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REVIEW: A NEW PROSPECTIVE OF NANOEMULGEL

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ABSTRACT
Newly found chemical substances are hydrophobic which makes them hard to disperse across water, there has been a lot of interest in utilizing nanoemulsions for administering for medical active compounds. Normal emulsions have particle sizes ranging from 1 to 20 µm range and in nanoemulsions from 10 to 200 nm. Transdermal drug delivery methods include transdermal patches, gels, and emulgels. Nanoemulsion combines with hydrogel to form nanoemulgel. It is currently among the most fascinating topical delivery methods. Nanoemulgel bonds higher to the skin's surface and has a greater solubilizing ability, it creates a larger concentration gradient that leads to better skin penetration and its characterization including improved physical stability, non-toxicity, and non-irritating aspects. Nanoemulgel formulation could be considered a potential and promising option for topical delivery of lipophilic drugs in the future.

KEYWORDS: Nanoemulgel, Nanoemulsion, lipophilic.

INTRODUCTION

Since 40% of newly discovered chemical entities are hydrophobic in nature and are difficult to distribute via water, nanoemulsions have garnered a lot of attention in the administration of therapeutically active chemicals. The size and form of the particles scattered in the continuous phase are the primary differences between emulsions and nanoemulsions. Particle sizes in normal emulsions range from 1 to 20 µm, while those in nanoemulsions are between 10 and 200 nm. The benefits of nanoemulsion include improved medication solubility, strong thermodynamic stability, and an increase in transdermal absorption.[1]

Nanoemulgel contains both a hydrogel and a nanoemulsion release control system, it has become one of the most intriguing topical delivery systems. Gelling agents improve the stability of nanoemulsions by decreasing surface and interfacial tension and increasing the aqueous phase's viscosity for topical medication administration. The drug supplied through nanoemulgel has a higher solubilizing capacity and superior adherence on the skin's surface, resulting in a bigger concentration gradient towards the skin and improved skin penetration.[2]

Transdermal gels, emulgels, and patches are examples of transdermal medication delivery systems. It has recently been discovered that nanoemulgel, a novel method for topical distribution of hydrophobic medicines, offers various advantageous qualities, such as enhanced physical stability, non-toxicity, and non-irritating nature. In comparison to other conventional formulations, nanoemulgel offers better medication efficacy for treating a variety of skin conditions as well as bacterial and fungal infections.[3]

Modification of the rheological behavior of nanoemulsion has already been investigated using biocompatible gels with weak contact with surfactants. Xanthan gum, carrageen, carbomer 980, carbomer 940, and carbomer 934 variant gel matrices have all been used to boost the viscosity of nanoemulsions intended for transdermal administration. When nano emulsion is incorporated into a gel matrix, nanoemulgel is produced, which may be more appropriate for transdermal application than nanoemulsion. Because the concentration gradient of the drug given through nanoemulgel is bigger towards the skin, it effects skin penetration more effectively.[4]

Nanoemulsion

Oil-in-water (O/W) and water-in-oil (W/O) nanoemulsions are dispersions of two immiscible liquids that have been stabilized with the right surfactant. Usually, a mean droplet diameter of less than 500 nm is reached. They seem clear or hazy due to their small droplet size, as opposed to the milky white colour associated with coarse emulsion.[5]

Benefits of a nanoemulsion

- It can be utilized as an alternative to liposomes and vesicles and enhances the drug's bioavailability.
- By nature, it is non-toxic and non-irritating.
- The physical stability has increased.

- The microscopic droplets of nanoemulsions have a larger surface area, which increases absorption.[6]

Negative aspects of nanoemulsion

- The creation of nanoemulsions requires sophisticated equipment and labour-intensive procedures due to the challenging nature of size reduction of droplets. Consider the homogenizer.
- The nanoemulsion's unsatisfactory stability poses a serious issue when storing formulations for extended periods of time.
- A decrease in the supply of surfactant and cosurfactant needed to produce nanoemulsion.[7]

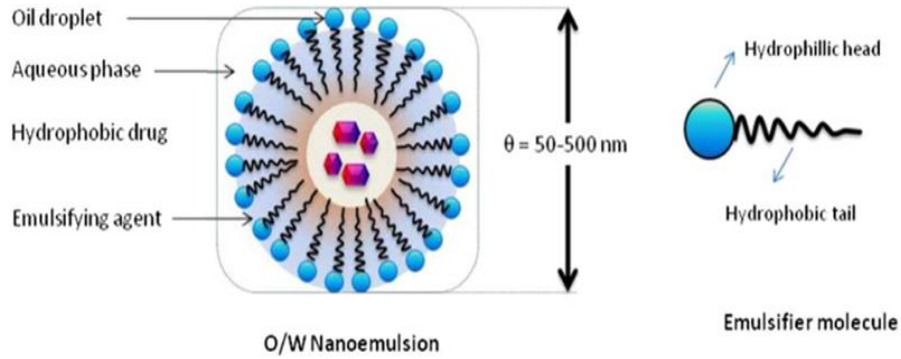

Fig. 1: Emulsion oil formation in the water type, where a medication that is hydrophobic is trapped in the internal oil phase.[8]

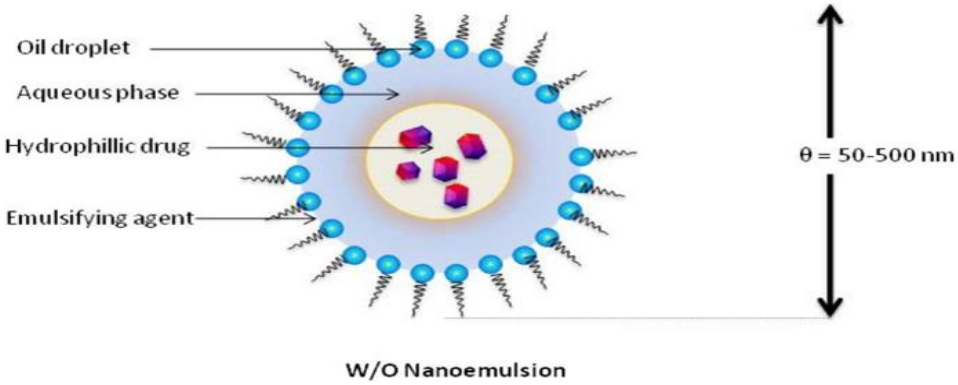

Fig. 2: Emulsion water formation in oil type where a hydrophilic medication is trapped in an interior aqueous phase.[8]

Emulgel

Emulgel is a gel and emulsion combination, where the emulsion is utilized as a vehicle to deliver a specific medicine to the skin. It can be either type W/O or O/W. The gelling agent-containing water phase transforms a conventional emulsion into an emulgel.[9]

Benefits of emulgel

Fig. 3: Advantages of emulgel delivery system. [10]

Drawbacks of emulgel

- In patients with contact dermatitis, the medication and/or excipients may cause skin irritation.
- Some drugs don't pass easily through the skin.
- The potential for allergic responses.
- Drugs with larger particle sizes are more difficult to absorb via the skin. [11]

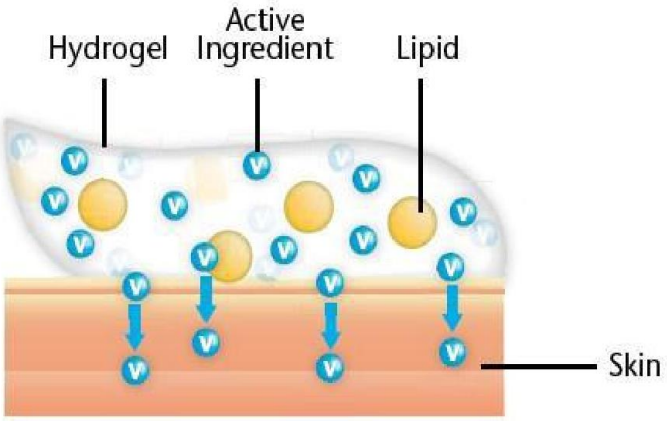

Fig. 4: Structure of emulgel.[12]

Nanoemulgel

The insertion of a nanoemulsion system intergraded into a gel matrix, which promotes improved skin penetration, is known as nanoemulgel formation. When nanoemulgel is applied to skin that is still intact, oil droplets are released from the gel. These droplets enter the skin's stratum corneum and transport the medication to the desired location.[13]

Benefits of nanoemulgel

- Its resistance to first-pass metabolism.
- Its shown efficacy as a controlled, long-term drug delivery strategy.
- Suitable for self-administration.
- The patient takes it in stride.
- The huge surface area and free energy provided by nanoemulgel make it an effective delivery mechanism.
- Nanoemulgel does not contain emulsion defects such as creaming, phase separation, flocculation, and coalescence.
- Because the nanosized particles may more easily pass through the rough skin surface, it exhibits improved medication penetration.[14]

Drawbacks of nanoemulgel

- The surfactant used in pharmaceutical applications should not be toxic.
- The potential for allergic responses.
- Dermatitis on contact causing skin discomfort.[14]

Formulation components consideration

An oil phase and an aqueous phase make up an o/w or w/o nanoemulsion. A thin layer of surfactant, occasionally enhanced by the presence of cosurfactant, enervates the microscopic dispersed phase. The connected section provides an overview of oil selection techniques that make use of a number of the incorporated oil's intrinsic features.[15]

Oil Selection

The lipid, or oil, component of the nanoemulgel is one of its key ingredients. To choose an acceptable oil phase based on the formed nanoemulsion's viscosity, permeability, and stability, various research is needed. Vegetable oils (of long-chain fatty acids) have been found to have weak emulsification characteristics, which leads to unstable nanoemulsions, depending on the oil's source. Less hydrophobicity in the oil was shown to improve its emulsification properties. Because of its anti-inflammatory, analgesic, anesthetic, antipruritic, and antioxidant qualities, emu oil has also attracted interest from the pharmaceutical industry. Emu oil's moisturizing properties for skin infections have made it popular not only in the pharmaceutical but also in the beauty industry.[15]

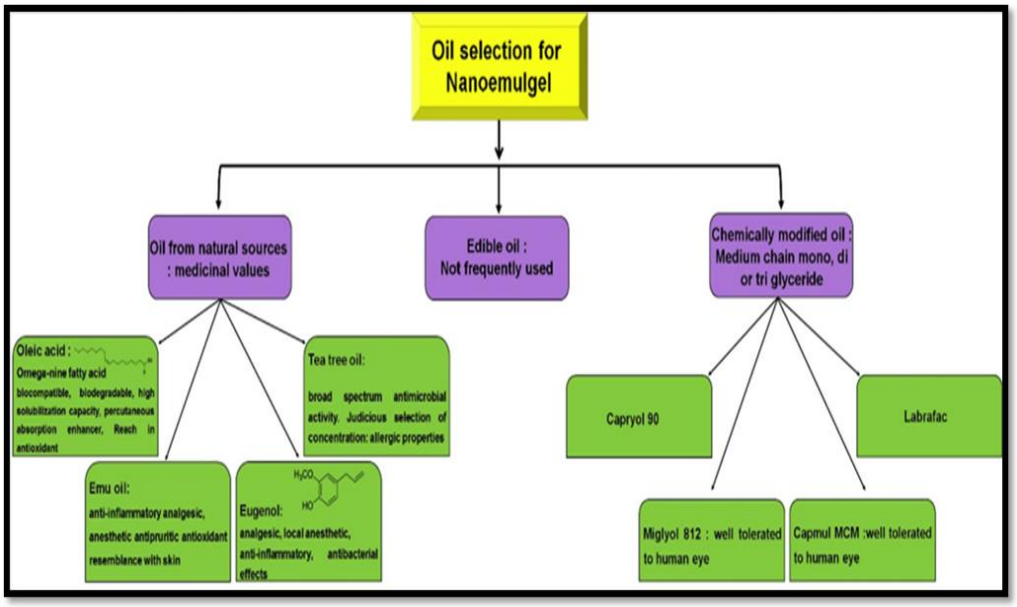

Fig. 5: Strategies for oil phase selection in the course of nanoemulgel formulation development.[15]

Aqueous material

Nanoemulgel are frequently made with distilled or ultra-purified water in order to maximize the aqueous phase. When an emulsion changes phases and contains a gelling agent, emulgel are created.[16]

Permeation enhancers: It is among the best methods for speeding up transport through the skin and its surrounding layers. A topical drug delivery system needs a permeation enhancer, and the optimum carrier to accomplish this is a nanoemulsion or nanoemulgel. This is because the topically applied nanoemulsion or nanoemulgel is a water-based solution. These permeation enhancers act essentially by enhancing the ability to permeate of the skin by transiently and permanently binding to skin constituents. to increase the pace at which chemicals can pass through a barrier. It also gives the process of a drug penetrating the skin a little extra push. Lecithin, isopropyl myristate, linoleic acid, and oleic acid are among the substances added to the nanoemulgel to increase penetration.[16] **Gelling agents** give consistency to nanoemulgel by forming a poorly cohesive three-dimensional in form structured networks containing a significant amount of cross-linking, possibly chemical or physically, when added to the correct media as a colloidal mixture. These variables are essential for assessing the formulation's uniformity, rheological features, bio-adhesive traits, pharmacokinetics, spreadability, and extrudability, amongst other aspects.[17]

Antioxidants

These are the chemical elements that were included in the mixture to stop the various ingredients from oxidizing. This is the reason they have been included in the first place. Ascorbyl palmitate, butylated hydroxyl anisole, and butylated hydroxyl toluene are the antioxidants that tend to be used in topical nano-lipoidal formulation above other antioxidants.[16]

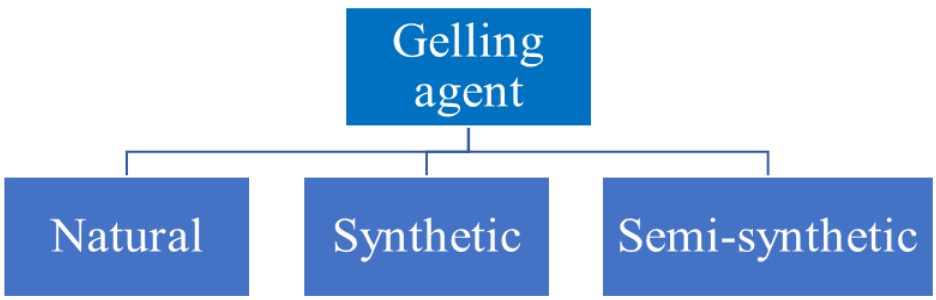

Fig. 6: Types of gelling agents. [17]

Natural gelling agent: The proteins and bio-polysaccharides, or their substitutes, are natural gelling agents. Bio-polysaccharides including pectin, gelatine, locust bean gum, carrageenan and alginic acid; bio-polysaccharides are derived substances of these substances that include xanthan gum, starch, dextran, and acacia gum. Protein and bio-polysaccharides, or their derivatives, are natural gelling agents. These compounds usually involve cellulose derivatives, including sodium alginate, hydroxypropyl cellulose, and ethyl cellulose.[17]

Synthetic gelling agent: Chemical synthesis is utilized for generating synthetic gelling agents; others, such carbomers and poloxamers, have FDA approval.[17]

Semi-synthetic agent: In comparison to gelling agents, semisynthetic substances show higher stability and are better responsive to fluctuations in chemical, biological, and environmental variables that include pH and temperature.[17]

Surfactant

The key components of stabilizing the nanoemulsion system include surfactant. In this system, surfactants of the anionic, cationic, and non-ionic categories were utilized. According to their unique chemical properties, selecting suitable surfactants becomes crucial for building an effective delivery system. In order to develop a stable nanoemulsion, surfactants with an acceptable HLB value must be used.[18]

Co-surfactants

Co-surfactants enhanced the flow of an interface and diminished tension at the interface, accordingly being necessary for generating a nanoemulsion with a small quantity of surfactant. A single-phase system known as Smix had been employed to completely solubilize multiple co-surfactants with an assigned surfactant (1:1). Phase diagram construction would be performed to evaluate the performance of this Smix combination for nano-emulsification potential subsequent the aqueous titration. For the purpose to facilitate continuous aqueous titration, the Smix was dispersed in oil phase at various ratios. The comparison was made between the nano-emulsification zone seen in phase diagrams for a certain co-surfactant combination.[19]

e.g. Polyethylene glycol 400, propylene glycol and ethanol

Emulsifiers

An emulsifier is used to improve the preparation's emulsification process in order to improve shelf-life stability. Emulsifying agents included substances such as stearic acid, Tween 20, Span 80, and Tween 80.[20]

Techniques used to create emulgel

Step 1: Formulation of O/W or W/O emulsions

The solubility of water-soluble substances in the aqueous vehicle and oil-soluble elements in the oil vehicle comprise the initial step in emulsion formulation. In order to guarantee the dispersion of the two phases into droplets, the two phases were combined in a turbulent mixing medium. When emulsification for industrial use, mechanical stirrers, ultrasonifers, homogenizers, or colloid mills are usually utilized, although a mechanical stirrer is employed throughout the production of emulsions.[21]

Step 2: Formulation of gel base

In a mixture vessel, the water-soluble substances or excipients are mechanically agitated until they completely dissolve in the aqueous vehicle. Stir the fluid and gradually add the hydrophilic polymer. Continue stirring until the polymer dissolves and the pH stays within the range that is suitable. Air may get stuck in beneficial gels if they are stirred excessively, hence the rate of mixing should be reasonable.[21]

Step 3: Addition of emulsion into gel base with steady blending

To produce emulgel, the gel and emulsion stages mix together at a 1:1 ratio.[21]

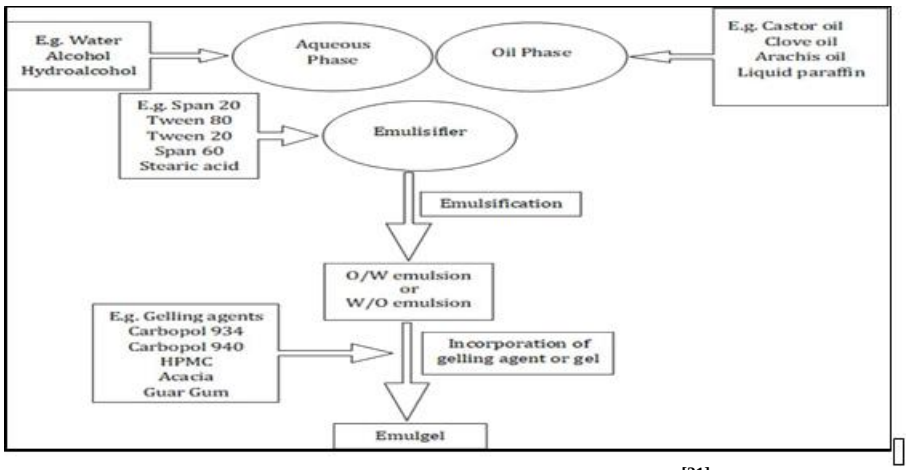

Fig. 7: Method of preparation of emulgels.[21]

Preparation of gel phase
Using a mechanical shaker, the polymer is dispersed in purified water then agitated constantly at a moderate speed to produce the gel phase in the formulations. Triethanolamine (TEA) is subsequently utilized to adjust the pH to 6-6.5.[22]

Preparation of oil phase of emulsion
Emulsifiers, such as span 20, are dissolved in the oil phase of the emulsion to create light liquid paraffin.[22]

Preparation of aqueous phase
Emulsifier including Tween 20, dissolve in purified water to produce the aqueous phase.[22]

Preparation of drug solution
The drug is dissolved in ethanol.[22]

Method of preparation of nanoemulsion

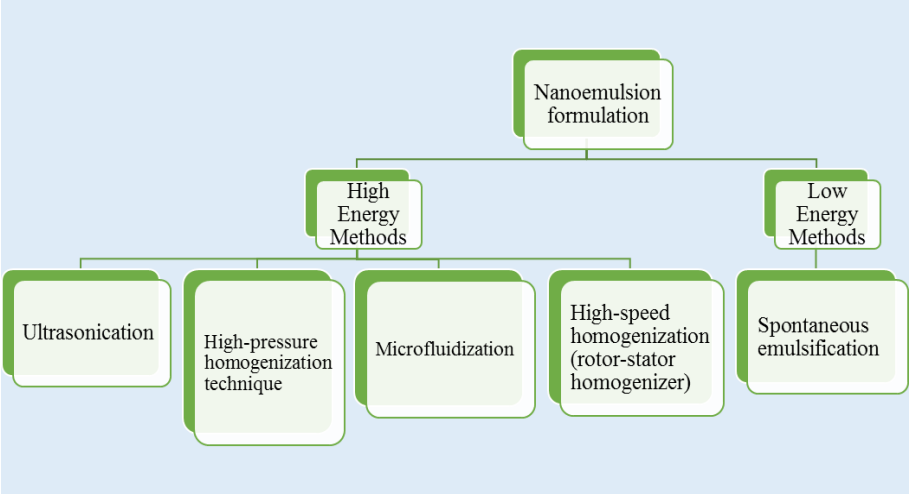

Fig. 8: Preparation of nanoemulsion.[14]

1. High energy methods
Since the typical size of a nanoemulsion droplet is between 5 and 500 nm, a significant amount of mechanical energy is needed to achieve this size. The main advantage of utilizing a high-energy mediated nanoemulsion formulation is the utilization of low emulsifier concentrations. The first step in applying high-energy techniques is the mechanical stirring that creates an emulsion with droplet sizes in the micron range. The main advantage of utilizing a high-energy mediated nanoemulsion formulation is the utilization of low emulsifier concentrations. The second phase involves using high-energy equipment to split large droplets into tiny droplets, which will transform the emulsion into a nanoemulsion. [14,23]

Ultrasonication
Applying a sonicator probe, the rough emulsion can be transformed into desired nano-sized emulsion droplets. The sonicator probe generates high-intensity sound waves at a frequency of higher than 20 kHz. which may fragment the hard emulsion into droplets the size of nanometres (5-500nm). These are various types of probes with different sizes which can be minimized in size up to specified values. The droplet scale is impacted by the time, type of probe, and intensity of the sonication input. [23]

Microfluidization
This technique generates very small sub-micron particles by forcing the product through an interaction chamber with stainless steel microchannels on the contact region utilizing a microfluidizer equipment which employs a high-pressure positive displacement pump (500 - 20,000 psi). The resulting mixture is passed through the microfluidizer continuously until the desired particle size has been obtained. The final outcome is filtered to generate a homogenous nanoemulsion by segregating the larger and smaller droplets. [23]

High-pressure homogenization technique
A variety of forces, particularly cavitation, extreme turbulence, and hydraulic shear, are often employed in the creation of nanoemulsions. To be able to formulate nanoemulsions, surfactants and cosurfactants are forced through a piston homogenizer's tiny opening at high pressures (500–5000 psi). High-pressure homogenization is an inexpensive, highly productive technique that may be applied on small and large scales to create nanoemulsions with particles as small as 1 nm. The solution to the coalescence issue that can arise is to add extra surfactants to the mixture. The dispersed and continuous phase viscosities, as well as homogenization cycles, affect the droplet size. [14]

High-speed homogenization (Rotor-stator homogenizer)
In industry, high-speed homogenizers are frequently used for comminution, dispersion, and emulsification processes. They are easy to install in tanks and containers that already exist. In many manufacturing industries, rotor-stator procedures are the preferred

emulsification technique. They use rotor-stator methods to create nanoscale droplets. It demands that the procedure and formulation parameters be chosen precisely.[14]

1. Low energy methods

After researching the cumulative behaviour of the oil, surfactants, co-surfactants, drug, aqueous component, hydrophilic lipophilic balance of the used oil surfactant blend, and operating temperature, low-energy emulsification techniques were established. One low-energy method is emulsification that occurs spontaneously. These techniques use the system's stored energy to create minuscule droplets. Depending on the type of oil and emulsifier available, low energy techniques may not always be possible.[5]

Spontaneous emulsification

The process of spontaneous emulsification is similar to the nanoprecipitation technique used to create polymeric nanoparticles. Oil is utilized in place of polymer. The process comprises the manufacture of two phases: an oil-soluble surfactant called Span, an organic solvent that is partially water miscible such acetone or ethyl acetate, and an organic or oil phase like mygliol that contains a medication. To create small nanoscale emulsions, the organic phase is added dropwise to the aqueous stirring phase (but the opposite, that is, adding water to oil, is as conceivable in the case of W/O emulsions).[5]

Application of nanoemulgel

Anti- Inflammatory application

A primary response of the body to an infection, irritation, or other injury is inflammation, which is characterized by redness, warmth, swelling, and discomfort. The reaction of the body's tissues to damage is called inflammation.[24]

A number of studies have demonstrated that anti-inflammatory drugs exhibit higher activity when applied topically through a nanoemulsion compared to a traditional emulsion. Because of the plant's many sections' bioactivity as anti-inflammatory, anti-mutagenic, and anti-tumor agents have employed in Swietenia macrophylla oil. Hydrogel and nanoemulsion were used to create Swietenia macrophylla oil nanoemulgels.[25]

Anti- Psoriatic application

Psoriasis is an autoimmune disorder of the skin are represented by recurrent bouts of inflammatory lesions and hyperkeratotic plaques. Numerous genetic and environmental variables, including trauma, medications, infections, alcohol, smoking, and stress, have been associated with psoriasis. [26]

A safe and reliable psoriasis treatment is growing greater due to new treatment which utilize nanotechnology and better understanding of the condition. Novel topical carriers have been developed a nanogel composed of methotrexate loaded nanostructured lipid carrier and to evaluate its potential in imiquimod-induced psoriasis model to ameliorate symptoms of psoriasis. [27]

Application of antifungals

An increasing number of individuals have been losing their lives or getting seriously ill due to fungal infections, especially those with impaired immune systems.[28]

Luliconazole is a broad-spectrum antifungal medication which includes the imidazole moiety with ketone dithioacetate. It has demonstrated efficacy against a variety of fungus, particularly filamentous fungi like dermatophytes. Study was attempted to develop and optimize Luliconazole loaded nanoemulgel for improved efficacy against fungal infection by enhancing the solubility and simultaneously the permeability across the skin barrier.[29]

Alopecia

Alopecia areata is the most common type of hair loss or alopecia in humans. It is a type of autoimmune disorder that usually has a varied history, relapsing or remitting, and can be permanent, particularly in cases of significant hair loss.[30]

The strong vasodilator (antihypertensive) drugs like minoxidil directly relax the smooth muscle of the arteries without having a significant impact on venous capacitance. Minoxidil is the only FDA approved topical medication with proven efficacy for the treatment of androgenic alopecia.[31]

Table 1: Examples of marketed emulgels for topical application.

Marketed Product	Active Pharmaceutical Ingredient	Manufacturing Company
Isofen Emulgel	Ibuprofen	Beit Jala Pharmaceutical Co.
Derma Feet	Urea	Herbitas
Voltaren Emulgel	Diclofenac diethylamine	Novartis Pharma
Coolnac gel	Diclofenac diethylamine	Community Pharmacy Public Co Ltd
Nucoxia Emulgel	Etoricoxib	Zydus Candila Healthcare Ltd

CONCLUSION

A recently developed technique for topical drug administration termed nanoemulgels works effectively in place of mixing hydrophilic and hydrophobic pharmaceuticals, and it can also be used to add hydrophobic therapeutics. Emulgels have the potential to be an effective option for inventive topical drug delivery formulations in the future due to their non-greasy, gel-

like properties and relatively high drug release rates. When applied directly to the skin, the nanoemulgel system has immense potential as a safe, effective, and internationally accepted drug delivery method for lipophilic medications. Topical application of lipophilic drugs, nanoemulgel formulation appears to be the future standard. To improve patient compliance, topical medicine delivery will be utilized extensively.

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