Topical Nanoemulgel: A Novel Pathway for Investigating Alopecia

Gurjot Kaur1*, Bedi PMS1 and Jasjeet K Narang2
1Department of Pharmaceutical sciences, Guru Nanak Dev University, Amritsar-143005, India
2Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar-143001, India

Abstract

Alopecia areata (hair loss) is an autoimmune disease occurs in both sexes and is characterized by partial, complete and total loss of body hair. The severity of the condition and the patient’s age are the tailored factors responsible for the hair loss. The FDA approved Minoxidil as a topical medication with proven efficacy for treating different types of alopecia’s. This review will discuss the effect of topical nanoemulgel over other formulations for the treatment of alopecia areata. The nanoemulgel will shows better solubility and permeability of the active components at the site of application via opening of hair follicles or other routes, as compared to other formulations.

Keywords: Alopecia areata; Minoxidil; Nanoemulsion; Topical nanoemulgel; Higher permeability

Introduction

Alopecia is the type of hair loss characterized as partial, complete and total loss of body hair [1]. Alopecia areata and androgenic alopecia (AGA) (male pattern baldness) are the other types which affects the scalp hair loss [2].

Recently, a genome-wide association study demonstrated a genetic predisposition to alopecia areata. The factors like viral infections, trauma, or psychosocial stress, have also been suspected to possibly contribute to the development of the disease [3].

The treatments for the alopecia areata include topical, locally injected, or systemic steroids; topical immunotherapy; topical minoxidil; topical irritants such as anthralin; and systemic immunosuppressants such as cyclosporine or methotrexate. Success rates vary depending on the extent and duration of disease [3]. The FDA had approved only minoxidil and finasteride for the treatment of AGA. Minoxidil, the FDA approved topical medication with proven efficacy is the best option for investigating the different factors responsible for alopecia [4].

Minoxidil acting pathway

The Minoxidil exert its action by transforming into active metabolite (minoxidilsulfate) with the help of sulfotranspherase enzyme mainly present in the scalp [5]. The hair cycle is the most preferred pathway for minoxidil to exert its action. It also increases the hair diameter and lengthen the anagen phase by proliferative and anti-apoptotic effects on dermal papilla cells of the hair follicles [2]. It also increases the blood supply to the scalp allowing more oxygen, blood, and nutrients to the follicle. The oral use of minoxidil results in several side effects like weight gain, severe water retention, etc. In order to avoid these side effects, the topical formulations of minoxidil are going to be the best treatment for alopecia by showing its better efficacy and prolong drug action [6].

Advantages of nanoemulgel

The nanoemulgel offers various advantages over other investigated topical formulations [8] which are [9]:

- Avoid first pass metabolism.
- Easy acceptable for patient
- Suitably for self-medication.
- Provide local drug delivery.
- Easy termination of medication.
- Easily acceptable for skin environment.
- Proven efficacy for controlled and sustained drug delivery system.

Formulation of topical nanoemulgel

Topical nanoemulgel is formulated by adding gelling agent to the optimized nanoemulsion formulation and therefore exhibit characteristics both of nanoemulsions and gels.

Nanoemulsions

Nanoemulsion system is an ideal drug delivery for most of the drugs with objective of maximizing efficacy while minimizing toxicity. In the advancement of research, researchers have excogitate the simple drug delivery to eminently refined novel dosage forms [10].

Nanoemulsion system comprises the mixture of nanoranges of two immiscible liquids (water and oil) to form a homogeneous system by adding suitable surfactant/cosurfactants with appropriate HLB value. This thermodynamically stable system ranges from 10-100 nm [11]. Figure 2 explain the different compartments of a stabilized nanoemulsion.

*Corresponding author: Gurjot Kaur, Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar-143005, Punjab, India, Tel: 917837552182; E-mail: gurjotk.06@gmail.com

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Surfactant: Surfactants are the important component used for stabilizing the nanoemulsion system. The anionic, cationic, and nonionic types of surfactants are used in this system. Due to their different chemical nature, proper selection of surfactants (Table 2) becomes a crucial factor to obtain a stabilized delivery system. For the formation of a stable nanoemulsion, surfactants having proper HLB value are required [13,16].

Cosurfactant: Cosurfactant plays an important role in reducing the polarity of surfactant to obtain a stabilized nanoemulsion. There are varieties of cosurfactants (Table 3), which acts on surfactants interface, such as short- to medium-chain length alcohols (C3-C8). These are also helpful in increasing the penetrability of oil to get a stabilized formulation [15].

**Components of nanoemulsion**

The main components of nanoemulsion are as follows:

Oils: The selection of oil phase is the most important parameter in order to obtain a stabilized nanoemulsion, so that maximum amount of drug could solubilise in it [13]. Usually, the oil which has maximum solubilising potential for selected drug candidate is selected as an oily phase for the formulation of nanoemulsions. This helps to achieve maximum drug loading in the nanoemulsions [14]. Mixture of oils can also be used to solubilised the maximum amount of drug [15]. The different oils used for the nanoemulsion formulation are enlisted in Table 1.

<table>
<thead>
<tr>
<th>Oils</th>
<th>Botanical Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachis oil</td>
<td>Arachis hypogaea</td>
</tr>
<tr>
<td>Brahmi oil</td>
<td>Bacopa monnieri</td>
</tr>
<tr>
<td>Clove oil</td>
<td>Syzygium aromaticum</td>
</tr>
<tr>
<td>Linseed oil</td>
<td>Linum usitatissimum</td>
</tr>
<tr>
<td>Eucalyptus oil</td>
<td>Eucalyptus globules</td>
</tr>
<tr>
<td>Jojoba oil</td>
<td>Buxus chinsenis</td>
</tr>
<tr>
<td>Peppermint oil</td>
<td>Mentha piperita</td>
</tr>
<tr>
<td>Neem oil</td>
<td>Azadirachta oil</td>
</tr>
<tr>
<td>Tea tree oil</td>
<td>Melaleuca alternifolia</td>
</tr>
</tbody>
</table>

**Table 1: List of oils used in nanoemulsion.**

<table>
<thead>
<tr>
<th>Surfactants</th>
<th>Chemical Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolliphor RH 40</td>
<td>Macrogolglycerol hydroxystearate</td>
</tr>
<tr>
<td>Ursolic acid</td>
<td>3β-Hydroxy-12-ursen-28-ic acid</td>
</tr>
<tr>
<td>Labrafil M 1944 CS</td>
<td>Oleoyl polyoxyglycerides</td>
</tr>
<tr>
<td>Lauroglycol FCC</td>
<td>Propylene glycol monolaurate</td>
</tr>
<tr>
<td>PEG MW=4000</td>
<td>Carbowax, polyglycol</td>
</tr>
<tr>
<td>Plurol Oleique CC 497</td>
<td>Polyglyceryl-3 dioleate</td>
</tr>
<tr>
<td>Poloxamer 188</td>
<td>Poly(ethylene glycol)-block-poly(propylene glycol)-block-polylethylene glycol)</td>
</tr>
</tbody>
</table>

**Table 2: List of surfactants used in nanoemulsion.**
nanoemulsion is obtained [19].

In this, cavitation is the preferable mechanism for vibrations are used to obtain stabilized nanoemulsion with reduced particle size. In this manner. They have high drug loading capacity, biocompatibility, and potential to deliver drugs in controlled, sustained and targetable delivery system [21].

Preparation of nanoemulgel formulation
Nanoemulsion base gels are prepared by incorporation of 1 g of gelling agent in a sufficient quantity of distilled water. This gelling agent solution is place under dark conditions for 25 hours until complete swelling system obtained. Then the drug loaded nanoemulsion is slowly added to the viscous solution of gelling agent under magnetic stirring. The pH is stabilized by the addition of 0.1 ml of triethanolamine (TEA). The formed nanoemulgels are kept for 24 h to obtain a homogeneous dispersion of gel [22].

Characterization of Nanoemulgel Formulations
The nanoemulgel formulations are characterized by the following techniques:

Physicochemical parameters
The prepared nanoemulgel formulations are inspected visually for their color, homogeneity, consistency and phase separation [23].

pH Determination
The pH of the prepared formulations is determined by pH using meter. In this, the formulations are place in 250 ml beaker and immersing the pH meter into the formulation and record the readings. Same process is repeated for three times with same formulation [24].

Rheological investigation
The viscosity of the different nanoemulgel formulations is determined at 25°C using a cone and plate viscometer or Brookfield viscometer with appropriate spindle and connected to a thermostatically controlled circulating water bath [15].

Globule size distribution in nanoemulgel
Globule size and distribution are determined by Malvern zetasizer. A 1 g sample is dissolved in purified water and agitated to get homogeneous dispersion. Sample is injected into photocell of zetasizer to obtain mean globule diameter and distribution [25].

Spreading coefficient
Spreadability is determined by apparatus which consists of a wooden block, which is provided by a pulley at one end. The spreadability is measured on the basis of ‘Slip’ and ‘Drag’ characteristics of nanoemulgels. A ground glass slide is fixed on this block. An excess of nanoemulgel (about 2 g) under study is placed on this ground slide. The nanoemulgel is then sandwiched between this slide and another glass slide. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the nanoemulgel between the slides. By putting weight of 80 g, the time (in seconds) required by the top slide to cover a distance of 7.5 cm with the help of string attached to the hook is noted [24].

A shorter interval indicates better spreadability, which is calculated by the formulae:

\[ S = \frac{M \cdot L}{T} \]

Where, \( S \) = Spreadability,
\( M \) = Weight tied to upper slide,
\( L \) = Length of glass slides
\( T \) = Time taken to separate the slides completely from each other.

<table>
<thead>
<tr>
<th>Name of gelling agent</th>
<th>Molecular formula</th>
<th>Molecular weight (g/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poloxamer</td>
<td>C₅H₁₀O₂</td>
<td>102.133</td>
</tr>
<tr>
<td>Polycrylamide</td>
<td>C₃H₅NO</td>
<td>71.077</td>
</tr>
<tr>
<td>Hydrin rubber, neoprene</td>
<td>C₃H₅Cl</td>
<td>88.534</td>
</tr>
<tr>
<td>HPMC 55</td>
<td>C₃H₈O</td>
<td>59.087</td>
</tr>
<tr>
<td>Carbomer 934</td>
<td>C₃H₈O₂</td>
<td>3,000,000</td>
</tr>
</tbody>
</table>

Table 3: List of co-surfactants used in nanoemulsion.

Table 4: Examples of gelling agents.

Aqueous phase: The nature of aqueous phase mainly influenced the droplet size and the stability of nanoemulsion. The physiological milieu has diverse pH ranges varying from pH 1.2 (pH in stomach) to 7.4 and greater (pH of blood and intestine). In addition, the presence of various ions in the physiological milieu can also have considerable effect on the properties of nanoemulsions [15].

Fabrication methods for preparing stabilized nanoemulsions
In order to get clear and stabilized nanoemulsion formulations, proper fabrication techniques should be adopted [17]. The techniques are mandatory in reducing the droplet size to nanoscale [18].

Homogenization using high pressure: For the preparation of stabilized nanoemulsion with particle size 1 nm, the high-pressure homogenizer piston is used by applying several forces, such as cavitation, etc. This process will continue until a desired nanosize formulation is obtained [13].

Microfluidization: Microfluidization of the prepared formulation is done by the use of device known as microfluidizer. The use of high pressure forces the product into microchannels in order to get a submicron range particle. The process is repeated until a stabilized nanoemulsion is obtained [19].

Ultrasonication: In case of ultrasonication technique, ultrasonic vibrations are used to obtain stabilized nanoemulsion with reduced particle size. In this, cavitation is the preferable mechanism for obtaining desired nanosized formulation [17].

Phase inversion method
A stabilized nanoemulsion is obtained by using phase inversion method which endorses chemical energy for phase transition with the help of emulsification process under a constant temperature [18].

Gelling agents (hydrogels)
The unique physical properties of hydrogels have reflected particular interest in drug delivery applications. These are the semisolid system with three-dimensional, cross-linked network of organic and inorganic molecules and imbibition by liquid due to high porosity [20].

Due to rapid researches in nanotechnology, there is sudden change which welcomes the new nanogel systems. Table 4 has proven their potential to deliver drugs in 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 [21].
Extrudability study (tube test)

This test is used to measure the force required to extrude the material from tube. The evaluation of extrudability is based upon the quantity of nanoemulgel extruded from lacquered aluminium collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of nanoemulgel in 10 seconds. The better extrudability is depend upon the quantity extruded [25]. The extrudability is than calculated by using the following formula

\[
\text{Extrudability} = \frac{\text{Applied weight to extrude nanoemulgel from tube (in g)}}{\text{Area (in cm}^2)}.
\]

Drug content determination

The drug content is determined by mixing appropriate amount of nanoemulgel formulation in suitable solvent. Then the solution is passed through whatman filter paper and filtrate is analyze for drug content by uv spectrophotometrically using the same standard plot by putting the value of absorbance as given by More et al. [24].

Skin irritation test (patch test)

The preparation is applied on the properly shaven skin of rat and undesirable changes in colour, change in skin morphology should be checked up to 24 hours. If no irritation occurs the test is passed [26].

In vitro release study

The Franz diffusion cell (with effective diffusion area 3.14 cm² and 15.5 ml cell volume) is used for the drug release studies. Nanoemulgel is applied onto the surface of dialysis membrane evenly and clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber is filled with freshly prepared phosphate buffer saline pH 5.5 solutions to solubilise the drug. The receptor chamber is stirred by magnetic stirrer. The samples (1.0 ml aliquots) are collected at suitable time interval. Samples are analyzed for drug content by UV visible after appropriate dilutions. The cumulative amount of drug released across the dialysis membrane is determined [27].

Drug release kinetic study

To analyze the mechanism of drug release from the topical nanoemulgel, the release data [28] are fitted to following equations:

Zero-order equation:
\[
Q = K_0 t
\]
Where \( Q \) is the amount of drug released at time \( t \), and \( K_0 \) is the zero-order release rate.

First-order equation:
\[
\ln(100-Q) = \ln 100 - K_1 t
\]
Where \( Q \) is the percentage of drug release at time \( t \), and \( K_1 \) is the first-order release rate constant.

Higuchi’s equation:
\[
Q = K_2 \sqrt{t}
\]
Where \( Q \) is the percentage of drug release at time \( t \), and \( K_2 \) is the diffusion rate constant.

Stability studies

The prepared nanoemulgels are packed in aluminium collapsible tubes (5 g) and subjected to stability studies at 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for a period of 3 months. Samples are withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profile [23].

Accelerated stability studies of gellified nanoemulsion

Stability studies are performed according to ICH guidelines. The formulations are stored in hot air oven at 37 ± 2°C, 45 ± 2°C and 60 ± 2°C for a period of 3 months. The samples are analyzed for drug content every two weeks by UV-Visible spectrophotometer. Stability study is carried out by measuring the change in pH of formulation at regular interval of time [29].

Conclusion

There are a number of products suit to treat hair loss contributing to the big market worldwide. There are many patents for potential useful or doubtful anti-hair loss agents. Some agents advertised as effective “anti-hair loss” remedies, but are not supported by convincing studies. These unsupported results from inefficient drug action and insufficient assessment of the basic pathology of hair loss. This is the reason why “great expectations” turn into plenty of disappointments. Research has revealed that the nanomaterials enhance the benefits of active ingredients when engineered into hair care. For the development of tailored products and new technologies capable of achieving improved hair care, enhanced knowledge of the composition of the hair fiber and an understanding of follicular targeting pathways should be there. Although there are already developed nanoformulations existing in market, nanoemulgels are going to be the promising products for better hair care and an effective and safe topical delivery system for the treatment of alopecia areata.

References