Research Article

Development and Characterization of Film Forming Spray of 5% Minoxidil for Baldness Due to Androgenetic Alopecia

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ABSTRACT

This study focuses on the treatment of Androgenetic Alopecia (AGA), a common type of hair loss that affects both men and women. The research problem addressed in this study is the need for effective and safe treatment options for AGA. The primary aim is to evaluate the safety and efficacy of minoxidil, a commonly used medication for AGA, and to explore novel topical delivery systems to enhance treatment outcomes and reduce side effects. The methodology employed in this study involves a comprehensive review of existing literature on AGA treatment, with a focus on minoxidil. Various studies and clinical trials exploring the safety and efficacy of minoxidil in the treatment of AGA are analyzed. Additionally, novel topical delivery systems for minoxidil, such as film-forming sprays, are discussed as potential solutions to enhance treatment outcomes. The findings of the study suggest that minoxidil is effective in promoting hair growth in patients with AGA, with variable levels of success reported in different studies. However, the use of traditional minoxidil formulations containing high ethyl alcohol and propylene glycol may lead to side effects such as dry scalp, irritation, and allergic reactions. Novel delivery systems like film-forming sprays offer a promising solution to reduce side effects and improve treatment efficacy. The implications of this study highlight the importance of exploring innovative delivery systems for existing medications to enhance their therapeutic effects and minimize adverse reactions. By developing novel formulations like film-forming sprays, healthcare providers can offer a more effective and patient-friendly treatment option for individuals with AGA.

Keywords: Androgenic alopecia, minoxidil, hair loss, treatment, topical delivery systems, film-forming sprays.

INTRODUCTION

Hair follicles control hair growth by using immunological cells, neuroproteins, and hormones. The intricate interplay among hair follicles found in various body parts results in the production of distinct hair types. The phases of hair growth are Anagen, which is the active growth stage; Catagen, which is the resting stage; Telogen, which is the hair follicle's regression phase; Exogen, which is the active phase of hair erosion; and Kenogen, which is the interval between the time when a hair follicle is empty and when new hair grows. The follicle has a bulbous bottom during the growing phase, with the dermal papilla located in the center. The papilla receives nourishment and oxygen from tiny blood vessels, which removes waste products and Hormones have a great effect on the papilla. This is the area where body's hormones and chemicals, either secreted or injected, affect the growth of hair, causing it to grow at a different rate or not at all. An increase in the amount of hair that falls out every day (effluvium) or noticeable hairlessness (alopecia) can both be referred to as "hair loss" in complaints. A normal day can see up to 100 hairs fall out. Hair loss is caused by several factors. It can be brought on by genetics, food, endocrine disorders, systemic diseases, drug use, and abnormalities in the hair shaft. The clinical examination should start with a thorough examination of the entire skin as well as the distribution of body and scalp hair. Particularly for androgenetic alopecia (AGA) and alopecia areata, grading systems have been developed. The Hamilton-Norwood scale is the most widely used classification for male pattern baldness. The most well-known 3-point Ludwig scale for female pattern AGA is used with females. The Savin scale has eight differentiation classes and the Gan-Sinclair scale has five; both are more accurate at defining specifications and are now widely used. The scientific term for the genetic predisposition for pattern baldness or pattern hair loss in both men and women is androgenetic alopecia. Alopecia areata is an immune system disorder that results in the loss of hair growth from hair follicles. Hair loss that appears suddenly in small patches on the head is a typical sign. Alopecia universalis, which causes all body hair to disappear, and alopecia totalis, which results in the loss of all hair on the head, are advanced forms of the disorder. Androgenetic alopecia (AGA), a common type of alopecia, is a multifactorial, age- related chronic illness that has a major negative impact on the psychological well-being and quality of life of its patients. By the age of 70, it is estimated that between 80% and 50% of Caucasian men and women will have some form of AGA. The Food and Drug Administration (FDA) has approved finasteride, an oral medication, and minoxidil (2% and 5%) as topical formulations for the treatment of men with AGA. It is still unknown how precisely pilosebaceous transport mechanisms work.[1-13]

Minoxidil is an effective oral medication for severe hypertension. As a hypertension treatment, it was first made available in the early 1970s. One common side-effect of minoxidil was hypertrichosis, which included hair growth in male baldness. When taken systemically for

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hypertension, minoxidil functions as a vasodilator; however, when it comes to hair loss, its mode of action is through direct stimulation of the follicular hair matrix cell or dermal papillae. Although the exact mechanism by which minoxidil stimulates hair growth is still unknown, Hair follicle miniaturization is reversed by minoxidil's angiogenic effects, which also seem to lengthen the anagen phase. By doing this, the formation of hair is not inhibited by epidermal growth factor. Hair growth is thereby encouraged. The creation of novel topical delivery systems for minoxidil is necessary to reduce side effects and increase therapeutic efficacy. Minor side effects such as allergic contact dermatitis and scalp pruritus have been associated with topical minoxidil. Several earlier studies that looked into the safety and effectiveness of 5% minoxidil in the treatment of AGA discovered that 54-62% of patients had variable levels of hair growth. [14-19]

Pharmacokinetics of Minoxidil: https://www.ncbi.nlm.nih.gov/books/NBK482378/

Absorption: The skin absorbs only 65% of topical minoxidil, **Distribution**: There is no binding affinity of minoxidil to plasma proteins. With a distribution volume ranging from 2.8 to 3.3 L/kg, this medication has a wide distribution. **Metabolism**: Topical minoxidil is converted to minoxidil sulfate in hair follicles through the action of the sulfotransferase enzyme, **Elimination**: Although minoxidil has a 3 to 4-hour elimination half-life, the drug's hypotensive effects can last up to 72 hours. Notably, the kidneys are primarily responsible for excreting minoxidil and its metabolites.

Structure: [21]

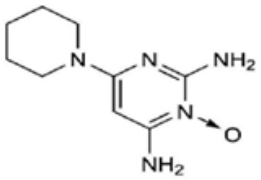

Figure 1: Minoxidil chemical structure

Advantages: [22] Treatment of androgenetic alopecia, treatment of female pattern hair loss, alopecia areata, beard enhancement, eyebrow enhancement, chemotherapy-induced alopecia, doesn't induce hypotension, frontal fibrosing alopecia, etc.

Disadvantages:[14] hair loss (telogen effluvium), scalp pruritus, scaling, irritant, allergic contact dermatitis, itching, erythema, etc.

FILM-FORMING SPRAY [FFS]

Numerous advancements have been made in recent decades to produce effective and efficient spray preparations. In general, FFS is made up of polymers, enhancers, and active ingredients dissolved in organic solvents. In contrast to other common topical preparations, a thin, non- sticky film can form that can prolong the drug's contact time and permeability, resulting in continuous drug release. It can also prevent crystallization, increasing the amount of drug available to provide therapeutic effects.[39] A transdermal spray that forms a film would function more effectively, show more efficacy, cause fewer side effects, require fewer doses, and have a longer retention period. Through the formation of a uniform thin layer on the skin, the developed formulation will facilitate the rapid evaporation of solvents, resulting in a cooling effect and lowering the tendency to rub off. Because the formulation will stick to the skin longer and penetrate the skin more quickly, it will take effect quickly.[40] A non-solid dosage form that forms a film in Situ or after being implemented to the pores and skin or another frame surface. These structures incorporate the drug and movie-forming excipients in a solvent that evaporates whilst coming in touch with the skin, leaving a movie of excipients and the drug behind the produced film can be a solid polymeric material that works as a matrix for drug release to the skin over time or a residual liquid film that is quickly absorbed in the stratum corneum.[41] The film-forming transdermal spray keeps the same level of medication effectiveness but requires a much lower dosage, and it even eliminates more side effects.[22] The sprayability of FFS is greatly influenced by the kind of nozzle, the size of the aperture, the pressure of the spray, and the type of liquid. Studying the viscoelastic, in situ gel, pH, and heat- sensitive characteristics of FFS is crucial to figuring out what factors to take into account when choosing polymers, solvents, and other excipients.[39]

FILM-FORMING SPRAY OF 5% MINOXIDIL

A derivative of piperidine and pyrimidine, minoxidil has the following chemical structure: 2,6-diamino-4-piperidinopyrimidine-1-oxide (C9H15N5O).The metabolite (minoxidil sulfate) is the primary factor contributing to minoxidil's beneficial effects on hair growth, While, Sulfotransferase, an enzyme found in hair follicles and with varying levels of production across individuals, is responsible for this conversion of minoxidil to minoxidil sulfate.[22] Moreover, minoxidil is a 5-alpha reductase (5AR) inhibitor used in the pharmacologic therapy of AGA to reduce dihydrotestosterone (DHT) and stimulate hair follicles[10]. However, Hair thinning in an "M" shape characterizes androgenetic alopecia (AGA), also known as male-pattern baldness; the back and sides of the head are spared while the temples and crown of the head experience hair loss. Most people's distribution of androgen-sensitive follicles is reflected in this pattern. Androgens cause follicular miniaturization and shorten the anagen phase beginning at puberty, which results in the formation of vellus-like hair and progressive hair thinning.[7] The 2% minoxidil solution was first launched in the market in 1986, followed by the 5% solution in 1993.Additionally, MDX exhibits side effects like redness, swelling, and itching, which makes treatment more difficult because a twice-daily application is advised for the recommended long-term course of care.

Furthermore, most commercially available (CA) formulations of MXD dissolve in propylene glycol (PG)

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and/or ethanol due to the drug's poor water solubility; one such formulation is marketed using a mixture solvent of PG, water, and ethanol (20/30/50, v/v/v).[30] To address minoxidil solution side effects a new form of drug delivery system is developed called film- forming spray. FFS is made up of polymers, enhancers, and active ingredients dissolved in organic solvents. In contrast to other common topical preparations, a thin, non-sticky film can form that can prolong the drug's contact time and permeability, resulting in continuous drug release. It can also prevent crystallization, increasing the amount of drug available to provide therapeutic effects.[39] A transdermal spray that forms a film would function more effectively, show more efficacy, cause fewer side effects, require fewer doses, and have a longer retention period. Through the formation of a uniform thin layer on the skin, the developed formulation will facilitate the rapid evaporation of solvents, resulting in a cooling effect and lowering the tendency to rub off. Because the formulation will stick to the skin longer and penetrate the skin more quickly, it will take effect quickly.[40] Depending on the volume of solution sprayed, drug dosages in film-forming sprays can also be adjusted to regulate either local or systemic effects. Prescriptions are dispersed efficiently and uniformly thanks to an FFS. Additionally, ease of use can increase patient compliance. Removing the thin layer with water is an easy task. This thin, non-sticky film improves patient comfort during activities in contrast to patches, ointments, gels, and other moisture products that dry out harshly and become sticky when applied. In addition, the thin film facilitates wound/skin penetration, preserving equilibrium. Insufficient wound/skin humidity may cause irritation or infection, just like when patch preparations are used. Droplets are created using the film-forming solution. The film-forming fluid is sprayed with the usage of any sort of sprayer. Even though they are all intended for medical use, each sprayer has unique features and purposes. The different types of sprayers that could be used as drug delivery systems in film-forming systems.[42] **BENEFITS:** Low Incidence of Irritation, Sterility of the dosage, excellent coverage of the skin, Adjustable Dosage, Increase the contact time, Increase the Permeability of the drug, Continuous drug release, Prevent crystallization, No Irritation, No Contamination Due to Repeat Exposure of Hands.

Application*:* Treatment of androgenetic alopecia, Treatment of Alopecia areata, Treatment of Chemotherapy-induced alopecia, Treatment of Hair transplant, Treatment of Scarring alopecia, Treatment of monilethri, Treatment of Hereditary alopecia or hypotrichosis.

MATERIALS AND METHODS

Formulation of Film- Forming Spray[81]

Method used for hydrophilic drug:

Take solvent in a beaker. Dissolve film forming agents completely(polymer) and then add the drug. Lastly add Plasticizer and stabilizer of different grades according to formulation and dissolve completely. Transfer this FFS into a Spray bottle (container). Mixing time can vary according to the polymer and solvent used for film formations

Method Used for Hydrophobic Drugs:[40]

First, 0.5% w/w plasticizer (PEG-400) and film formers [EC: Eudragit(:1:2 ratio)] were dissolved in the eutectic mixture, which contained equal amounts of menthol and camphor. A vehicle blend comprising 80 parts alcohol and 20 parts acetone was used to separately dissolve 0.5% w/w drugs. The mixture was then sonicated for 20 minutes in an ultrasonic cleaner. The final mixture was put into an assembly of containers. Mixing time can vary according to the polymer and solvent used for film formations**.**

Preparation of Formulation

first, Mix Ethanol and Acetone in a beaker (8:2), then, Dissolve Film-forming agents (HPMC E15) completely, and then add the drug, and mix it on a magnetic stirrer till it becomes homogeneous for 20 min. Lastly, add PEG 400 and glycerin to the formulation and stir it again for 15 minutes, then Transfer this FFS (film-forming solution) into a Spray bottle (container).

Figure 1: Film-forming formulation of different concentrations of ingredients

Figure 2: Film of minoxidil 5% film-forming spray

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Table 1: Formulation composition

Ingredients	F1	F2	F3
Minoxidil	5	5	5
HPMC E15	1.2	1.8	2.4
PEG 400	0.25	0.25	0.25
Glycerin	0.5	0.5	0.5
Ethanol	60	60	60

EVALUATION PARAMETERS

PH: A digital pH meter that has been calibrated is used to measure the pH of the optimized formulation. The film-forming solution being tested is dipped into the pH meter's rod, and the meter's reading is recorded. [40]

Viscosity: Using a Brookfield viscometer at room temperature, the viscosity of the prepared spray formulations was determined.[40] The film-forming solution's viscosity is a crucial parameter, particularly in MDS, as it impacts its spray ability. The spray's coverage area may decrease as the film- forming solution's concentration rises.[39]

Film Formation: A Petri dish was used to administer film-forming systems. The film is labeled as either transparent or opaque, sticky or dry, and detachable or non-detachable based on its visual properties.[82]

Drying Duration: To measure the drying time, the formulation is applied to the inner forearm sides of a volunteer or on a petri dish. After a set period, a glass slide is gently placed on the film. When there are no discernible liquid remnants on the glass slide following removal, the film is said to be dry. A minimum drying time should be a part of an efficient FFS to avoid making the patient wait a long time.[82]

Water Washability: The dried film is used to evaluate the film's wetting ease. After being cleaned with water, the film is rated on an ordinal scale: easily, partially, and poorly cleaned.

Spray Angle[69]: The pigmentation technique of a spray-on slip of paper was used to calculate the spray angle. The nozzle was positioned 15 cm away from the white paper, and the sprays were activated horizontally. To help with visual representation, 10 mg of Sudan red was dissolved in the formulation. Using the formula below, the spray angle was determined. spray angle (θ) = tan-1(l/r), Where, r = circle's mean radius, l = distance between the nozzle and sheet.

Volume Actuated Upon Each Spray[69]: After each actuation, the weight difference was recorded and the volume delivered was estimated using the formula, WT = WO - AL/Dn, Where, AL = amount of solution delivered with each actuation, WT = formulation's load following an actuation, WO = formulation's initial weight before an actuation, Dn = density.

Drug Content[69]: A ml of the prepared formulation was immersed for four hours at 100 rpm in phosphate buffer with a pH of 7.4 to assess the drug content. After filtering, the samples were suitably diluted. The mixture obtained was subjected to additional sonication, and spectrophotometric absorbance measurements were made at λmax.

Stickiness: Using cotton wool, gently press the dried film. The amount of cotton wool fibers adhered to the film serves as a proxy for the viscosity of the material. If the attached fiber is thick, the film adhesiveness is deemed high; if the attached fiber is thin, it is deemed medium; and if there is little to no attached fiber, it is deemed low. [83]

Flexibility: If the film is flexible and free of skin fixation disorders or cracks, it will be deemed flexible. [66]

***In-Vitro* Drug Permeation Studies:** The Franz diffusion cell's onion membrane was used for the *in-vitro* drug permeation process. The shape and size of the membrane used in the permeation studies were cut to match the dimensions of the diffusion cell. 7.4 pH phosphate buffer was added to the diffusion cell's receptor compartment. The donor and receptor compartments were separated by a 2.4 cm- diameter onion membrane. The film-forming solution was taken and added to the receptor compartment in an amount of 1 mL, which is equivalent to 5 mg of the drug. Subsequently, the stirrer was adjusted to 100 revolutions per minute. At precise intervals, 1 mL of sample were taken out of the receptor chamber. A U.V. spectrophotometer was used to measure the absorbance of these samples, which were prepared up to 10 mL in a volumetric flask and recorded at λmax.[41]

RESULTS AND DISCUSSION

Viscosity, pH, Spray Angle, Volume Actuated Upon Each Spray, Evaporation Time, And Drug Content

The pH of the solutions was found to be between 5.5 and 6.5, which is within the normal range for the pH of the skin and scalp and is therefore it not irritating to the scalp. All formulations from F1 to F6, however, have viscosities between 26 and 48 cps. Additionally, the film- forming spray's uniform delivery on the scalp's surface is demonstrated by its spray angle, which lies between 36 and 40 degrees. The volume activated during each spray was within a narrow range and changed slightly in response to changes in the polymer's concentration. The concentration of polymers added to the formulation directly affects the drying time or timing of the film's formation; the higher the concentration, the longer the film takes to form while changing. Nevertheless, the drug concentration of the formulation was observed in spectrophotometry at λ max of 279 nm. Drug content was also not affected significantly by changes in the concentration of polymers in the formulation.

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Table 2: Result of Viscosity, pH, spray angle, volume actuated upon each spray, evaporation time, and drug content

Formulation number	pH	Viscosity cps	Spray angle	Volume actuated upon each spray (ml)	Evaporation time (min)	Drug content
F1	5.7	26.86	36.8±0.2	0.2436	5.5	98
F2	6.2	36.92	37.95±0.1	0.3665	6	97
F3	5.9	41.68	39.69±0.05	0.508	7.5	95

Film Washability, Stickiness, and Flexibility: The washability and stickiness of films were observed which is followed by rupturing and flexibility tests of film shown in table.

Table 3: Result of Film washability, stickiness, and flexibility.

Formulation number	Flexibility	Stickiness	Washability
F1	++	+++	+++
F2	++	+++	+++
F3	+	++	+++

Good (+++), moderate (++), poor(+).

***In vitro* permeation study of 5% minoxidil film-forming spray using a thin layer of onion.**

Using an onion-thin layer, an in vitro drug permeation experiment was conducted for each formulation, in which F1 exhibited the highest drug content and cumulative drug release percentage. The percentage of cumulative permeation was then plotted against time. The above % cdr shows that the kinetic release of drug shows zero order kinetics.

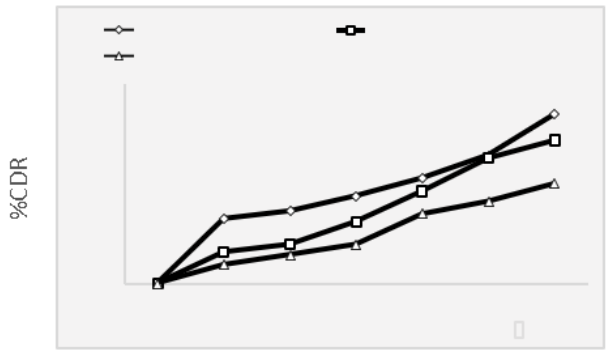

Figure 3: Cumulative drug release of formulation F1, F2, F3

CONCLUSION

In this work, an attempt is made to create and describe a minoxidil film-forming spray by employing polymer at varying concentrations to create a consistent film after the solution is sprayed. The prepared formulation was examined for several evaluation factors, such as pH, drying time, and spray angle. Based on the above results, it was determined that formulation F2, which contains 1.8% hydroxy properly methyl cellulose E15, has good physical properties, good drug concentration, and cumulative drug release. Considering the outcomes of evaluation studies, it can be concluded that film-forming spray formulation can be a good alternative approach for treating patchy hair loss or baldness in men who have androgenetic alopecia.

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