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A REVIEW: PROMISING TECHNOLOGY FOR EFFECTIVE TOPICAL DELIVERY OF DRUGS

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ABSTRACT

A **Nanoemulgel** is a nanoparticle composed of a hydrogel—a crosslinked hydrophilic polymer network. Nanogels are most often composed of synthetic polymers or biopolymers which are chemically or physically crosslinked. Nanogels are usually in the tens to hundreds of nanometers in diameter. Like hydrogels, nanogels have low density of macromolecules and their pores (spaces between the macromolecular chains) can be filled with small molecules or macromolecules, and their properties, such as swelling, degradation, and chemical functionality, can be controlled. Current review deals with the study to for finding nanomeulgel a promising technique for topical delivery of poorly water soluble drugs. Some latest researches concluded that nanogels formulation has proven bioavalibility and safety issues to those drugs which are available in traditional formulations and their adverse effects are of major concern. Nanoemulgels are also overcome the solubilty issues to poorly water soluble drugs. Latest studies have started gaining interest of researchers with nanogels as they are non-greasy, better patient compatibility and easy spreadibilty and good therapeutic efficacy and safety.

KEYWORDS: Nanoemulsion, Nanoemulgels, Nanogels, Drug delivery.

INTRODUCTION

An emulsion is the dispersed system in which the small droplets are dispersed throughout the dispersion medium using emulsifying agent. Depending on the droplet size the emulsions are further classified as Macroemulsion having droplet of 1 to 100 μm of diameter is also known as the conventional emulsion/colloid. These types of emulsion are usually unstable and phase inversions are common problem.[1] Droplets with diameter between (10-100nm are termed as microemulsion, liquid system having uniform size with excellent physicochemical properties and emulsion with droplet diameter 20-200nm fall under category of nanoemulsion which are more stable.

The formulation is further converted to nanoemulgel by adding a suitable gelling agentwhere nano sized emulsion globules are prepared by different techniques.Nanoemulsions are incorporated to hydrogel matrix and finally get converted into Nanoemulgel, which also enhances the skin permeation of the formulation. It acts as a reservoir for the drug from where release of drug from inner phase to outer phase and then to skin. The nanogel when applied on skin gets intact with skin and release oil droplets from gel network directly to statum corneum and permeation of drug starts directly through the statum corneum. By decreasing surface and interfacial tension the stablility nanoemulsion formulation is enhanced and the viscosity of aqueos phase is increased in nanoemulgel, and which leads the viscosity of the aqueous phase to be increased. Emulsifier and thickeners been added to hold the gelling capability of hydrogel serves a better stability, permeation and suitable viscosity for the delivery of topical drug-loaded nanoemulsion.[2]

NANOEMULSION

For most medicines, the nanoemulsion technology is among most drug delivery to optimize drug deliveryandreducing toxicity associated with drug. Nanoemulsion system consist of combination of two immiscible liquids (water and oil) to form ahomogeneous solution by adding appropriate emulsifying agent (may be mixture of surfactant and co-surfactant) within an acceptable limits of HLB values. The thermodynamically stable, system ranges diameter of globule from 10-100nm. The figure-1 describes the various compartments of astable nanoemulsion. Nanoemulsion is a promising technique to enhance the solubility of poorly soluble drugs as well as to increase the permeation of drug through the skin, improving drug absorption time in the affected site and minimal side effects.[2] Nano size globule was loaded with drugs thus enhances drug permeation and make overall system thermodynamically stable.

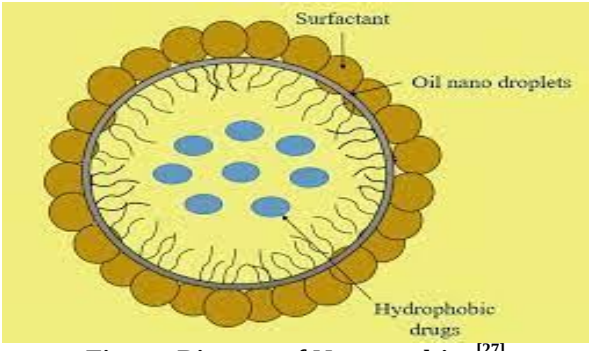

Figure: Diagram of Nanoemulsion[27]

Components of Nanoemulgels[8]

The main components of Nanoemulsion are as follows.

Oil

Selection of oil phase is most important part and drug solubility is determined with various oils and oil having best solubility is selected. It attains maximum drug loading in nanoemulsions. Mixture of oils can also be selected for maximum drug solubility. Different oils which can be used for preparation of nanoemulsion as listed in table 3.

Table 3: List of oils used in nanoemulsion.

Oils	Botanical Names
Arachis oil (Peanut oil)	*Arachishypogaea*
Brahmi oil	*Baopamonnieri*
Clove oil	*Syzygiumaromaticum*
Linseed oil (Flax seed oil)	*Linumusitatissimum*
Eucalpytus oil	*Eucalyptus globules*
Jojoba oil	Buxuschinensis
Peppermint oil	Menthapiperita
Neem oil	Azadirachta oil
Tea tree oil	*Melaleuca alternifolia*

Surfactant

Surfactants plays vital role in formulating stable nanoemulsions. The anionic, cationic, and nonionic types of surfactants were utilized in formulating nanoelusions.[9] Due to their different HLB Value, proper selection of surfactants (Table 4) is important factor for consideration for obtaining Nanoemlsion.[8]

Table 4: List of surfactants used in Nanoemulsion.

Surfactants	Chemical Names
Kolliphor RH 40	Macrogolglycerolhydroxystearate
Ursolic acid	3β-Hydroxy-12-ursen-28-ic acid
Labrafil M 1944 CS	Oleoylpolyoxylglycerides
Lauroglycol FCC	Propylene glycol monolaurate
PEG MW>4000	Carbowax, polyglycol
PlurolOleique CC 497	Polyglyceryl-3 dioleate
Poloxamer 188	Poly(ethyleneglycol)-block-poly (propylene glycol)- block-poly (ethylene glycol)

Gelling agents (hydrogels)

Application of hydrogels and their unique feature of gelling are among most suitable process of drug delivery. Hydrogels are semisolid system cross-linked network of organic and inorganic. Due to vast area of research of nanotechnology, nanogels are widely accepted by researchers.[8] List of sufactants mentioned in Table 5 has proved potential for delivery of drugs in a controlled, sustained and targetable manner. They have high drug loading capacity, biocompatibility, and biodegradability, which are the key points to design an effective drug delivery system. (Table 5).

Table 5: Examples of gelling agents.

Name of the gelling agent	Molecular formula	Molecular weight (g/mol)
Poloxamer	C5H10O2	102.133
Polyacrylamide	C3H5NO	71.077
Hydrin rubber, neoprene	C4H5Cl	88.534
HPMC 55	C3H7O	59.087
Carbomer 934	C3H4O2	3,000,000

Cosurfactant

Polarity of the surfactant is reduced by cosurfactant in order to obtain a stabilenanoemulsion.[10] There are wide varieties of cosurfactants acts on surfactant interface, such as short- to medium chain length alcohols (C3-C8). The penetrability of oil is enhanced by these cosurfactantsto get stable form of nanoemulsion.(Table 7).

Table 6: List of co-surfactants used in nanoemulsion.[8]

Cosurfactants	Molecular Formula	Molecular weight
Transcutol P	C6H14O3	134.175 g/mol
Glycerol	C3H8O3	92.09382 g/mol
Propylene glycol	C3H8O2	76.095 g/mol
Ethanol	C2H6O	46.068 g/mol
Propanol	C3H8O	60.095 g/mol

Biomedical application of different Nanoemulsion formulation

Nanoemulsion of diclofenac was formulated using oil of cloves with adequate amount of surfactants and cosurfactants, and it had been converted to hydrogel form using the gelling agent Carbopol 980. The Droplet size of the oil globules in the nanoemulsion was found to be 64.07±2.65 nm with a low polydispersity index (0.238±0.02) along with high negative zeta potential (-39.06 mV). The developed nanoemulgel exhibited non-Newtonian and pseudoplastic behavior. Thein- vitro release profile of the developed nanoemulgel was higher as compared to marketed and conventional gel. The carrageenan-induced paw edema test was performed in rats to evaluate the anti-inflammatory activity of developed nanoemulgel. the developed nanoemulgel showed significantly higher ($p<0.01$) effect in reducing

pain and inflammation symptoms as compared to marketed as well as conventional gel of diclofenac.[4]

Nitric oxide (NO), a radical gas molecule produced by nitric oxide synthase, plays a key role in the human body. When endogenous NO is overproduced by physiological disorders, severe inflammatory diseases such as rheumatoid arthritis (RA) can occur. Therefore, scavenging NO may be an alternative strategy for treating inflammatory disorders. In previous study, developed NO-responsive macrosized hydrogel by incorporating a NO-cleavable cross-linker (NOCCL); it was furthur evaluated the effectiveness of the NO-scavenging nanosized hydrogel (NO-Scv gel) for treating RA. NO-Scv gel is simply prepared by solution polymerization between acrylamide and NOCCL. When the NO-Scv gel is exposed to NO, NOCCL is readily cleaved by consuming the NO molecule, as demonstrated in a Griess assay. The NO-Scv gel reduces inflammation levels by scavenging NO in vitro and shows excellent biocompatibility. Furthermore, the more promising therapeutic effect of the NO-Scv gel in suppressing the onset of RA is observed in vivo in a mouse RA model when compared to the effects of dexamethasone, a commercial drug. Therefore, our findings suggest the potential of the NO-Scv gel for biomedical applications and further clinical translation.[5]

Curcumin and emu oil derived from emu bird (Dromaiusnovaehollandiae) has shown promising results against inflammation. The delivery of curcumin is hindered due to low solubility and poor permeation. The current investigation was designed to evaluate the antiinflammatory potential of curcumin in combination with emu oil from a nanoemulgel formulation in experimental inflammation and arthritic in vivo models. Nanoemulsion was prepared using emu oil, Cremophor RH 40 and Labrafil M2125CS as oil phase, surfactant and co-surfactant. The optimized curcumin loaded nanoemulsion with emu oil was incorporated into carbopol gel for convenient application by topical route. The anti-inflammatory efficacy was evaluated in carrageenan induced paw edema and FCA induced arthritic rat model in terms of paw swelling, weight indices of the liver and spleen, pathological changes in nuclear factor kappa B, iNOS, COX-2 expression and inflammatory cytokines. Arthritic scoring, paw volume, biochemical, molecular, radiological and histological examinations indicated significant improvement in anti-inflammatory activity with formulations containing curcumin in combination with emu oil compared to pure curcumin. These encouraging results demonstrate the potential of formulations containing curcumin and emu oil combination in rheumatoid arthritis.[5]

O/W Nanoemulsions were prepared using aqueous titration method oleic acid was chosen as the oil phase, Tween20, ethanol were used as surfactant and cosurfactant respectively, on the basis of solubility studies and emulsification studies in the formulation of nanoemulsion. Pseudoternary phase diagrams were constructed to obtain the nanoemulsion region. Further optimized Naoemulsion was incorporated into different concentration of Carbopol-940 to get a gel for improving convenience in superficial application of the drug. The optimized formulation was compared to conventional gel formulation and it showed higher permeation rate invitro and ex-vivo which justifies the nanoemulsion gel to be a promising carrier for transdermal delivery of aceclofenac. The optimized formulation showed higher drug release of 90.2%, compared to conventional gel that released68.2% release in about 9 hrs.[7]

NANOEMULGEL

The nanoemulsion component of the nanoemulgelprotects to the active drug by preventing the enzymatic degradation and inhibits hydrolysis reactions. The conversion to gel imparts the formulation thermodynamic stability by enhancing the viscosity of the aqueous phase by decreasing the interfacial and surface tension.[7] This feature has attracted many researchers towards delivery drugs for skin disorders or delivery of drugs induced orally having greater changes of toxicity or side-effects are delivered by this technique with improved bioavailability and minimal side-effects.

Advantages of Nanoemulgels[8]

The nanoemulgel offers various advantages over other investigated topical formulations which are.

- Nanoemulgels avoids first pass metabolism.
- Easy Patient Compliance
- Easy self-Medication by patient
- Topically application.
- Easily accepted by skin.
- Nanoemulgels efficacy is proven for controlled / sustained drug delivery system.

Nanoemulgel formulation methods

Methods are involved in formulation of Nanoemulgel followed by high pressure homogenization.

1. Preparation of Nanoemulsion,
2. Preparation of hydrogel and.
3. Finally, nanoemulgel are going to be produced by the incorporation of Nanoemulsion into the gel with continuous stirring.[6]

The production process of nanoemulgel is diagrammatically presented in Fig.2.

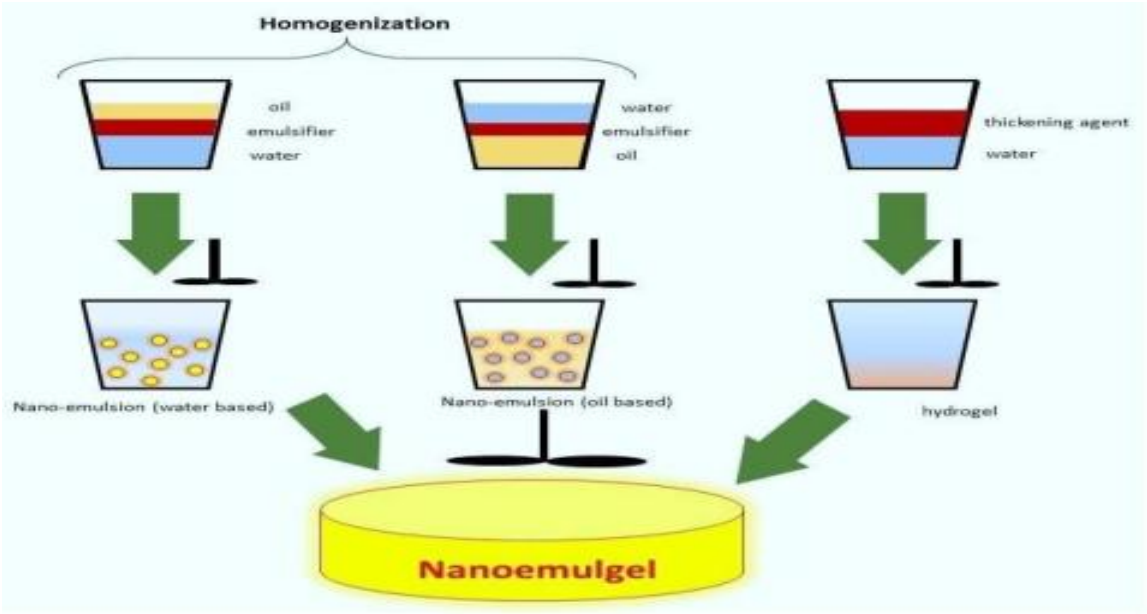

Figure 2: Steps for formulation of Nanoemulgels.[28]

Preparation of nanoemulgel formulation

Nanoemulsion based gels were prepared by the incorporation of 1g of gelling agent in a sufficient quantity of distilled water. This gelling agent solution is a place under dark conditions for 25 hours until the complete swelling system obtained. Then the drug-loaded nanoemulsion is slowly added to the viscous solution of a gelling agent under magnetic stirring.

Aqueous phase

The nature of aqueous phase mainly influenced the droplet size and the stability of nanoemulsion. The physiological environment has diverse pH ranges varying from pH 1.2 (pH in the stomach) to 7.4 and greater (pH of blood and intestine). Also, the presence of various ions in the physiological milieu can have a considerable effect on the properties of nanoemulsions.[11]

Marketed formulations of Nanoemulgel, as shown in Table 1. On the otherhand, Table 2 shows article published on nanoemulgel formulations.

Table 1: Emulgel Product current in market.

VoltarenEmulgel©	Novartis Consumer Health	Active ingredient: 100 g Diclofenac diethylamine corresponding to 1g diclofenac sodium, propylene glycol. Base: Fatty emulsion in an aqueous gel towhich isopropanol and propylene glycol have been added.
ReumadepEmulgel©	ErbozetaEnergia Verde	Arnica, Ashwagandha, Myrrh, Ginger, Rosemary, Cloves, Mint.
EmulgelLevoragMonodose©	THD LAB Farmaceutici	
MeloxicEmulgel©	Provet	Meloxicam
BenzolaitAzEmulgel©	Rordermal	Benzoylperossido 10%
Coolnac Gel Emulgel 1 %©	Chumchon	Diclofenac Diethylammonium

Table 2: Researchers on Nanoemulgel Formulations.

Author	Year	Formulation
Shivakumar*et al.*	2020	diclofenac sodium by topical nanoemulgel
Lee*et al.*	2019	Nitric Oxide-Scavenging Nanogel
Nair*et al.*	2019	Atorvaststin loaded emulgel for wound healing activity
Ahmad*et al.*	2020	Nanoemulgel for improved topical delivery of retinyl palmitate
Kohli*et al.*	2016	Formulation development of novel *in situ*nanoemulgel (NEG) of ketoprofen
Dhawan*et al.*	2014	Enhanced transdermal permeability of piroxicam through novel nanoemulgel formulation

CONCLUSION

Nanomeulgel a promising technique for topical delivery of poorly water soluble drugs. *Ahmad et al* finds - vitro release profile of the developed nanoemulgel was higher as compared to marketed and conventional gel, asthe developed nanoemulgel showed significantly higher ($p<0.01$) effect in reducing pain and inflammation symptoms as compared to marketed as well as conventional gel of diclofenac.[4] *Lee et al*. concludes that Nitric Oxide (NO)-Scavenging gel reduces inflammation levels by scavenging NO in vitro and shows excellent biocompatibility, he promising therapeutic effect of the NO-Scv gel in suppressing the onset of RA is observed in vivo in a mouse RA model when compared to the effects of dexamethasone, a commercial drug.[5] *Vishnu et al*. found that Arthritic scoring, paw volume, biochemical, molecular, radiological and histological examinations indicated significant improvement in anti-inflammatory activity with formulations containing curcumin in combination with emu oil (in nanogel formulation) compared to pure curcumin.[6] *Gupta et al.* observed that optimized formulation of Aceclofenac emulgel was compared to conventional gel formulation and it showed higher permeation rate invitro and ex-vivo which justifies the nanoemulsion gel to be a promising carrier for transdermal delivery of aceclofenac. The optimized formulation showed higher drug release of 90.2%, compared to conventional gel that released68.2% release in about 9 hrs.[7]

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CONFLICT OF INTEREST

There is no conflict of interest among authors

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