Review Article

A Review on Nano-Emulgel as a Novel Carrier for Topical Drug Delivery System

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ABSTRACT

Nano-emulgel, a new transdermal delivery method, has demonstrated unexpected advantages for lipophilic medicines over conventional formulations. Because most contemporary medications introduced in this modern period are lipophilic, they have poor oral bioavailability, irregular absorption, and variable pharmacokinetics. In order to prevent such disruptions, it has been demonstrated that this innovative transdermal delivery method is superior to traditional oral and topical drug delivery methods. These nano-emulgel are essentially gelled oil-in-water nano-emulsions that have been mixed with a gelling agent. The new technique created by adding nano-emulsion to gel increases stability and permits quick and regulated release of the medicine. In addition, it can prevent first-pass metabolism, alleviate the user of gastric or systemic incompatibilities, and be more precisely targeted to the site of action. The new system created by adding nano-emulsion to gel enhances stability and permits controlled and immediate release of medication. Because of its safety profile, lack of gastrointestinal breakdown or first-pass metabolism, ease of application, and capacity for targeted delivery, nano-emulgel has also gained more attention. This review focused on the formulation components, preparation, and characterization of nano-emulgel.

Keywords: Nano-emulgel, Surfactants, Topical delivery, Oils, Gelling Agent, Characterization.

INTRODUCTION

Modern dosing systems have been developed by pharmacists since the beginning of pharmaceutical culture in Mesopotamia (2600 BC), when disease was first treated with plants and water. Research in this area has introduced a number of routes of administration to deliver the developed modern dosage form, which are primarily dependent on the physicochemical properties of the active compounds.[1] According to recent statistical reports on new chemical entities, poor aqueous solubility (70%) has surprised the earlier reports estimate of only about 40% new chemical entities with poor solubility.[2] The lipophilic properties of the newly developed drug molecules lead to issues such as poor oral B.A. erratic absorption, inter- and intra-subject pK variations, and lack of dose proportionality. To minimize these problems and focus on the solubility enhancement approach, a continuous developing process.[3-5]

To increase the solubility of drug, a variety of techniques can be used such as physical modification, chemical modification, formulation development, which include particle size reduction, complexation, amorphization, and nanocarrier drug delivery system.[6-8] The solubility of poorly water-soluble pharmaceuticals has been improved using a variety of formulation techniques, such as a particle size reduction to give through a variety of lipids formulation techniques, such as nanocarrier systems, crystal engineering, amorphous formulation etc.[9-10] Incorporating a lipophilic component into an inert vehicle,[11,12] creating micro or nano-emulsion,[13] self-emulsifying formulations, liposomes, solid-lipid nanoparticles, or lipid nano carriers are some of the recent lipid formulation approaches used to overcome the problem of these lipophilic compound.[14-16] As a result, many routes of administration have been investigated to deliver such formulation based on their individual benefits and drawback with regards to the topical system the severity of the disease, the age and conditions of the patients, accessible dosage form and ultimately for the user's compliance.[17-18]

The most popular route, based on patient compliance, is oral administration; nevertheless, oral administration is more likely to cause hepatic first-pass metabolism, requires a higher dose. Additionally, the main restriction on the presence of surfactants in lipid-based formulations is stomach irritation. At the same time, the body's ability to absorb drugs may cause unfavorable adverse effects. To overcome these issues of oral administration, the non-invasive, non-paining, topical delivery of formulations gives several advantages, such as the delivery of drugs to specific sites of action, reducing systemic toxicity, avoiding first-pass metabolism and gastric irritation, increasing the release rate of the formation, and improving percutaneous absorption.[19-21] For example, disease-modifying antirheumatic drugs (DMARDs) orally administered for the treatment of arthritis have various side effects like carcinogenicity, hepatotoxicity, and hematologic toxicity. These side effects can be reduced by delivering drugs through the topical route.[22-23]

In topical drug delivery, various mechanisms have been explored to enhance drug penetration through the outermost layer of epidermis called stratum corneum (the first and firmest layer to overcome drug penetration into skin).[24] This mechanism includes chemical penetration enhancers, ultrasound, ionophoresis, sonophoresis, electroporation, and microneedles by use of novel carriers.[25] The topical administration using novel carriers also includes emulsions (nano/micro), micelles, dendrimers, liposomes, solid lipid nanoparticles, and nano-structural lipid carriers. In which nanoemulsion are found to be a potential drug delivery system due to their high drug loading capacities, solubilizing capacities, ease of manufacturing, stability, and controlled release patterns.[26-28] In comparison of other novel carriers like liposomes, nano-emulsion have their own lipophilic core, which allows the movement of more lipophilic molecules across the topical membrane.[29]

Nano-emulsions

Nano-emulsions are heterogenous colloidal mixtures of oil and water with disperse and continuous phase, stabilized by an emulsifying agent reduces the surface tension of the disperse and continuous phases. Nano-emulsions have high thermodynamic stability, which provides longer half-life in comparison to simple emulsions and other formulations. Among these advantages, nano-emulsion have some limitations, such as low viscosity due to low viscosity retention time and spreadability problems. These problems can be resolved by modifying the nano- emulsion into a nano- emulgel by using suitable gelling agents.[30-32]

Nano-emulgel

Nano-emulsion have various advantages, but due to the lack of spreadability and retention time (due to their low viscosity), they have limitations for clinical application. Nano-emulgel is the best option to solve the problem of nano-emulsion, by adding a gelling agent to the nano-emulsion. Gels are prepared by adding huge quantity of aqueous and hydroalcoholic bases to a colloidal particulate system. By incorporating nano-emulsion into a hydrogel matrix, nano-emulgel is formed, which reduces the thermodynamic instability of nano-emulsion. A controlled-release dosage form for topical administration, nano-emulgel is advantageous for medication with a short half-life because of the improved retention time and thermodynamic instability that allow the formation to release drugs over time. [33-36]

Nano-emulgel have gel properties with specific characteristics of nano-emulsion such as particle size and thermodynamic stability. Nano-emulgel enhance skin penetration, provide high loading capacity of the active moiety, less irritation, and more spreadability. Nano-emulgel show better patient compliance due to their nonirritant, nongreasy nature, and also increase pharmacokinetic properties like bioavailability and reduce side effects.[37,38]

Table 1: Comparison between Nano-emulgel and Nano-emulsion.

Parameters	Nano-emulgel	Nano-emulsion
Preparation	Low energy or high energy technique	High energy technique
Particle size	Less than 100 nm	Greater than 500 nm
Thermodynamic stability	More stable	less stable due to sedimentation or creaming
Permeation	High permeation dur to particle size	Lower permeation
Bioavailability	High	Less in comparison to nano-emulgel
Systemic absorption	High	Low in comparison to nano-emulgel
Ability to cross BBB	Cross BBB	Less in comparison to nano-emulgel

Formulation considerations of Nano-emulgel

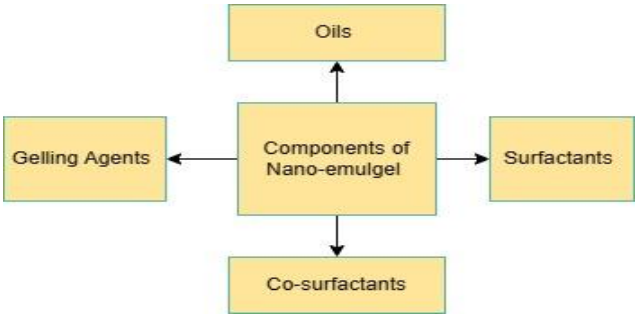

Figure 1: Various components of Nano-emulgel.

Nano-emulgel composed of two systems one is nano-emulsion (which consist nanoparticles or droplets), which may be O/W or O/W, and the other is gelling agents. Gelling agents (gel bases) contain polymers that swell by absorbing liquids and form gel bases. There are various components that are used in the formulation of nano-emulgel like oil, surfactant, cosurfactant, polymers.[39]

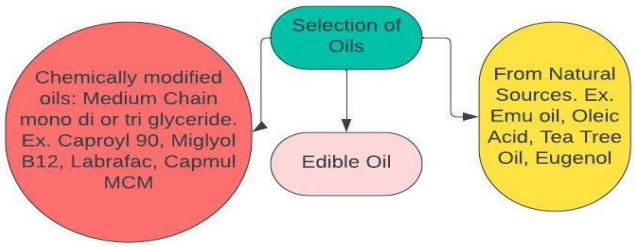

Figure 2: Selection of the Oil Phase for Nano-emulgel preparation.

Oil selection (oil phase)

The selection of the oil phase is one of the most critical and important parts of the formulation development of nano-

emulgel and nano-emulsion. There are some characteristics that are considered at the time of oil selection, such as viscosity, permeability, stability, oil nature, and quality. Which depends the application and utilization of nano-emulgel. In case of pharmaceutical and cosmetic applications of nano-emulgel the oil phase may natural, or synthetic lipids, and some time it may be act as an active ingredient in formulation. The hydrophobicity of the oil phase plays a critical role in forming nano-emulgel in term of stability, solubility of drugs (lipophilic drugs).[40]

Natural oil

Oleic acid

It is a biocompatible and biodegradable omega-nine fatty acid with high solubilizing properties, and well-known percutaneous absorption characteristics, obtained from vegetable as well as animal sources. Besides it also has some additional properties like antioxidant (repair cell damage). Due to these properties, it is used as a penetration enhancer in many drug formulations for the development of topical nano-emulgel. E.g.- Piroxicam, ketoprofen.[41]

Emu bird (Emu oil)

It has anti-inflammatory, analgesic, antipruritic, anesthetic, and antioxidant activity is also used to moisturize the skin because it has high amount of unsaturated fatty acids like oleic, which improve the skin penetration of the drug.[42-43]

Tea tree oil (Terpinene oil)

It has antimicrobial activity, used antifungal and antibacterial agent in various formulations e.g.- itraconazole. It provides synergistic effect against vaginal candidiasis when used with itraconazole. Along with these advantages, it its transdermal delivery is limited by its allergic properties.[44-45]

Eugenol (Eugenia Aromatica)

It is a phenolic compound have analgesic, local anesthetic, anti-inflammatory, and antibacterial properties. E.g. ketoprofen, provides super-additive synergistic antibacterial activity with ketoprofen when preparing nano-emulgel formulations against Staphylococcus aureus and Escherichia coli.[46] Swietenia macrophylla is also used in the oil phase and provide higher anti-inflammatory properties when delivered through nano-emulgel as compared to its parent form.

There are some other edible or vegetable oils mention in the earlier discussions but they are not frequently used due to their poor ability to dissolve lipophilic drugs and their poor emulsifying properties. Some chemically modified oils are also used as oil phases like medium-chain triglycerides or mono- or diglycerides e.g.- caproyl 90, Labrafac (Labrafac TM lipophile WL1349), capsules MCM, and miglyol 812.[47]

Table 2: List of Different Oils used in Nano-emulgel Formulation.

Oil	Drug	Author Name	Reference
Oleic acid	Ketoprofen	Arora et al.	37
Emu oil	Curcumin	Jeengar et al.	43
Oleic acid	Piroxicam	Dhawan et al.	75
Capmul MCM	Fluconazole	Pathak et al.	74
Eugenol oil	Ketoprofen	Srivastava et al.	47
Tea tree oil	Itraconazole	Bhusan et al.	76
Capryol 90	Ketoprofen	Arora et al.	37

Surfactants and Co-surfactant

Surfactants are important ingredients for nano-emulsion formulation. It reduces the interfacial tension between the disperse and continuous (dispersion) phases, and stabilizes the thermodynamic instable mixture of two immiscible liquids by changing dispersion entropy. Along with safety, stability, and high drug loading capacity, it provides good emulsification properties. Surfactants are the most basic integrated part of nano-emulsion formulation. Surfactants reduce the interfacial tension between the two immiscible liquids, show quick absorption, and prevent the coalescence of the nanodroplets.[48-49]

Surfactants are mainly categorized into two types based on HLB value and ionic nature. The selection of surfactant based on the HLB value of the surfactants may be classified as either O/W type (HLB 3-8) or O/W type (HLB 8-16). [50-51] Based on ionic charge, surfactants can be classified as cationic (amines and quaternary ammonium compounds, cetyl-trimethyl ammonium bromide, lecithin, hexadecyl trimethyl ammonium bromide, etc), anionic (carboxylate group, sodium directly sulfates), nonionic (poloxamers 124, 188, tween 20, 60, 80 and caproyl 90), or zwitterionic nature. [52-55] Anionic surfactants are toxic and non-biocompatible so they are less used. Nonionic surfactant is safe, biocompatible, and unaffected by pH.[56-57]

Among this synthetic surfactant, some natural surfactants (biosurfactants) are also used for formulation development, and they are safer and more biocompatible than synthetic surfactant. They are obtained from natural sources such as the cells of microorganisms like bacteria, Fungi, and animals. Biosurfactants are used potentially because of their safety, biocompatibility, and biodegradability. They are amphiphilic in nature and decrease surface tension the same as synthetic surfactants with the same mechanism because of their polar head and short fatty acid tail, which are for both hydrophilic and hydrophobic. These surfactants are safer and more biocompatible than synthetic surfactants.[58]

In nano system, co-surfactant is also used with surfactant, which helps during the emulsification of oil in the aqueous phase by decreasing interfacial tension. The selection of co-surfactant is also important in the preparation of Nano emulsion because it is associated with the surfactant and

partitioning of the immiscible phase of the drug and determine the drug release from nano-emulgel. Examples of surfactants are PEG-400, transcutol HP, absolute ethyl alcohol, and carbitol. The most preferred co-surfactant is alcohol base because it has the ability to partition between the oil and aqueous phases by improving their miscibility.[59-60]

Gelling Agents

Gelling agents are more important for the formulation of nano-emulgel. When these are added to a colloidal mixture, they produce a weakly cohesive three-dimensional structure network with high crosslinking and provide physical and chemical consistency to nano-emulgel.[61-63] Gelling agents are also used to stabilize the topical formulation in order to produce optimal drug delivery through the skin. They are crucial in determining formulation qualities such as consistency, theological properties, bio-adhesive properties, pharmacokinetics, spreadability and extruded ability. The gelling agents are classified as natural, synthetic or semisynthetic based on their origin.[64-65]

Table 3: List of Surfactant and Co-surfactant used in Nano-emulgel Preparation.

Sr. No.	Surfactants and Co-surfactants	Drug	Author Name	Reference
1.	Tween 80 (HLB-15) and span 80 (HLB 4.3)	-	Noor EL-Din et. al.	77
2.	Tween 20 and propylene glycol	Indomethacin	Abdelaziz et al.	78
3.	Tween 20 and tween 80	Ropinirole, Ketoprofen	Azeem et al., Arora et al.	79,80
4.	Tween 20 tween 80, Labrasol, Cremophore Rh 40, Cremophore EL	Leflunomide	Pund et al.	81
5.	Tween 80 and Transcutol (co-surfactant)	Aceclofenac	Shakeel et al.	82

Table 4: List of Gelling agents used in Nano-emulgel Preparation.

Sr. No.	Gelling Agent	Drug	Formulation	Author Name	Reference
1.	HPMC	Metronidazole	Topical Emugel	Dadoo et al.	83
2.	NaCMC	Acyclovir	Novel Emugel	Dixi et al.	84
3.	Poloxamer – 124, 182, 188, 407	Resveratrol	Nasal Emugel	Salem et al.	85
4.	HPMC and Carbopol combination	Clotrimazole	Oil based emulsion gel formulation	Sahin et al.	86

Preparation of Nano-emulgel

Nano-emulgel prepared by various method which is based on order of addition of oil phase and aqueous phase. In preparation, nano-emulgel drugs (API) are stabilized in the oil phase (phase I) and gelling agents (known as gel phases) are stabilized in aqueous phase (Phase II) separately. Then phase I is transferred in gel phase by continuous stirring followed by homogenization to form a homogeneous emulsion.[66-67]

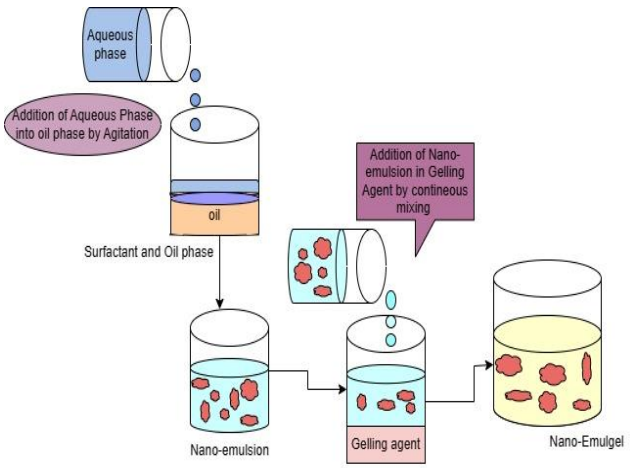

Figure 3: Preparation of Nano-Emulgel.

Ther are two steps involved in the preparation of nano-emulgel, one is the preparation of nano-emulsion, and another step is the addition of nano-emulsion in to gelling agents. Which is shown in fig. 3.

CHARACTERIZATIONS OF NANO-EMULGEL

Quality and consistency of pharmaceutical products are important for their therapeutic activity. There are some common tests used to evaluate the quality of a topical product (dosage form), such as water content uniformity, microbial limits, pH, particle size, sterility, etc. and some other tests are also used for the characterization of nano-emulgel because nano-emulgel contain nano-size globules, which is evaluated by zeta potential, PDI, spreadability, in-vitro release, bio-adhesive, skin irritation, and permeability test etc.

Zeta potential

Zeta potential is used to compare consistency between batches based on an indirect measurement of the net charge. If zeta potential is high, the products repulsion and stability of formulation is increase. Surfactants are used to maintain zetapotential in nano-emulgel. Instruments used for measuring zeta potential are Malvern nano-sizer/ zeta-sizer.[68-69]

Droplet size measurement and poly-dispersibility Index (PDI)

The hydrodynamic diameter of a globule in a nano-emulgel is the diameter of an analogue of a hard sphere that diffuses at the same rate as the active moiety.[70] The standard deviation of droplet size divided by the mean droplet size is known as the PDI, which determines the distribution of droplet size. Droplet size and PDI are closely connected to the drug release and stability (in-vivo and ex-vivo performance) and also provide consistency between the batches. It is measured by zeta size, which is work on the principal of dynamic light scattering.[71-72]

Rheological characteristics

Flow properties of the material are determined by rheology. The viscoelastic flow behaviors of the formulation are show by the rheological characteristics of materials. This effect is caused by the concentration of oil, surfactants, gelling agents. Formulation stability, drug release, and other in-vivo properties may be affected by variations in its viscosity and flow characteristics. Rheological behavior is an important factor for nano-emulgel due to their thinning tendency, which generates a thin layer on the skin surface, and improved permeability. Various types of viscometers are used to determine rheological behavior.[73]

Spreadability testing

The spreadability of the nano-emulgel significantly affected by the viscosity of the formulation. The parallel-plate method is commonly used for the determination of spreadability. In this method, two glass slides of the same length are used. In which one is stationarily attached to the wooden block and another slide is attached to a pulley at one end to measure spreadability. The nano-emulgel dosage form will be placed on a stationary glass slide, which is then squeezed in between the both slides. The known weight is added to the pully until the upper slide slips off from the lower slide. The time required for slipping off is recoded, which is used to calculate spreadability by using formula.[2]

$$S = M*L/T$$

Where- s is Spreadability.

M- is weight bounded to the upper slide.

L- is the length of the slide.

T- is the time taken to detach the slide.

In-Vitro Release Test (IVRT)

in-vitro release of semi-solid dosage form is determined by using the vertical diffusion cell or immersion cell method. The vertical diffusion has a receptor and donor chamber separated by a receptor membrane. The donor chamber contains a sample of nano-emulsion and the receptor chamber holds the receptor media (which may be buffer or hydroalcoholic solution). A membrane is selected that act as a skin cell membrane, and the temperature of the media is maintained at 37 ± 1° C for topical product 37±1^{0}C for mucosal product.[76]

Bio-adhesive Properties

Bio-adhesive properties is important for topical drug delivery to produce prolonged action. This is an in-vivo test performed on pig and rat skin because this skin resembles to human skin. Texture analyzer is used for measurement of bio-adhesive strength.[2]

CONCLUSION

This viscous formulation may have better and more effective topical drug delivery than nano-emulsion because of reduced interfacial tension and dispersed phase mobility. This is especially true for lipophilic drug molecules, which aim to improve skin permeation across the deeper layer of the skin through improved contact time for the formation of a thin layer over the skin, and skin hydration. The qualities of a nano-emulgel are largely determined by the choice of ingredients and the proper ratios between them. A departure from this could have an impact on the thermodynamic stability and the transformation of a nano-emulsion into a nano-emulgel. Because the properties of the various constituents in nano-emulgel- surfactant, cosurfactant, oil, and gelling agent—vary from component to component, careful selection and determination of the intended concentration of these constituents call for specialized knowledge. Because of its less mobile dispersed phase and decreased interfacial tension, the nano-emulgel is more stable than the nano-emulsion. Therefore, better pharmacokinetics and improved permeation make the former a better option for delivering lipophilic moieties, which in turn improves the pharmacological effect.

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