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Review On Formulation And Evaluation Of In-Situ Gel Of Minoxidil

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ABSTRACT

The review focuses on the formulation and evaluation of in-situ gel of minoxidil Androgenic alopecia (AGA) significantly affects both physical appearance and psychological well-being, leading to progressive hair thinning due to genetic and hormonal factors. Minoxidil, an FDA-approved treatment, has long been a cornerstone for addressing AGA. Originally developed for hypertension, it was repurposed after its hair growth-promoting effects were discovered. Despite its effectiveness, conventional minoxidil formulations require frequent applications and can cause scalp irritation, limiting their overall eficacy and patient adherence. Main Body Hair growth cycles through anagen (growth), catagen (transition), and telogen (resting) phases. In AGA, the anagen phase shortens while the telogen phase lengthens, resulting in thinner hair. Minoxidil helps by extending the anagen phase and enlarging hair follicles. However, traditional formulations suffer from rapid solvent evaporation, leading to crystallization on the scalp and irritation. In-situ gels offer a novel solution, transforming from liquid to gel upon exposure to physiological conditions like temperature or pH changes. This allows for sustained release of minoxidil, maintaining effective drug concentrations on the scalp for longer periods and reducing the frequency of application. This approach enhances patient compliance and minimizes side effects. Conclusion In-situ gels represent a significant advancement in treating AGA by providing controlled, sustained drug release. They overcome the limitations of conventional minoxidil formulations, improving therapeutic outcomes and patient adherence. As research continues, in-situ gels hold the potential to revolutionize hair loss management.

KEYWORDS: Hair loss, androgenic alopecia, minoxidil, in-situ gels, drug delivery systems.

INTRODUCTION

Skin is the largest organ in the human body and serves several vital functions. It acts as a protective barrier, shielding the body from physical harm, pathogens, and UV radiation. Additionally, skin regulates body temperature, helps with the sensation of touch, and plays a role in the synthesis of vitamin D.

The skin consists of three main layers:

- **Epidermis**: This is the outermost layer of the skin and acts as a protective barrier. It contains several types of cells, including keratinocytes that produce a protein called keratin, which helps waterproof the skin. The epidermis also contains melanocytes, which produce melanin, the pigment responsible for skin color, and Langerhans cells, which are involved in the immune response.
- **Dermis**: The dermis lies beneath the epidermis and contains blood vessels, nerves, hair follicles, and sweat glands. It provides structural support to the skin and is responsible for temperature regulation and sensation. Collagen and elastin fibers in the dermis give the skin its strength and elasticity.
- **Subcutaneous tissue (Hypodermis):** This layer is located beneath the dermis and consists of fat and connective tissue. It provides insulation, stores energy, and serves as a cushion to protect internal organs and bones.

Epidermis

The epidermis is the outermost layer of the skin and is responsible for several crucial functions in the body. It serves as a protective barrier that separates the internal organs and tissues from the external environment.

The primary functions of the epidermis include:

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Protection: The epidermis provides a physical barrier that shields the body from various external threats, such as pathogens (bacteria, viruses, and fungi), physical injury, and UV radiation from the sun. The outermost layer of the epidermis, called the stratum corneum, consists of dead, keratinized cells that provide an effective barrier.

Regulation of Water Loss: The epidermis helps regulate the loss of water from the body by preventing excessive evaporation and maintaining proper hydration. The stratum corneum's outermost layer helps to minimize water loss.[3]

Sensation: The epidermis contains specialized cells called Merkel cells and sensory nerve endings, which are responsible for the sensation of touch, pressure, temperature, and pain. These cells and nerve endings transmit sensory information to the brain.

Melanin Production: Within the epidermis, there are melanocytes, specialized cells that produce melanin, a pigment responsible for skin, hair, and eye color. Melanin plays a crucial role in protecting the skin from the harmful effects of UV radiation by absorbing and dissipating it.

Immune Response: The epidermis houses immune cells called Langerhans cells, which are part of the body's immune system. These cells help protect against infections and play a role in initiating immune responses when the skin is exposed to pathogens or foreign substances.

Vitamin D Synthesis: The epidermis is involved in the synthesis of vitamin D when exposed to sunlight. Vitamin D is essential for various bodily functions, including calcium absorption in the bones.

The epidermis consists of multiple layers, with the deepest layer known as the stratum basale or basal layer, and the outermost layer being the stratum corneum. As skin cells progress from the basal layer to the surface, they undergo a process of differentiation and keratinization, transforming into tough, flattened, and dead cells that make up the stratum corneum. This process ensures the formation of a protective barrier.

The epidermis continuously renews itself through a process called skin cell turnover, where older, dead skin cells are shed from the surface and replaced by newer cells from the basal layer. This turnover process is essential for maintaining healthy and functional skin.

Dermis

The dermis is the middle layer of the skin, situated beneath the epidermis and above the subcutaneous tissue (hypodermis). It is a vital component of the skin and is responsible for various functions that contribute to the skin's strength, elasticity, and overall functionality.

Here are some key characteristics and functions of the dermis:

Structural Support: The dermis provides structural support to the skin. It contains an intricate network of collagen and elastin fibers, which give the skin its strength and elasticity. Collagen provides tensile strength, while elastin allows the skin to stretch and return to its original shape.

Blood Vessels: The dermis contains an extensive network of blood vessels, including arteries, veins, and capillaries. These blood vessels supply oxygen and nutrients to the skin cells and help regulate body temperature by directing blood flow to the skin's surface when needed for cooling.

Nerves and Sensation: The dermis is rich in sensory nerve endings, which allow the skin to perceive various sensations, including touch, pressure, temperature, and pain. Different types of nerve receptors in the dermis transmit sensory information to the brain.[6]

Hair Follicles: Hair follicles, which produce and support hair growth, are embedded in the dermis. Each hair

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follicle is associated with sebaceous glands that secrete sebum, an oily substance that lubricates the hair and skin.

Sweat Glands: Eccrine and apocrine sweat glands are located in the dermis and are responsible for producing sweat, which plays a crucial role in regulating body temperature and eliminating waste products through perspiration.

Immune Cells: The dermis contains immune cells, such as macrophages and mast cells, which help protect the skin from infections and respond to foreign substances or pathogens that breach the skin's barrier.

Extracellular Matrix: The dermal extracellular matrix consists of proteins, glycosaminoglycan's, and other molecules that provide structural support and maintain tissue integrity.

Wound Healing: The dermis plays a critical role in wound healing and tissue repair. When the skin is injured, cells in the dermis are involved in the formation of new collagen fibers and tissue regeneration.[7]

Subcutaneous tissue (Hypodermis)

The hypodermis, also known as the subcutaneous tissue or subcutaneous layer, is the deepest layer of the skin, situated below the dermis. While not technically part of the skin, it is closely associated with it and serves several important functions:

Insulation: One of the primary functions of the hypodermis isto provide insulation for the body. It consists mainly of adipose (fat) tissue, which acts as an insulating layer. Fat is an excellent thermal insulator that helps regulate body temperature by preventing heat loss from the body. It also provides padding and cushioning to protect underlying structures.

Energy Storage: The hypodermis stores energy in the form of fat cells (adipocytes). This stored fat can be mobilized and used by the body as an energy source when needed.

Shock Absorption: The layer of fat in the hypodermis provides shock absorption, protecting internal organs and bones from external trauma or injury.

Blood Vessels and Nerves: The hypodermis contains blood vessels that supply nutrients and oxygen to the surrounding tissues. Additionally, nerves and nerve endings extend into the hypodermis, providing sensation and transmitting sensory information.

Attachment to the Dermis: The hypodermis is not firmly attached to the dermis but is loosely connected to it by fibrous bands called septa. This loose connection allows for movement between the two layers and helps to prevent shearing forces that could damage the skin.

Temperature Regulation: While the primary role of temperature regulation lies in the dermis, the hypodermis also plays a role in thermal regulation by providing insulation.

Cosmetic Applications: In cosmetic medicine, injections into the hypodermis are commonly used for procedures such as dermal fillers and liposuction. Dermal fillers can be injected into the hypodermis to add volume to specific areas of the face, while liposuction involves removing fat from the hypodermis for body contouring.

The thickness of the hypodermis can vary among individuals and across different body regions. It tends to be thicker in areas with a higher concentration of adipose tissue, such as the buttocks and abdomen.

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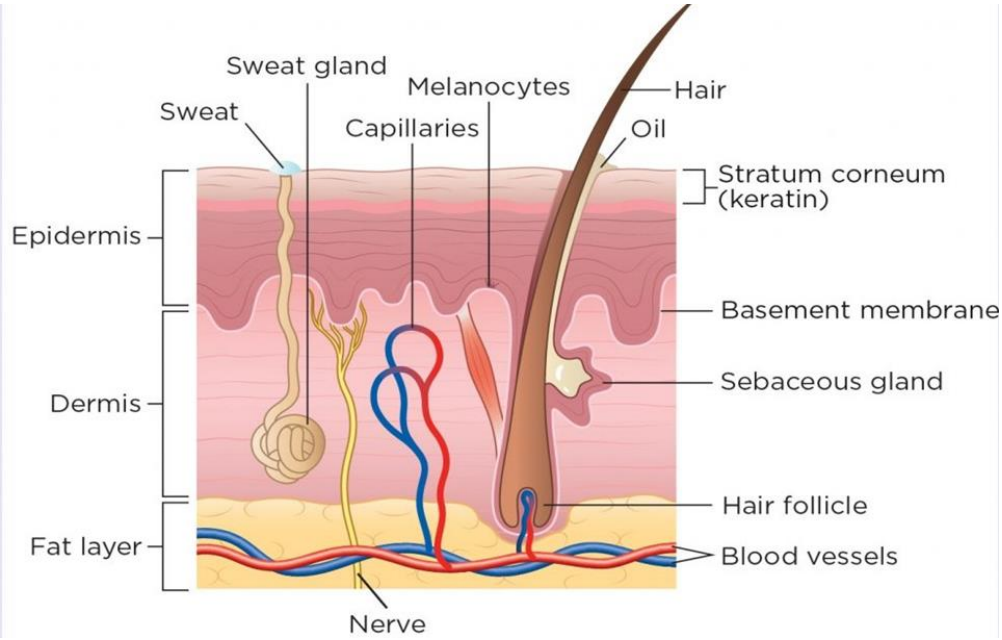

Alopecia

Alopecia refers to a condition characterized by hair loss, which can occur on the scalp or other parts of the body. The severity and pattern of hair loss can vary widely. There are different types of alopecia, and some of the common ones include:

Androgenetic Alopecia (Male and Female Pattern Baldness): This is the most common form of hair loss and is often hereditary. In men, it typically results in a receding hairline and baldness on the top of the head. In women, it usually leads to thinning of the hair on the crown of the scalp.

Alopecia Areata: This is an autoimmune condition where the immune system mistakenly attacks hair follicles, leading to hair loss. It can occur suddenly and result in small, round patches of hair loss on the scalp or other parts of the body.

Alopecia Totalis: This is a more severe form of alopecia areata where all the hair on the scalp is lost.

Alopecia Universalis: The most extreme form of alopecia areata, causing the loss of all body hair, including scalp hair, eyebrows, and eyelashes.

Telogen Effluvium: This type of hair loss is often triggered by significant stress, illness, or hormonal changes. It results in a widespread thinning of the hair rather than distinct bald patches.

Cicatricial Alopecia (Scarring Alopecia): This rare type of alopecia occurs when inflammation and scarring destroy hair follicles, preventing hair regrowth.

The exact cause of alopecia can vary depending on the type. Genetics, autoimmune factors, hormonal changes, and environmental factors can all play a role. Diagnosis and treatment may involve a combination of medical history, physical examination, and, in some cases, blood tests or a biopsy of the affected skin.

Treatment options also vary depending on the type of alopecia and its underlying cause. Some common treatments include medications, such as minoxidil or corticosteroids, and in certain cases, immune suppressants. Hair transplants may be an option for some individuals.

It's important for individuals experiencing hair loss to consult with a healthcare professional or a dermatologist to determine the underlying cause and discuss appropriate treatment options based on their specific condition.

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Androgenic alopecia

Androgenetic alopecia, often referred to as male pattern baldness (in men) and female pattern baldness (in women), is the most common form of hair loss. It is a hereditary condition that can affect both men and women, but the patterns of hair loss differ between the sexes.

In Men:

Typically, male pattern baldness begins with a receding hairline.
Hair at the temples and crown of the head gradually thins and eventually falls out, leading to partial or complete baldness on the top of the head.

In Women:

Female pattern baldness usually involves overall thinning of hair across the scalp.
Unlike in men, women usually do not experience a receding hairline. Instead, they may notice widening of the part or a more visible scalp.

Causes:

Genetics play a significant role in androgenetic alopecia. If your parents or grandparents experienced hair loss, you may be more prone to it.

Hormones, specifically androgens (male hormones), contribute to the development of androgenetic alopecia. In both men and women, an enzyme called 5-alpha reductase converts testosterone into di-hydrotestosterone (DHT). Hair follicles that are genetically sensitive to DHT will shrink over time, leading to shorter and finer hair until they eventually stop growing.

Symptoms:

Gradual hair thinning, usually starting at the temples or crown of the head.
In men, a receding hairline.
In women, a widening part or diffuse thinning.

Treatment:

Minoxidil: A topical solution or foam applied to the scalp. It is available over-the-counter and is one of the most common treatments for androgenetic alopecia.

Finasteride: An oral prescription medication for men that inhibits the production of DHT. It is not typically prescribed for women of childbearing age due to potential risks during pregnancy.

Hair Transplant: Involves removing hair follicles from areas of the scalp where hair is still growing well and transplanting them to thinning or bald areas.

Low-Level Laser Therapy (LLLT): Some people use devices that emit low-level lasers or light-emitting diodes to stimulate hair growth.
It's essential to note that the effectiveness of treatments can vary from person to person, and not everyone will respond to the same therapies. Consulting with a dermatologist or healthcare professional can help determine the most appropriate treatment plan based on individual circ

***In-situ* gel**

"*In situ* gel" refers to a type of gel that forms or undergoes a gelation process directly at the site of application or administration. This is often encountered in pharmaceutical and biomedical applications, where the gel transitions from a liquid to a gel state in response to specific physiological conditions or external triggers. The objective is to provide a controlled and sustained release of active substances.

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Key points about *in-situ* gels:

Site-Specific Gelation: Unlike pre-formed gels, *in-situ* gels are designed to undergo gelation after application or administration at the target site. This property is advantageous for certain drug delivery systems as it allows for precise localization and sustained release of therapeutic agents.

- **Triggers for Gelation**: *In-situ* gelation can be triggered by various factors, including changes in temperature, pH, ion concentration, or other environmental conditions. The idea is to take advantage of the specific conditions at the targeted site to induce gel formation.
- **Biomedical Applications**: *In-situ* gels are commonly used in biomedical and pharmaceutical applications, especially for drug delivery. For example, a liquid formulation containing a drug may be administered, and once in contact with the target tissue or physiological environment, the formulation undergoes gelation, providing sustained drug release.
- **Controlled Drug Release**: *In-situ* gels can offer controlled and sustained drug release, reducing the need for frequent administrations. This can be particularly beneficial for conditions that require long-term treatment or for drugs with a narrow therapeutic window.
- **Examples of Triggered Gelation**: Some in situ gels are designed to gel in response to temperature changes (thermo sensitive gels), changes in pH (pH-sensitive gels), or the presence of ions (ion-sensitive gels).
- **Ophthalmic and Injectable Formulations**: *In-situ* gels are commonly used in ophthalmic formulations (eye drops) and injectable formulations. For instance, a liquid formulation injected into the eye may form a gel upon contact with the ocular tissues, providing prolonged contact time and sustained drug release.

In-situ gels represent an innovative approach to drug delivery, offering the potential for improved therapeutic outcomes and patient compliance. The specific design and formulation of in situ gels depend on the intended application and the properties of the active substances involved. Researchers and pharmaceutical scientists continue to explore and develop new formulations to optimize the performance of in situ gels in various medical applications.

Minoxidil

Minoxidil is a medication commonly used to treat hair loss, and it is available over-the-counter in various formulations, including topical solutions and foams. Here are key points about minoxidil:

Mechanism of Action: The exact mechanism of how minoxidil promotes hair growth is not fully understood, but it is believed to increase blood flow to the hair follicles, leading to improved follicular function and stimulation of hair growth.

Application:

Minoxidil is typically applied directly to the scalp in the form of a liquid solution or foam.

The recommended application involves placing a specified amount of the product on the affected areas of the scalp.

It should be applied to a dry scalp and left on for a certain period before washing.

Indications:

Minoxidil is primarily used to treat androgenetic alopecia (male pattern baldness and female pattern baldness). It is also sometimes used to promote hair growth in other types of hair loss, such as alopecia areata.

Effectiveness:

Minoxidil has been shown to be effective in promoting hair growth in some individuals.

Results can vary from person to person, and it may take several months before noticeable changes occur.

The medication is generally more effective at slowing down or stopping hair loss than regrowing significant amounts of hair.

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Side Effects:
Common side effects may include itching, redness, or irritation at the application site.
Some users may experience increased hair shedding initially, but this is often temporary.
Allergic reactions are possible but rare.

Availability:
Minoxidil is available over-the-counter in many countries.
There are different concentrations (usually 2% and 5% for men, and 2% for women) and formulations (liquid and foam).

Continued Use:
To maintain the benefits of minoxidil, it generally needs to be used continuously. Discontinuing use may lead to a gradual return of hair loss.

Combination Therapy:
Some individuals use minoxidil in combination with other treatments, such as Finasteride (an oral medication), for a more comprehensive approach to hair loss.

Consultation with a Healthcare Professional:
Before starting any treatment with minoxidil, it's advisable to consult with a healthcare professional or dermatologist to discuss the suitability of the treatment and to address any concerns or questions.
While minoxidil is a widely used and generally well-tolerated treatment for hair loss, it may not be effective for everyone. Individual responses can vary, and it's essential to manage expectations and discuss any concerns with a healthcare professional.

Evaluation Test for*In-situ* gel
Clarity
The developed formulations were inspected visually for their clarity both in their sol state and gel state.

Determination of Sol-Gel Temperature
To determine the Tsol-gel of the *in-situ* gels, 20 g of the cold formulation will be loaded into a beaker and placed in a temperature-controlled magnetic stirrer. Afterwards, a Digital Thermometer will be immersed in the solution and it was constantly monitored. Following, the heating of the solution was conducted at a rate of 2°C/min by continuous stirring (200 rpm). As gelation temperature, it will be reported the temperature at which the magnetic bar stopped. The maximum limit of gelation will be examined up to 60°C and the study will be triplicated to ensure the results.

Determination of pH
The pH of the gel will be evaluated via a calibrated pH meter. The pH measurement will be repeated at least 3 times and the average pH values of the formulations were calculated.

Viscosity
Viscosity determinations of the prepared in situ gels as well as sols will be carried out on a cone and plate geometry viscometer, using spindle No 40. Viscosity of in situ gelling solutions was measured at different angular velocities at a temperature of 37°. A typical run comprised changing of the angular velocity from 0.0 to 100 rpm. The averages of two readings were used to calculate the viscosity. Evaluations were conducted in triplicate.

Spread ability

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For the determination of spread ability, excess of sample was applied between the two glass slides and was compressed to uniform thickness by placing 1000 g weight for 5 min. Weight (50 g) was added to the pan. The time required to separate the two slides, i.e. the time in which the upper glass slide moves over the lower plate was taken as measure of spread ability (S). S=M×L/T, where M = weight tide to upper slide, L = length moved on the glass slide, T = time taken.

***In-vitro* drug release studies**

In-vitro release studies will be conducted via dialysis method using a dialysis membrane, as it will be previously reported. 2 mL of in situ gel will be separated from 100 mL release media. The release of minoxidil will be carried out in ethanol and PBS pH 7.4 (50:50) to ensure sink conditions at 150 rpm at 32±0.5°C. At specific time intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours), 1 mL of sample was withdrawn and analyzed with UV spectrophotometer. The experiment was triplicated.

Optimization of *In-situ* gel

Formulation Design

1. **Identify Factors and Levels**:

Factor 1 (A): Gellan Gum concentration (e.g., 0.1%, 0.55% and 1.1864%)
Factor 2 (B): Carbopol concentration (e.g., 0.1%, 0.55%and 1%)
Define the levels for each factor:
Low (-1): 0.1% (Gellan Gum), 0.1% (Carbopol)
Medium (0): 0.55% (Gellan Gum), 0.55% (Carbopol)
High (+1): 1% (Gellan Gum), 1.1864% (Carbopol)

2. **Central Composite Design Layout**:

Design the experiment using CCD, which includes:
Factorial points: All combinations of low and high levels.
Axial points: Points beyond the high and low levels (e.g., 0.1% Gellan Gum with 0.55% Carbopol).
Center points: Replicate runs at the center level for statistical validity.

3. **Generate Experimental Runs**:

Use Design Expert Software to generate a list of formulation codes (e.g., F1, F2, ... F10) and their respective factor combinations

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