small droplets with high-energy equipment's11.

Ultrasonication

The rough emulsion is converted into desirable nano-sized emulsion droplets using a sonicator probe. High-intensity sound waves having a frequency of even more than 20 kHz are generated by the sonicator probe. which has the ability to shatter the rough emulsion into nano-sized droplets (5-500nm). Different types of probes with varying dimensions are available for reduction in size up to recommended values. The sonication input intensity, time, and the probe type affect the droplet scale [12].

High-pressure homogenization technique

Numerous forces such as hydraulic shear, severe turbulence, and cavitation, are frequently utilized for the development of nanoemulsions. The surfactants and co-surfactants that are passed through a small orifice of a piston homogenizer under high pressure (500-5000 psi) to generate nanoemulsions. The problem of coalescence that would occur can be solved by incorporating excess surfactants into the mixture. High-pressure homogenization is a highly effective method and a cost-effective technology that can be used on both a small and a large scale to produce nanoemulsions of extremely low particle size (up to 1 nm). The droplet size varies according to homogenization cycles and dispersed and continuous phase viscosities. The main drawbacks include consumption of a lot of energy and raising the temperature during the processing, which may lead to component deterioration. This approach works well for a nanoemulsion that has a 20% oil content since a high volume of oil in the formulation decreases the method's productivity13.

Microfluidization This approach uses a microfluidizer device, which utilizes a high-pressure positive displacement pump (500- 20,000 psi) to force the product through an interaction chamber with stainless steel microchannels on the contact area, resulting in the creation of very small sub-micron particles. The mixture is circulated through the microfluidizer till it reaches the desired particle size. The final product is filtered to separate the smaller droplets from the bigger ones and produce a homogeneous nanoemulsion14.

High-speed homogenization (rotor-stator homogenizer) High-speed homogenizers are commonly used in industry for emulsification, dispersion, and comminution. They are simple to mount in existing vessels and tanks, and they are inexpensive to buy. Rotor-stator processes are often the emulsification method of preference in many manufacturing industries. Many studies prove that it is possible to produce nanoscale droplets through using rotor-stator processes. However, this necessitates the precise selection of method and formulation parameters [15].

Low-energy method

The production of nanoemulsions using a low-energy emulsification process uses less energy than high-energy methods. They produce nanoemulsions by utilizing the system's inherent chemical energy and just requiring mild stirring. Low-energy approaches include phase inversion methods and spontaneous emulsification [16].

Spontaneous emulsification

One of the most practical methods of nanoemulsion preparation is spontaneous emulsification. It has two liquid components, one of which is aqueous and the other is organic. Solvents, surfactants, and co-surfactants that are water miscible are shifted from the organic phase to the aqueous phase. The process starts with an organic phase, such as oil and surfactant, being introduced into an aqueous phase, which is made up of water and co-surfactant. Massive turbulence at the phase interface is caused by the rapid migration of water-miscible components into the aqueous phase, which increases the oil–water interfacial area. As a result, small oil droplets form spontaneously [17].

Step 2: preparation of nanoemulgel The gel base is produced by dissolving the polymer in purified water and continually stirring it with a mechanical stirrer (4). Following the preparation of the nanoemulsion and the gelling agent, the two are continuously stirred until a nanoemulgel is formed. Water in oil (w/o) or oil in water (o/w) nanoemulsion is turned into thick and semisolid nanoemulgels with the aid of different polymeric gelling agents [18].

Advantages

1. The ability to resist First-pass metabolism.
2. Effectiveness for a managed and long-term drug delivery system has been proven.
3. Skin friendly.
4. Appropriate for self-medication.
5. Patient accepts it quickly.
6. Nanoemulsion provides large surface area and free energy which make an efficient delivery system.
7. Emulsion defect like Creaming, phase separation, flocculation, and coalescence is not found in nanoemulsion.
8. Nanoemulsion prepared in variety of formulations, foams, creams, sprays and much other cosmetic formulation.
9. It is safe on transdermal application due to its non-toxic nature.
10. By using biocompatible surfactant in nanoemulsion [31]. Formulation, it can be administered orally.
11. It shows better penetration of drug because the nano-sized particles can easily enter by the rough skin surface.
12. By the process of precipitation and interfacial poly-condensation of nanoemulsion, nanocapsule and nanosperes are prepared [19].

Disadvantages

1.Bubbles formed during emulgel formulation.
2. For utilization in pharmaceutical application, surfactant used ought to be non-poisonous.
3. Possibility of allergenic reactions.
4. Skin irritation on contact dermatitis [20].

Evaluation of nanoemulgel

1 Visual inspection The prepared nanoemulgel could be checked visually to detect the color, appearance and homogeneity of the nanoemulgels [5].

2 pH measurement The pH of nanoemulgel depends on the applications whether for skin or for other mucous membrane, for example the pH of human skin is known to be between 4.5 and 6.

3 Determination of Viscosity The gel's viscosity is crucial for effective application to the skin. It is important for gel to know the rheological behavior. Viscosity can be defined as the resistance of fluid to flow and higher viscosity means higher resistance to flow. Fluids generally are classified into Newtonian and non-Newtonian systems. In Newtonian flow, the fluid with higher viscosity requires greater force per unit area (shear stress) to generate a certain shear rate. In Newtonian flow, the viscosity is constant with different shear rate. In contrast to the Newtonian fluid, non-Newtonian flow does not comply with newton low and the viscosity is changed with the differences in shear rate [22].

4 Spreadability measurement The therapeutic efficacy of the developed formulation will be determined by the spreadability of the topical preparation. The ease with which a gel spreads over the application site on the skin and the affected area is referred to as spreadability. The 'Slip' and 'Drag' properties of nanoemulgels are used to determine their spreadability [23].

5 Droplet Size Measurement and Polydispersity Index (PDI) Droplet size is typically determined using the dynamic light scattering (DLS) approach. The polydispersity index (PDI) measurement provides information on the droplet size homogeneity within the prepared nanoemulsion [24].

6 Zeta Potential Because nanoemulgel is made up of nanoemulsion and a gelling agent, the formulation can acquire an electrical charge as a result of the presence of different surface-active ingredients25.

7 Drug content Drug content is a very important parameter which determines the total amount of drug that is present in the prepared formulae and higher drug content is associated with little loss of drug during production steps [26].

8 Accelerated stability study Accelerated stability study should be conducted in accordance with International Council for Harmonization (ICH) regulations. The formulations should be kept 3 months in the oven at 37±2°C, 45±2°C, and 60±2°C. The samples IN PRESS Azeez, Alkotaji: Nanuemulgel should be tested every two weeks using an appropriate analytical procedure to determine the drug content. The change in pH of the gel or drug deterioration is used to measure the stability [27,28].

Marketed formulation

Currently available marketed emulgel products for the treatment of acne and pimple, inflammation, and pain caused by osteoarthritis and rheumatoid arthritis and skin infection have been listed in Table 1

Table 1: Marketed formulation

Product brand name	Active pharmaceutical ingredient (s)	Manufacturers	Application
Benzolait AZ emulgel	Benzoylperoxide	Roydermal	Pimple and blacks on skin
Coolnac Gel emulgel 1%	Diclofenac diethyl ammonium	Chumchon	Inflammation and pain due to trauma
Diclobar emulgel	Diclofenac diethyl amine	Barakat Pharma	Inflammation due to trauma and rheumatic diseases
Levorage emulgel	Liquorice, hibiscus, and natural extract	THD Ltd	Anal fissures
Meloxic emulgel	Meloxicum	Laboratories Provet	Musculoskeletal pain management and inflammation
Miconaz-H-emulgel	Miconazole nitrate, hydrocortisone	Medical Union Pharmaceutics	Skin infection by candida
Reumadep emulgel	Ashwagandha, myrrh, arnica, rosemary, mint, and cloves	Erbozeta	Inflammation and pain due to trauma
Voltaren emulgel	Diclofenac diethyl ammonium	Novartis Pharma	Osteoarthritis joint pain
Voveron emulgel	Diclofenac diethyl amine	Novartis Pharma	Osteoarthritis joint pain

Current and Future Prospects of Nanoemulgel

Delivering hydrophobic drugs to the biological systems has been a major challenge in formulation development owing to their low solubility, leading to poor bioavailability. Some of the topical formulations include creams, ointments, and lotions. They possess good emollient characteristics, however, has slow drug release kinetics due to the presence of hydrophobic oleaginous bases such as petrolatum, beeswax, and vegetable oils, which inhibit the incorporation of water or aqueous phase. On contrary, topical aqueous-based formulations like gels enhance the drug release from the medication since it provides an aqueous environment for medicament. Therefore, hydrophobic APIs are blended with oily bases to form an emulgel, which further undergoes nanonization to form a nanoemulgel with enhanced properties. The superior properties of a nanoemulgel like thermodynamic stability, permeation enhancement, and sustained release make it an excellent dosage form. There are several marketed emulgels and patents being filed for the same, demonstrating its tremendous progress in this field. By making advancements in the ongoing research, nanoemulgel, as a delivery system would outshine, in formulating the drugs that are being eliminated from the development pipeline owing to their poor bioavailability, therapeutic non-efficacy, etc. Despite these advantages, the manufacturing of nano-emulsion limits its commercialization. However, with the progressing technology, commercially feasible and profitable manufacturing techniques could be possible in the future. With the advantages of nano-emulgel over other formulations, a tremendous increase in the production of nano-emulgel can be foreseen

Conclusion

Nanoemulgel topical has proven to be the best choice for an efficient and convenient drug delivery system. Its gel-like and non-greasy properties help patients with greater compliance and oil deficiency as a substrate provides better drug release than other formulations. Incorporation of the nanoemulsion into the gel matrix makes formulation a dual control system release. Gel loaded with nanoemulsion offers greater efficacy in some topical disorders. Future of formulation Nanomulsion Gel may provide a better and reliable solution for hydrophobic drug delivery. A large number of drugs used in the treatment of skin infections are hydrophobic and these drugs can be successfully delivered in the form of Nanoemulgel in which the drug is incorporated into the oil phase of the drug. Nanoemulsion and then fused with the base of the gel. Although has barrier pairs, nanoemulgel likely possesses focal points for in situ transport for future lipophilic drugs.

Acknowledgment

None

Conflict of interest

Authors are declared that no conflict of interest

Funding

No Funding

Ethical Consideration and Inform Consent

Not Applicable

Refrences

1. Kalepu S., Nekkanti V. Insoluble Drug Delivery Strategies: Review of Recent Advances and Business Prospects. *Acta Pharm. Sin. B.* 2015;5:442–453.
2. Anyanwu NCJ, Adogo LY, Ajide B. Development and evaluation of in situ gelling gastroretentive formulations of Meloxicam. Universal Journal of Pharmaceutical Research 2017; 2(3): 10-13.
3. Donthi M.R., Munnangi S.R., Krishna K.V., Marathe S.A., Saha R.N., Singhvi G., Dubey S.K. Formulating Ternary Inclusion Complex of Sorafenib Tosylate Using β-Cyclodextrin and Hydrophilic Polymers: Physicochemical Characterization and In Vitro Assessment. *AAPS PharmSciTech.* 2022;23:1–15.
4. Obanewa OA, Oyeniran OT. Development and estimation of anti-inflammatory activity of topical etoricoxib emulgel by carrageenan induced paw oedema method. Universal Journal of Pharmaceutical Research 2019;4(3):22-26.
5. Singh G., Singh D., Choudhari M., Kaur S.D., Dubey S.K., Arora S., Bedi N. Exemestane Encapsulated Copolymers L121/F127/GL44 Based Mixed Micelles: Solubility Enhancement and in Vitro Cytotoxicity Evaluation Using MCF-7 Breast Cancer Cells. *J. Pharm. Investig.* 2021;51:701–714.
6. Ugochukwu AE, Nnedimkpa OJ, Rita NO. Preparation and characterization of Tolterodine tartrate proniosomes, Universal Journal of Pharmaceutical Research 2017; 2(2): 1-3.
7. Alekya T., Narendar D., Mahipal D., Arjun N., Nagaraj B. Design and Evaluation of Chronomodulated Drug Delivery of Tramadol Hydrochloride. *Drug Res.* 2018;68:174–180.
8. Umar S, Onyekachi MK. Development and evaluation of transdermal gel of Lornoxicam. Universal Journal of Pharmaceutical Research 2017; 2(1): 15-18.
9. Homayun B., Lin X., Choi H.J. Challenges and Recent Progress in Oral Drug Delivery Systems for Biopharmaceuticals. *Pharmaceutics.* 2019;11:129.
10. Paliwal S, Kaur G, Arya KKR. Formulation and characterization of topical nano emulgel of terbinafine. Universal Journal of Pharmaceutical Research 2018;3(6):28-34.
11. Donthi M.R., Dudhipala N.R., Komalla D.R., Suram D., Banala N. Preparation and Evaluation of Fixed Combination of Ketoprofen Enteric Coated and Famotidine Floating Mini Tablets by Single Unit Encapsulation System. *J. Bioequiv. Availab.* 2015;7:1–5.
12. Mursyid AM, Waris R. Formulation and evaluation of pharmaceuticaly stable serum of D. indica (Arbenan). Universal Journal of Pharmaceutical Research 2021; 6(1):38-42.
13. Wang W., Zhou H., Liu L. Side Effects of Methotrexate Therapy for Rheumatoid Arthritis: A Systematic Review. *Eur. J. Med. Chem.* 2018;158:502–516.
14. Türkmen A, Esentürk-Güzel İ, Kara BA. Innovative drug delivery systems for infectious diseases of the skin. Universal Journal of Pharmaceutical Research 2022; 7(4):68-76.
15. Rajitha R., Narendar D., Arjun N., Nagaraj B. Colon Delivery of Naproxen: Preparation, Characterization and Clinical Evaluation in Healthy Volunteers. *Int. J. Pharm. Sci. Nanotechnol.* 2016;9:3383–3389.
16. Hamsinah, Meylinda A, Khusnia, Mario R, Ummum A, Safitri D. Application of lutein-zeaxanthin of egg yolk based hydrogel eye mask as a preventive effort against Computer Vision Syndrome (CVS). Universal Journal of Pharmaceutical Research 2021; 6(5):24-29.
17. Garg N.K., Singh B., Tyagi R.K., Sharma G., Katare O.P. Effective Transdermal Delivery of Methotrexate through Nanostructured Lipid Carriers in an Experimentally Induced Arthritis Model. *Colloids Surf. B Biointerfaces.* 2016;147:17–24.
18. Gurpınar SS, Devrim B, Eryılmaz M. In-vitro antibacterial activity of lactobacilli metabolites loaded hydrogel formulations against *Pseudomonas aeruginosa*. Universal Journal of Pharm Research 2019; 4(4):9-11.
19. Szumała P., Macierzanka A. Topical Delivery of Pharmaceutical and Cosmetic Macromolecules Using Microemulsion Systems. *Int. J. Pharm.* 2022;615:121488.
20. Elsaied EH, Dawaba HM, Ibrahim EA, Afouna MI. Investigation of proniosomes gel as a promising carrier for transdermal delivery of Glimepiride. Universal Journal of Pharmaceutical Research 2016; 1(2): 1-10.
21. Gupta R., Dwadasi B.S., Rai B., Mitragotri S. Effect of Chemical Permeation Enhancers on Skin Permeability: In Silico Screening Using Molecular Dynamics Simulations. *Sci. Rep.* 2019;9:1456.
22. Saka R., Jain H., Kommineni N., Chella N., Khan W. Enhanced Penetration and Improved Therapeutic Efficacy of Bexarotene via Topical Liposomal Gel in Imiquimod Induced Psoriatic Plaque Model in BALB/c Mice. *J. Drug Deliv. Sci. Technol.* 2020;58:101691.
23. Pandi P., Jain A., Kommineni N., Ionov M., Bryszewska M., Khan W. Dendrimer as a New Potential Carrier for Topical Delivery of SiRNA: A Comparative Study of Dendriplex vs. Lipoplex for Delivery of TNF-$α$ SiRNA. *Int. J. Pharm.* 2018;550:240–250.
24. Sarathlal K.C.S., Kakoty V., Krishna K.V., Dubey S.K., Chitkara D., Taliyan R. Neuroprotective Efficacy of Co-Encapsulated Rosiglitazone and Vorinostat Nanoparticle on Streptozotocin Induced Mice Model of Alzheimer Disease. *ACS Chem. Neurosci.* 2021;12:1528–1541.
25. Nafisi S., Maibach H.I. *Cosmetic Science and Technology: Theoretical Principles and Applications.* Elsevier; Amsterdam, The Netherlands: 2017. Nanotechnology in Cosmetics; pp. 337–369.

26. Tiwari N., Osorio-Blanco E.R., Sonzogni A., Esporr\'\in-Ubieto D., Wang H., Calderon M. Nanocarriers for Skin Applications: Where Do We Stand? *Angew. Chem. Int. Ed.* 2022;61:e202107960.
27. Shukla T., Upmanyu N., Agrawal M., Saraf S., Saraf S., Alexander A. Biomedical Applications of Microemulsion through Dermal and Transdermal Route. *Biomed. Pharmacother.* 2018;108:1477–1494.
28. Nastiti C.M.R.R., Ponto T., Abd E., Grice J.E., Benson H.A.E., Roberts M.S. Topical Nano and Microemulsions for Skin Delivery. *Pharmaceutics.* 2017;9:37.