

TOPICAL COMPOSITION COMPRISING DUTASTERIDE AND MINOXIDIL FOR ALOPECIA

RELATED APPLICATION

5 This application claims the benefit of Indian Provisional Application No. 202321086964 filed on December 19, 2023; which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

10 The invention relates to a composition comprising minoxidil and dutasteride with one or more pharmaceutically acceptable excipient. Further the invention relates to process of preparing such composition. Further the invention relates to topical application of the composition for preventing hair loss and/or stimulating hair growth. Further invention relates to achieving acceptable pharmacokinetic parameters to give beneficial therapeutic effect with
15 minimal side effects.

BACKGROUND

 Hair loss is a natural phenomenon. Hair growth follows a cycle which involves the birth and development of the follicle, a stationary phase, and a final phase during which the hair is
20 expelled. This alternation between the phases of growth (the anagenic phase), regression (the catagenic phase), and the rest (the telogenic phase) is due to the specific secretion of the hair follicle which acts as a gland, and progressively produces a mass of keratin which it eliminates and replaces after a resting period.

 The cycle begins with the development of the hair follicle that rises up from the dermis
25 which contains large numbers of mesenchymatous cells, resulting in the formation of a dermal papilla. In the final stage (the anagenic phase) the cells surrounding the dermal papilla divide actively every 12 hours in order to produce cells which line up, grow longer, and begin to keratinize. This is hair growth. During the catagenic phase mitosis no longer occurs and the bulb detaches itself from the papilla and rises towards the surface. In the telogenic phase the
30 hair is fully keratinized and is ready to be expelled. After three to four months, another mitotic cycle begins in the germination zone of the hair and another hair follicle is formed.

 Male pattern alopecia is dependent on male hormones and is thus directly related to the amount of male hormones. Therefore, extensive research aimed at preventing and treating hair loss by inhibiting the activity of male hormones has recently been reported. The mechanism of

hair loss related to male hormones is briefly described below. The testosterone, which is one of the male hormones, is converted into dihydrotestosterone, which is an active male hormone, by a 5 α -reductase, and the active male hormone binds to a specific receptor to produce a protein that triggers hair loss, thus causing hair loss. Also, this mechanism produces excessive sebum, which causes acne or seborrheic dermatitis, eventually causing hair loss accompanied by inflammation in the scalp. As a result, the cause of male pattern alopecia is the synthesis of excessive dihydrotestosterone and thus it is possible to effectively prevent and treat male pattern alopecia by competitive inhibition with the androgen dihydrotestosterone from binding to androgen receptors in the sebaceous gland and hair follicles.

Treatments for the various forms of hair loss have limited success. Three medications have evidence to support their use in male pattern hair loss: oral finasteride (PROPECIA®, Merck), oral dutasteride and topical minoxidil (ROGAINE®, Pfizer/Johnson & Johnson). These treatments require prolonged usage of the drug and if treatment is stopped any benefits gained will be lost and the hair thickness will regress to levels as if no treatment was undertaken. Reversible side effects associated with the use of these androgen inhibitors have been reported such as decreased libido, erectile dysfunction and dermatologic discomfort.

The mechanism of action of minoxidil which is approved for use in hair loss treatment by the U.S. Food and Drug Administration (FDA) in 1979 has not been clearly elucidated. However, the action mechanism of minoxidil has been explained by a hypothesis that the minoxidil increases blood flow to the follicles to cause an increase in blood flow, thus stimulating the growth of hair, and a hypothesis that the minoxidil acts directly on the follicular epithelium to induce the growth of hair. However, hair restorers comprising minoxidil should be applied several times daily to maintain the hair growth effect, which is very cumbersome and easy to forget. Therefore, in many cases, the hair growth effect is not sufficiently obtained due to irregular application and arbitrary discontinuation of treatment. Also if topical application of minoxidil is stopped or topical application is discontinued subjects gradually lose any regrown hair.

IN 378724 discloses a topical composition comprising one or more hair growth promoting agents, at least one acidifying agent, and a suitable carrier system.

US 10993934 B2 discloses a topical composition of dutasteride for preventing hair loss, androgenic alopecia (AA) and stimulating hair growth. The composition for topical application for preventing hair loss and stimulating hair growth provides equal or superior hair loss prevention and hair growth stimulating effects while using much smaller dosage than the conventional compositions (oral dosage form) which use finasteride and dutasteride.

US 2012/0258972A1 a method for treating hair loss caused by androgenic alopecia and/or male pattern baldness.

Androgenetic alopecia is a common form of hair loss in both men and women. In men, this condition is also known as male-pattern baldness. Some of the current challenges in AGA
5 include:

Understanding the underlying causes: Despite significant progress in the understanding of the genetics and biology of AGA, there is still much that is not fully understood about the condition. Researchers are still working to identify the precise genetic and environmental factors that contribute to AGA.

10 Developing effective treatments: Although there are several treatments available for AGA, including medications and hair transplant surgery, there is still no cure for the condition. Current treatments are often expensive, time-consuming, and may have side effects.

Addressing psychological impact: AGA can have a significant psychological impact on those affected, causing anxiety, depression, and low self-esteem. More research is needed to
15 better understand the psychological aspects of AGA and develop effective interventions to address these issues.

Preventing hair loss: While there are treatments available to slow down or even reverse hair loss in some cases, preventing hair loss altogether remains a challenge. Lifestyle changes, such as reducing stress and eating a healthy diet, may be beneficial, but more research is needed
20 to determine the most effective ways to prevent hair loss.

Overall, the challenges in AGA highlight the need for continued research and development of new and more effective treatments, as well as increased focus on the psychological impact of the condition.

The method described herein constitute a major improvement to the currently available
25 therapies of alopecia, and specifically AGA, and would allow the physicians to have an effective, valuable and safe treatment of alopecia, and in particular AGA.

SUMMARY OF THE INVENTION

The invention relates to composition comprising: a. a pharmaceutically effective
30 amount of a 5 α -reductase inhibitor, b. a pharmaceutically effective amount of a vasodilator and c. pharmaceutically acceptable vehicle.

The invention relates to the composition for treating hair loss and/or stimulating hair growth comprising: a. a pharmaceutically effective amount of a 5 α -reductase inhibitor, b. a pharmaceutically effective amount of a vasodilator and c. pharmaceutically acceptable vehicle.

The invention relates to composition comprising: a. a pharmaceutically effective amount of a dutasteride, b. a pharmaceutically effective amount of a minoxidil, and c. pharmaceutically acceptable vehicle.

The invention relates to the composition for treating hair loss and/or stimulating hair growth comprising: a. a pharmaceutically effective amount of a dutasteride, b. a pharmaceutically effective amount of a minoxidil, and c. pharmaceutically acceptable vehicle.

Inventors of the present invention have surprisingly found that the combination therapy with dutasteride and minoxidil is an effective approach for treating androgenetic alopecia (AGA).

When used in combination, dutasteride and minoxidil target different aspects of the hair loss process, potentially providing more comprehensive and effective treatment for AGA. However, it is important to note that combination therapy may also increase the risk of side effects, such as scalp irritation, dizziness, and sexual dysfunction.

The invention relates to the composition comprising: a. dutasteride, b. minoxidil, and c. pharmaceutically acceptable vehicle, wherein at least one of the active is partially solubilized.

In another embodiment, the invention relates to a composition comprising: a. dutasteride, b. minoxidil, and c. pharmaceutically acceptable vehicle, wherein dutasteride is partially solubilized or supersaturated or suspended.

In another embodiment, the invention relates to a composition comprising: a. dutasteride, b. minoxidil, c. pharmaceutically acceptable vehicle, wherein minoxidil is partially solubilized or supersaturated or suspended.

In another embodiment, the invention relates to a composition comprising: a. dutasteride, b. minoxidil, c. pharmaceutically acceptable vehicle, wherein dutasteride and minoxidil are fully solubilized.

In another embodiment, the invention relates to a stable composition comprising: a. dutasteride, b. minoxidil, and c. pharmaceutically acceptable vehicle.

In another embodiment, the invention relates to a composition for treating hair loss and/or stimulating hair growth comprising: a. dutasteride, b. minoxidil, c. pharmaceutically acceptable vehicle, wherein dutasteride is partially solubilized; minoxidil is solubilized.

In another embodiment, the invention relates to a composition comprising: a. dutasteride, b. minoxidil, c. pharmaceutically acceptable vehicle, wherein minoxidil is partially solubilized; dutasteride is solubilized.

In another embodiment, the invention is based on sol-gel technology in sol-gel, *in situ* gel-forming formulations, which undergo phase transition from liquid to gel upon

exposure to physiological environments. This technology combines advantages of being convenient for administration to patients and prolonging drug delivery.

In another embodiment, the invention relates to a stable composition comprising: a. dutasteride, b. minoxidil, c. pharmaceutically acceptable vehicle, wherein the composition is stable at least for a period of about 1 month at room temperature.

In another embodiment, the invention relates to a stable composition for treating hair loss and/or stimulating hair growth comprising: a. dutasteride, b. minoxidil, c. pharmaceutically acceptable vehicle, wherein the composition is stable at least for a period of about 2 months at room temperature.

In another embodiment, the invention relates to a stable composition for treating hair loss and/or stimulating hair growth comprising: a. dutasteride, b. minoxidil, c. pharmaceutically acceptable vehicle, wherein the composition is stable at least for a period of about 3 months at room temperature.

In another aspect, the invention relates to a topical composition comprising a. dutasteride, b. minoxidil, c. a pharmaceutically acceptable vehicle comprising one or more penetration enhancer(s).

In another aspect, the invention relates to a topical composition comprising a. dutasteride, b. minoxidil, c. a pharmaceutically acceptable vehicle comprising one or more solubilizer(s).

In another aspect, the invention relates to a topical composition: a. dutasteride, b. minoxidil, c. a pharmaceutically acceptable vehicle comprising one or more stabilizer(s).

In another aspect, the invention relates to a topical composition: a. dutasteride, b. minoxidil, c. a pharmaceutically acceptable vehicle comprising one or more surfactant(s).

In another aspect, the invention relates to a topical composition: a. dutasteride, b. minoxidil, c. a pharmaceutically acceptable vehicle comprising one or more viscosity agent(s).

In another aspect, the invention relates to a topical composition: a. dutasteride, b. minoxidil, c. a pharmaceutically acceptable vehicle comprising one or more solvent(s).

In another aspect, the invention relates to a topical composition: a. dutasteride, b. minoxidil, c. a pharmaceutically acceptable vehicle comprising one or more acidulant(s).

In another aspect, the invention relates to a topical composition: a. dutasteride, b. minoxidil, c. a pharmaceutically acceptable vehicle comprising one or more emulsifier(s).

In another aspect, the invention relates to a topical composition comprising a. about 0.001% w/w to about 1% w/w of the dutasteride or a pharmaceutically acceptable salt thereof,

b. about 1% w/w to about 20% w/w of the minoxidil or a pharmaceutically acceptable salt thereof and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates to a topical composition comprising a. about 0.01% w/w to about 0.1% w/w of the dutasteride or a pharmaceutically acceptable salt thereof,
5 b. about 2% w/w to about 15% w/w of the minoxidil or a pharmaceutically acceptable salt thereof and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates to a topical composition comprising a. about 0.02% w/w to about 0.08% of the dutasteride or a pharmaceutically acceptable salt thereof, b. about 5% w/w to about 10% w/w of the minoxidil or a pharmaceutically acceptable salt thereof,
10 and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates to a topical composition comprising a. about 0.04% w/w to about 0.06% of the dutasteride or a pharmaceutically acceptable salt thereof, b. about 5% w/w to about 10% w/w of the minoxidil or a pharmaceutically acceptable salt thereof, and c. a pharmaceutically acceptable vehicle.

15 In another aspect, the invention relates to a topical composition comprising a. about 0.05% w/w of the dutasteride or a pharmaceutically acceptable salt thereof, b. about 5% w/w of the minoxidil or a pharmaceutically acceptable salt thereof, and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates method of treating hair loss and/or stimulating
20 hair growth in a subject in need thereof applying a formulation to a desired area of scalp in the form of the composition for external application, selected from the group consisting of hair tonic, solution, dispersion, suspension, emulsion, microemulsion, colloidal solution, cream, ointment, lotion, hair dye, shampoo, rinse, gel, patch, hair serum, foam, and spray.

In another aspect, the invention relates to composition for external application, selected
25 from the group consisting of hair tonic, solution, dispersion, suspension, emulsion, microemulsion, colloidal solution, cream, ointment, lotion, hair dye, shampoo, rinse, gel, patch, hair serum, foam, and spray.

BRIEF DESCRIPTION OF THE DRAWINGS

30 Figure-1A: Effect of hair growth formulations on hair coverage: line graph showing daywise hair coverage score.

Figure-1B: Effect of hair growth formulations on hair coverage: bar graph showing terminal hair coverage score.

Figure-2. Effect of hair growth formulations on anagen phase onset: line graph showing daywise number of mice in anagen phase.

Figure-3: Terminal macroscopic photos of mice: topical placebo.

Figure-4: Terminal macroscopic photos of mice: topical dutasteride 0.05%

5 Figure-5: Terminal macroscopic photos of mice: topical minoxidil 5%

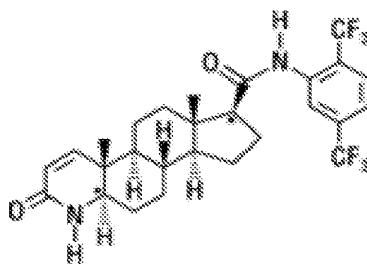
Figure-6: Terminal macroscopic photos of mice: topical dutasteride 0.05% and minoxidil 5% combination composition.

DETAILED DESCRIPTION

10 Disclosed herein are detailed descriptions of specific aspects of the invention of a topical composition in the form of a cream, ointment, gel, lotion, hair tonic, patch, hair serum, emulgel, emulsion, aerosol foam, solution, spray, suspension, swab, sponge, powder or paste. It will be understood that the disclosed embodiments are merely examples of the way in which certain aspects of the application can be implemented and do not represent an exhaustive list of all of
15 the ways the application may be embodied.

A. Dutasteride:

Dutasteride has a chemical name (5 α ,17 β)-N-{2,5-bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. It has the structural formula shown as Formula I.



20

Formula I

Dutasteride is a synthetic 4-azasteroid compound that is a selective inhibitor of both type I and type II isoforms of steroid 5 α -reductase (5AR), an intracellular enzyme that converts testosterone to 5 α -dihydrotestosterone (DHT), and is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men. A pharmaceutical product containing dutasteride
25 as the active ingredient is commercially available as AVODART® from GlaxoSmithKline, in the form of soft gelatin capsules for oral administration and containing 0.5 mg of the active ingredient.

R. Clerk et al., Journal of Clinical Endocrinology and Metabolism, Vol. 89, pages 2179-2184, 2004, demonstrated approximately 3 times higher potency of dutasteride at inhibiting

type II 5 α -reductase and more than 100 times higher potency at inhibiting the type I isoform, as compared with finasteride.

While type I 5 α -reductase has been reported to be located predominantly in the skin, both in hair follicles and sebaceous glands, as well as in the liver, prostate, and kidney, type II 5 α -reductase is found in the male genitalia, prostate and hair follicles. Due to the distribution of both isoforms of 5 α -reductase in skin, it has been hypothesized that dutasteride, being a dual inhibitor, would be more useful for treatment of AA when compared to the selective type I inhibitor such as finasteride. (S. Marihart et. al., Reviews in Urology, Vol. 7, pages 203-210, 2005).

Dutasteride (0.5 mg/day) is approved for treatment of androgenic alopecia in South Korea, Japan, and Taiwan. However, efficacy and safety data for dutasteride is largely derived from short-term clinical trials and post-marketing surveillance studies. Long-term, real-world evidence for the effectiveness of dutasteride in androgenic alopecia is limited.

Orally administered dutasteride acts by stopping the conversion of testosterone to DHT in the body so that the DHT doesn't have the chance to reach the hair follicles. Due to its oral use it has potential side effects associated with sexual dysfunction and neuropsychiatric side effects. Some of the side effects are depression, chest pains, swelling, sexual dysfunction, and suicidal thoughts.

Dutasteride when used topically can provide the local effective concentrations and minimal systemic concentration. When applied topically, it works by stopping DHT conversion in the hair follicles, the site of action.

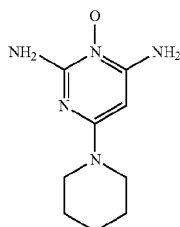
Further topical use of dutasteride being targeted to hair follicle helps in reducing the concentration of dutasteride compared to that administered orally, which further helps in reducing the side effects.

The therapeutically effective amount of dutasteride is from about 0.001% w/w to 1% w/w or from about at least 0.01% w/w to about 0.5% w/w, or preferably from about at least 0.01% w/w to about 0.07% w/w, or preferably of about 0.03% w/w, most preferably about 0.05% w/w based on the total weight of the composition.

In a specific aspect, the concentration of dutasteride in the composition is selected from about 0.001% w/w, 0.002% w/w, 0.003% w/w, 0.004% w/w, 0.005% w/w, 0.006% w/w, 0.007% w/w, 0.008% w/w, 0.009% w/w, 0.01% w/w, 0.02% w/w, 0.03% w/w, 0.04% w/w, 0.05% w/w, 0.06% w/w, 0.07% w/w, 0.08% w/w, 0.09% w/w, 0.1% w/w, 0.11% w/w, 0.12% w/w, 0.13% w/w, 0.14% w/w, 0.15% w/w, 0.16% w/w, 0.17% w/w, 0.18% w/w, 0.19% w/w, 0.2% w/w, 0.21% w/w, 0.22% w/w, 0.23% w/w, 0.24% w/w, 0.25% w/w, 0.26% w/w, 0.27%

w/w, 0.28% w/w, 0.29% w/w, 0.3% w/w, 0.31% w/w, 0.32% w/w, 0.33% w/w, 0.34% w/w, 0.35% w/w, 0.36% w/w, 0.37% w/w, 0.38% w/w, 0.39% w/w, 0.4% w/w, 0.41% w/w, 0.42% w/w, 0.43% w/w, 0.44% w/w, 0.45% w/w, 0.46% w/w, 0.47% w/w, 0.48% w/w, 0.49% w/w, 0.5% w/w, 0.51% w/w, 0.52% w/w, 0.53% w/w, 0.54% w/w, 0.55% w/w, 0.56% w/w, 0.57% w/w, 0.58% w/w, 0.59% w/w, 0.6% w/w, 0.61% w/w, 0.62% w/w, 0.63% w/w, 0.64% w/w, 0.65%, 0.66% w/w, 0.67% w/w, 0.68% w/w, 0.69% w/w, 0.7% w/w, 0.71% w/w, 0.72% w/w, 0.73% w/w, 0.74% w/w, 0.75% w/w, 0.76% w/w, 0.77% w/w, 0.78% w/w, 0.79% w/w, 0.80% w/w, 0.80% w/w, 0.80% w/w, 0.81% w/w, 0.82% w/w, 0.83% w/w, 0.84% w/w, 0.85% w/w, 0.86% w/w, 0.87% w/w, 0.88% w/w, 0.89% w/w, 0.9% w/w, 0.91% w/w, 0.92% w/w, 0.93% w/w, 0.94% w/w, 0.95% w/w, 0.96% w/w, 0.97% w/w, 0.98% w/w, 0.99% w/w or 1% w/w.

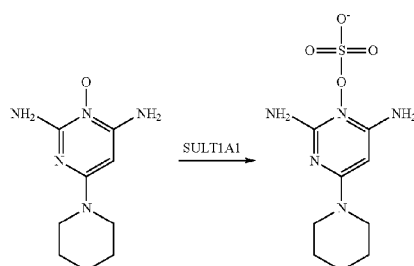
B. Minoxidil:



Formula II

Minoxidil is believed to open adenosine triphosphate (ATP)-sensitive potassium channels and dilates blood vessels allowing more nutrients, blood and oxygen into the follicles. In the late telogen phase of the hair follicle growth cycle, stem cells located in the bulge region differentiate and re-enter anagen phase. In patients suffering from androgenetic alopecia hair follicles become smaller and anagen phase is shortened in duration. Minoxidil increases the amount of intracellular Ca^{2+} , which may upregulate the enzyme adenosine triphosphate (ATP) synthase, independent of its role in ATP synthesis, and promotes stem cell differentiation. It is theorized that minoxidil induced Ca^{2+} influx can increase stem cell differentiation and may be a factor in the mechanism by which minoxidil facilitates hair growth (Mechanism of Action of Minoxidil in the Treatment of Androgenetic Alopecia), A. Gren et al., J Biol Regul Homeost Agents 31(4):1049-1053 (2017).

There is some evidence that minoxidil may cause hair in the telogen phase to shed, which are replaced by newer and thicker hairs in the anagen phase. Minoxidil is a prodrug which converts to minoxidil sulphate by the sulfotransferase enzyme SULT1A1.



Further, minoxidil sulphate as compared to minoxidil is a much more potent hair growth agent. Some studies speculate that the amount of enzyme SULT1A1 in and around the hair follicles is what determines whether individuals respond well to minoxidil.

- 5 The therapeutically effective amount of minoxidil is from about 1% w/w to 20% w/w, or from about at least 2% w/w to about 15% w/w, or preferably from about at least 5% w/w to about 10% w/w based on the total weight of the composition, or most preferably of about 5% w/w. In a specific aspect, the concentration of minoxidil in the composition is selected from
- 10 1.8% w/w, 1.9% w/w, 2% w/w, 2.1% w/w, 2.2% w/w, 2.3% w/w, 2.4% w/w, 2.5% w/w, 2.6% w/w, 2.7% w/w, 2.8% w/w, 2.9% w/w, 3% w/w, 3.1% w/w, 3.2% w/w, 3.3% w/w, 3.4% w/w, 3.5% w/w, 3.6% w/w, 3.7% w/w, 3.8% w/w, 3.9% w/w, 4% w/w, 4.1% w/w, 4.2% w/w, 4.3% w/w, 4.4% w/w, 4.5% w/w, 4.6% w/w, 4.7% w/w, 4.8% w/w, 4.9% w/w, 5% w/w, 5.1% w/w, 5.2% w/w, 5.3% w/w, 5.4% w/w, 5.5% w/w, 5.6% w/w, 5.7% w/w, 5.8% w/w, 5.9% w/w, 6%
- 15 w/w, 6.1% w/w, 6.2% w/w, 6.3% w/w, 6.4% w/w, 6.5% w/w, 6.6% w/w, 6.7% w/w, 6.8% w/w, 6.9% w/w, 7% w/w, 7.1% w/w, 7.2% w/w, 7.3% w/w, 7.4% w/w, 7.5% w/w, 7.6% w/w, 7.7% w/w, 7.8% w/w, 7.9% w/w, 8% w/w, 8.1% w/w, 8.2% w/w, 8.3% w/w, 8.4% w/w, 8.5% w/w, 8.6% w/w, 8.7% w/w, 8.8% w/w, 8.9% w/w, 9% w/w, 9.1% w/w, 9.2% w/w, 9.3% w/w, 9.4% w/w, 9.5% w/w, 9.6% w/w, 9.7% w/w, 9.8% w/w, 9.9% w/w, 10% w/w, 10.1% w/w, 10.2%
- 20 w/w, 10.3% w/w, 10.4% w/w, 10.5% w/w, 10.6% w/w, 10.7% w/w, 10.8% w/w, 10.9% w/w, 11% w/w, 11.1% w/w, 11.2% w/w, 11.3% w/w, 11.4% w/w, 11.5% w/w, 11.6% w/w, 11.7% w/w, 11.8% w/w, 11.9% w/w, 12% w/w, 12.1% w/w, 12.2% w/w, 12.3% w/w, 12.4% w/w, 12.5% w/w, 12.6% w/w, 12.7% w/w, 12.8% w/w, 12.9% w/w, 13% w/w, 13.1% w/w, 13.2% w/w, 13.3% w/w, 13.4% w/w, 13.5% w/w, 13.6% w/w, 13.7% w/w, 13.8% w/w, 13.9% w/w,
- 25 14% w/w, 14.1% w/w, 14.2% w/w, 14.3% w/w, 14.4% w/w, 14.5% w/w, 14.6% w/w, 14.7% w/w, 14.8% w/w, 14.9% w/w, 15% w/w, 15.1% w/w, 15.2% w/w, 15.3% w/w, 15.4% w/w, 15.5% w/w, 15.6% w/w, 15.7% w/w, 15.8% w/w, 15.9% w/w, 16% w/w, 16.1% w/w, 16.2% w/w, 16.3% w/w, 16.4% w/w, 16.5% w/w, 16.6% w/w, 16.7% w/w, 16.8% w/w, 16.9% w/w, 17% w/w, 17.1% w/w, 17.2% w/w, 17.3% w/w, 17.4% w/w, 17.5% w/w, 17.6% w/w, 17.7%

w/w, 17.8% w/w, 17.9% w/w, 18% w/w, 18.1% w/w, 18.2% w/w, 18.3% w/w, 18.4% w/w, 18.5% w/w, 18.6% w/w, 18.7% w/w, 18.8% w/w, 18.9% w/w, 19% w/w, 19.1% w/w, 19.2% w/w, 19.3% w/w, 19.4% w/w, 19.5% w/w, 19.6% w/w, 19.7% w/w, 19.8% w/w, 19.9% w/w or 20 % w/w based on total weight of the composition.

5 **Definitions:**

The terms “active” and “active agent” as used herein refers to therapeutically active agent used in the treatment of a disease or disorder. For example, therapeutically active agent used herein is useful for the treatment, alleviation or prevention of hair loss, and/or the stimulation of hair growth. Exemplary agents are a hair growth stimulant, and/or hair growth
10 stimulating agent and/or hair density increasing agent and/or hair loss prevention agent.

For example, an active agent may be dutasteride or minoxidil or combination thereof.

The term “effective amount” refers to an amount that is sufficient to achieve the desired modification of a physical property of the composition or material. For example, an “effective amount” of a therapeutic agent refers to an amount that is sufficient to achieve the desired
15 improvement in clinical condition modulated by the formulation component, e.g. achieving the desired level of hair growth or mitigation of hair loss. Therapeutic agents should be understood to include the neutral forms of the drug and pharmaceutically acceptable forms thereof. “Pharmaceutically acceptable” refers to those compounds, materials, compositions, salts and/or dosage forms which, are suitable for administration to patients without excessive toxicity,
20 irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio, when used in the compositions of the invention, including when the compositions are applied topically according to methods described herein.

The term “solution state stability” refers to formulation is stable chemically and physically, e.g. physical stability can be attributed to no visible particulate matters/ dispersed
25 particles in the formulation, and chemical stability can be attributed to within acceptable limit of degradant/impurities.

By “pharmaceutically acceptable forms” thereof is meant any pharmaceutically acceptable derivative or variation, including stereoisomers, stereoisomer mixtures, enantiomers, solvates, hydrates, isomorphs, polymorphs, pseudomorphs, salt forms and
30 prodrugs. Preferably in some aspects, the pharmaceutically acceptable forms include salt forms. In other preferable aspects the pharmaceutically acceptable forms include, any stereoisomer or stereoisomeric mixture of the therapeutic agent. The specific level in terms of % w/w in a composition required as an effective amount will depend upon a variety of factors including the

amount and type of therapeutic agent and formulation type, e.g., solution, emulsion, suspension, spray, ointment, cream, gel, and the like.

The term “comprising” is to be interpreted as specifying the presence of the stated features, integers, steps, or components as referred to, but does not preclude the presence or
5 addition of one or more features, integers, steps, or components, or groups thereof. Moreover, each of the terms “by”, “comprising”, “comprises”, “comprised of”, “including”, “includes”, “included”, “involving”, “involves”, “involved”, and “such as” are used in their open, non-limiting sense and may be used interchangeably. Further, the term “comprising” is intended to include examples and aspects encompassed by the terms “consisting essentially of” and
10 “consisting of.” Similarly, the term “consisting essentially of” is intended to include examples encompassed by the term “consisting of”.

The term “safe and effective amount” as used herein means an amount of a compound or composition sufficient to significantly induce a positive benefit, for example, hair growth, but low enough to avoid serious side effects, i.e., to provide a reasonable benefit to risk ratio,
15 within the scope of sound judgment of the skilled artisan.

The term “hair growth”, “regulating hair growth”, “hair growth regulation”, and “regulating the growth of hair”, are meant to include: stimulating hair growth; promoting hair growth; stimulating hair thickening; preventing, reducing, arresting and/or retarding the loss of hair; preventing, reducing, arresting and/or retarding the thinning of hair or hair loss; increasing
20 the rate of hair growth; inducing the formation of a greater number of hair strands; increasing the diameter of the hair strand; lengthening the hair strand; changing the hair follicle from a vellus or miniaturized follicle to a large terminal follicle; inducing the formation of vellus and terminal follicles.

The term “stability” or “stable” as used herein, includes both chemical stability and
25 physical/polymorphic stability of the topical composition of the present invention, wherein said composition remains within the established specifications to maintain its identity, strength, quality and purity throughout the storage, retest or expiry period and do not change or decompose due to internal reaction, or due to the effects of oxygen, heat, light, moisture or pressure; and wherein the drug is present in an amount of at least about 95% to about 100% of
30 the originally specified amount and total impurity of not more than about 5.0% for at least about 1 months upon storage at 2-8°C or 25°C / 60% relative humidity (RH), 30°C / 65% RH or at 40°C / 75% RH.

As used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example,

reference to “a silicone base,” “a gel base for gel-cream emulsions,” or “a heavy cream base,” including, but not limited to, two or more such silicone bases, gel bases for gel-cream emulsions, or heavy cream base, and the like.

It should be noted that ratios, concentrations, amounts, and other numerical data can be expressed herein in a range format. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as “about” that particular value in addition to the value itself. For example, if the value “10” is disclosed, then “about 10” is also disclosed. Ranges can be expressed herein as from “about” one particular value, and/or to “about” another particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms a further aspect. For example, if the value “about 10” is disclosed, then “10” is also disclosed.

It is to be understood that such a range format is used for convenience and brevity, and thus, should be interpreted in a flexible manner to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. To illustrate, a numerical range of “about 0.1% to 5%” should be interpreted to include not only the explicitly recited values of about 0.1% to about 5%, but also include individual values (e.g., about 1%, about 2%, about 3%, and about 4%) and the sub-ranges (e.g., about 0.5% to about 1.1%; about 5% to about 2.4%; about 0.5% to about 3.2%, and about 0.5% to about 4.4%, and other possible sub-ranges) within the indicated range.

The term “alopecia” as used herein refers to, collectively, or individually as specified, androgenetic alopecia (AGA), alopecia areata (including diffuse alopecia areata, alopecia areata monolocularis, alopecia areata multilocularis, ophiasis, alopecia totalis, and alopecia universalis), telogen effluvium, anagen effluvium, and traction alopecia.

As used herein, the terms “about,” “approximate,” “at or about,” and “substantially” mean that the amount or value in question can be the exact value or a value that provides equivalent results or effects as recited in the claims or taught herein. That is, it is understood that amounts, sizes, formulations, parameters, and other quantities and characteristics are not and need not be exact, but may be approximate and/or larger or smaller, as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art such that equivalent results or effects are obtained. In some circumstances, the value that provides equivalent results or effects cannot be reasonably

determined. In such cases, it is generally understood, as used herein, that “about” and “at or about” mean the nominal value indicated $\pm 20\%$ variation unless otherwise indicated or inferred. In general, an amount, size, formulation, parameter or other quantity or characteristic is “about,” “approximate,” or “at or about” whether or not expressly stated to be such. It is understood that
5 where “about,” “approximate,” or “at or about” is used before a quantitative value, the parameter also includes the specific quantitative value itself, unless specifically stated otherwise.

As used herein, the terms “optional” or “optionally” means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances
10 where said event or circumstance occurs and instances where it does not.

As used herein, the term “administration” refers to the act of administering a drug, prodrug, or other active agent, or therapeutic treatment (e.g., compositions of the invention) to a subject. Exemplary routes of administration to the human body can be on the skin, e.g., on the scalp. Administration may be in one or more administrations, applications or dosages, and
15 is not intended to be limited to a particular time period. “Administered” and “applied” are used to describe the act of “administration” and are used synonymously.

The term “oil-based,” as used herein, refers to a composition in which the major component is an oil.

The term “aqueous-based,” as used herein, refers to a composition in which the major
20 component is water or water miscible or soluble excipients.

The phrase “alcohol free” means that a composition does not contain short chain alcohol.

The phrase “propylene glycol free” means that a composition does not contain propylene glycol.

25 The term “substantially free” is meant that the component content in the composition is less than about 10% w/w. For example, a composition that is substantially free of petrolatum has a petrolatum content that is less than about 10% of the final composition. In some aspects, the term “substantially free” refers to a component that is in the composition less than about 10% w/w or less than about 1% w/w or less than about 5% w/w or about 1% w/w or about 0 %
30 w/w based on the total weight of the composition.

The term “substantially solubilized,” as used herein, means that the therapeutic agent is dissolved in the compositions and is at a concentration which is less than about its solubility limit in the compositions.

The term “partially solubilized,” as used herein, means that the therapeutic agent is insoluble in the compositions and is at a concentration which is less than about its solubility limit in the compositions.

5 The term “topical” or “topically” in reference to administration or application of a composition or a product refers to epicutaneous administration or application, or administration onto the surface of the skin. The term “topically active agent” as used herein refers to a compound that is effective in a treatment of a skin condition when administered topically. The term “topical,” when used in reference to a composition, formulation or a product refers to a composition or a product formulated for topical application. “Formulation” and “composition”
10 can be interchangeable.

The term “pharmaceutical composition” as used herein refers to compositions comprising 5 α -reductase inhibitors, and vasodilator together with one or more pharmaceutically acceptable excipients as required to prepare a dosage form for the effective delivery of the active agent. Such pharmaceutical compositions can be in the form of solutions, ointments,
15 creams, gels, lotions, suspensions, sprays, foams, microspheres, microemulsions, nanoemulsions, nanoparticles, nanosuspensions, dermal sticks, roll-ons, pumps, patches, tapes, and the like.

“Scalp” according to the present invention means the skin covering the head and is bordered by the face anteriorly and the neck to the sides and posteriorly.

20 The term “treatment duration” as used herein, means that the composition prescribed or used or administered for said period of time for example one month, two months, six months, 1 year or two year).

The term “solvent” as used herein refers to a substance that solubilizes active agent and provides uniform distribution of active agent throughout the composition. As used herein
25 “solvent” and “solubilizer” can be interchangeable.

“Penetration enhancement” or “permeation enhancement” means an increase in the permeability of a biological membrane (i.e. skin or mucosa) to a drug, so as to increase the rate at which the drug is transported through the membrane. “Permeation enhancer”, “enhancer”, “penetration enhancer”, or similar terms mean a material that achieves such permeation or
30 penetration enhancement, and an “effective amount” of an enhancer means an amount effective to enhance penetration through the skin or mucosa of a selected agent to a desired degree.

The term “subject” as used herein refers to human subject or an animal including mammals (such as monkeys, guinea pig, domestic pets, for instance cats and dogs).

The term “silicone excipient” as used herein refers to a silicon-based materials used in the composition for various function such as gelling agent(s), solvent(s), emulsifier(s), volatile solvent(s), polymer(s) and wax(es).

The pharmaceutically acceptable vehicle according to the present invention include, but
5 are not limited to: paraffin oils; esters of C₈-C₁₈ organic acids like isopropyl myristate; C₈-C₃₀ fatty alcohols; silicone oils; vegetable oils; fractionated or hydrogenated vegetable oils; monoglycerides; diglycerides; triglycerides; phospholipids; dimethyl isosorbide; volatile solvents; N-methylpyrrolidone; N,N-dimethylacetamide and N,N-dimethylformamide; dimethylsulphoxide; alcohols such as ethanol and isopropyl alcohol; glycols such as propylene
10 glycol, polyethylene glycol and glycerol; cyclodextrins such as beta-cyclodextrin, beta-hydroxy cyclodextrin, gamma-cyclodextrin, and hydroxypropyl cyclodextrin; and any mixtures thereof.

The pharmaceutically acceptable excipient(s) are selected from solvent, emulsifying agent, co-emulsifying agent, gelling agent, polymer, thickening agent, viscosity-enhancing agent, co-solvent, emollient, pH adjusting agent, penetration enhancing agent, antioxidant,
15 preservative, and any combination of any of the foregoing thereof.

In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, comprising topically administering an effective amount of the pharmaceutical formulation, once daily to the subject.

In another embodiment, the invention provides a method of preventing hair loss and/or
20 stimulating hair growth, comprising topically administering an effective amount of the pharmaceutical formulation, twice daily to the subject.

In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, comprising topically administering an effective amount of the pharmaceutical formulation, once in a two day to the subject.

25 In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, the method comprising topically administering to a subject in need thereof an effective amount of the topical pharmaceutical formulation, wherein the topical administration of the formulation for at six months is free from systemic side-effects associated with dutasteride and/or minoxidil.

30 In another embodiment, the subject is free from systemic side-effects associated with dutasteride and/or minoxidil for at least one month or at least two months or at least three months or at least four months or at least five months.

In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, the method comprising topically administering to a subject in need

thereof an effective amount of the topical pharmaceutical formulation, wherein once a day topical administration of the formulation for at least one month achieves hair growth comparable to hair growth observed upon administration of formulation of topical minoxidil available commercially for the same period of time.

5 In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, the method comprising topically administering to a subject in need thereof an effective amount of the topical pharmaceutical formulation, wherein twice a day topical administration of the formulation for at least one month achieves hair growth comparable to hair growth observed upon administration of formulation of topical minoxidil
10 available commercially for the same period of time.

 In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, the method comprising topically administering to a subject in need thereof an effective amount of the topical pharmaceutical formulation, wherein once a day topical administration of the formulation for at least two month achieves hair growth
15 comparable to hair growth observed upon administration of formulation of topical minoxidil available commercially for the same period of time.

 In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, the method comprising topically administering to a subject in need thereof an effective amount of the topical pharmaceutical formulation, wherein twice a day
20 topical administration of the formulation for at least two month achieves hair growth comparable to hair growth observed upon administration of formulation of topical minoxidil available commercially for the same period of time.

 In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, the method comprising topically administering to a subject in need thereof an effective amount of the topical pharmaceutical formulation, wherein once a day
25 topical administration of the formulation for at least six month achieves hair growth comparable to hair growth observed upon administration of formulation of topical minoxidil available commercially for the same period of time.

 In another embodiment, the invention provides a method of preventing hair loss and/or
30 stimulating hair growth, the method comprising topically administering to a subject in need thereof an effective amount of the topical pharmaceutical formulation, wherein twice a day topical administration of the formulation for at least six month achieves hair growth comparable to hair growth observed upon administration of formulation of topical minoxidil available commercially for the same period of time.

In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, comprising topically administering an effective amount of the pharmaceutical formulation during treatment duration, wherein after discontinuation of administration of pharmaceutical formulation, the reversal of prevention of hair loss and/or stimulation of hair growth is delayed for at least one month.

In another embodiment, the treatment duration is at least one month or at least two months or at least three months or at least four months or at least five month or at least six months or at least seven months or at least eight months or at least nine months or at least ten months or at least at least eleven months or at least one year or at least two years.

In another embodiment, the reversal of prevention of hair loss and/or stimulation of hair growth is delayed for at least one month or at least two months or at least three months or at least four months or at least five month or at least six months after the treatment duration of at least one month.

In another embodiment, the reversal of prevention of hair loss and/or stimulation of hair growth is delayed for at least one month or at least two months or at least three months or at least four months or at least five month or at least six months after the treatment duration of at least two months.

In another embodiment, the reversal of prevention of hair loss and/or stimulation of hair growth is delayed for at least one month or at least two months or at least three months or at least four months or at least five month or at least six months after the treatment duration of at least three months.

In another embodiment, the reversal of prevention of hair loss and/or stimulation of hair growth is delayed for at least one month or at least two months or at least three months or at least four months or at least five month or at least six months after the treatment duration of at least four months.

In another embodiment, the reversal of prevention of hair loss and/or stimulation of hair growth is delayed for at least one month or at least two months or at least three months or at least four months or at least five month or at least six months after the treatment duration of at least five months.

In another embodiment, the reversal of prevention of hair loss and/or stimulation of hair growth is delayed for at least one month or at least two months or at least three months or at least four months or at least five month or at least six months after the treatment duration of at least six months.

In another embodiment, the reversal of prevention of hair loss and/or stimulation of hair growth is delayed for at least one month or at least two months or at least three months or at least four months or at least five month or at least six months after the treatment duration of at least one year.

5 In another embodiment, the reversal of prevention of hair loss and/or stimulation of hair growth is delayed for at least one month or at least two months or at least three months or at least four months or at least five month or at least six months after the treatment duration of at least two years.

10 In another embodiment, invention provides a method of preventing hair loss and/or stimulating hair growth, comprising topically administering an effective amount of the pharmaceutical formulation, wherein after discontinuation of administration of pharmaceutical formulation, prevention of hair loss and/or stimulation of hair growth is maintained for at least one month.

15 In another embodiment, prevention of hair loss and/or stimulation of hair growth is maintained for at least one month or at least two months or at least three months or at least four months or at least five month or at least six months after discontinuation of administration of pharmaceutical formulation.

20 In embodiments, topical pharmaceutical compositions according to the present invention provide improved local delivery of an active agent, i.e., a 5 α -reductase inhibitor, such as dutasteride, that results in enhanced bioavailability and is substantially comparable in effect to an oral or injectable formulation of the 5 α -reductase inhibitor.

25 In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, the method comprising topically administering to a subject in need thereof an effective amount of the topical pharmaceutical formulation comprising one or more actives selected from dutasteride, minoxidil and at least one acidifying agent, wherein said actives are present in a ratio of about 1:0.1 to about 1:0.4, preferably in a ratio of about 1:0.2 to about 1:0.3.

In an aspect of the above embodiment, said dutasteride and acidifying agent are present in a ratio of about 1:10 to about 1:40.

30 In an aspect of the above embodiments, said dutasteride and acidifying agent are present in a ratio of about 1:15 to about 1:35.

In an aspect of the above embodiments, said dutasteride and acidifying agent are present in a ratio of about 1:20 to about 1:30.

In an aspect of the above embodiments, said dutasteride and acidifying agent are present in a ratio of about 1:28.

In an aspect of the above embodiment, said minoxidil and acidifying agent are present in a ratio of about 1:0.1 to about 1:0.4.

5 In an aspect of the above embodiments, said minoxidil and acidifying agent are present in a ratio of about 1:20 to about 1:30.

In an aspect of the above embodiments, said minoxidil and acidifying agent are present in a ratio of about 1:28.

10 In another embodiment, the invention provides a method of preventing hair loss and/or stimulating hair growth, the method comprising topically administering to a subject in need thereof an effective amount of the topical pharmaceutical formulation comprising one or more actives selected from dutasteride, minoxidil and at least one thermoreversible polymer, wherein said actives are present in a ratio of about 1:0.5 to about 1:0.4, preferably in a ratio of about 1:0.1 to about 1:0.3, most preferably in a ratio of about 1:0.15 to about 1:0.25.

15 In an aspect of the above embodiment, said dutasteride and poloxamer are present in a ratio of about 1:5 to about 1:40.

In an aspect of the above embodiment, said dutasteride and poloxamer are present in a ratio of about 1:10 to about 1:35.

20 In an aspect of the above embodiment, said dutasteride and poloxamer are present in a ratio of about 1:15 to about 1:30.

In an aspect of the above embodiment, said dutasteride and poloxamer are present in a ratio of about 1:15 to about 1:25.

In an aspect of the above embodiment, said dutasteride and poloxamer are present in a ratio of about 1:20.

25 In an aspect of the above embodiment, said minoxidil and poloxamer are present in a ratio of about 1:0.5 to about 1:0.4.

In an aspect of the above embodiment, said minoxidil and poloxamer are present in a ratio of about 1:0.1 to about 1:0.3.

30 In an aspect of the above embodiment, said minoxidil and poloxamer are present in a ratio of about 1:0.15 to about 1:0.25.

In an aspect of the above embodiment, said minoxidil and poloxamer are present in a ratio of about 1:0.2.

In one of the aspect, invention provides a method of preventing hair loss and/or stimulating hair growth in a patient in need thereof, comprising topically administering to the

subject a pharmaceutical formulation comprising about 0.05% w/w of dutasteride, about 5% w/w of minoxidil, and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or stimulating hair growth in a patient in need thereof, comprising topically administering to the
5 subject a pharmaceutical formulation comprising about 0.02% w/w of dutasteride, about 5% w/w of minoxidil, and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or stimulating hair growth in a patient in need thereof, comprising topically administering to the
10 subject a pharmaceutical formulation comprising about 0.01% w/w of dutasteride, about 5% w/w of minoxidil, and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or stimulating hair growth in a patient in need thereof, comprising topically administering to the
subject a pharmaceutical formulation comprising about 0.05% w/w of dutasteride, about 2% w/w of minoxidil, and a pharmaceutically acceptable vehicle.

15 In one of the aspect, invention provides a method of preventing hair loss and/or stimulating hair growth in a patient in need thereof, comprising topically administering to the
subject a pharmaceutical formulation comprising about 0.02% w/w of dutasteride, about 2% w/w of minoxidil, and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or
20 stimulating hair growth in a patient in need thereof, comprising topically administering to the
subject a pharmaceutical formulation comprising about 0.1% w/w of dutasteride, about 5% w/w of minoxidil, and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or
stimulating hair growth in a patient in need thereof, comprising topically administering to the
25 subject a pharmaceutical formulation comprising about 0.1% w/w of dutasteride, about 2% w/w of minoxidil, and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or
stimulating hair growth in a patient in need thereof, comprising topically administering to the
subject a pharmaceutical formulation comprising about 0.01% w/w of dutasteride, about 2%
30 w/w of minoxidil, and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or
stimulating hair growth in a patient in need thereof, comprising topically administering to the
subject a pharmaceutical formulation comprising about 0.05% w/w of dutasteride, about 7.5%
w/w of minoxidil, and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or stimulating hair growth in a patient in need thereof, comprising topically administering to the subject a pharmaceutical formulation comprising about 0.02% w/w of dutasteride, about 7.5% w/w of minoxidil, and a pharmaceutically acceptable vehicle.

5 In one of the aspect, invention provides a method of preventing hair loss and/or stimulating hair growth in a patient in need thereof, comprising topically administering to the subject a pharmaceutical formulation comprising about 0.01% w/w of dutasteride, about 7.5% w/w of minoxidil, and a pharmaceutically acceptable vehicle.

10 In one of the aspect, invention relates to a synergistic composition for preventing hair loss and/or stimulating hair growth in a patient in need thereof comprising about 0.01% w/w to 0.2% w/w of dutasteride, about 2% w/w to about 10% w/w of minoxidil, and pharmaceutically acceptable vehicle.

15 In one of the aspect, invention relates to a synergistic composition for preventing hair loss and/or stimulating hair growth in a patient in need thereof comprising of about 0.05% w/w of dutasteride, about 5% w/w of minoxidil, and pharmaceutically acceptable vehicle.

In one of the aspect, invention relates to a synergistic composition for preventing hair loss and/or stimulating hair growth in a patient in need thereof comprising of about 0.05% w/w of dutasteride, about 5% w/w of minoxidil, and pharmaceutically acceptable vehicle.

20 In another embodiment, the oil phase can include one or more oils having long chain triglycerides, such as vegetable oils, fish oils, animal fats, hydrogenated vegetable oils, partially hydrogenated vegetable oils, semi-synthetic triglycerides, synthetic triglycerides, or mixtures thereof. Fractionated, refined or purified oils of these types can also be used. The oil may be present in an amount of between about 1% w/w to about 95% w/w.

25 Specific examples of suitable long chain triglyceride-comprising oils suitable for use in the compositions of the invention include almond oil; castor oil; coconut oil; corn oil; cottonseed oil; emu oil; evening primrose oil; flax seed oil; grapeseed oil; groundnut oil; mustard seed oil; olive oil; palm oil; palm kernel oil; peanut oil; rapeseed oil; safflower oil; sesame oil; shark liver oil; soybean oil; sunflower oil; hydrogenated castor oil; hydrogenated coconut oil; hydrogenated palm oil; hydrogenated soybean oil; hydrogenated vegetable oil; a mixture of hydrogenated cottonseed oil and hydrogenated castor oil; partially hydrogenated soybean oil; a mixture of partially hydrogenated soybean oil and partially hydrogenated cottonseed oil; glyceryl trioleate; glyceryl trilinoleate; glyceryl trilinolenate; a Ω 3 polyunsaturated fatty acid triglyceride comprising oil; and mixtures thereof.

30

Preferred long chain triglyceride comprising oils include coconut oil; corn oil; olive oil; palm oil; peanut oil; safflower oil; sesame oil; soybean oil; hydrogenated castor oil; hydrogenated coconut oil; partially hydrogenated soybean oil; glyceryl trioleate; glyceryl trilinoleate; glyceryl trilinolenate; $\Omega 3$ polyunsaturated fatty acid triglyceride comprising oil; and mixtures thereof. Most preferably long chain triglyceride comprising oils include coconut oil and hydrogenated castor oil. The oil may be present in an amount of between about 1% w/w to about 95% w/w, preferably about 5% w/w to about 50%, most preferably about 1% w/w to about 20% w/w.

In certain embodiments, the antioxidant of the invention is selected from one or more ascorbic acid, monothioglycerol, potassium metabisulfite, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium sulfite, sodium thiosulfate, tocopherol or its derivative such as dl- α -tocopherol, sodium metabisulfite, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate, propyl gallate, acai oil, alpha lipoic acid, green tea extract, retinol, vitamin C, coenzyme Q10 (Co Q-10), isoflavones, polyphenols, curcumin, turmeric, pomegranate, rosemary extract, glutathione, selenium, zinc, a chelating molecule, ethylenediaminetetraacetic acid (EDTA), disodium EDTA, tetrasodium EDTA, pentasodium penetate, sodium metasilicate and phosphate derivatives, etidronic acid and/or its derivatives, and/or galactaric acid. The antioxidant may be present in an amount of between about 0.01% w/w to about 5% w/w, preferably about 0.01% w/w to about 1%, most preferably about 0.01% w/w to about 0.05% w/w.

In some aspects antioxidant enhances the activity of at least one active.

In some aspects antioxidant enhances the activity of dutasteride.

In some aspects antioxidant enhances the activity of minoxidil.

In certain embodiments, the preservative of the invention is selected from one or more sodium benzoate, benzoic acid, phenol, cresol, alcohol, chlorbutanol, benzalkonium chloride, methyl paraben or its salts, propyl paraben or its salts, methyl paraben or its salts. The preservative may be present in an amount of between about 0.01% w/w to about 5% w/w, preferably about 0.01% w/w to about 1%, most preferably about 0.01% w/w to about 0.05% w/w.

In an aspect, invention relates to a method for delivering a topical composition for the treatment of hair loss of a human user, said method comprising the steps of: providing a topical composition comprising a hair growth constituents comprising a about 0.01% w/w to about 0.2% w/w dutasteride; about 1% w/w to about 20% w/w minoxidil, and at least one of an penetration enhancer, wherein said penetration enhancer is in a concentration sufficient to aid

said one or more active compound in penetrating the skin surface merely to a depth of approximately the depth of hair bulbs.

In an aspect, invention relates to a method for delivering a topical composition for the treatment of hair loss of a human user, said method comprising the steps of: providing a topical
5 composition comprising: a hair growth constituents comprising a about 0.01% w/w to about 0.1% w/w dutasteride; about 1% w/w to about 15% w/w minoxidil, and at least one antioxidant, wherein said antioxidant is in a concentration sufficient to enhance therapeutic benefit of said one or more active compound when compare to composition without said antioxidant.

In an aspect, the invention relates to a composition for treating hair loss and/or
10 stimulating hair growth comprising a. dutasteride, b. minoxidil, and c. pharmaceutically acceptable vehicle; substantially free of ethanol and propylene glycol.

In a particular embodiment, the invention relates to a composition for treating hair loss and/or stimulating hair growth comprising a. dutasteride, b. minoxidil, and c. pharmaceutically acceptable vehicle; wherein the composition is substantially free of ethanol.

15 In a particular embodiment, the invention relates to a composition for treating hair loss and/or stimulating hair growth comprising: a. dutasteride, b. minoxidil, and c. pharmaceutically acceptable vehicle; wherein the composition is substantially free of propylene glycol.

In a particular embodiment, the invention relates to a composition for treating hair loss and/or stimulating hair growth comprising: a. dutasteride, b. minoxidil, and c. pharmaceutically
20 acceptable vehicle; substantially free of ethanol and propylene glycol.

In an aspect, the invention relates to a composition comprising a. dutasteride b. minoxidil, and c. a pharmaceutically acceptable carrier comprising one or more penetration enhancer(s), one or more solubilizer(s), one or more stabilizer(s) or a mixture thereof.

In certain embodiments, the solubilizer of the invention is selected from one or more
25 alcohol(s); one or more polyhydric alcohol(s) such as propylene glycol, polypropylene glycol, pentylene glycol, glycerin; ethyl acetate, phenoxyethanol, Diisopropyl adipate, isopropyl myristate, diethyl sebacate, dibutylee sebacate, dimethyl isosorbide, dimethyl sulfoxide and mixtures thereof. In certain embodiments, the solubilizer comprises ethanol, isopropanol, pentylene glycol, propylene glycol, ethyl acetate, polyethylene glycol and mixtures thereof. The
30 solubilizer may be present in an amount of between about 1% w/w to about 50% w/w, preferably about 5% w/w to about 30% w/w, most preferably about 10% w/w to about 25% w/w.

In some aspects, the solubilizer of the invention is glycol selected from ethylene glycol, polyethylene glycol, propylene glycol, dipropylene glycol, butylene glycol, pentylene glycol,

hexylene glycol, propylene glycol dipelargonate, diethylene glycol monoethyl ether, propylene laurate glycol dicaprylate dicaprate propylene glycol, and diethylene glycol monoethyl ether, ethanol, dimethyl isosorbide, methyl pyrrolidone, oleic acid, capric / caprylic glycerides and any combination of any of the foregoing. The solubilizer may be present in an amount of
5 between about 1% w/w to about 50% w/w, preferably about 5% w/w to about 30% w/w, most preferably about 10% w/w to about 25% w/w.

In an aspect, the invention relates to a composition comprising a. dutasteride b. minoxidil, and c. a pharmaceutically acceptable carrier comprising one or more a crystal growth inhibitor.

10 In some aspects the crystal growth inhibitor is glycol or its derivatives, selected from ethylene glycol, polyethylene glycol, propylene glycol, dipropylene glycol, butylene glycol, pentylene 20 glycol, hexylene glycol, propylene glycol dipelargonate, diethylene glycol monoethyl ether, propylene laurate glycol dicaprylate dicaprate propylene glycol, and diethylene glycol monoethyl ether.

15 The present invention is directed to the addition of hexylene glycol to a pharmaceutical composition comprising a. dutasteride and b. minoxidil, that contains a pharmaceutically acceptable solvent, including water, to inhibit growth of at least one of the active in the composition. For topical solution products designed to contain solubilized composition of
20 actives, the addition of hexylene glycol to a composition, will inhibit the growth of crystals of precipitated actives over the shelf life of the product or during temperature excursion of labelled storage condition of a product for any duration whether during transportation or distribution to assure consistent bioavailability. Inhibiting crystal growth assures that any precipitated active will quickly return to being completely dissolved once the product is returned to controlled room temperature.

25 Preferably, hexylene glycol is added to compositions containing 2% w/w to about 15% w/w.

In an aspect, the invention relates to a composition comprising a. dutasteride b. minoxidil, and c. a pharmaceutically acceptable carrier comprising one or more a solubilizer(s) is selected from monohydric or polyhydric simple alcohols, including, but not limited to, water,
30 C1-C3 alcohols (such as methanol, ethanol, n-propanol, isopropyl alcohol), n-butanol such as 1-butanol, n-hexanol, 2-ethyl-1-hexanol, polyhydric alcohols (such as ethylene glycol, propylene glycol, polypropylene glycol [e.g., polyethylene glycol 200 (PEG 200), polyethylene glycol 400 (PEG 400)], pentylene glycol, the butanediol isomers, 1,5 pentane diol, 1,2,6-trihydroxyhexane, 1 2-ethyl-1,3-hexanediol, 1,7-hepatanediol, or glycerin); ether alcohols, such

as, for example, 1-methoxy-2-propanol, 3-ethyl-3-hydroxymethyloxetan, tetrahydrofurfuryl alcohol, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol monobutyl ether, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol or dipropylene glycol, xylene, chlorobenzene, ethyl acetate, butyl acetate, diethylene glycol dimethyl ether, dipropylene glycol dimethyl ether, ethylene glycol monomethyl or monoethyl ether acetate, diethylene glycol ethyl and butyl ether acetate, propylene glycol monomethyl ether acetate, 1-methoxypropyl-2-acetate, 3-methoxy-n-butylacetate, propylene glycol diacetate, N-methylpyrrolidone and N-methylcaprolactam, dimethylsulfoxide (DMSO), tocopheryl polyethylene glycol succinate (TPGS), dimethylformamide (DMF), dimethylacetamide (DMA), capryl-caproyl macrogol 8-glyceride (Labrasol); polymeric solubilizer such as is selected from the group consisting of cyclodextrin, vinyl polymers such as ethylene-vinyl acetates: ethylene vinyl acetates, polyvinyl alcohol, povidone, copovidone or any combination of any of the foregoing.

15 In certain embodiments, the one or more solubilizer(s) is in the composition in an amount of from about 0.1% to about 60%, optionally, from about 0.1% to about 50%, or, optionally, from about 0.1% to about 40%, by weight of the total composition.

The one aspect of the invention relates to a composition comprising: at least one cyclodextrin.

20 In one of the embodiment, the cyclodextrin of the composition of the invention is selected from the group consisting of α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin or mixtures thereof. Preferably, the cyclodextrin in said list is a hydroxypropyl-cyclodextrin.

In some aspects, the topical composition comprises one or more water-immiscible substance(s) selected from mineral oil, wax(es), paraffin(s), petrolatum, vegetable oil(s), fatty alcohol(s), fatty acid(s), fatty alcohol ether(s), fatty acid ester(s), mono or diester(s) of fatty acid(s) and any combination of any of the foregoing. The water-immiscible substance may be present in an amount of between about 1% w/w to about 95% w/w, preferably about 5% w/w to about 50%, most preferably about 1% w/w to about 20% w/w.

30 In some aspects of the present invention, the topical foam composition comprises one or more aromatic alcohol. In one embodiment, the aromatic alcohol is benzyl alcohol. The present composition further includes one or more foam structuring agents, such as one or more fatty alcohols. The one or more fatty alcohols included in the composition of the present invention have a linear or branched carbon backbone that has 6-22 carbon atoms.

In one embodiment the fatty alcohol is selected from the group consisting of lauryl alcohol, myristyl alcohol, cetyl alcohol, lauryl alcohol, stearyl alcohol, octyldodecanol, and combinations thereof.

In one embodiment, the fatty alcohol, such as cetyl alcohol and or stearyl alcohol, is included in the composition at between about 0.2-2% w/w, 0.04-1.8% w/w, 0.6-1.6% w/w, 0.8-1.4% w/w.

In another embodiment, composition further includes one or more foam structuring agents, such as one or more non-ionic surfactants. Non-ionic surfactants that may be used in the composition of the present invention generally include ethoxylated alcohols. Non-ionic surfactants that may be used in the composition of the present invention include glyceryl stearate, PEG 100-stearate, polyoxyl-20-cetostearyl ether, glyceryl monooleate, glyceryl palmitostearate, polyoxyl-20-stearate, polyoxyl-40-stearate, polyoxyl-60-stearate, polyoxyl-80-stearate, polyoxyl-20-oleate, polyoxyl-40-oleate, polyoxyl-60-oleate, polyoxyl-80-oleate, polyoxyl-20-palmitate, polyoxyl-40-palmitate, polyoxyl-60-palmitate, polyoxyl-80-palmitate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, laureth-2, laureth-4, laureth-6, and laureth-8. Yet other non-ionic surfactants will be apparent to those of skill in the art. In a preferred embodiment, the non-ionic surfactant is polyoxyethylene (20) sorbitan monostearate. In embodiment, the non-ionic surfactant, such as polyoxyethylene (20) sorbitan monostearate, is included in the composition at between about 0.05-1.0% w/w, 0.06-0.95% w/w, 0.07-0.9% w/w, 0.08-0.75% w/w, 0.09-0.7% w/w, 0.1-0.65% w/w, 0.15-0.6% w/w, 0.2-0.5% w/w; or in an amount of about 0.15% w/w, 0.16% w/w, 0.17% w/w, 0.18% w/w, 0.19% w/w, 0.2% w/w, 0.21% w/w, 0.22% w/w, 0.23% w/w, 0.24% w/w, 0.25% w/w, 0.26% w/w, 0.27% w/w, 0.28% w/w, 0.29% w/w, 0.3% w/w, 0.31% w/w, 0.32% w/w, 0.33% w/w, 0.34% w/w, 0.35% w/w, 0.36% w/w, 0.37% w/w, 0.38% w/w, 0.39% w/w, 0.40% w/w, 0.41% w/w, 0.42% w/w, 0.43% w/w, 0.44% w/w, 0.45% w/w, 0.46% w/w, 0.47% w/w, 0.48% w/w, 0.49% w/w, 0.50% w/w.

In another embodiment, composition further includes one or more pH adjusting agents. The pH of the formulation plays critical role in stabilizing the formulation and solubilizing the drug. Use of acidifying agents and basifying agents for adjusting the pH essential for the solubilization for drug may not be suitable for topical application to scalp or skin, and can cause itching, irritation at the site of application.

Suitable examples of acidifying agent that may be used in the present application include, but are not limited to, citric acid, citric acid anhydrous, citric acid monohydrate, DL-

lactic acid, DL-malic acid, DL-tartaric acid, fumaric acid, L-malic acid, L-tartaric acid, salicylic acid, glycol acid, potassium acid tartrate, potassium citrate, potassium DL-bitartrate, potassium gluconate, sodium lactate, sodium L-tartrate, sodium citrate, ascorbic acid, sorbic acid, methane sulfonic acid, or any combinations thereof.

5 In an embodiment, the present application relates to an aqueous based topical composition comprising one or more hair growth promoting agents and at least one acidifying agent, wherein said acidifying agent is present in an amount from about 0.1% to about 5%, based on the total weight of the composition.

 In one of the embodiments, said acidifying agent is lactic acid.

10 In some aspects of the above embodiments, said acidifying agent is malic acid.

 In some aspects of the above embodiments, said acidifying agent is tartaric acid.

 In some aspects of the above embodiments, said acidifying agent is fumaric acid.

 In some aspects of the above embodiments, said acidifying agent is citric acid.

 In some aspects of the above embodiments, the pH of the said composition ranges from
15 about 3 to about 8.

 In some aspects of the above embodiments, the pH of the said composition ranges from about 3.5 to about 7.5.

 In some aspects of the above embodiments, the pH of the said composition ranges from about 4 to about 7.

20 In some aspects of the above embodiments, the pH of the said composition ranges from about 4.5 to about 6.5.

 In some aspects of the above embodiments, the pH of the said composition ranges from about 5 to about 6.

 Minoxidil is a base and is very slightly soluble in water. minoxidil is soluble under
25 acidic conditions. lactic acid helps to solubilize minoxidil in the formulation without affecting the overall pH of the formulation. Without wishing to bound by any theory investors have surprisingly found that dutasteride, which is highly sensitive to acid and base which is stabilized by acidic environment.

 In one of the embodiment lactic acid is preferable acidifying agents. Lactic acid has the
30 ability to exfoliate the scalp and remove build-up. Lactic acid can also help to increase hair elasticity, making it less likely to break. Lactic acid has humectant properties, which means it helps to draw moisture into the hair shaft and promotes healthy hydration levels that help to prevent dryness and frizziness.

In one aspect, the formulation of the invention contains a thickening agent (viscosity agent) to provide viscosity so that the formulation may be provided in the form of a solution, serum, lotion, gel, cream, or ointment. Preferably but not necessarily, the thickening agent is miscible or soluble in an aqueous fluid. Examples of suitable thickening agents include acacia, alginic acid, bentonite, carbomers, also known as carboxy vinyl polymers, such as sold under the tradename Carbopol® (Lubrizol, Wickliffe, Ohio), carboxymethylcellulose, ethylcellulose, Sepineo P 600 (Acrylamide / Sodium Acryloyldimethyl Taurate Copolymer / Isohexadecane & Polysorbate 80) polymer, which is pH independent thickening agent gelatin, hydroxyethylcellulose, hydroxypropyl cellulose, magnesium aluminum silicate, methylcellulose, poloxamers, polyvinyl alcohol, sodium alginate, tragacanth, and xanthan gum. The thickening agent may also reside in the oil or lipophilic portion of the formulation. Examples of suitable lipophilic thickening agents include cetyl alcohol, stearyl alcohol, glyceryl stearate, white beeswax, microcrystalline wax, hydrogenated polyisobutane polymers, and emulsifying wax. The thickening agent may be present in an amount of between about 0.1% w/w to about 20% w/w, preferably about 1% w/w to about 15%, most preferably about 2% w/w to about 10% w/w.

In one of the aspect viscosity agent is cyclopentasiloxane, polysilicone-11, C₃₀₋₄₅ alkyl cetearyl dimethicone crosspolymer, dimethiconol, phenyl trimethicone, PEG PPG dimethicone, cyclomethicon and simethicone.

In some aspects, if desired or required in order to obtain the form of the formulation desired, a surfactant or emulsifier may be included. The emulsifier is preferably a non-ionic emulsifier such as a sorbitan ester, a polyoxyethylene derivative of a sorbitan ester or a glyceryl ester; a polymeric emulsifier such as a acrylates/C10-C30 alkyl acrylate crosspolymer such as those sold under the tradename PEMULEN® (The Lubrizol Corporation, Wickliffe, Ohio); or an anionic emulsifier such as an alkali soap such as sodium or potassium oleate, an amine soap such as triethanolamine stearate, a detergent such as sodium lauryl sulfate, sodium dioctyl sulfosuccinate, and sodium docusate. Less preferred are cationic emulsifiers such as quaternary ammonium salts. Particular examples of suitable anionic and non-ionic emulsifiers include glyceryl monostearate, polyoxyethylene monooleate, polyoxyethylene monostearate, polyoxyethylene monolaurate, potassium oleate, sodium lauryl sulfate, sodium oleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, triethanolamine oleate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan tristearate, polyoxyethylene sorbitan monooleate, and

polyoxyethylene sorbitan trioleate. The surfactant or emulsifier may be present in an amount of between about 0.1% w/w to about 50% w/w or about 0.5% w/w to about 40%, preferably about 1% w/w to about 15%, most preferably about 2% w/w to about 10% w/w.

The formulation may contain other pharmaceutically acceptable excipients, preferably, the formulation contains a humectant such as glycerin, sorbitol, hexylene glycol, urea, or propylene glycol. Preferably, the formulation contains an emollient such as petrolatum, lanolin, mineral oil, light mineral oil, stearic acid, cyclomethicone, or dimethicone. pH adjusting agents such as sodium hydroxide, chelating agents such as EDTA and its salts, and buffers.

The formulation of the invention may be made by any method known to make a uniphase or multiphase pharmaceutical formulation for topical administration. In order to make a multiphase formulation such as an emulsion, for example, the components of the aqueous phase and of the oil phase may be separately combined and mixed until homogenous solutions are obtained and then the aqueous solution and the oil solution may be combined and mixed, such as by shear mixing, to form the formulation. The oil phase may be added to the water phase, or the water phase may be added to the oil phase. The phases may be combined and mixed, such as at elevated temperatures of 35-90° C. or at room temperature, that is between 20-30° C., or at a temperature between room temperature and the elevated temperatures.

In one of the embodiment composition according to invention comprises a. dutasteride b. minoxidil, and c. a pharmaceutically acceptable carrier comprising water, one or more penetration enhancer(s), one or more solubilizer(s), one or more stabilizer(s) or a mixture thereof; wherein the pharmaceutically acceptable carrier is nonirritant upon application to the surface of the skin or scalp of a recipient, the active agent penetrates the dermal layer of the skin and with minimal systemic blood levels.

In one embodiment invention relates to a topical composition comprising: a. dutasteride b. minoxidil, and c. a pharmaceutically acceptable carrier comprising water, one or more penetration enhancer(s), one or more solubilizer(s), one or more stabilizer(s) or a mixture thereof; wherein said composition is substantially free from systemic blood levels.

In one of the embodiment composition according to invention relates to a topical composition comprising active ingredients consisting of: a. dutasteride, at a concentration of about 0.05% w/w of the composition; b. minoxidil at a concentration of about 5% w/w by weight of the composition, and c. a pharmaceutically acceptable carrier; wherein the composition is a aqueous solution; wherein solution comprises a solvent; and wherein the composition comprising the dutasteride, and minoxidil at said concentrations is capable of

providing synergistic efficacy and synergistic reduction of at least an adverse event associated with either of dutasteride and minoxidil.

In another embodiment sol-gel technology in particular is thermoreversible gels. Use of an aqueous liquid which can be applied at room temperature as a liquid, but which forms a semisolid gel when warmed to body temperature, has been utilized as a vehicle for drug delivery since such a system combines ease of application with greater retention at the site requiring treatment than would be the case if the aqueous composition were not converted to a gel.

The useful polymers which provide the sol-gel characteristics of the pharmaceutical compositions of the invention are, preferably, ethylene oxide/propylene oxide triblock copolymer. A preferred family of hydrogel polymers is group of tri-block copolymers designated as PEG-PPG-PEG (PEG = Polyethylene glycol and PPG = Polypropylene glycol) and called Poloxamers, which produces reverse thermal gelation compositions, i.e., with the characteristic that their viscosity increases with increasing temperature up to a point from which viscosity again decreases.

In particular, Poloxamer 407 possesses a gelling temperature which is above 10° C. but below the human body temperature, i.e., 37° C. This characteristic has allowed Poloxamer 407 (PF-127) to be used as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes. Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene triblock copolymers in a concentration ranging from 20-30%. At low concentrations (10-4 \-10-5%) they form monomolecular micelles, but higher concentrations result in multimolecular aggregates consisting of a hydrophobic central core with their hydrophilic polyoxyethylene chains facing the external medium. Micellization occurs in dilute solutions of block copolymers in selected solvents above the critical micellar concentration, at a given temperature. At higher concentrations, above a critical gel concentration, the micelles can order into a lattice.

Aqueous solutions of poloxamers are stable in the presence of acids, alkalis, and metal ions. Commonly used poloxamers include the 88 (F-68 grade), 237 (F-87 grade), 338 (F-108 grade) and 407 (F-127 grade) types, which are freely soluble in water. The "F" designation refers to the flake form of the product. PF-127 has a good solubilizing capacity, low toxicity and is, therefore, considered a good carrier for topical drug delivery.

PF-127 is a commercially available polyoxyethylene-polyoxypropylene triblock copolymer that possesses a general formula E101 P56 E101, with an average molar mass of 13,000. It contains approximately 70% ethylene oxide, which accounts for its hydrophilicity. It is one of the series of poloxamer ABA block copolymers. As said above, PF-127 aqueous

solutions of 20 to 30% w/w have the interesting characteristic of reverse thermal gelation, i.e., they are liquid at refrigerated temperatures (4-5° C.), but gel upon warming to room temperature. The gelation is reversible upon cooling. This phenomenon, therefore, suggests that when poured onto the skin, the gel preparation will form a solid artificial barrier and a sustained
5 release depot. Furthermore, PF-127 has been reported to be the least toxic of commercially available copolymers.

In one of the embodiment poloxamer polymers are present, preferably, in the amount of about 1 to about 10% w/w. If desired, the drug delivery vehicle may also contain preservatives, co-solvents, suspending agents, viscosity enhancing agents, osmolality adjusters, colouring
10 agents, and other excipients in addition to the medicament and buffering agents. Suitable water soluble preservatives which may be employed in the drug delivery vehicle are sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric borate, parabens, benzyl alcohol and phenyl ethanol, and others. These agents may be present in amounts of about 0.001% to about 5% by weight and, preferably, in the
15 amount of about 0.01 to about 2% by weight.

In a preferred embodiment, the compositions of the invention can be delivered to the area of the application requiring a low viscosity liquid at ambient temperatures which, upon contact with the subject body, forms a semisolid gel having a high viscosity.

In one embodiment amounts of an ethylene oxide/propylene oxide block copolymer
20 effective to produce a composition of sufficiently low viscosity at room temperature to be dispensed from dispensing device or applicator to the area of scalp. At body temperature, the material exhibits a much higher viscosity and will stably adhere to the scalp. As the material dissolves, a therapeutic agent incorporated therein is slowly released to hair follicles.

In one of the embodiment of the present invention, the use of a thermoreversible
25 hydrogel composition for delivery of a therapeutic agent to the for the treatment of hair loss and/or stimulating hair growth, is characterized in that said thermoreversible hydrogel composition comprises a thermoreversible hydrogel characterized by: a viscosity of less than 200 Pa·s over a temperature range of 4° C to 12° C.; a viscosity of greater than 10³ Pa·s at 37° C.

30 In one of the embodiment of the present invention, the use of a thermoreversible hydrogel composition for delivery of a therapeutic agent to the for the treatment of hair loss and/or stimulating hair growth, is characterized in that said thermoreversible hydrogel composition comprises a thermoreversible hydrogel characterized by: a viscosity of less than 50 cP over a temperature range of 5° C to 25° C. In one particular embodiment viscosity is less

than 30 cP. In one particular embodiment viscosity is less than 20 cP. In one particular embodiment viscosity is less than 10 cP. In one particular embodiment viscosity is of about 5 cP to less than 15 cP. In one embodiment the composition flowable liquid or solution composition, wherein such composition uses hydrogel, in particular thermoreversible hydrogel such as one or more poloxamer.

It one of the embodiment of the present invention, the use of a thermoreversible hydrogel composition for delivery of a therapeutic agent to the for the treatment of hair loss and/or stimulating hair growth, is characterized in that said thermoreversible hydrogel composition comprises a thermoreversible hydrogel characterized by: a viscosity of less than 5 Pa·s over a temperature range of 4° C. - 12° C.; a viscosity of greater than 10^3 at 37° C.

In some embodiments of the invention, said thermoreversible hydrogel is further characterized by a viscosity of less than 5 Pa·s over a temperature range of 4° C. - 12° C. In some embodiments of the invention, the said thermoreversible hydrogel is further characterized by a viscosity of less than 0.5 Pa·s over a temperature range of 4° C. - 12° C. In some embodiments of the invention, the thermoreversible hydrogel is further characterized by a viscosity of greater than 3×10^3 at 37° C.

In one of the embodiment, the present invention to disclose a hydrophilic sustained-release material comprising poloxamer in amounts effective to produce a hydrogel composition of sufficiently low viscosity at room temperature to be applied to the scalp.

In one of the embodiment composition according to invention relates to a topical composition comprising active ingredients consisting of: a. dutasteride, at a concentration of about 0.05% w/w of the composition; b. minoxidil at a concentration of about 5% w/w by weight of the composition and c. a pharmaceutically acceptable carrier; wherein the composition is a aqueous solution; wherein solution comprises a solvent; and wherein the composition comprising the dutasteride and minoxidil at said concentrations is capable of providing synergistic efficacy and synergistic reduction of at least an adverse event associated with either of dutasteride and minoxidil.

In one of the embodiment composition according to invention comprises a composition for treatment of alopecia and/or promoting hair regrowth, said composition comprising: (a) at least one therapeutic agent selected from a 5α -reductase inhibitor and vasodilator; (b) at least one solubilizer; (c) water, and wherein said composition is substantially free from greasiness.

In one of the embodiment composition according to invention, comprises a composition suitable for preventing hair loss and / or stimulating hair growth, comprising: (a) active agent comprising: (i) minoxidil from about 2% w/w to about 7% w/w, (ii) dutasteride from about 0.02

to about 0.07% w/w, and (b) a means for solubilization of one or more active agent to provide sufficient solution state stability, wherein the composition provides pH of about 3 to about 7.

In one aspect of above embodiment, the means for solubilization comprises one or more solvents, one or more solubilizer, one or more crystal growth inhibitor.

5 In one aspect of above embodiment, the solvent is selected from ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol monobutyl ether, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol, N-methylpyrrolidone and N-methylcaprolactam, dimethylsulfoxide (DMSO), tocopheryl polyethylene glycol succinate (TPGS),
10 dimethylformamide (DMF), dimethylacetamide (DMA), capryl-caproyl macrogol 8-glyceride

In one aspect of above embodiment, the solubilizer is selected from one or more of glycerol, aliphatic alcohols or aromatic alcohols containing 4 or more carbon atoms, polyoxyl castor oil, polyoxyl hydrogenated castor oil, cyclodextrin, ethylene vinyl acetates, polyvinyl alcohol, povidone, copovidone or any combination of any of the foregoing or any combinations
15 thereof.

In one aspect of above embodiment, the stabilizer or antioxidant is selected from sodium sulfite, sodium thiosulfate, tocopherol or its derivative such as dl-alfa tocopherol, sodium metabisulfite, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate.

20 In one aspect of above embodiment, the crystal growth inhibitor is selected from is glycol or its derivatives, selected from ethylene glycol, polyethylene glycol, propylene glycol, dipropylene glycol, butylene glycol, pentylene 20 glycol, hexylene glycol, propylene glycol dipelargonate, diethylene glycol monoethyl ether, propylene laurate glycol dicaprylate dicaprate propylene glycol, and diethylene glycol monoethyl ether.

25 In one aspect of above embodiment, composition further comprises acidifying agent selected from citric acid, citric acid anhydrous, citric acid monohydrate, DL-lactic acid, DL-malic acid, DL-tartaric acid, fumaric acid, L-malic acid, L-tartaric acid, salicylic acid, glycol acid, potassium acid tartrate, potassium citrate, potassium DL-bitartrate, potassium gluconate, sodium lactate, sodium L-tartrate, sodium citrate, ascorbic acid, sorbic acid, methane sulfonic
30 acid, or any combinations thereof.

In one aspect of above embodiment, composition further comprises thermoreversible polymer.

In one of the embodiment composition according to invention, comprises a composition suitable for preventing hair loss and / or stimulating hair growth, comprising: (a) active agent

comprising: (i) minoxidil from about 2% w/w to about 7% w/w, (ii) dutasteride from about 0.02 to about 0.07% w/w, and (b) acidifying agent wherein the ratio of said active agents to acidifying agent is in the range of about 1:0.1 to about 1:0.4.

In one aspect of the above embodiment, the ratio of dutasteride to acidifying agent is in
5 the range of about 1:10 to about 1:40.

In one of the embodiment composition according to invention, comprises a composition suitable for preventing hair loss and / or stimulating hair growth, comprising: (a) active agent comprising: (i) minoxidil from about 2% w/w to about 7% w/w, (ii) dutasteride from about 0.02 to about 0.1% w/w, (b) a means for solubilization of one or more active agent to provide
10 sufficient solution state stability, wherein the composition provides pH of about 3 to about 7.

In one aspect of above embodiment, the means for solubilization comprises one or more solvents, one or more solubilizer, one or more crystal growth inhibitor.

In one aspect of above embodiment, the solvent is selected from ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol monobutyl ether,
15 diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol, N-methylpyrrolidone and N-methylcaprolactam, dimethylsulfoxide (DMSO), tocopheryl polyethylene glycol succinate (TPGS), dimethylformamide (DMF), dimethylacetamide (DMA), capryl-caproyl macrogol 8-glyceride.

In one aspect of above embodiment, the solubilizer is selected from one or more of
20 glycerol, aliphatic alcohols or aromatic alcohols containing 4 or more carbon atoms, polyoxyl castor oil, polyoxyl hydrogenated castor oil, cyclodextrin, ethylene vinyl acetates, polyvinyl alcohol, povidone, copovidone or any combination of any of the foregoing or any combinations thereof.

In one aspect of above embodiment, the crystal growth inhibitor is selected from is
25 glycol or its derivatives, selected from ethylene glycol, polyethylene glycol, propylene glycol, dipropylene glycol, butylene glycol, pentylene 20 glycol, hexylene glycol, propylene glycol dipelargonate, diethylene glycol monoethyl ether, propylene laurate glycol dicaprylate dicaprate propylene glycol, and diethylene glycol monoethyl ether.

In one aspect of above embodiment, composition further comprises acidifying agent
30 selected from citric acid, citric acid anhydrous, citric acid monohydrate, DL-lactic acid, DL-malic acid, DL-tartaric acid, fumaric acid, L-malic acid, L-tartaric acid, salicylic acid, glycolic acid, potassium acid tartrate, potassium citrate, potassium DL-bitartarate, potassium gluconate, sodium lactate, sodium L-tartrate, sodium citrate, ascorbic acid, sorbic acid, methane sulfonic acid, or any combinations thereof.

In one aspect of above embodiment, composition further comprises thermoreversible polymer.

In one of the embodiment composition according to invention, comprises a composition suitable for preventing hair loss and / or stimulating hair growth, comprising: (a) active agent
5 comprising: (i) minoxidil from about 2% w/w to about 7% w/w, (ii) dutasteride from about 0.02 to about 0.07% w/w (b) acidifying agent wherein the ratio of said active agents to acidifying agent is in the range of about 1:0.1 to about 1:0.4.

In one aspect of the above embodiment, the ratio of dutasteride to acidifying agent is in the range of about 1:10 to about 1:40.

10 In one of the embodiment composition according to invention comprises a composition for treatment hair loss and/or promoting hair growth, the composition comprising: a. dutasteride, at a concentration of about 0.05% w/w of the composition; b. minoxidil at a concentration of about 5% w/w by weight of the composition, and c. a pharmaceutically acceptable carrier; wherein the composition comprises a means for penetration of at least
15 dutasteride or minoxidil.

In one of the embodiment composition according to invention comprises a composition for treatment hair loss and/or promoting hair growth, the composition comprising: (a) active ingredients consisting of: (i) dutasteride, at a concentration of about 0.05% w/w of the composition; (ii) minoxidil at a concentration of about 5% w/w by weight of the composition,
20 and (b) a pharmaceutically acceptable carrier; wherein the composition is a solution.

In one of the embodiment composition according to invention comprises a composition for treatment hair loss and/or promoting hair growth, the composition comprising: (a) active ingredients consisting of: (i) dutasteride, at a concentration of about 0.05% w/w of the composition; (ii) minoxidil at a concentration of about 5% w/w by weight of the composition,
25 and (b) a pharmaceutically acceptable carrier; wherein the composition is a dispersion.

In one of the embodiment invention comprises composition for treatment of alopecia and/or promoting hair regrowth, said composition comprising: (a) at least one therapeutic agent selected from a 5-alpha reductase inhibitors and a vasodilator; (b) at least one solvent; (c) a viscosity agent; (d) water, and wherein said composition is substantially free from alcohol and
30 propylene glycol.

In one of the embodiment composition according to the invention comprises solution formulation comprising of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; diethylene glycol monoethyl ether at about 5.0-50.0% w/w; glycerin at about 1.0-10.0% w/w; lactic acid at about 0.5-2.0% w/w; polysorbate 60 at about 0.2-2.0% w/w; benzyl

alcohol at about 0.5-3.0% w/w; purified water at about 15-30.0% w/w; and isopropyl alcohol to 100% w/w.

In one of the embodiment composition according to the invention comprises thermoreversible sol-gel spray formulation comprising of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; diethylene glycol monoethyl ether at about 5.0-50.0% w/w; poloxamer at about 1.0-5.0% w/w; glycerin at about 1.0-10.0% w/w; lactic acid at about 0.5-2.0% w/w; polysorbate 60 at about 0.2-2.0% w/w; benzyl alcohol at about 0.5-3.0% w/w; purified water to 100% w/w.

In one of the embodiment composition according to the invention comprises foam formulation of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; diethylene glycol monoethyl ether at about 5.0-50.0% w/w; glycerin at about 1.0-10.0% w/w; lactic acid at about 0.5-2.0% w/w; polysorbate 60 at about 0.2-2.0% w/w; benzyl alcohol at about 0.5-3.0% w/w; cetyl alcohol at about 0.5-2.5% w/w; stearyl alcohol at about 0.2-1.5% w/w; purified water at about 20-50% w/w and propellant (NIP-70) of about 1.0-5.0gm/60gm can.

In one of the embodiment composition according to the invention comprises microsphere formulation of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; anhydrous citric acid at about 0.01-0.1% w/w; cetrimonium chloride at about 0.05-0.5% w/w; cetyl alcohol at about 1-5% w/w; cyclomethicone at about 1-5% w/w; edetate disodium at about 0.01-0.2% w/w; glycerin at about 1.0-10.0% w/w; diethylene glycol monoethyl ether at about 5.0-50.0% w/w; lactic acid at about 0.5-2.0% w/w; macrogol stearate type I at about 1.0-5.0% w/w; mono and di-glycerides at about 1.0-10.0% w/w; phenoxyethanol at about 0.5-5.0% w/w; silicon dioxide at about 2.0-10.0% w/w; polyquaternium-7 at about 0.5-5.0% w/w; sodium hydroxide for pH adjustment; purified water to 100% w/w.

In one of the embodiment composition according to the invention comprises solution formulation comprising of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; diethylene glycol monoethyl ether at about 5.0-50.0% w/w; glycerin at about 1.0-10.0% w/w; lactic acid at about 0.5-2.0% w/w; polysorbate 60 at about 0.2-2.0% w/w; benzyl alcohol at about 0.5-3.0% w/w; purified water at about 15-40.0% w/w; and isopropyl alcohol to 100% w/w.

In one of the embodiment composition according to the invention comprises thermoreversible sol-gel spray formulation comprising of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; diethylene glycol monoethyl ether at about 5.0-50.0% w/w; poloxamer at about 1.0-5.0% w/w; glycerin at about 1.0-10.0% w/w; lactic acid at about

0.5-2.0% w/w; polysorbate 60 at about 0.2-2.0% w/w; benzyl alcohol at about 0.5-3.0% w/w; purified water to 100% w/w.

In one of the embodiment composition according to the invention comprises foam formulation of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; diethylene glycol monoethyl ether at about 5.0-50.0% w/w; glycerin at about 1.0-10.0% w/w; lactic acid at about 0.5-2.0% w/w; polysorbate 60 at about 0.2-2.0% w/w; benzyl alcohol at about 0.5-3.0% w/w; cetyl alcohol at about 0.5-2.5% w/w; stearyl alcohol at about 0.2-1.5% w/w; purified water at about 20-50% w/w and propellant (NIP-70) of about 1.0-5.0gm/60gm can.

In one of the embodiment composition according to the invention comprises microsphere formulation of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; anhydrous citric acid at about 0.01-0.1% w/w; cetrimonium chloride at about 0.05-0.5% w/w; cetyl alcohol at about 1-5% w/w; cyclomethicone at about 1-5% w/w; edetate disodium at about 0.01-0.2% w/w; glycerin at about 1.0-10.0% w/w; diethylene glycol monoethyl ether at about 5.0-50.0% w/w; lactic acid at about 0.5-2.0% w/w; macrogol stearate type I at about 1.0-5.0% w/w; mono and di-glycerides at about 1.0-10.0% w/w; phenoxyethanol at about 0.5-5.0% w/w; silicon dioxide at about 2.0-10.0% w/w; polyquaternium-7 at about 0.5-5.0% w/w; sodium hydroxide for pH adjustment; purified water to 100% w/w.

In one of the embodiment composition according to the invention comprises solution formulation comprising of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; diethylene glycol monoethyl ether at about 15.0-35.0% w/w; glycerin at about 1.0-10.0% w/w; lactic acid at about 0.5-2.0% w/w; phenoxyethanol at about 0.2-2.0% w/w; dl-alfa tocopherol acetate at about 0.001- 0.01% w/w; isopropyl alcohol at about 10-30% w/w; polyoxyl 40 hydrogenated castor oil at about 0.1-5% w/w; hexylene glycol at about 5-20% w/w; poloxamer at about 0.1-5%; purified water to 100% w/w.

In one of the embodiment composition according to the invention comprises solution formulation comprising of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; diethylene glycol monoethyl ether at about 10.0-50.0% w/w; glycerin at about 1.0-10.0% w/w; lactic acid at about 0.5-2.0% w/w; phenoxyethanol at about 0.2-2.0% w/w; dl-alfa tocopherol acetate at about 0.001- 0.01% w/w; isopropyl alcohol at about 15-40% w/w; polyoxyl 40 hydrogenated castor oil at about 0.1-5% w/w; hexylene glycol at about 5-20% w/w; poloxamer at about 0.1-5%; purified water to 100% w/w.

In one of the embodiment composition according to the invention comprises solution formulation comprising of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to

5.0% w/w; diethylene glycol monoethyl ether at about 15.0-35.0% w/w; glycerin at about 1.0-10.0% w/w; lactic acid at about 0.5-2.0% w/w; phenoxyethanol at about 0.2-2.0% w/w; dl-alfa tocopherol acetate at about 0.001- 0.01% w/w; isopropyl alcohol at about 10-30% w/w; polyoxyl 40 hydrogenated castor oil at about 0.1-5% w/w; hexylene glycol at about 5-20% w/w; poloxamer at about 0.1-5%; purified water to 100% w/w.

In one of the embodiment composition according to the invention comprises solution formulation comprising of dutasteride at about 0.01 to 0.05% w/w; minoxidil at about 2.0 to 5.0% w/w; diethylene glycol monoethyl ether at about 10.0-50.0% w/w; glycerin at about 1.0-10.0% w/w; lactic acid at about 0.5-2.0% w/w; phenoxyethanol at about 0.2-2.0% w/w; dl-alfa tocopherol acetate at about 0.001- 0.01% w/w; isopropyl alcohol at about 15-40% w/w; Polyoxyl 40 hydrogenated castor oil at about 0.1-5% w/w; hexylene glycol at about 5-20% w/w; poloxamer at about 0.1-5%; purified water to 100% w/w.

In one of the aspect invention pertain to reduce the amount of at least one of the active that is available to enter the systemic circulation following the topical administration of dutasteride, and minoxidil.

In some aspects concentrations of minoxidil is at the same level, that is at 2% w/w or 5% w/w, 10% w/w, 15% w/w or 20% w/w.

In some aspects concentrations of minoxidil is at the same level, that is at 2% w/w or 5% w/w or higher with further reduction of at least one of the side effect associated with minoxidil compared to same concentration of minoxidil in comparative composition.

In some aspects concentrations of minoxidil is at the same level, that is at 2% w/w or 5% w/w or higher with further enhancement of efficacy compared to same concentration of minoxidil in comparative composition and simultaneous reduction of at least one of the side effect associated with minoxidil compared to same concentration of minoxidil in comparative composition.

Example-1: Dutasteride + Minoxidil Cream

Ingredients	% w/w
Dutasteride	0.05
Minoxidil	5.0
Anhydrous citric acid	0.05
Cetrimonium chloride	0.1
Cetyl alcohol	3.0
Cyclomethicone	1.5

Ingredients	% w/w
Edetate disodium	0.05
Glycerin	5.0
Diethylene glycol monoethyl ether	40
Lactic acid	1.0
Macrogol stearate Type I	3.0
Mono and di-glycerides	5.0
Phenoxyethanol	1.0
Silicon dioxide	3.4
Polyquaternium-7	1.0
Sodium hydroxide	Q.S to pH
Purified water	Q.S to 100%

Manufacturing process: Oil phase is prepared by mixing cetyl alcohol, cyclomethicone, macrogol stearate type I, mono and di-glycerides, phenoxyethanol in SS vessel and heated. Separately, to SS vessel added diethylene glycol monoethyl ether, purified water, anhydrous

5 citric acid, glycerin, lactic acid, disodium EDTA and heated; minoxidil is added to above phase under stirring to get the clear drug phase. Separately, solution of sodium hydroxide is prepared in purified water. Separately dutasteride microspheres prepared by loading in silicon base, polyquaternium-7 microspheres. Minoxidil drug phase is transferred to main manufacturing vessel; oil phase is transferred in to main manufacturing vessel under homogenization and

10 homogenize is carried out; dutasteride microspheres are added in to above phase under homogenization; mixture is cooled under stirring; pH of cream adjusted with sodium hydroxide solution if required.

Example-2: Dutasteride + Minoxidil Thermoreversible Spray

Ingredients	% w/w
Dutasteride	0.05
Minoxidil	5.0
Diethylene glycol monoethyl ether	40.00
Poloxamer	5.00
Glycerin	2.00
Lactic acid	1.10
Polysorbate 60	0.42

Ingredients	% w/w
Benzyl alcohol	1.00
Purified water	45.40

Manufacturing process: To SS vessel added diethylene glycol monoethyl ether, glycerin, lactic acid, polysorbate 60, and benzyl alcohol and purified water and heated; to this minoxidil is added and dissolved under stirring; minoxidil drug phase is cooled; dutasteride is added and dissolved in to above phase under stirring. To a separate SS vessel purified water is added; to this added Poloxamer under stirring to get uniform lump free dispersion of gel; to this gel phase, drug phase is added under stirring and mixed.

Example-3: Dutasteride + Minoxidil Foam

Ingredients	% w/w
Dutasteride	0.05
Minoxidil	5.00
Diethylene glycol monoethyl ether	40.0
Glycerin	2.00
Lactic Acid	1.10
Polysorbate 60	0.42
Benzyl Alcohol	1.0
Purified Water	48.71
Cetyl Alcohol	1.16
Stearyl Alcohol	0.53
Propellant (NIP-70)	3.0gm/60gm can

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Manufacturing process: To SS vessel added diethylene glycol monoethyl ether, glycerin, lactic acid, polysorbate 60, and benzyl alcohol and purified water and purified water; cetyl alcohol is added to this phase under stirring to get clear phase; stearyl alcohol is added under stirring to get clear phase; to this minoxidil is added under stirring; the phase is allowed to cool under stirring; dutasteride is added and dissolved in to above phase under stirring. Mixing is carried out under stirring. Aluminum cans were filled with the pre-foam, finally the crimping of filled can and filling of Propellant (NIP-70) carried out.

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Example-4: Dutasteride + Minoxidil solution

Ingredients	% w/w
Dutasteride	0.05
Minoxidil	5.0
diethylene glycol monoethyl ether	40.00
Glycerin	2.0
Lactic Acid	1.10
Polysorbate 60	0.42
Benzyl Alcohol	1.00
Purified Water	10.00
Isopropyl Alcohol	40.43

Manufacturing process: Drug phase of minoxidil is prepared by adding to mixture of diethylene glycol monoethyl ether, glycerin, lactic acid, polysorbate 60, benzyl alcohol and purified water under stirring at temperature 45-55°C, allowed to cool to temperature; isopropyl alcohol is added to minoxidil drug phase and then dutasteride is added. Mixing is carried out under stirring to get clear solution.

Example-5: Dutasteride + Minoxidil solution

Ingredients	% w/w
Dutasteride	0.05
Minoxidil	5.0
Diethylene glycol monoethyl ether	25.00
Glycerin	5.0
Lactic acid	1.40
Phenoxyethanol	1.0
DL-Alfa tocopherol acetate	0.002
Isopropyl alcohol	20.0
Polyoxyl 40 hydrogenated castor oil	1.0
Hexylene glycol	10.0
Poloxamer	2.0
Purified Water	29.52

Manufacturing process: Purified water, part of quantity of diethylene glycol monoethyl ether, glycerin, lactic acid, polyoxyl 40 hydrogenated castor oil, phenoxyethanol and hexylene glycol were mixed and heated. Minoxidil was added under stirring. Separately dutasteride drug phase was prepared by adding it to part of diethylene glycol monoethyl ether under stirring and added in to minoxidil drug phase under stirring. Vitamin E acetate in part of isopropyl alcohol was mixed under stirring and added to minoxidil phase and mixed. Remaining quantity of isopropyl alcohol is added to get clear colorless to pale yellow solution. Poloxamer was added under stirring in to above phase and mixed to get clear colorless to pale yellow solution.

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Example-6: Dutasteride + Minoxidil solution

Ingredients	% w/w
Dutasteride	0.05
Minoxidil	5.0
Diethylene glycol monoethyl ether	40.00
Glycerin	5.0
Lactic Acid	1.40
Phenoxyethanol	1.0
DL-Alfa tocopherol acetate	0.002
Isopropyl Alcohol	30.0
Polyoxyl 40 hydrogenated castor oil	1.0
Hexylene Glycol	5.0
Poloxamer	2.0
Purified Water	9.5

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Manufacturing process: Purified water, part of quantity of diethylene glycol monoethyl ether, glycerin, lactic acid, polyoxyl 40 hydrogenated castor oil, phenoxyethanol and hexylene glycol. Minoxidil was added under stirring to above phase. Separately dutasteride drug phase was prepared by adding to part of diethylene glycol monoethyl ether under stirring and added to dutasteride drug phase. Vitamin E acetate in part of isopropyl alcohol was mixed under stirring and added into minoxidil drug phase. Remaining quantity of isopropyl alcohol is added to above phase under stirring. Poloxamer was added under stirring in to above phase and mixed to get clear colorless to pale yellow solution.

Example-7: The stability study results of Example 6 at 25 °C/60% RH & 40 °C/75% RH is shown in Table-1.

Table-1:

Storage condition	Period	Description	% Assay of Dutasteride	% Assay of Minoxidil	Specific gravity	Viscosity	pH
Stability specification		Clear colorless to pale yellow solution	90-110%	90-110%	0.8-1.2	1-20cP	3.0-7.0
-	Initial	Clear colorless to pale yellow solution	99.95	102.3	0.06	9.42	5.89
25 °C/60% RH	1M		99.0	101.9	0.94	9.40	5.97
	2M		99.8	101.5	0.94	9.60	5.94
	3M		98.8	101.6	0.95	9.64	5.95
	6M		99.8	100.2	0.95	9.34	5.92
40 °C/75% RH	1M		100.5	103.2	0.94	9.42	5.92
	2M		99.6	100.4	0.94	9.38	5.99
	3M		97.7	101.5	0.94	9.62	5.98
	6M		99.9	100.6	0.95	9.24	6.01

- 5 The stability study results impurity profile of Example 6 – minoxidil component at 25 °C/60% RH & 40 °C/75% RH is shown in Table-2.

Table-2:

		Related substances of Minoxidil				
		Pyrimidine oxide analog (Impurity A)	Pyrimidine analog (Impurity B)	Deoxyminoxidil (Impurity E)	Single max impurity	Total impurities
Specification		-	-	-	Not more than 0.5%	Not more than 3%
25 °C/60% RH	Initial	ND	ND	BLQ (<0.01)	0.01	0.01
	1M	0.05	ND	BLQ (<0.01)	0.04	0.12
	2M	ND	ND	ND	0.02	0.03
	3M	BLQ (<0.01)	ND	ND	0.02	0.06
	6M	ND	ND	0.01	0.04	0.07
40 °C/75% RH	1M	0.04	ND	BLQ (<0.01)	0.04	0.15
	2M	ND	ND	ND	0.05	0.09
	3M	0.01	ND	ND	0.05	0.13
	6M	ND	ND	0.01	0.08	0.14

ND: Not detected

BLQ: below limit of quantification

The stability study results impurity profile of Example 6 – dutasteride component at 25 °C/60% RH & 40 °C/75% RH is shown in Table-3.

Table-3:

Related substances of Dutasteride														
		Impurity A	Impurity B	Impurity C	Impurity D	Impurity E	Impurity F	Impurity G	B-Isomer	Impurity H	Impurity I	Dihydro dutasteride	Highest individual unspecified impurity	Total impurities
Specification		-	-	-	-	-	-	-	-	-	-	-	Not more than 1%	Not more than 3%
Initial	-	ND	ND	0.05	ND	ND	ND	ND	ND	ND	ND	ND	0.17	0.34
25 °C/60% RH	1M	ND	ND	0.05	ND	ND	ND	ND	ND	ND	ND	ND	0.022	0.076
	2M	ND	ND	0.03	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.03
	3M	ND	ND	0.06	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.06
	6M	ND	ND	0.06	ND	ND	ND	ND	ND	ND	ND	ND	0.10	0.16
40 °C/75% RH	1M	ND	ND	0.04	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.04
	2M	ND	ND	0.06	ND	ND	ND	ND	ND	ND	ND	0.02	0.06	0.18
	3M	ND	ND	0.04	ND	ND	ND	ND	ND	ND	ND	0.03	ND	0.07
	6M	ND	ND	0.05	ND	ND	ND	ND	ND	ND	ND	0.03	ND	0.07

5

Example-8: Animal Dermal toxicity study

A study was conducted to determine the dermal concentration, plasma concentration, dermal irritation and sensitization potential dutasteride and minoxidil formulation according to the present invention as per Example 6.

A. 14-day dermal toxicity study with dutasteride + minoxidil topical solution in rats.

10 Study design:

Test species: Male Sprague Dawley Rats

Table-4: Treatment & dose

Treatment arm	Dose
Placebo of topical solution	-
Dutasteride 0.05% + minoxidil 5% topical solution	14-day: 1x & 5x dose
Dutasteride 0.05% topical solution	14-day: 5x clinical dose
Minoxidil 5% topical solution	14-day: 5x clinical dose

15 Exposure: Test formulation and Placebo were applied to 10% body surface area (BSA) of hair clipped rats. Exposure period was 6 hours/day.

Parameters: Formulation was evaluated for toxicology parameters (Plasma: Day 1, 14, 30 and 90; Skin: Day 14 and 90) and histopathology of application site. Additionally, skin reactions scoring for edema/erythema everyday post exposure were evaluated.

20 Results: No local site reactions or any clinical signs was noticed. No treatment-related effect on body wt., hematology, clinical chemistry, organ wt. & gross pathology was observed. No

histopathology findings at the application site & in any tissues/organs up to 5x the maximum recommended human dose (MRHD) was observed.

Below are the AUC, $C_{\max}$ and Skin concentration parameters at the NOAEL (no observed adverse effect level) dose of 0.25/25 mg/kg/day of Dutasteride + Minoxidil topical solution (Table-5).

Table-5:

Analyte	Parameters	Day 14
Dutasteride 0.25 mg/kg	AUC (h.ng/mL)	41.197
	$C_{\max}$ (ng/mL)	1.925
	Skin Conc (ng/g)	134
Minoxidil 25 mg/kg	AUC (h.ng/mL)	126.06
	$C_{\max}$ (ng/mL)	34.5
	Skin Conc (ng/g)	9042

In 14-Day dermal study in rats, the NOAEL doses were 0.25/25 mg/kg/day of Dutasteride + Minoxidil topical solution (5x the MRHD [1 ml applied OD] on mg/m² basis).

Plasma exposure of dutasteride was low and plasma exposure of Minoxidil was higher compared to dutasteride. Skin concentration at application site for all dutasteride (~70 fold), Minoxidil (~260 fold), were significantly higher compared to their plasma exposure. Higher skin concentration was not associated local dermal toxicity.

B. 14-day dermal toxicity study with dutasteride + minoxidil topical solution in Rabbits.

Study design:

Test species: Male New Zealand White Rabbits

Table-6: Treatment & dose

Treatment arm	Dose
Placebo of topical solution	-
Dutasteride 0.05% + minoxidil 5% topical solution	14-day: 1x & 5x dose
Dutasteride 0.05% Topical Solution	14-day: 5x clinical dose
Minoxidil 5% Topical Solution	14-day: 5x clinical dose

Exposure: Test formulation and Placebo were applied to 10% body surface area (BSA) of hair clipped rabbits. Exposure period was 6 hours/day.

Parameters: Formulation was evaluated for toxicology parameters (Plasma: Day 1, 14, 30 and 90; Skin: Day 14 and 90) and histopathology of application site. Additionally, skin reactions scoring for edema/erythema everyday post exposure were evaluated.

Results: No local site reactions or any clinical signs was noticed. No treatment-related effect on body wt., hematology, clinical chemistry, organ wt. & gross pathology was observed. No histopathology findings at the application site & in any tissues/organs up to 5x the maximum recommended human dose (MRHD) was observed.

Below are the AUC, C_{max} and Skin concentration parameters at the NOAEL (no observed adverse effect level) dose of 0.125/12.5 mg/kg/day mg/kg/day of Dutasteride + Minoxidil topical solution (Table-7).

Table-7:

Analyte	Parameters	Day 14
Dutasteride 0.125 mg/kg	AUC (h.ng/mL)	32.54
	C _{max} (ng/mL)	2.37
	Skin Conc (ng/g)	583
Minoxidil 12.5 mg/kg	AUC (h.ng/mL)	298.83
	C _{max} (ng/mL)	38.65
	Skin Conc (ng/g)	288500

In 14-Day dermal study in rabbits, the NOAEL doses were 0.125/12.5 mg/kg/day of Dutasteride + Minoxidil topical solution (5x the MRHD [1 ml applied OD] on mg/m² basis). Plasma exposure of dutasteride was low and plasma exposure of minoxidil was higher compared to dutasteride. Skin concentration at application site for all dutasteride (~245 fold), Minoxidil (~7460 fold), were significantly higher compared to their plasma exposure. Higher skin concentration was not associated local dermal toxicity.

Example-9: Pre-Clinical Trials for Evaluation of Hair Growth

The hair growth measurement to be conducted in C3H mice (6 – 7 weeks old). C3H mice divided into eight groups, each group having about 7 animals as provided in Table 8. The study on the C3H mice is planned for sufficient number of days.

Formulations:

- 1) Placebo Vehicle
- 2) Dutasteride 0.05%

3) Minoxidil 5%

4) Topical Dutasteride 0.05% + Topical Minoxidil 5%

Table-8:

Group	Treatment Formulation	Number of animals
A	Placebo vehicle	7
B	Topical Dutasteride 0.05%	7
C	Topical Minoxidil 5%	7
D	Topical Dutasteride 0.05% + Topical Minoxidil 5%	7

5 Procedure:

Mice were housed in approximately sized cages in an environmentally controlled room with a 12-hour light-12-hour dark photoperiod and supplied with food and water ad libitum. Animal care was based on the “Guide for the Care and Use of Laboratory Animals”, NIH Publication No. 85-23. Once all mice entered their prolonged telogen/resting phase of the hair cycle, they were clipped over the dorsal area (Wahl Clippers KM10 series, Blade # 40). Ten female mice per group were clipped while sedated with isoflurane anesthesia.

Determination of Accelerated Onset of Anagen Phase:

The mice were shaved with short hair clipper to hairless on their back as determined by visual inspection at the start of the study. The test articles were applied once daily to the shaved areas of the mice daily at 0.2 ml per dose. Both the hair anagen phase and the hair coverage were observed by visual inspection and recorded 5 days a week for each mouse’s hair condition (Telogen phase: resting phase in hair growth cycle-shaved skin shown no dark hair bulbs/roots; Anagen phase: anagen follicles, i.e. follicles in the growth state of the hair growth cycle-shaved skin shows dark hair bulbs/roots). A study log (or, Anagen Phase Log) documenting day-to-day observations of mice entering anagen (grey skin, the first visual clue to a new hair growth) were recorded. Treatments continued for 8 weeks.

The groups were ranked in order of highest degree of terminal hair coverage to lowest degree of terminal hair coverage according to the following hair coverage scoring system.

Hair Coverage Scoring System	
Grading	Description
0	No hair at all
1	A few patches of hair growth, less than ¼ of the dorsal area

Hair Coverage Scoring System	
Grading	Description
2	Hair growth covering about ¼ of the dorsal area
3	Hair growth covering about 1/2 of the dorsal area
4	Hair growth covering more than 1/2 of the dorsal area
5	Hair growth completely covering treatment area

Histological Analysis:

At the end of experiment, skin was surgically removed from the mice after euthanizing using CO₂ asphyxiation to examine the histological features at the end of the treatment period.

- 5 The skin samples were fixed in phosphate-buffered 10% formalin for 24 h. The samples were embedded in paraffin blocks. Paraffin section were processed for histological analysis. General histology was examined by hematoxylin and eosin staining. The number of hair follicles were counted and subcutis thickness was measured.

Statistical Analysis:

- 10 All statistical analyses were carried out using Prism 8 software (GraphPad Software, San Diego, CA, USA). The hair growth area was evaluated by two-way repeated measures ANOVA followed by Tukey's multiple comparison post hoc test.

Results:

15 Hair coverage score

- Healthy six to seven weeks old female C3H mice were taken. Mice were shaved on the back to hairless. Next day mice were randomized on the basis of body weight. Hair coverage scoring and application composition of example 6 was initiated. Composition of example 6 was applied for 48 days and scoring was also done all along the study. As depicted in figure 1A, 20 topical application of composition of example 6 containing dutasteride 0.05% w/w & minoxidil 5% w/w showed faster hair growth as compared to mono treatment groups & placebo. As depicted in figure 1B, topical application of composition of example 6 containing dutasteride 0.05% w/w & minoxidil 5% w/w w/w showed significantly increased hair coverage score terminally as compared to mono treatment groups & placebo (Table-9 – Mean hair coverage 25 score).

Table-9:

Day / Treatment	Placebo	Dutasteride 0.05%	Minoxidil 5%	Dutasteride 0.05% + Minoxidil 5%
1	0.0	0.0	0.0	0.0
2	0.0	0.0	0.0	0.0
3	0.0	0.0	0.0	1.4
4	0.0	0.0	0.0	1.4
5	0.0	0.0	0.0	1.4
6	0.0	0.0	0.0	1.4
7	0.0	0.0	0.0	1.6
8	0.0	0.0	0.0	1.6
9	0.0	0.0	0.0	1.6
10	0.0	0.0	0.0	1.6
13	0.0	0.0	0.0	1.6
14	0.0	0.0	0.0	1.6
15	0.0	0.0	0.0	1.9
16	0.0	0.0	0.0	1.9
17	0.0	0.0	0.0	1.9
20	0.0	0.0	0.0	1.9
21	0.0	0.0	0.0	1.9
22	0.0	0.0	0.0	1.9
23	0.0	0.0	0.0	1.9
24	0.0	0.0	0.0	1.9
27	0.0	0.0	0.1	2.1
28	0.0	0.0	0.1	2.1
29	0.0	0.0	0.1	2.1
30	0.0	0.0	0.3	2.1
31	0.0	0.0	0.3	2.3
34	0.0	0.0	0.6	2.6
35	0.0	0.0	1.0	2.9
36	0.0	0.0	1.0	3.0
37	0.0	0.0	1.0	3.4
38	0.0	0.0	1.3	3.6
41	0.0	0.0	1.9	3.7

Day / Treatment	Placebo	Dutasteride 0.05%	Minoxidil 5%	Dutasteride 0.05% + Minoxidil 5%
42	0.0	0.0	1.9	3.9
43	0.0	0.0	2.0	4.0
44	0.1	0.0	2.3	4.0
45	0.3	0.0	2.4	4.6
48	0.3	0.0	2.4	4.6
49	0.4	0.3	2.6	5.0

Anagen phase onset log

After hair growth formulations application initiation, number of mice showing growth phase (anagen phase) from resting phase (telogen phase) were recorded in anagen phase log.

- 5 On day 3 of treatment application, significantly more number of mice showed anagen phase in combination group as compared to mono treatments and placebo vehicle (Figure-2, Table-10).

Table-10:

Day / Treatment	Placebo	Dutasteride 0.05%	Minoxidil 5%	Dutasteride 0.05% + Minoxidil 5%
1	0	0	0	0
2	0	0	0	0
3	0	0	0	4
4	0	0	0	4
5	0	0	0	4
6	0	0	0	4
7	0	0	0	4
8	0	0	0	4
9	0	0	0	4
10	0	0	0	4
13	0	0	0	4
14	0	0	0	4
15	0	0	0	4
16	0	0	0	4
17	0	0	0	4
20	0	0	0	4

Day / Treatment	Placebo	Dutasteride 0.05%	Minoxidil 5%	Dutasteride 0.05% + Minoxidil 5%
21	0	0	0	4
22	0	0	0	4
23	0	0	0	4
24	0	0	0	4
27	0	0	1	4
28	0	0	1	4
29	0	0	1	4
30	0	0	2	4
31	0	0	2	4
34	0	0	3	6
35	0	0	3	6
36	0	0	3	6
37	0	0	3	6
38	0	0	3	6
41	0	0	6	7
42	0	0	6	7
43	0	0	6	7
44	1	0	6	7
45	2	0	6	7
48	2	0	6	7
49	2	2	6	7

The results of the embodiment show that the combination formulation of minoxidil and dutasteride in the present invention has better efficacy than a composition of mono minoxidil composition or a dutasteride composition.

5 The results of the example 6 show that compared with the mono minoxidil preparation or dutasteride preparation, the topical composition of minoxidil and dutasteride in the present invention has better efficacy; compared with the composition with only minoxidil or only dutasteride.

10 As such, it is evident that androgenetic alopecia patients should dramatically benefit from the combination treatment of dutasteride plus minoxidil.

The phraseology or terminology herein is for the purpose of description and not of limitation. As such, the terminology and/or phraseology of the present specification should be interpreted by the skilled artisan in light of the teachings and guidance herein.

The breadth and scope of the present invention should not be limited by any of the
5 above-described exemplary embodiments but should be defined only in accordance with the
following claims and their equivalents.

We Claim:

1. A pharmaceutical composition comprising:
 - (a) active agent comprising:
 - (i) minoxidil of about 2% w/w to about 7% w/w,
 - 5 (ii) dutasteride of about 0.02 to about 0.07% w/w, and
 - (b) a means for solubilization of one or more active agent to provide solution state stability, and
 - (c) an acidifying agent,
 wherein the composition provides pH of about 3 to about 7 and
- 10 wherein the pharmaceutical composition prevents hair loss and / or stimulate hair growth.
2. The pharmaceutical composition of claim 1, wherein the means for solubilization comprises one or more solvents, one or more solubilizer, one or more crystal growth inhibitor.
3. The pharmaceutical composition of claim 2, wherein said solvent comprises ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol monobutyl ether,
 15 diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol, N-methylpyrrolidone and N-methylcaprolactam, dimethylsulfoxide (DMSO), tocopheryl polyethylene glycol succinate (TPGS), dimethylformamide (DMF), dimethylacetamide (DMA), capryl-caproyl macrogol 8-glyceride
- 20 4. The pharmaceutical composition of claim 2, wherein said solubilizer comprises one or more of glycerol, aliphatic alcohols or aromatic alcohols containing 4 or more carbon atoms, polyoxyl castor oil, polyoxyl hydrogenated castor oil, cyclodextrin, ethylene vinyl acetates, polyvinyl alcohol, povidone, copovidone or any combination of any of the foregoing or any combinations thereof.
- 25 5. The pharmaceutical composition of claim 2, wherein said crystal growth inhibitor comprises glycol or its derivatives, selected from ethylene glycol, polyethylene glycol, propylene glycol, dipropylene glycol, butylene glycol, pentylene 20 glycol, hexylene glycol, propylene glycol dipelargonate, diethylene glycol monoethyl ether, propylene laurate glycol dicaprylate dicaprinate propylene glycol, and diethylene glycol monoethyl
 30 ether.
6. The pharmaceutical composition of claim 1, further comprises stabilizer.
7. The pharmaceutical composition of claim 6, wherein said stabilizer comprises sodium sulfite, sodium thiosulfate, tocopherol or its derivative such as dl-alfa tocopherol, sodium

metabisulfite, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and ascorbyl palmitate.

8. The pharmaceutical composition of claim 1, wherein said acidifying agent comprises citric acid, citric acid anhydrous, citric acid monohydrate, dl-lactic acid, dl-malic acid, dl-tartaric acid, fumaric acid, l-malic acid, l-tartaric acid, salicylic acid, glycol acid, potassium acid tartrate, potassium citrate, potassium dl-bitartrate, potassium gluconate, sodium lactate, sodium l-tartrate, sodium citrate, ascorbic acid, sorbic acid, methane sulfonic acid, or any combinations thereof.
9. The pharmaceutical composition of claim 1, wherein the composition is selected from the group consisting of hair tonic, solution, dispersion, suspension, emulsion, microemulsion, colloidal solution, cream, ointment, lotion, hair dye, shampoo, rinse, gel, patch, hair serum, foam, and spray.
10. The pharmaceutical composition of claim 1, further comprises thermoreversible polymer.
11. The pharmaceutical composition of claim 1, wherein ratio of dutasteride to acidifying agent is in the range of about 1:10 to about 1:40.
12. The pharmaceutical composition of claim 1, wherein the acidifying agent is lactic acid.
13. A pharmaceutical composition comprising:
 - (a) active agent comprising:
 - (i) minoxidil of about 2% w/w to about 7% w/w,
 - (ii) dutasteride of about 0.02 to about 0.07% w/w, and
 - (b) a means for solubilization of one or more active agent to provide solution state stability, and
 - (c) an acidifying agent,wherein the composition is capable of providing synergistic efficacy to prevent hair loss and / or stimulate hair growth.
14. A pharmaceutical composition of claim 13, further comprise a dermatologically acceptable carrier comprising about 1.0% and about 5.0% w/w of an ethylene oxide/propylene oxide triblock copolymer.
15. A pharmaceutical composition of claim 13, wherein the pH of the composition is about 3 to about 7.
16. A pharmaceutical composition of claim 13, where in the composition is having pH of about 5 to about 6.5.
17. A pharmaceutical composition of claim 13, where in the composition provides a viscosity of less than 50 cP at temperature of about 5° C to 25° C.

18. A method for preventing hair loss and / or stimulating hair growth, comprising:

(a) active agent comprising:

(i) minoxidil from about 2% w/w to about 7% w/w,

(ii) dutasteride from about 0.02 to about 0.07% w/w, and

5 (c) an acidifying agent,

(b) a means for solubilization of one or more active agent to provide sufficient solution state stability,

wherein the composition provides pH of about 3 to about 7,

wherein method comprises administration once daily or twice daily to the subject.

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