Journal of Pharmaceutical Research International

33(39B): 326-351, 2021; Article no.JPRI.71885
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Recent Advances in Topical Nanotechnological Strategies for Treatment of Alopecia

Mehak[1], Karanbir Singh[1], Ravika Nanda[1] and Jasjeet Kaur Narang[1*]

[1]Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i39B32211
Editor(s):
(1) Dr. Ana Cláudia Coelho, University of Trás-os-Montes and Alto Douro, Portugal.
Reviewers:
(1) Kirty Nahar, Apollo Hospitals International Ltd, India.
(2) Eman Alaaeldin Abdelzziz, Minia University, Egypt.
Complete Peer review History: https://www.sdiarticle4.com/review-history/71885

Review Article

Received 22 May 2021
Accepted 28 July 2021
Published 04 August 2021

ABSTRACT

Alopecia can be characterized as a hair-related disorder leading to decreased hair growth, especially on the scalp. It has affected approximately 2% of the world population. The hair loss may emerge due to genetic or environmental factors like stress, infectious agents, tensile forces or medications. The pathogenetic pathway of induction of alopecia comprises of different factors, but exploitation of hair follicle immune privilege system (HFIP) is the most prominent one. Alopecia can be classified into two types: scarring alopecia or non-scarring alopecia. Although, many conventional dosage forms have been formulated against alopecia, but they have been associated with different adverse effects such as weight gain, palpitations, itching etc. In order to overcome the adverse effects associated with conventional dosage forms, the topical nano-formulations have been used for the treatment of dermatological disorders. Nano-formulations are known to increase the contact time of drug with the target site, thereby, achieving sustained and controlled release of the drug leading to enhanced therapeutic compliance. This review provides an in-depth study of developed nanocarriers like liposomes, nano-emulsions, ethosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs) along with their composition, method of preparation, results obtained after formulation, suitable use and along with their potential use in treatment of different forms of alopecia.

**Corresponding author: E-mail: jasjeet2975@yahoo.com;*

Keywords: Alopecia; immune privilege; scarring; dermatological; conventional.

1. INTRODUCTION

Alopecia, also recognized as hair loss, is a dermatological disorder in which confluent, diffuse or patchy pattern hair loss originates from different regions of the body, especially from the scalp [1]. In the contemporary scenario, it is considered as a severe problem as it encloses a variety of conditions that can either be congenital or acquired. Both congenital and acquired hair loss may be irrecoverable, leading to hair follicle devastation and swapping by fibrous group of cells [2]. The overall population has an approximately 2% possibility to develop alopecia at any time of their life without any gender preponderance [3]. It is encountered that alopecia is present in two different forms: Alopecia totalis (AT) or Alopecia universalis (AU) respectively. The former is known to affect the entire scalp, while the latter has an impact on whole body [4].

The aetiology of subsequent growth of alopecia is still a mystery, but it is an autoimmune disorder that emerges from a mixture of environmental and genetic factors [5]. Several theories have suggested the belief of involvement of different stimulating factors such as stress, hormones, infectious agents and many others in the pathology of alopecia [6,7]. The occurrence of alopecia is accompanied with psychological damage which gives rise to excruciating emotional stress and leads to different psycho-social problems. As a repercussion, patients with alopecia experience high incidence of mood changes, depression and anxiety disorders [8].

Hair follicle targeted drug delivery is the major and constantly growing market in the pharmaceutical field for treating various hair-related disorders. It is regarded as the most efficacious route especially when the active ingredient (drug) is incorporated into nanocarriers as it leads to enhanced drug penetration and deeper release in the skin stratum corneum [9]. Nanotechnology is are markably novel field that utilizes “therapeutically active nanomaterials” having unique physicochemical features for targeting it into the hair follicles [10]. High permeation of drug linked to nanocarrier can be clearly explained by rachet effect.It means that, when the drug containing nano-formulationcomes in contact with the hair follicles, it starts acting as a drug reservoir (drug depot formation), which leads to sustained drug release, decreased side effects and elevated patient compliance [11].

2. EPIDEMIOLOGY

Alopecia is the most prevalent and depressing disorder, affecting many people with the incidence of 1.7-2.0% in the general population, without any gender or racial predominance. The prevalence rate of alopecia varies throughout the world. This disorder has affected 2.1% of people in United States, 0.7% of people in India and 3.8% of population in Singapore respectively [12]. Generally, there is no age restriction for development of alopecia, but it mostly arises during second and third decades of life [13]. As per the statistical data registered in the literature, people belonging to 20-50 years age group are more vulnerable to alopeciaand 60% of patients affirm the first episode of the disease before 20 years of age [14].

3. PATHOPHYSIOLOGY OF ALOPECIA

The exact mechanism of pathophysiology of the disease named alopecia is still not clear. However, many genetic and environmental factors are believed to induce different forms of alopecia. The involvement of environmental factors such as microtrauma, bacterial autoantigens, viral infections or stress cause the collapse of hair follicle immune privilege by activating the action of IFN-γ and CXCL 10 in the hair bulbs, leading to immense hair loss [15]. The pathophysiologic pathway linked with alopecia is summarized in Fig. 1 and different factors included in the induction of alopecia are discussed as follows:

3.1 Genetic Factors

Genetics plays a vital role in the pathogenesis of alopecia. Different observations have shown the significant correlation between alopecia and family history. Recent reports have also confirmed the presence of human leukocyte antigen-DR (HLA-DR) on chromosome 6 as a largest risk factor for alopecia. The HLA genes are further highly attached to $CD4^+$ and $CD8^+$ T-cells, which are considered as the main effector cells in many forms of alopecia [16]. Moreover, the involvement of $BCL2^-$ like protein (BAM), effectors of JAK pathway, T-regulatory cells etc.

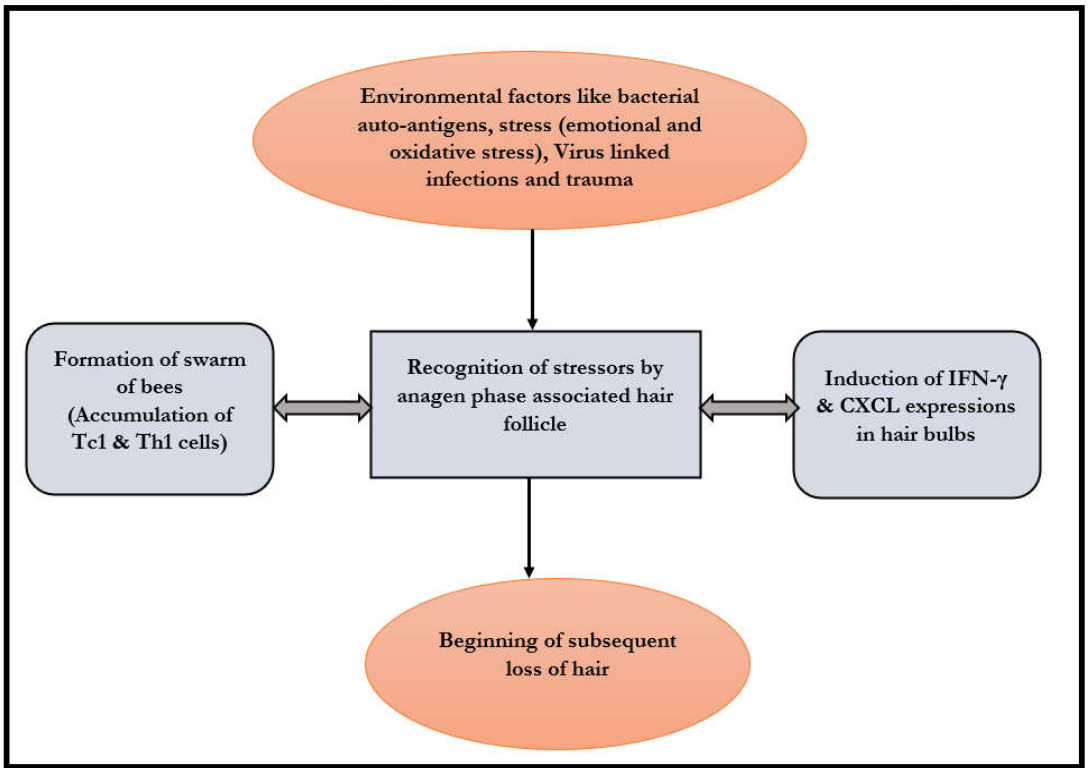

Fig. 1. Pathophysiological mechanism of initiation of alopecia

in the pathogenesis of this disease has also been implicated [17].

3.2 Environmental Factors

Environmental factors such as stress, hormonal fluctuations, vaccinations, medications etc. are more likely to develop alopecia. The human hair follicle is comprised of functional peripheral which is largely affected by different stressors such as ultraviolet radiations, mechanical injury, chemical and biological insults [18]. The increased levels of adrenocorticotropic hormone, corticosterone, and estradiol in correlation with increased cytokine level in the skin also contributes in induction of alopecia [19].

3.3 Swarm of Bees and Collapse of Hair Follicle Immune Privilege

The most interesting feature of hair biology is the immune privilege system, which is present during the resting phase of hair follicle, but usually absent during the telogen or catagen phase. The collapse of human immune privilege system is thought to play a major role in the development of alopecia. It is hypothesized that different environmental factors induce the activation of interferon (IFN)-γ or Interleukin (IL-II) after the recognition of anagen-associated hair autoantigens which further leads to the infiltration of CD^{+4} and CD^{+8} and other inflammatory cells, thereby, proceeding to accumulation of these autoreactive cells around the hair follicle and leading to inflammation of hair follicle and results in alopecia [20].

4. CLASSIFICATION OF ALOPECIA

Based on occurrence, Alopecia can be classified into two broad categories, i.e.Non-Scarring alopecia, also termed as non-cicatricial, reversible or temporary alopecia and scarring alopecia, which can also be called as Cicatricial, irreversible or permanent hair loss [21]. Cicatricial hair loss is associated with inflammation, which consequently exploits the hair follicle, leading to permanent loss of hair.On the other hand, non-scarring alopecia is not permanent and reversible in nature [22]. Different subtypes of Cicatricial and Non-cicatricial alopecia are enumerated in Fig. 2.

4.1 Non-Scarring Alopecia

Non scarring hair loss, also known as non-cicatricial alopecia is defined as the loss of hair without the presence of any kind of scarring [23]. It results in little inflammation and irritation, but loss of hair is eloquent. It can occur suddenly or gradually with concurrent stress [24]. The details of different forms of non-scarring alopecia are given in Table 1.

4.1.1 Diffuse non-scarring alopecia

4.1.1.1 Androgenetic Alopecia (AGA)

Androgenetic alopecia (AGA) or male-pattern hair loss can be described as illness regarding

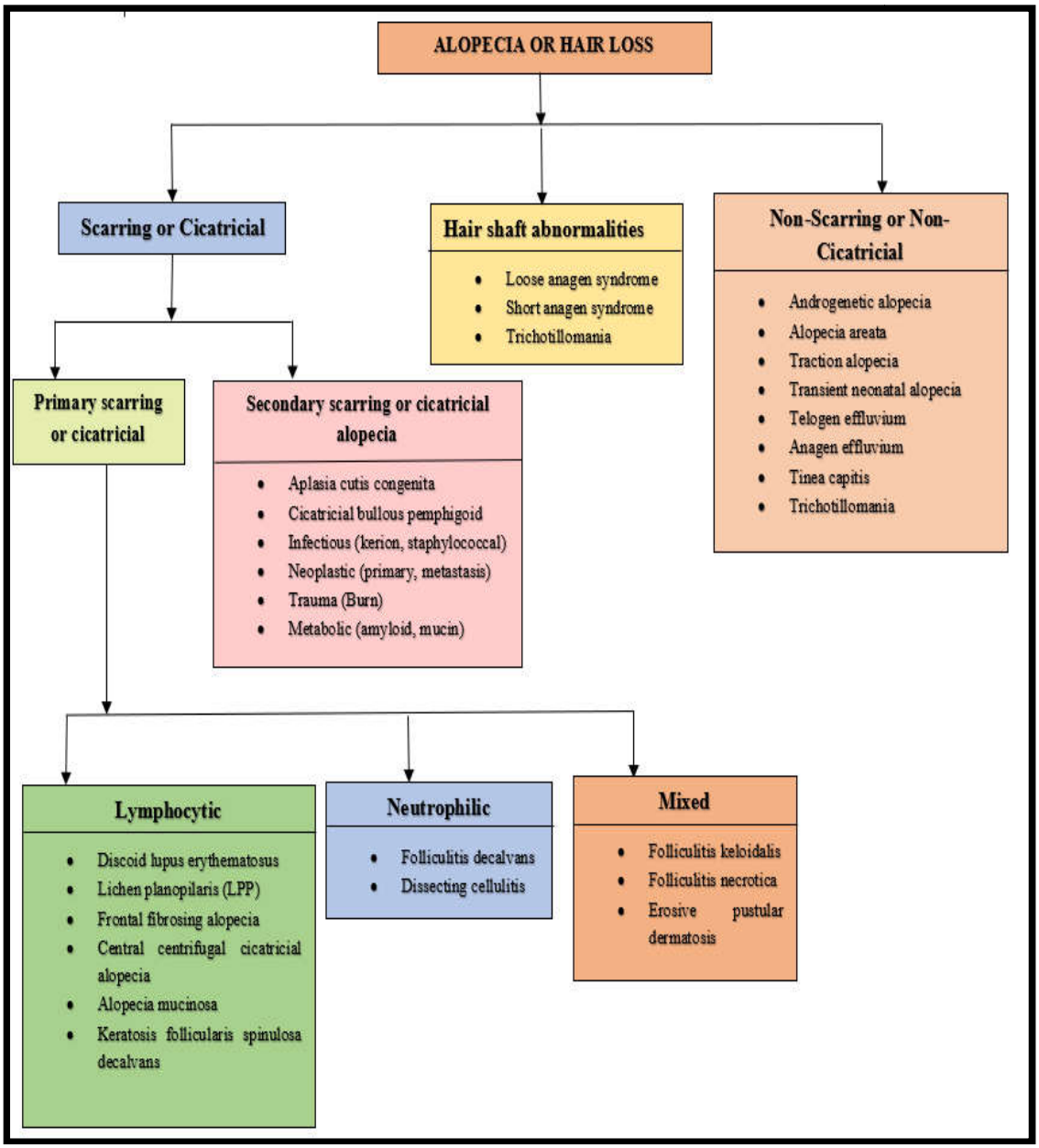

Fig. 2. Etiologies of different forms of alopecia

hair with ongoing hair loss patterns, influencing multifarious males and females who are natively susceptible to an androgen named dihydrotestosterone (DHT), which plays a vital role in reducing the follicular growth [25]. The incidence of male-pattern hair loss is found to be age associated, affecting mainly Caucasian population [23]. There is no clarity of pathophysiological pathway of AGA till now. Although, the studies revealed that androgenetic alopecia (AGA) favours the hair follicle contraction due to anagen phase shortening, leading to reduction in the hair diameter and hair density and subsequently, increase in the growth of vellus hair [26].

4.1.1.2 Telogen effluvium (TE)

Telogen effluvium is defined as a reversible hair-cycle disorder, which is characterized by hair transitions from anagen to telogen phase, leading to an increase in hair shedding [27]. The disturbance in hair growth cycle is generally due to medicines, surgical operations, metabolic or nutritional disruptions, or marked exposure to stress and different vaccinations [28].

4.1.1.3 Anagen effluvium (AE)

Anagen effluviumis a diffuse non-cicatricial form of alopecia, which occurs in patients having a remarkable history of ingesting antineoplastic agents, colchicine, radiotherapy and exposure topoisonous chemicals like mercury, boron etc. [29]. This type of hair loss affects 90% of the scalp within few days or weeks [30].

4.1.1.4 Female Pattern Hair loss (FPHL)

This type of alopecia is another form of Androgenetic alopecia (AGA), commonly seen in females. Unlike Androgenetic alopecia (AGA), it is presented as central scattered thinning, which mainly begins during the reproductive years [31]. However, FPHL has affected 12% of women who are 29 years old, 25% women of 49 years old, 41% (with age of 69 years) and > 50% women having age of 79 years [32].

4.1.2 Patchy non-scarring alopecia

4.1.2.1 Alopecia areata (AA)

It is defined as a chronic, auto-immune inflammatory hair loss linked with hair follicles present in growth phase resulting in reversible, temporary alopecia. It is commonly presented as confined patches on the scalp or dispersed loss of hair throughout the body, including the eyelashes and eyebrows [33]. The onset of alopecia areata occurs in people susceptible to auto-immune disorders (vitiligo, thyroid diseases etc.) [34]. The pathogenesis of AA also suggested the involvement of genes such as interleukins, leukocyte antigens [35].

4.1.2.2 Tinea Capitis

The term 'Tinea capitis' is referred to a dermophyte infection which particularly affects scalp of children, mainly infants. Tinea capitis is also named as ringworm infection and herpes tonsurans infection [36]. Trichophytontonsurans, Microsporum and Epidermophyton are the major dermophytes which are known to induce tinea capitis [37].

4.1.3 Focal non-scarring alopecia

4.1.3.1 Traction Alopecia (TA)

Traction alopecia is an acquired distressing form of alopecia which occurs due to the continuous exposure of scalp hair to the highly tensile forces or painful hair styling practices. Traction alopecia is predominantly affecting the black women [38]. In the beginning, it is found to be non-scarring, but prolonged and high pressure gives rise to mechanical detachment of the hair shaft from the follicle, eventually resulting in follicular diminution and irreversible hair loss [39].

4.1.3.2 Transient Neonatal Hair Loss (TNHL)

This hair loss is also known as friction alopecia or neonatal occipital hair losswhich involves the progression of bald patches in occipital area or other locations during the stage of early infancy or in 2-months old baby. It is induced by friction and different sleeping positions of individual which particularly affects occiput [40].

4.1.3.3 Trichotillomania

Trichotillomania is an enfeebling maniac situation in which a person repetitively pulls one's scalp hair, promoting alopecia and pronounced occupational disturbances [41]. This hair pulling disorder may produce unnecessary medical issues such as ingestion of hair after plucking them out resulting in intestinal disturbances along with the production of abdominal hair-balls, demanding surgical interference in most cases [42].

Table 1. Clinical features and Management of different forms of Non-Scarring Alopecia

Type	Clinical Histopathological feature	Pattern	Treatment	Reference
Androgenetic alopecia (AGA)	Diminished hair follicles with reduced anagen to telogen ratio, hyperplasia of sebaceous glands and increased levels of dihydrotestosterone (androgen)	Diffuse or patchy	Minoxidil topical solution (2% and 5%), Oral dutasteride, oral finasteride, Cyproterone acetate	[32]
Alopecia areata (AA)	Exclamation vellus hairs on scalp surface with subsequent trachyonychia	Patchy, diffuse or complete hair loss.	Squaric acid dibutyl ester, systemic immunomodulators, topical corticosteroids and diphencyclopropenone	[17]
Traction alopecia (TA)	Fringe skin with reduced terminal hair follicles and subsequent trichotillomania features	Patchy	Topical minoxidil solution (2%), Topical and oral anti-inflammatory preparations.	[43]
Trichotillomania	Lack of inflammatory follicular infiltrate,inter and perifollicular bleeding	Patchy	Clomipramine, SSRIs etc.	[44]
Female pattern hair loss (FPHL)	Discrete thinning of hair in frontal regions, little to no effect of androgen excess	Diffuse	Topical minoxidil, finasteride and spironolactone	[45]
Tinea Capitis	Presence of black dot hairs, dorsal lymphadenopathy at cervix	Patchy	Oral antifungal preparations, Ketoconazole 2% shampoo	[46]
Telogen effluvium (TE)	Apoptosis of follicular stem cell with large number of hair follicles in resting phase	Diffuse	Minoxidil, β-blockers, retinoids and anti-coagulants etc.	[47]
Transient Neonatal hair loss (TNHL)	No histopathological change	Focal	Improves with age	[40]
Anagen effluvium (AE)	Breakage at posterior hair shaft	Diffuse	Topical minoxidil, topical dexamethasone, calcitriol	[29]

4.2 Scarring Alopecia

Scarring alopecia or Cicatricial alopecia referred to a grouping of conditions which involves the replacement of hair follicles by vertical pulpy strands or deteriorated collagen [48]. Based on the causes, the scarring alopecia can be divided into two classes: primary or secondary cicatricial alopecia. Primary Cicatricial hair loss comprises of different hair-related disorders which characterize thefollicular destruction due to an inflammation process but, the intrafollicular skin is exempted from this process [49]. The details of different Scarring alopecia are given in Table 2.

4.2.1 Primary lymphocytic scarring alopecia

4.2.1.1 Central Centrifugal Cicatricial Alopecia (CCCA)

It is defined as a form of scarring hair loss which begins with the progression of hair loss that appears in the form of patches usually at the vertex followed by slow centrifugal circulation throughout the scalp [50]. The middle-aged African women are extremely affected by this type of alopecia along with some children [51]. It has been suggested that this condition is the outcome of premature deterioration of the inner root sheath (IRS) of the hair follicle [52].

4.2.1.2 Discoid Lupus erythematosus (DLE)

This is an inflammatory immune-mediated disorder which is usually presented as pruritic, patchy head and neck that can easily scatter to different skin regions [53]. Discoid lupus affects all ages related to different ethnic groups. However, it originates more rapidly in women than in men, but the preference towards women is not marked as in systemic lupus [54].

4.2.1.3 Lichen planopilaris (LPP)

Lichen planopilaris (LPP) is comparatively rare skin disease associated with severe lymphocytic (T-cell) inflammation, which causes critical hair follicle wreckage [55]. The term “Lichen planopilaris” is used to describe hair follicle related lichen planus, whereas onset of cutaneous or mucosal lichen planus affects 30% patients [56].

4.2.1.4 Keratosis follicularis spinulosa decalvans (KFSD)

Keratosis follicularis spinulosa decalvans (KFSD) is an uncommon inherited dermatosis depicted by keratosis pilaris and progressive scarring hair loss at the scalp, eyebrows, and eyelashes. Itis a genetic disorder which develops during stage of infancy and usually caused by a transformation in the *MBTPS2* gene [57].

4.2.1.5 Alopecia mucinosa

It is also known as hair follicle mucinosa which is a cutaneous disorder, which develops due to the mucin accumulation in the pilosebaceous units of the hair follicles [58]. Alopecia mucinosa is presented in two forms: an abiogenic form and lymphocytic form [59].

4.2.1.6 Frontal fibrosing alopecia

Frontal fibrosing alopecia is one of the primary cicatricial alopecia with characteristic detached form of continuous collapse of the occipital or transient hairline, usually in the form of bands. This condition was first described in women after menopause and presented in three forms [60]. Firstly, the linear FFA is the strip of collapsed occipital hairline without any loss in the hair density, while the second diffuse zig-zag pattern is similar tofirst one but is known to reduce the density of hair. The third pseudo-fringe pattern showed the resemblance with traction alopecia (hence the term ‘pseudo’ is used) where the existence of properly preserved temporal hair justifies the presence of fringe word [61].

4.2.2 Primary neutrophilic scarring alopecia

4.2.2.1 Folliculitis decalvans

Folliculitis decalvans (FD) is referred to a neutrophilic scalp inflammation, which is linked to the repeated or excruciating follicular transudation. It predominantly affects young and middle-aged adults [72]. Etiopathogenesis of folliculitis decalvans is not understood yet, while the presence of *Staphylococcus aureus* and the abnormal changes in the local immune response of patients have been considered as important triggering agents [73].

4.2.2.2 Dissecting cellulitis

It is a neutrophilic scarring alopecia which can be defined as keratinization of the hair follicle, leading to hair follicle hinderance, followed by bacterial infection [74].

Table 2. Clinical features and management of different forms of scarring alopecia

Type	Clinical Histopathological feature	Pattern	Treatment	Reference
Central Centrifugal Cicatricial alopecia (CCCA)	Lamellar fibroplasias along with inflammation of lymphocytes	Patchy	Topical or Intralesional steroids	[62]
Lichen planopilaris (LP)	Lichenoid skin infection with symptoms of erythema and atrophy of scalp	Patchy or diffuse	Potent topical corticosteroids, I/L triamcinolone acetonide, oral tetracycline and cyclosporin	[63]
Discoid Lupus erythematosus	Hair follicle plugging linked with vacuolar skin infection	Patchy or diffuse	Oral and topical corticosteroids, topical tacrolimus, retinoids	[53]
Alopecia mucinosa	Deactivation of sebum glands and follicular papules breakage	Diffuse	Potent topical corticosteroids, topical and oral indomethacin	[64]
Frontal Fibrosing alopecia (FFA)	Loss of follicular duct with evidence of hyperkeratosis and erythema on hairline	Diffuse	5-α-reductase inhibitors, oral retinoids and hydroxychloroquine	[65]
Keratosis follicularis spinulosa decalvans	Hyper-granulation of follicular bumps with adventitial fibrosis	X-linked inheritance	Topical treatment with keratolytics, systemic retinoids like etretinate and dapsone	[66]
Dissecting cellulitis	Maturation of excruciating nodules with bulge formation at infundibulum	Patchy	Oral isotretinoin, oral and topical antibiotics, topical retinoids, dapsone	[67]
Erosive pustular dermatosis	Epidermal erosions leading to atrophy	Diffuse	Topical corticosteroids, oral isotretinoin and topical immunomodulators	[68]
Folliculitis necrotica	Keratin cells virulence with presence of lymphocytic infiltrate	Patchy	Oral antibiotics and oral isotretinoin, I/L triamcinolone	[69]
Folliculitis Keliodalis	Lack of sebum secreting glands by the formation of perifollicular and intrafollicular lymphocytic infiltrate	Diffuse	Potent topical steroids, oral antibiotics, I/L Triamcinolone	[70]
Folliculitis decalvans	Excruciated follicular pustules and fibrosis	Diffuse	Anti-inflammatory and anti-bacterial solutions, oral antibiotics like rifampicin, clindamycin	[71]

4.2.3 Primary mixed scarring alopecia

4.2.3.1 Erosive pustular dermatosis

This type of scarring alopecia is an uncommon, inflammatory condition disease which occurs without any microbial cause. It is an abiogenic pustular eruption with a severe course of repetitive relapses and identified by the existence of erythematosus scalp lesions, skin atrophy, attrition and thick crusts [75].

4.2.3.2 Folliculitis necrotica

Follicular necrotica, also called acne necrotica varioliformis refers to a skin disease of adults of obscure aetiology, featuring necrosis of the hair follicles and resulting in the appearance of varioliform scars [76]. These lesions are seen in the occipital hair region as well as in the seborrheic face areas [77].

4.2.3.3 Folliculitis keloidalis

Acne Keloidalis nuchae (AKN) is a severe condition which is characterized by scalp inflammation, resulting in scar formation in hair follicles, on the tape of the neck and occipital scalp [78]. Several studies reported that acne keloidalis nuchae occurs in people after adolescence and it is more prevalent in African men with skin injuries and abnormal immune reactions being the prominent reasons [79].

4.2.4 Secondary scarring alopecia

In secondary cicatricial alopecia, the hair follicle devastation takes place due to an unusual dermis interruption, as in the case of thermal burns or blistering disorders. This type of hair loss develops as an outcome of different skin inflammation causing phenomenon or by traumatic situations [80]. Recently, no effective treatment is available to cure secondary cicatricial alopecia apart from diminishing the inflammation progression induced by infections or damages linked with tissue. Besides this, the medicines involved in the treatment of SCAs are highly potent corticosteroids (topical), immunosuppressive drugs and antibacterial drugs [81].

4.3 Hair Shaft Disorders

These disorders are characterized as inherited or acquired hair structure impairments. Patients suffering from hair shaft disorders are frequently associated with hair elongation failure, abnormal hair texture or appearance [82]. The two major hair shaft disorders are reported as follows:

4.3.1 Loose anagen syndrome

Loose anagen syndrome is related to poor fixing of anagen hairs to follicle, producing relative pain-free hair loss with gentle pulling [83]. It is also considered to be linked with different genetic growth situations like Noonan syndrome. Mostly, patients do not require any kind of treatment for treating LAS as the hair automatically becomes normal after few years with the avoidance of hair styling products. Topical minoxidil seems to be efficient for LAS patients with severe symptoms [84].

4.3.2 Short anagen syndrome

It is defined as an inherited hair-related disease in which the anagen phase (hair growth phase) becomes shorter, resulting in an incapability to get longer hair and prolongation of telogen or resting phase [85]. It has mostly affected the young children of 2-3 years age. However, people in adulthood stage are also influenced by it.This condition is usually is a treatable condition and the majority of patients improve by the stage of puberty [86].

The management and clinical features of different hair shaft disorders are discussed in Table 3.

Table 3. Clinical features and Management of different Hair shaft disorders

Type	Clinical Histopathological feature	Pattern	Treatment	Reference
Loose anagen Syndrome	Early keratinization of inner root sheath of hair follicle	Diffuse	Topical minoxidil	[83]
Short anagen Syndrome	No histopathological change but reduced hair density	Diffuse	Improves with puberty	[85]

5. NANOTECHNOLOGICAL STRATEGIES FOR TREATING ALOPECIA

Nanotechnology based formulations offer the development of drug delivery systems that are able to deliver lower drug doses with maximized therapeutic effects by maintaining drug's stability, high permeation profile, therapeutic adherence and by reducing drug toxicity and treatment resistance [87]. Nano-systems will possess an improved drug delivery via skin due to the small size and increased surface area of nanoparticles, leading to a close and extended contact with the stratum corneum. Besides this, the conventional drug delivery systems used for alopecia are often linked with the limitations of marked irritation, itching and formation of patchy scales on scalp due to the presence of certain ingredients like ethanol or propylene glycol. These delivery systems also offer limited contact time with the scalp, which have a remarkable influence on the total drug concentration at the target site [25]. In order to overcome certain drawbacks associated with the traditional products, application of nanotechnology is escalating in the area of cosmeceuticals. Nevertheless, the topical drug delivery by using nanotechnology-based formulations offers several benefits which are illustrated in Fig. 3 [88].

The different nanotechnological strategies used for treating alopecia are:

5.1 Nanostructured Lipid Carriers (NLCs)

Uprit et al. [89] developed the MXD loaded topical NLC based gel to reduce the incidence of alopecia and promote hair growth. The cholesterol and soya lecithin were utilized as lipids for the preparation of different MXD-NLC formulations. The technique used for the preparation of MXD-NLCs was melt dispersion ultrasonication method. The optimized NLC-3 formulation was obtained by assessing particle size, shape, polydispersity index, drug entrapment efficiency and *in vitro* release profile. The results showed that the optimized NLC-3 was a suitable formulation to be converted into gel. The developed NLC-gel formulation was evaluated and found to be homogeneous with good consistency and spreadability values. The prepared NLC based gel formulation showed a good rheological behaviour with maximum drug content, non-irritant pH value and good *in vitro* release characteristics. The developed Minoxidil loaded NLC-based gel formulation exhibited faster release and prolonged activity up to 16 hours.

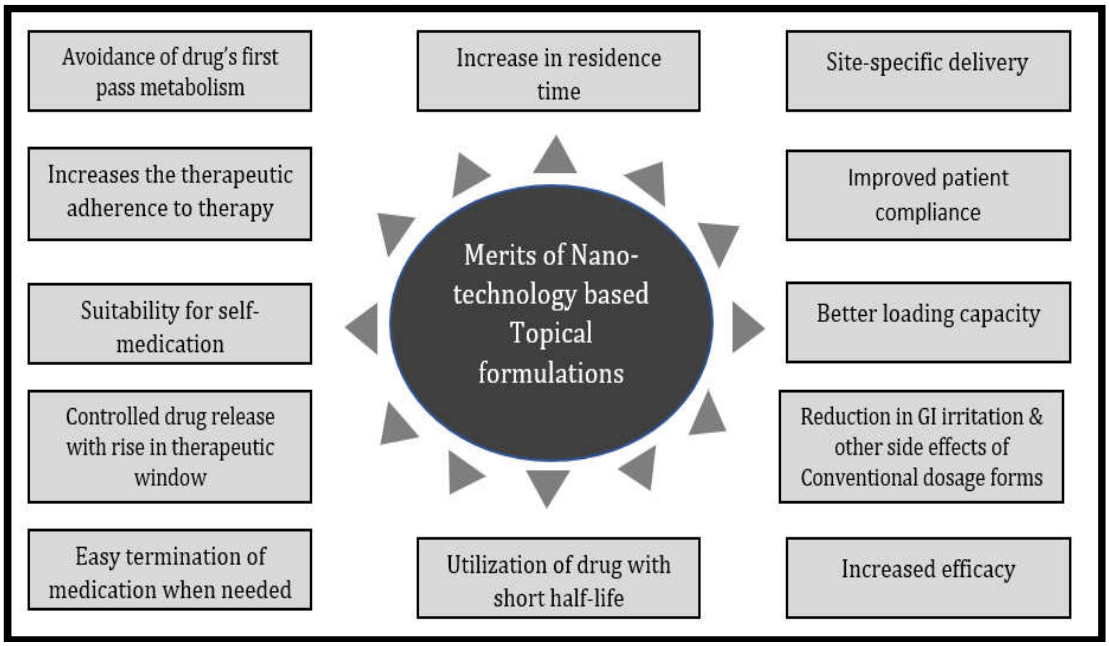

Fig. 3. Benefits of Topical Nano-formulations designed for Alopecia

Gomes et al. [90] prepared nanostructured lipid carriers to deliver a combination of minoxidil and finasteride into the dermis and hair follicles. NLCs were prepared by ultrasonication method and they exhibited particle size of 200 nm and zeta potential around -30mV. The formulations were stored over 28 days and all prepared NLC formulations were found to be stable over that period. After 28-days, finasteride-NLC formulations showed higher loading efficiency (between 70 and 90%) in comparison with MXD-NLCs formulations (less than 30%). The controlled release assays performed at sink conditions demonstrated that release of drug from MXD-NLCs occurred for a prolonged time. Penetration studies were performed using skin excised from pig's ear and low penetration of finasteride and minoxidil from nanoparticles was also observed. Thereby, the authors proposed that the prepared novel NLC formulation containing a combination of finasteride and minoxidil exhibited several good characteristics and it can be preferrable for dermal delivery to treat the problem of alopecia.

Shamma et al. [91] designed spironolactone loaded nanostructured lipid carriers to enhance drug efficiency and safety in the treatment of alopecia. The methods used for the preparation of spironolactone containing nanostructured lipid carriers were emulsion solvent diffusion technique or method of evaporation. The optimization of prepared formulations was done and the prepared SL-loaded NLCs were found to be spherical with nano size of 215.6–834.3 nm and entrapment encapsulation (%EE) greater than 74%. The amorphous character of spironolactone was confirmed by differential Scanning calorimetry and X-ray diffraction. The SL-loaded nanostructured lipid carrier initially released the free drug present on the surface in a burst, but after some time, it followed the controlled drug release pattern. The spironolactone containing NLCs delivered the drug into the hair follicles which was estimated using confocal laser scanning, thereby recommending the localized potential of efficient follicular drug delivery.

Aljuffali et al. [92] formulated lipidic squarticle-based NLCs coupled with anti-platelet-derived growth factor (PDGF)-receptor β antibody to achieve site-specific follicular drug delivery. The PDGF-squarticle NLCs exhibited a mean diameter of 195 nm, zeta potential of −46 mV along with an increased drug accumulation (0.11 to 0.23 mcg/mg). From the results of *in vivo* study, it was revealed that a three-fold higher follicular uptake was seen in case of squalene based NLCs in contrast to the control solution. Both the skin sections showed a uniform dispersal of conjugated NLCs in the different hair and skin regions. The entrapped minoxidil demonstrated multiplication of dermal papillae cells and activation of growth factors such as VEGF. The results confirmed that prepared MXD-squarticle based NLCs were beneficial in treatment of hair loss disorders.

Wang et al. [93] formulated minoxidil loaded nanostructured lipid carriers (NLCs) for topical delivery. NLCs were prepared by using stearic acid (Solid lipid) and oleic acid (liquid lipid) that exhibited the maximum solubilization capacity for minoxidil. The method used for NLCs was high pressure homogenization method. The optimized MXD-NLCs were observed to be spherical in shape with an optimum mean diameter value (281.4 ± 7.4 nm) and uniform particle size distribution (0.207 ± 0.009). The zeta potential of minoxidil loaded NLCs was −32.90 ± 1.23 mV with a high drug entrapment efficiency (92.48 ± 0.31%), and loading capacity of 13.85 ± 0.47%. The stability studies of the optimized NLCs were done and the results confirmed that average particle size and %EE of the minoxidil loaded NLCs did not show any change after storage period of 3 months. Moreover, the drug release, *in vitro* permeability and retention of minoxidil was also determined and it was found to be higher in case of NLCs than from SLNs. From the results, it was confirmed that the minoxidil loaded nanostructured lipid carriers could act as a beneficial nanotechnological strategy for treatment of alopecia.

Noor et al. [94] developed topical NLC formulation containing dutasteride (DST) with the enhanced potential to deliver drug into the hair follicles and overcoming the systemic side effects. Optimization of prepared NLC formulation was also done. The stearic acid-chitosan solution was utilized in different concentrations for coating of the formulation. The 5% stearic acid-chitosan solution coated NLCs exhibited enhanced particle size (187.6 ± 7.0 nm to 220.1 ± 11.9 nm). There was a significant difference in the zeta potential value of the uncoated (−18.3 ± 0.9 mV) and coated DST-NLCs (+25.8 ± 1.1 mV) respectively. The nanoparticles were found to be spherical in shape. Both the coated and uncoated DST-NLCs showed no variation in particle size value during the storage period of 60 days at 4–8 °C. The

particle size of all formulations which were stored at 25 °C was checked and marked aggregation was observed in case of coated DST-NLCs. All the DST-NLC formulations showed fast release while the dutasteride loaded NLC formulations which were uncoated released the drug at a very fastest rate. A Franz diffusion cell was used for conducting permeation study by using skin samples excised from pig ear and the cumulative amount of dutasteride permeated in the skin was significantly different ($p < 0.05$) for uncoated DST loaded NLCs (6.09 ± 1.09 mcg/cm^2), SA-CSO (5%) coated DST-NLCs (2.82 ± 0.40 mcg/cm^2), soya lecithin-chitosan solution (10%) coated DST-NLCs (2.70 ± 0.35 mcg/cm^2) and chitosan solution-coated NLCs (2.11 ± 0.64 mcg/cm$^{2)}$. A marked difference was also observed in the cell-toxicity of drug alone and when loaded in NLCs. These results confirmed that a stable, positively charged dutasteride loaded NLC formulation containing stearic acid-chitosan conjugate with less cytotoxicity was successfully prepared and had a potential for promotion of hair growth.

Ghasemiyeh et al. [95] formulated a cyproterone acetate loaded NLCs for the treatment of different dermatological diseases skin disorders like alopecia etc. As cyproterone acetate undergoes limited penetration into the skin, thus, the formation of nanostructured lipid carriers (NLCs) with different size ranges (100, 300 and 600 nm) was designed. The different CPA-NLCs formulation were prepared and characterized on the basis of loading capacity, drug release study and morphological examination and *ex vivo* skin permeation study. The prepared NLC formulations were further examined their potential to deliver drug into the hair follicles to compare the results obtained with those obtained from rhodamine B-loaded micro and nanoparticles. The drug release study was conducted for 72 hrs and the results confirmed that CPA-NLCs released approximately 85% of drug. The prepared cyproterone acetate loaded NLCs possessed an optimum particle size (600 nm) with good drug permeation characteristics and retention in deeper skin layers. A significantly higher drug permeation was observed in case of CPA-NLC (size range of 100 nm) in contrast to CPA loaded NLCs (having size of 300 nm) and unentrapped drug. The CPA-loaded NLCs with size range of 300 nm had the higher potential to retain high concentration of CPA in the hair follicles, thus achieving site specific hair follicle delivery. Therefore, all the results confirmed that 300 nm sized cyproterone nanostructured lipid carriers could be an efficient nano-approach for the treatment of different skin disorders.

Angelo et al. [96] proposed the formulation of clobetasol propionate (CLO) loaded nanostructured lipid carriers to investigate its epidermal targeting potential. In this study, the hair follicle uptake provided by CLO-NLCs were evaluated in comparison to a commercial cream and investigation of the effect of different physical stimuli such as infrared irradiation (with and without metallic nanoparticles-MNP), ultrasound (with and without vibration) and mechanical massage on their follicular targeting potential. CLO-NLCs exhibited a size around 180 nm, PdI value lesser than 0.2 and a negative zeta potential. The formulation showed stability for at least 30 days at 5 °C. The release of drug from CLO-loaded NLCs followed sustained release pattern and passively increased CLO follicular growth in contrast to the commercial cream. The enhanced delivery of drug to hair follicles was confirmed by confocal imaging. The application of IR irradiation at higher temperatures to the prepared CLO-NLCs manifested no effect on the hair follicle targeting. However, in the case of ultrasound vibration, there occurred a significantly higher ($p<0.05$) drug retention in the deeper skin layers. After ultrasound treatment of clobetasol loaded NLCs, the mechanical vibration was also applied and a higher follicular drug accumulation took place in comparison with that obtained after passive exposure to NLC. The study concluded that the clobetasol loaded nanostructured lipid carriers (CLO-NLCs) exhibited higher drug delivery capability into the hair follicles and double follicular retention could be retained by simple massage.

5.2 Solid Lipid Nanoparticles (SLNs)

Padois et al. [97] formulated MXD loaded solid lipid nanoparticles (SLNs) by utilizing different lipids. SLNs containing 5% minoxidil were made of various components such as triglycerides and polysorbate. The prepared systems were evaluated on the basis of different parameters. The skin corrosion was also examined and the results of these studies were compared with those obtained from commercial solutions. The minoxidil loaded SLN suspensions showed effective drug permeation with no evidence of corrosion whereas the commercial solutions were found to be corrosive. Thus, MXD-SLNs

could be considered as an efficient approach for treating the problem of alopecia.

Matos et al. [98] prepared minoxidil sulphate-loaded topical chitosan solid lipid nanoparticles (MXS-NP) for site-specific hair follicle delivery to achieve controlled release of drug. The monomodal distribution was presented by MXS-SLN along with hydrodynamic diameter (235.5 ± 99.9 nm) and polydispersity index value of 0.31 ± 0.01 and positive zeta potential (+38.6 ± 6.0 mV). The spherical shape of solid lipid nanoparticles was confirmed by SEM analysis. The selected polymer and drug ratio for the preparation of minoxidil loaded solid lipid nanoparticles was 1:1 w/w and the drug loading efficiency was found to be 73.0 ± 0.3%. The drug release study was also conducted by using cellulose acetate membranes and MXS-NP exhibited 5 times more sustained release (188.9 ± 6.0 μg/cm^2/h) when compared to diffusion rate of minoxidil solution (35.4 ± 1.8 μg/cm^2/h). The *in vitro* permeation studies revealed that minoxidil loaded chitosan nanoparticles has higher potential to deliver the maximum amount of minoxidil (5.9 ± 0.6 μg/cm2) into the hair follicles after 6 hrs, in contrast to the control solution (2.9 ± 0.8 μg/cm2). Thus, the results confirmed that the MXS loaded nanoparticles could appear as a beneficial nano-carrier in terms of sustained drug release and targeted drug delivery into the hair follicles, thereby, improving the topical treatment of alopecia.

Hamishehkar et al. [99] designed and evaluated topical Flutamide loaded SLNs to treat androgenic alopecia. The method used for preparation of flutamide loaded solid lipid nanoparticles was hot melt homogenization method. The prepared nanoparticles were also subjected to drug permeation and drug retention studies to evaluate their *in vitro* and *in vivo* efficiency in delivering drug to the targeted site. The histological study was also performed using the male hamsters. The optimized solid lipid nanoparticle formulation possessed an optimum particle size (198 nm) with % EE of 65% and drug loading capacity of 3.27%. The formulation also showed good stability during storage for 2 months. XRD also confirmed the amorphous nature of flutamide and higher skin drug deposition was also observed from nanoparticle formulation in contrast to flutamide hydroalcoholic solution. The *in vivo* studies concluded that the extensive hair growth was observed in case of flutamide containing nanoparticles when compared to commercial solution. The maximum hair follicle growth was due to higher retention of drug at the follicular level. The controlled release from the nanoparticle formulation maximizes the contact time of hair follicle with the anti-androgenetic drug i.e. flutamide. Therefore, the results concluded that solid lipid nanoparticle formulation containing flutamide formulation could be an efficient or beneficial nano approach for the topical treatment of androgenic alopecia.

5.3 Polymeric Nanoparticles

Khalil et al. [100] prepared colchicine loaded topical polymeric nanoparticle formulation to evaluate its potential for treating hair loss disorders. Double emulsion solvent evaporation method was used to prepare colchicine loaded nanoparticles along with different polymers. A binary mixture of polymers (poly-D, L-lactic acid (PLA), and Eudragit RL) in the ratio 1:1 was chosen on the basis of different characterization parameters such as entrapment efficiency, the particle size and percent drug release. In order to reduce the solubility of colchicine, the pH of the outer water phase was maintained to 6 and combination of dichloromethane and acetone (1:1 % v/v) was chosen as solvent mixture. Calcium chloride was chosen as the counter ion additive and to enhance the entrapment efficiency, span was also utilized. Medium chain triglyceride (30%w/w) was observed to be very effective. After the optimization, the entrapment efficiency was found to be 44.6 % with the nano particle size and varying zeta potential value (31.1 mV to 45 mV). The shape of colchicine loaded nanoparticles was found to be spherical and the optimized NP formulation showed initial burst release in the first 8 hours. After 24 hours study, a sustained release (15-16%) was also observed.

Roque et al. [101] aimed to design polymeric nanoparticles for topically administering finasteride (anti-androgen) to achieve an efficient follicular targeting. Emulsification or solvent diffusion techniques were used for the preparation of polymeric NPs. The prepared nanoparticles possessed an optimum size (300 nm) with spherical shape, negative zeta potential and %EE of 79.49 ± 0.47% for targeting the drug into the hair follicles. The prepared FNS-NPs were also subjected to *in vitro* drug release studies and *in vitro* skin permeation assays. From the results of these studies, it was concluded that the drug release from FNS-NPs

was found to be sustained for at least 3 hours, while the nanoparticles exhibited less permeation of drug into the skin. The components used in the preparation of finasteride loaded polymeric nanoparticles were found to be safe. From this study, it was confirmed that the developed new nano-formulation of finasteride for targeting alopecia could be an efficient approach for site specific delivery of drug with enhanced contact time.

Fernandes et al. [102] developed topical Cyclosporin-Aloaded polymeric nanoparticles for treatment of alopecia. Cyclosporin A-loaded nanoparticles were prepared by using poly (D, L-lactide) (PLA) polymer nanoparticles with good physicochemical stability and evaluated on the basis of different parameters. The *ex vivo* skin permeation study was done using porcine skin and drug permeation or accumulation was found to be maximum in contrast to a non-colloidal formulation. The biocompatibility of cyclosporin A in NCTC2455 keratin cells (reference skin cell line) was enhanced with the addition of PLA nanoparticles. The study encouraged further *in vivo* study of Cyclosporin A loaded nanoparticles as an innovative approach for the treatment of alopecia.

5.4 Nano-emulsions

Abd et al. [103] developed minoxidil loaded nano-emulsions containing penetration enhancers to investigate the potential of nano-emulsion to increase drug delivery into the skin. The water-in-oil minoxidil loaded nano-emulsions were prepared by adding 2% w/w of minoxidil and the oleic acid or eucalyptol oil as oil phases. The oleic acid and eucalyptol oil also acted as a permeation enhancer. After the preparation of nano-emulsion, the permeation studies were conducted using the Franz diffusion cell. A full-thickness properly cut to size skin sample was mounted on Franz diffusion cell. 1 ml of prepared MXD nano-emulsion and minoxidil aqueous solution (control) were placed on the mounted skin. Different parameters like drug concentration in skin strata, hair follicles and flux were calculated after conducting 24 hrs study. Drug permeation was found to be significantly higher in case of minoxidil loaded nano-emulsions as compared to minoxidil aqueous solution. Minoxidil loaded nano-emulsions containing eucalyptol oil showed higher retention in skin stratum corneum when compared to oleic acid nano-emulsions. However, the follicular penetration was observed to be higher in case of oleic acid nano-emulsion formulation. Both the minoxidil loaded nano-emulsions (containing oleic acid or eucalyptol oil) exhibited enhanced flux which might be due to the high solubility of drug in both oil phases and better skin diffusion from both nano-emulsion systems. The major driving forces for flux enhancement could be higher skin drug diffusion, leading to enhanced division into skin strata, thereby recommending the concept of increased fluid character and impairment of skin layer lipids.

Cardoso et al. [104] proposed the concept of formulation and evaluation of minoxidil loaded nano-emulsions to provide a controlled and site-specific delivery of minoxidil into the hair follicles. The method used for preparation of minoxidil loaded nano-emulsions was ultrasonication method. The optimization of the prepared MXD-nano-emulsions were studied by evaluating the effect of 3 independent variables and the optimized minoxidil loaded nano-emulsions were NE 5, NE 6 and NE 8. The oil phase and surfactant used for the preparation of minoxidil nano-emulsions were clove oil and Kolliphor® P188 respectively. The optimized MXD-NEs (NE5, NE6 and NE8) were evaluated and exhibited PDI (<0.2) with the average particle size of 10 nm. The prepared nano-emulsions showed extensive stability against coalescence at 50% RH and two-fold higher sustained release of drug in contrast to control solutions. The release of drug from minoxidil loaded nano-emulsions followed Higuchi release model. The optimized minoxidil loaded nano-emulsions were also subjected to skin permeation study and the results of this study confirmed that drug permeation was 9-times higher in case of minoxidil loaded NEs as compared to that obtained from conventional minoxidil ethanolic solution. The total penetration into the hair follicles was also examined and efficient follicular drug penetration was observed from MXD-NEs in contrast to the control solution. Thus, from these results it can be estimated that the developed minoxidil loaded topical nano-emulsion containing clove oil as an oil phase could be considered as an efficient nano-carrier for the treatment of alopecia.

Upadhyay et al. [105] designed and characterized topical lipidic finasteride loaded nano-emulsion based gel for treatment of alopecia, to enhance drug's contact time with the skin to increase drug availability into the skin for a prolonged time and to investigate the *in vivo* drug's efficiency in promoting hair growth.

Finasteride containing nano-emulsion was prepared by a high-speed homogenization technique. The major components used in the preparation of FNS-NE were Vitamin E as oil along with cholesterol and soya lecithin as lipid phases. The prepared FNS-NE exhibited droplet size of 195.20 ± 9.43 nm, PDI value of 0.25 ± 0.08 and zeta potential of − 7.61 ± 1.35 mV and was converted into gel form using guar gum as a thickening agent. FNS-NEG was characterized on the basis of different evaluation parameters. From the results of characterization studies of FNS-NEG, it was observed that nano-emulsion based gel possessed a non-irritant pH value (5.37 ± 0.74) with *in vitro*gradual release (94.77%) of finasteride in 24 hrs study and confined penetration of drug (30.7%) into the skin. The prepared FNS-NEG was also subjected to macroscopic evaluation to investigate its efficiency to enhance hair diameter or length and the results revealed the maximum hair diameter and length elongation in case of nano-emulsion based gel in contrast to control group (treated with testosterone). After this, the histopathological study was also performed and the optimized formulation was subjected to storage period of 90 days. From these results, it was proved that FNS-loaded nano-emulsion based gel had a potential to treat hair-related disorders with high efficiency and prolonged residence time.

5.5 Liposomes

Kumar et al. [106] aimed to encapsulate an anti-androgen drug i.e. Finasteride inside the core of phospholipid vesicles to achieve an efficient trans-epidermal delivery of finasteride. The different compositions of multilamellar hydrogenated phospholipid containing liposomes were prepared by utilizing the method of thin hydration followed by sonication. The optimization of finasteride loaded liposomes was done on the basis of vesicle size (3.66 ± 1.6 µm), drug loading (2.9mg) and encapsulation efficiency (88.6%). The abdominal skin permeation of finasteride was examined and results revealed that the higher permeation and deposition of FNS was observed from prepared liposomes in contrast to conventional gel and solution formulations. The FNS loaded liposomal formulation was subjected to stability studies for 2 months and the prepared formulations were found to be stable at refrigerator temperature. Therefore, the results confirmed the efficient localized delivery of finasteride.

Jain et al. [107] proposed an idea to target pilosebaceous units of hair follicle by delivering liposomal formulation containing minoxidil, a drug associated with hypertrichosis. The thin film hydration method was used for the preparation of different concentrations of minoxidil containing liposomal formulations. The prepared formulations were characterized on the basis of different parameters such as vesicle size, morphology, lamellarity, encapsulation efficiency, *in vitro* drug release, skin permeation, retention and drug deposition into the pilosebaceous units. From the results, it was observed that the neutral liposomal formulation with vesicle size 3.83 ±0.18 µm exhibited higher drug deposition (5.8×10^3 to 7.25×10^3 µg) as compared to other formulations i.e positively charged liposomal formulation, negatively charged liposomal formulation and non-liposomal formulation. The results of stability studies revealed that the liposomal formulations must be stored at low temperatures for better stability profile. Thus, the prepared neutral minoxidil loaded formulations showed higher potential for targeting drug into pilosebaceous units as compared to other formulations.

Kochar et al. [108] formulated a liposomal gel formulation for delivering a combination of minoxidil and tretinoin for overcoming the adverse effects associated with conventional formulations. The liposomes were successfully prepared by thin film hydration method and evaluation was done on the basis of different parameters like *ex vivo* permeation study, size, encapsulation efficiency and morphological assessment. The prepared liposomes were also examined for stability and *in vivo* skin irritation studies. From the results, it was found that prepared liposomes had the ability to deliver the combination of two drugs with good stability and homogeneity characteristics. Conversion of liposomes into gel formulations increased the rate of drug permeation into the skin with no evidence of irritation to the skin. Thus, the liposomal hydrogel system containing minoxidil and tretinoin was found to be efficient for targeted delivery of combination of drugs.

5.6 Transferosomes

Ahmed et al. [109] formulated finasteride loaded nano-transferosomes based gel for delivering the drug into hair follicles and deeper skin layers and overcome the adverse effects associated with oral delivery of finasteride against androgenetic alopecia. Different concentrations of finasteride

were used for the preparation of elastic liposomal based gel formulation. The evaluation of nano-transferosomes based gel formulations (F1-F3) was done on the basis of entrapment efficiency, *ex vivo* permeation and vesicle size. From the results of evaluation study of elastic liposomal gel formulations, the vesicle size of three FIN loaded nano-transferosome based gel were 299.6 ± 45.6 for F1, 171 ± 25.6 for F2, and 197.4 ± 29.1 nm for F3, while the entrapment efficiency for F1, F2 and F3 were found to be 69.72 ± 8.36, 89.43 ± 6.82, and 93.1 ± 1.93% respectively. The permeation of finasteride from nano-transferosomes based gel was comparatively higher as compared to plain gel of finasteride. The skin penetration of nano-transferosomes based gel into the deeper skin layers was confirmed by fluorescence laser microscope. Therefore, finasteride loaded transferosome based gel had the potential to enhance the finasteride delivery into skin layers by reducing the adverse effects associated with oral delivery.

Ramezani et al. [110] designed elastic liposomes (transferosome) vesicles containing minoxidil and caffeine with a flexible membrane. An optimization design was used and the concentration ratio of tween 20 and tween 80 (edge activators) and volume of hydration media was investigated as the independent parameters, while the parameters studied as dependent variables were encapsulation efficiency, rate of drug release and stability study of prepared elastic liposomes. From the results of evaluation study, it was found that the optimized ratio of tween 20 and tween 80 showed the increased delivery of caffeine and minoxidil into the skin with an enhanced encapsulation efficiency. Thus, the simultaneous delivery of minoxidil and caffeine resulted in increased hair length and volume as proved in *in vivo* studies.

5.7 Niosomes

Mali et al. [111] formulated niosomes containing minoxidil by utilizing the technique of ethanol injection. First of all, the surfactants were screened for their potential to develop niosomal vesicles. Based on the results, span 60, span 20 and polysorbate 20 were found to be optimum. The optimized ratio of span 60 and cholesterol was1:2 which was obtained after the evaluation of minoxidil loaded niosomal formulation on the basis of encapsulation efficiency (34.70 ±1.1 %), stability and vesicle size (470±27 nm). The prepared MXD-niosomes were also subjected to skin permeation studies and the results showed that the increased permeation and retention (17.21 ±3.2 %) of minoxidil was due to an increased concentration of cholesterol. The drug retention from niosomal formulation was much higher in contrast to control solution of minoxidil.

Khatereh et al. [112] aimed to design topical niosomes by utilizing a combination of minoxidil (2%) and tretinoin (0.05%). For the preparation of niosomes, the non-ionic surfactants like Span 20, Span 40, Span 60, span 80 along with tweens were used with cholesterol. The method used for preparation of MXD-tretinoin niosomes was thin layer hydration The maximum confinement observed for minoxidil and tretinoin was 95% and 80% respectively. The stability studies showed changes in particle size values at refrigerator temperature. The noisome formulation showed significantly greater release than minoxidil solution. From the results, it was concluded that the prepared niosomes were efficient and showed controlled release pattern. Thus, they could be used for efficient treatment of alopecia.

5.8 Ethosomes

Wilson et al. [113] designed finasteride loaded ethosomes against androgenetic alopecia with an optimum size rang (100-300 nm) for efficiently delivering the drug into the pilosebaceous units. Ultra-probe sonicator method was used for the formulation of ethosomes and the prepared formulation was characterized on the basis of morphological appearance, vesicle size, zeta potential, permeation studies and encapsulation efficiency. The potential of finasteride loaded ethosomes to permeate across rat skin and human scalp was also examined in comparison with the unentrapped drug. The results indicated that the ethosomes showed higher permeation.

Pravalika et al. [114] formulated minoxidil containing ethosome based gel formulation in order to acquire an increased skin penetration with an efficient rate of drug release. For the preparation of minoxidil loaded ethosomes, minoxidil and phospholipids were taken in different ratios. The optimum ratio of minoxidil and phospholipids for the preparation of ethosomes were found to be 1:4. The prepared ethosomes were then evaluated on the basis of evaluation parameters such as vesicle size, morphology, encapsulation efficiency and drug

Table 4. Different nano-approaches for treatment of alopecia

Nano-formulation	Drug	Method of preparation	Components	Result	Reference
Nano-structured Lipid Carriers (NLCs)	Minoxidil	Melt dispersion ultrasonication technique	Oleic acid, tristearin, cholesterol and phosphatidylcholine, Tween 80 and Carbopol (thickening agent)	Faster onset and prolonged activity	[89]
	Minoxidil and Finasteride	Ultrasonication method	Cetylpalmitate, Precirol®, Tween 60, Miglyol® 812	Low level of drug penetration in MXD and FNS NLCs	[90]
	Spironolactone	Emulsion solvent diffusion or evaporation method	Olive oil, Compritol, Tween 80, Transcutol	Sustained release with localized delivery	[91]
	Minoxidil-squarticles	High speed homogenization and ultrasonication	Pluronic F68, water, squalene, soy phosphatidylcholine	Proliferation of dermal papillae cells and enhanced follicular uptake	[92]
	Minoxidil	Hot High pressure homogenization	Stearic acid, oleic acid, tween 80 and span 80	More retention and permeation of minoxidil with no evidence of erythema	[93]
	Dutasteride	Melt dispersion ultrasonication method	Stearic acid, Phosal® 53 MCT, Lutrol® micro68	Rapid release with enhanced cytotoxicity profile	[94]
	Cyproterone acetate	Solvent diffusion evaporation method	Stearic acid, cholesterol, triolein, acetone	Increased permeation with best accumulation capacity	[95]
	Clobetasol propionate	Hot microemulsion template method	Steric acid, oleic acid, lecithin and taurodeoxycholate	Sustained release with increased hair follicle uptake. No effect of IR radiation with an increased follicular growth by ultrasound vibration.	[96]
Solid Lipid Nanoparticles (SLNs)	Minoxidil	High pressure homogenization method	Suppocire® NAI50, Montane® 80PHA, Montanox® 20PHA and Phosal® 50PG	Non-corrosive and efficient drug penetration	[97]
	Minoxidil sulphate	Magnetic stirring	Chitosan, Sodium tripolyphosphate	Higher follicular uptake	[98]

Nano-formulation	Drug	Method of preparation	Components	Result	Reference
	Flutamide	Hot melt homogenization method	Precirol ATO 50, Span 80, Poloxamer 407, ethanol, water	Enhanced hair follicle growth	[99]
Polymeric Nanoparticles	Colchicine	Double emulsion solvent evaporation	Colchicine, dichloromethane, polycaprolactone, Eudragit RLPO, Eudragit RSPO, Poly-(D,L-lactide)	Sustained release	[100]
	Finasteride	Emulsification or solvent diffusion	Pluronic F68, Sodium polyacrylate, Carbopol	Prolonged release, Improved residence time with less permeation	[101]
	Cyclosporin-A	Rotary evaporator method	Pluronic F68, acetone, ethanol, Poly-(D,L-lactide)	Good physicochemical stability with increased permeation and hair follicle accumulation	[102]
Nano-emulsion	Minoxidil	Aqueous titration technique	Oleic acid, Eucalyptol, Volpo N10, water, PEG 6000, ethanol	High retention from Eucalyptol loaded nanoemulsion but high permeation from oleic acid nanoemulsion	[103]
	Minoxidil	Ultrasonication technique	Clove oil, Kolliphor P188, Cremophor RH40	Enhanced follicular drug penetration in contrast to control solution	[104]
	Finasteride	High-speed homogenization	Soya lecithin, Vitamin E oil, Cholesterol, PEG 600, water	Slow release with restricted permeation	[105]
Liposomes	Finasteride	Film hydration with sonication technique	Saturated phospholipid, Cholesterol	Increased permeation and deposition	[106]
	Minoxidil	Rotary evaporator	Phospholipid, cholesterol, stearylamine, diacetylphosphate	Higher drug deposition from neutral liposomes	[107]
	Minoxidil	Film hydration method	Phospholipon 90H, cholesterol, chloroform	Enhanced permeation with non-irritancy	[108]
Transferosomes	Finasteride	Thin film hydration	Span 65, Phospholipon	Improved and enhanced	[109]

Nano-formulation	Drug	Method of preparation	Components	Result	Reference
		method	90G, methanol	drug delivery into skin	
	Minoxidil and Caffeine	Thin film hydration method	Lecithin, tween 20, tween 80, chloroform, lactic acid	Enhanced delivery into skin with increased hair length	[110]
Niosomes	Minoxidil	Ethanol injection method	Ethanol, cholesterol, Span 60, Diacetyl phosphate	Increased permeation and retention of drug	[111]
	Minoxidil & Tretinoin	Thin film Hydration	Cholesterol, Sorbate esters & Polysorbate	Controlled release & highly stable	[112]
Ethosomes	Finasteride	Ultra-probe sonicator	Ethanol, Finasteride, phospholipid	Increased permeation due to the presence of permeation enhancer	[113]
	Minoxidil	Hot method	Phospholipid 90G, ethanol, water	Increased hair length and diameter in comparison with commercial product	[114]
Cubosomes	Hydroxy propyl β cyclodextrin-Minoxidil complex	Sonication	Hydroxy propyl β cyclodextrin, Minoxidil	Higher permeation and retention of drug	[115]
Metallic Nanoparticles	Ruxolitinib	-	-	Excessive multiplication of fibroblasts	[116]
	Minoxidil	Crush bead mill method	Methyl cellulose, p-hydroxy alkyl benzoates, Mannitol	Promoted hair growth	[117]
Liquid Crystalline Nanoparticles	Finasteride	Ultrasonication	Monoolein, Poloxamer 407, Polyethylene glycol, propylene glycol	Controlled drug release	[118]

diffusion studies. The drug release from prepared ethosomal formulation was significantly higher in comparison with other ethosomal formulations with 75% encapsulation efficiency. The *ex vivo* permeation studies were also conducted for prepared ethosome based gel formulations in comparison with commercial formulation. From all these results, it was concluded that the optimized minoxidil loaded gel formulation (E12) promoted hair growth and hair length.

5.9 Cubosomes

Kwon et al. [115] designed the encapsulation of Hydroxypropyl β-cyclodextrin or minoxidil ((HPβCD)/MXD) complex in Monoolein containing cubosomes. The different concentrations (1.0%/0.32%–19.4%/1.98%) of hydroxypropyl β-cyclodextrin-minoxidil complex were prepared and the concentration of minoxidil in the cubosomes was found to be dependent on the HPβCD. The method used for preparation of cubic phases was bath type sonication. Pluronic F127 was used as a dispersant. The size and structural composition was not dependent on the HPβCD/MXD complex. The *in vitro* skin permeation of minoxidil containing cubosomes (2.44 mg/cm^2) was significantly higher in contrast to the minoxidil dissolved in propylene glycol, water and ethanol mixture (20:30:50 % v/v/v) (1.91 mg/cm^2). However, the drug retention in the deeper skin layers was much higher as compared to minoxidil solution.

5.10 Metallic Nanoparticles

Boca et al. [116] developed Topical Ruxolitinib loaded gold nanoparticles for the treatment of different skin disorders. The technique of electron microscopy was used to examine the inner side of developed novel Ruxolitinib conjugated gold nanoparticles and the techniques of cell counting, western blotting etc. was also used to evaluate drug's potent effects. The results obtained showed that the inhibition of JAK2 protein resulted in excessive multiplication of fibrous cells. This effect is highly acceptable in case of humans as the administration of ruxolitinib would cause less systemic adverse effects.

Nagai et al. [117] prepared minoxidil loaded nanoparticles by utilizing zirconia beads to increase the delivery of minoxidil into the hair follicles. C57BL/6 mice was also used to evaluate the potential of minoxidil nanoparticles. The selected components were firstly dissolved in water and then milled by using suitable conditions.The prepared minoxidil loaded nanoparticles were characterized and found to exhibit oblong shape. The stability and toxicity studies were also conducted for minoxidil loaded nanoparticles and found to be stable for more than 15 days with no evidence of skin toxicity. The hair growth potential was also checked for minoxidil nanoparticles and the results showed that MXD-NPs exhibited less content in skin and maximum content in hair bulbs in contrast to conventional minoxidil formulations. The repetitive application of minoxidil loaded nanoparticles also enhanced the expression of IGF-1 and VEGF when compared to conventional formulations of minoxidil. Therefore, the minoxidil loaded metallic nanoparticles showed high potential for delivery maximum amount of drug into hair follicles.

5.11 Liquid Crystalline Nanoparticles

Madheswaran et al. [118] formulated finasteride loaded liquid crystalline nanoparticles to treat the problem of male-pattern baldness. The technique used for preparation of finasteride containing LCN was ultrasonication and the prepared liquid crystals were evaluated on the basis of different parameters. From the results of evaluation studies, the size range of nanoparticles were found to be 153.8 to 170.2 nm along with a sustained drug release pattern. The liquid crystalline nanoparticles were found to cubical in shape. Oleic acid had an immense effect on the permeation and retention rate of liquid crystalline nanoparticles containing finasteride. Therefore, finasteride containing liquid crystalline nanoparticles could be used as a beneficial nano-approach against androgenetic alopecia.

Furthermore, a few examples of developed nanotechnological based formulations for treating alopecia are depicted in Table 4.

6. CONCLUSION

Alopecia is a remarkably growing disorder presented in many societies and has emerged from different congenital or acquired conditions. Although it is not a life-threatening illness, but it is a form of disfigurement resulting in loss of individual's identity or self-esteem. Some forms of hair loss respond to the given therapeutic medications, while some get resolved over time with the avoidance of different stress conditions. Assessment of the different scarring and non-scarring hair loss can be done by using various

diagnostic approaches like biopsy, patient's age, scalp examinationetc. In the present times, several conventional treatment options which have been identified to treat hair-related disorders were not found to be effective. Thus, the application of nanotechnology has been frequently increased on regular basis to treat them. Nanotechnological approaches are known to overcome the side effects or limitations associated with conventional formulations such as less contact time of drug with the targeted site, palpitations, itching, weight gain etc. Nano-carrier systems like nano-emulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), phospholipid vesicles etc have been formulated for efficient treatment of alopecia and are known to act as drug reservoirs due to rachet effect. Therefore, the release of drug from the nanocarriers would result in presence of effective concentration of drug at the targeted site, thereby, recommending the great potential for treating different forms of alopecia.

7. FUTURE PERSPECTIVES

Development of Nanotechnology based formulations has been an extensively growing field for the treatment of hair-related disorders or for topically targeting the potent drugs into the hair follicles or dermal papillae cells (DPCs) to achieve maximum localized responses. However, the development of nano-approaches against alopecia is still confined to the usage of only two approved drugs: minoxidil or finasteride. Many other drugs which have the potential to promote the hair growth are not introduced yet. Therefore, there is a huge need for collaboration of researchers to increase the invention of nano-technological strategies for delivery of other potential drugs as well. Besides this, there is a scarcity of evaluation data of such nano-formulations which causes a clear restriction in the usage of nanotechnological strategies. Furthermore, the researchers have to give a deep insight over the data obtained on performing *in vitro* and *in vivo* performance assay to evoke the available substantial knowledge. Besides this, an insight into the nano-safety profile is a significant parameter and needs utmost guidance and regulation as it can hinder the commercialization of nano-formulationsin the market.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Norwood OT. Male–pattern baldness. Classification and incidence. South Med J. 1975;68(11):1359–1370.
2. Xu L, Liu KX, Senna MM. A Practical Approach to the Diagnosis and Management of hair Loss in Children and Adolescents. Front. Med. 2017;4(112):1-13.
3. Alshahrani AA, Tuwaijri RA, Abuoliat ZA, Alyabsi M, Alkjodair R. Prevalence and Clinical characteristics of Alopecia areata. Dermatology Research and Practice. 2020;1-4.
4. Likhitkar M, Shakur AA, Bansal KK, Pande M. Alopecia - reason and possible treatments. MOJ Drug Des Develop Ther. 2018;2(5):198-208.
5. Rivitti E. Alopecia areata:A revision and update. Bras Dermatol. 2005;80(1):57-68.
6. Wang E, McElwee KJ. Etiopathogenesis of alopecia areata:Why do our patients get it. Dermatol Ther. 2011;24:337-347.
7. Sunderberg JP, Silva KA, Zhang W, Sunderberg BA, Edwards K, King LE. Recombinant human hepatitis B vaccine initiating alopecia areata:Testing the hypothesis using the C3H/HeJ mouse model. Vet. Dermatol. 2009;20:99-104.
8. Hunt N, McHale S. The psychological impact of Alopecia. BMJ. 2005;331:1-3.
9. Knorr F, Lademann J, Patzelt A, Sterry W, Blume-Peytavi U, Vogt A. Follicular transport route–research progress and future perspectives. Eur. J. Pharm. Biopharm. 2009;71:173–180.
10. Bawa R. Nano-pharmaceuticals:Nano-pharmaceuticals. European Journal of Nanomedicine. 2010;3:34-40.
11. Radtke M, Patzelt A, Knorr F, Lademann J, Netz RR. Ratchet effect for nanoparticle transport in hair follicles. Eur. J. Pharm. Biopharm. 2017;116:125–130.
12. Kantor J, Kessler LJ, Brooks DG, Cotsarelis G. Decreased serum ferritin is associated with alopecia in women. J Invest Dermatol. 2003;121(5):985-988.

13. Farrant P, Messenger AG, McKillop J. British Association of Dermatologists-Guidelines for the management of Alopecia. Br J Dermatol. 2012;166(916):1-3.
14. Messenger AG. Medical management of male pattern hair loss. Int J Dermatol. 2000;39:585-586.
15. Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update:PartI. Clinical picture, histopathology, and pathogenesis. J Am Acad Dermatol. 2010;62:177-88.
16. McDonagh AJ, Tazi-Ahnini R. Epidemiology and genetics of alopecia areata. Clin Exp Dermatol 2002;27:405-9.
17. Biran R, Zlotogorski A, Ramot Y. The genetics of alopecia areata:New approaches, new findings, new treatments. J Dermatol Sci. 2015;78:11-23.
18. Güleç AT, Tanriverdi N, Dürü C, SarayY, Akçali C. The role of psychological factors in alopecia areata and the impact of the disease on the quality of life. Int J Dermatol 2004;43:352-6.
19. Brajac I, Tkalcic M, Dragojević DM, Gruber F. Roles of stress, stress perception and trait-anxiety in the onset and course of alopecia areata. J Dermatol 2003;30:871-8.
20. Ito T, Meyer K, Ito N, Paus R. Immune privilege and the skin;Current Directions in Autoimmunity:2008;10:27–52.
21. Moreno GA, Ferrando J. Alopecia areata. Med CutanIbero Latina Americana. 2000;28:294-312.
22. Stefenato CM. Histopathology of alopecia:A clinicopathological approach to diagnosis. Histopathology. 2010;56: 24-38.
23. Adil A, Godwin M. The effectiveness of treatments for Androgenic alopecia:A systematic review and meta-analysis. J. Am. Acad. Dermatol. 2017;77:136-141.
24. Al A, Ahmad M, Patrick M. Alopecia. StatPearls, Treasure Island (FL):StatPearls Publishing. 2020;
25. Santos AC, Silva MP, Guerra C, Costla D, Peixoto D, Pereira I, Pita I, Ribeiro AJ, Veiga F. Topical Minoxidil-Loaded nanotechnology Strategies for Alopecia. Cosmetics. 2020;7(21):1-25.
26. Santos Z, Avci P, Hamblin MR. Drug discovery for alopecia:Gone today, hair tomorrow. Expert Opin. Drug Discov. 2015;10:269–292.
27. Headington JT. Telogen effluvium. New concepts and review. Arch Dermatol. 1993;129(3):356–63.
28. Alves R, Grimalt R. Hair loss in children. Curr Probl Dermatol. 2015;47:55–66.
29. Kanwar AJ, Narang T. Anagen effluvium. Indian J Dermatol Venereol Leprol. 2013;79(5):604–12.
30. Tosti A, Misciali C, Piraccini BM, Peluso AM, Bardazzi F. Drug-induced hair loss and hair growth. Incidence, management and avoidance. Drug Saf. 1994;10(4):310–7.
31. Birch MP, Lalla SC, Messenger AG. Female pattern hair loss. Clin Exp Dermatol. 2002;27:383–388.
32. Olsen EA, Messenger AG, Shapiro J, Bergfeld WF, Hordinsky MK, Roberts JL. Evaluation and treatment of male and female pattern hair loss. J Am Acad Dermatol. 2005;52(2):301–11.
33. Darwin E, Fertig D, Delcanto G, Jimeniz JJ, Doliner B, Hirt PA. Alopecia Areata:Review of Epidemiology, Clinical features, Pathogenesis and New treatment Options. Int. J trichology. 2018;10(2):51-60.
34. Garza LA, Qi J. An overview of Alopecias. Cold Spring Harbor Perspectives in Medicine. 2014;4:1-14.
35. Price V. Alopecia areata. Clinical aspects. J Invest Dermatol. 1991;96:685.
36. Mirmirani P, Tucker LY. Epidemiologic trends in pediatric tinea capitis:a population-based study from Kaiser Permanente Northern California. J Am Acad Dermatol. 2013;69(6):916–21.
37. Abdel-Rahman SM, Farrand N, Schuenemann E, Stering TK, Preuett B, Magie R. The prevalence of infections with Trichophyton tonsurans in school children:the CAPITIS study. Pediatrics. 2010;125(5):966–73.
38. Hantash BM, Schwartz RA. Traction alopecia in children. Cutis. 2003;71(1):18–20.
39. Whiting DA. Traumatic Alopecia. Int J Dermatol. 1999;34-44.
40. Cutrone M, Grialt R. Transient neonatal hair loss:a common transient neonatal dermatosis. Eur J Pediatr. 2005;164(10):630-632.
41. Christenson GA, Pyle RL, Mitchell JE. Estimated lifetime prevalence of trichotillomania in college students. J Clin Psychiatry. 1991;52(10):415–417.

42. Grant JE, Odlaug BL. Clinical characteristics of trichotillomania with trichophagia. Compr Psychiatry. 2008; 49(6):579–84.
43. Akingbola CO, Vyas J. Traction Alopecia:A neglected entity in 2017. Indian J Dermatol Venereol leprol. 2017;83:644-649.
44. Siddappa K. Trichotillomania. Indian J DermatolVenereolLeprol. 2003;69:63-68.
45. Gatherwright J, Liu MT, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to female alopecia:A study of identical twins. Plast Reconstr Surg. 2012;130:1219-26.
46. Trovato MJ, Schwartz RA, Janniger CK. Tinea capitis:current concepts in clinical practice. Cutis. 2006;77(2):93–9.
47. Grover C, Khurana A. Telogen effluvium. Indian J Dermatol Venereol Leprol. 2013;79:591-603.
48. Abal L, Soria X, Casanova-Seuma JM. Alopecias cicatriciales. Actas Dermosifiliogr. 2012;103:376-87.
49. Bernardez C, Molina-Ruiz AM, Requena L. Histologic features of Alopecias:Part II:Scarring Alopecias. ACTAS Dermo-Sifiliograficas. 2014;261-270.
50. Gathers RC, Lim HW. Central centrifugal cicatricial alopecia:past, present, and future. J Am AcadDermatol. 2009;60(4):660–8.
51. Shah SK, Alexis AF. Central centrifugal cicatricial alopecia:retrospective chart review. J Cutan Med Surg. 2010;14(5):212–22.
52. Sperling LC, Sau P. The follicular degeneration syndrome in black patients. Hot comb alopecia revisited and revised. Arch Dermatol. 1992;128:68-74.
53. Miettunen PM, Bruecks A, Remington T. Dramatic response of scarring scalp discoid lupus erythematosus (DLE) to intravenous methylprednisolone, oral corticosteroids, and hydroxychloroquine in a 5-year-old child. Pediatr Dermatol. 2009:26(3):338–41.
54. Tebbe B, Orfanos CE. Epidemiology and socioeconomic impact of skin disease in lupus erythematosus. Lupus. 1997;6:96 – 104.
55. Lyakhovitsky A, Amichai B, Sizopoulou C, Barzilai A. A case series of 46 patients with lichen planopilaris:demographics, clinical evaluation, and treatment experience. J Dermatolog Treat. 2015;26(3):275–279.
56. Assouly P, Reigagne P. Lichen planopilaris:update on diagnosis and treatment. SeminCutan Med Surg. 2009;28(1):3–10.
57. Verma R, Bhatnagar A, Vasudevan B, Kumar S. Keratosis follicularis spinulosa decalvans. Indian J Dermatol Venereol Leprol. 2016;82:214–6.
58. Hempstead RW, Ackerman AB. Follicular mucinosis. A reaction pattern in follicular epithelium. Am J Dermato pathol, 1985;7:245-57.
59. Pinkus H. The relationship of alopecia mucinosa to malignant lymphoma. Dermatologica. 1964;129:266-70.
60. Kossard S. Postmenopausal frontal fibrosing alopecia. Scarring alopecia in a pattern distribution. Arch Dermatol. 1994;130:770–774.
61. Pirmez R, Duque-Estrada B, Abraham LS. It's not all traction:the pseudo 'fringe sign' in frontal fibrosing alopecia. Br J Dermatol. 2015;173:1336–8.
62. Harries MJ, Sinclair RD, Donald-Hull M, Whiting DA, Griffiths CE, Paus R. Management of primary cicatricial alopecia:Options for treatment. Br J Dermatol. 2008;159:1-22.
63. Rácz E, Gho C, Moorman PW, Noordhoek V, Neumann HA. Treatment of frontal fibrosing alopecia and lichen planopilaris:a systematic review. J Eur Acad Dermatol Venereol. 2013;27(12):1461–1470.
64. Ross EK, Tan E, Shapiro J. Update on primary cicatricial alopecia. J Am Acad Dermatol. 2005;53:1- 37.
65. Samrao A, Chew AL, Price V. Frontal fibrosing alopecia: A clinical review of 36 patients. Br J Dermatol. 2010;163:1296–1300.
66. Sequeira FF, Jayaseelan E. Keratosis follicularis spinulosa decalvans in a female. Indian J Dermatol Venereol Leprol. 2011;77:325–7.
67. Brooke RC, Griffiths CE. Folliculitis decalvans. Clin Exp Dermatol. 2001;26:120-2.
68. Salim A, David J, Holder J. Dissecting cellulitis of the scalp with associated spondyl arthropathy:case report and review. J Eur Acad Dermatol Venereol. 2003;17:689-91.
69. Séez M, Rodríguez-Martín M, Sidro M, Carnerero A, García-Bustínduy M, Noda A. Successful treatment of erosive pustular dermatosis of the scalp with topical tacrolimus. Clin Exp Dermatol. 2005;30:599-600.

70. Petiau P, Cribier B, Chartier C. Acne necrotica varioliformis:Resolution with isotretinoin. Eur J Dermatol. 1994;4:608-10.
71. Mahe A. Treatment of acne keloidalisnuchae:recommendations. Ann Dermatol Venereol. 1999;126:541-2.
72. Powell JJ, Dawber RPR, Gatter K. Folliculitis decalvans including tufted folliculitis:Clinical, histological and therapeutic findings. Br J Dermatol. 1999;140:328–33.
73. Annessi G, Lombardo G, Gobello T, Puddu P. A clinicopathologic study of scarring alopecia due to lichen planus:Comparison with scarring alopecia in discoid lupus erythematosus and pseudopelade. Am J Dermatopathol. 1999;21:324-31.
74. Badaoui A, Reygagne P, Cavelier-Balloy B. Dissecting cellulitis of the scalp:a retrospective study of 51 patients and review of literature. BrDermatol. 2016;174:421-423.
75. Burton JL, Peachey RD, Pye RJ. Erosive pustular dermatosis of the scalp-a definition. Br J Dermatol. 1988;119: 411.
76. Kossard S, Collins A, McCrossin I. Necrotizing lymphocytic folliculitis:The early lesion of acne necrotica (varioliformis). J Am Acad Dermatol. 1987;16:1007-14.
77. Stritzler C, Friedman R, Loveman AB. Acne nectrotica;relation to acne necrotica milaris and response to penicillin and other antibiotics. AMA Arch DermSyphilol. 1951;64(4):464-9.
78. Salami T, Omeife H, Samuel S. Prevalence of acne keloidalis nuchae in Nigerians. Int J Dermatol. 2007;46(5):482–484.
79. Kelly AP. Pseudofolliculitis barbae and acne keloidalis nuchae. Dermatol Clin. 2003;21(4):645–653.
80. Rongioletti F, Christana K. Cicatricial (scarring) alopecias:An overview of pathogenesis, classification, diagnosis, and treatment. American Journal of Clinical Dermatology. 2012;13(4):247-260.
81. Sundberg JP, Hordinsky MK, Bergfeld W, Lenzy YM, McMichael AJ, Christiano AM, et al. Cicatricial Alopecia Research Foundation Meeting, May 2016:Progress towards the diagnosis, treatment and cure of primary cicatricia alopecias. Experimental Dermatology. 2018 ;27(3):302-310.
82. Mirmirani P, Huang KP, Price VH. A practical, algorithmic approach to diagnosing hair shaft disorders. Int J Dermatol. 2011;50(1):1–12.
83. Cantatore-Francis J.L, Orlow SJ. Practical guidelines for evaluation of loose anagen hair syndrome. Arch Dermatol. 2009;145(10):1123–8.
84. Haskett M. Loose anagen syndrome. Australas J Dermatol. 1995;36(1):35–6.
85. Herskovitz I, de Sousa ICD, Simon J, Tosti A. Short anagen hair syndrome. Int J Trichol. 2013;5:45-46.
86. Barraud MM, Trüeb RM. Congenital hypotrichosis due to short anagen. Br J Dermatol. 2000;143(3):612–7.
87. Gupta S, Bansal R, Gupta S, Jindal N, Jindal A. Nanocarriers and nanoparticles for skin care and dermatological treatments. Indian Dermatol. Online J. 2013;4:267–272.
88. Vogt A, Wischke C, Neffe AT, Ma N, Alexiev U, Lendlein A. Nanocarriers for drug delivery into and through the skin—Do existing technologies match clinical challenges? J. Control. Release. 2016;242:3–15.
89. Uprit S, Sahu RK, Roy A, Pare A. Preparation and characterization of minoxidil loaded nanostructured lipid carrier gel for effective treatment of alopecia. Saudi Pharmaceutical Journal. 2013:21:379-385.
90. Gomes MJ, Martins S, Ferreira D, Segundo MA, Reis S. Lipid nanoparticles for topical and transdermal application for alopecia treatment:development, physicochemical characterization, and *in vitro* release and penetration studies. Int J Nanomedicine. 2014;9:1231-42.
91. Shamma RN, Aburahma MH. Follicular delivery of spironolactone via nanostructured lipid carriers for management of alopecia. International Journal of Nanomedicine, 2014;9:5449-5460.
92. Aljuffali JA. Anti-PDGF receptor β antibody-conjugated squarticles loaded with minoxidil for alopecia treatment by targeting hair follicles and dermal papilla cells. Nanomedicine Nanotechnology, Biology and Medicine. 2010;11:1321-1330.
93. Wang W, Chen L, Huang X, Shao A. Preparation and Evaluation of Minoxidil-Loaded Nanostructured Lipid carriers. American Association of Pharmaceutical Sciences. 2016;1530-9932.

94. Noor NM, Sheikh K, Somavarapu S, Taylor MG. Preparation and characterization of dutasteride-loaded nanostructured lipid carriers coated with stearic acid-chitosan oligomer for topical delivery. European Journal of Pharmaceutics and Biopharmaceutics. 2017;117:372-384.
95. Ghasemiyeh P, Azadi A, Daneshamouz S, Heidari R, Azarpira N, Mohammadi-Samani S. Cyproterone Acetate-Loaded Nanostructured Lipid Carriers:Effect of Particle Size on Skin Penetration and Follicular Targeting. Pharmaceutical Development and Technology. 2019;1–37.
96. Angelo T, El-Sayed N, Jurisic M. Effect of physical stimuli on hair follicle deposition of clobetasol-loaded Lipid Nanocarriers. Sci Rep. 2020;10:176.
97. Padois K, Centieni C, Bertholle V, Bardel C, Pirot F, Falson F. Solid lipid Nanoparticles versus Commercial solutions for dermal delivery of Minoxidil. International Journal of Pharmaceutics. 2011;416:300-304.
98. Matos BN, Reis TA, Gratieri T, Gelfuso GM. Chitosan Nanoparticles for targeting and sustaining Minoxidil sulpate delivery into hair follicles. International Journal of Biological Macromolecules. 2015;75:225-229.
99. Hamishehkar H, Ghanbarzadeh S, Sepehran S, Javadzadeh Y, Adib ZM, Kouhsoltani M. Histological assessment of follicular delivery of flutamide by solid lipid nanoparticles:potential tool for the treatment of androgenic alopecia. Drug Dev Ind Pharm. 2016;42(6):846-53.
100. Khalil R. Hashem F, Zaki H, El-Arini S. Polymeric Nanoparticles as potential carriers for topical delivery of Colchicine:Development and *in vitro* characterization. International Journal of Pharmaceutical Sciences and Research. 2014;5(5):1746-1756.
101. Roque LV, Dias IS, Cruz N, Rebelo A, Roberto A, Rijo P, Reis CP. Design of Finasteride-Loaded Nanoparticles for Potential Treatment of Alopecia. Skin Pharmacol Physiol. 2017;30(4):197-204.
102. Fernandes B, Matamá T, Andreia C Gomes, Cavaco-Paulo A. Cyclosporin A-loaded poly(d,l-lactide) nanoparticles:a promising tool for treating alopecia. Nanomedicine (Lond). 2020 Jun;15(15):1459-1469.
103. Abd E, Benson HAE, Roberts MS, Grice JE. Follicular penetration of caffeine from topically applied nanoemulsion formulations containing penetration enhancers in vitro human skin studies. Skin Pharmacol Physiol. 2018;31(5):252-60.
104. Cardoso SA, Baraddass TN. Developing Formulations for Drug Follicular targeting:Submicron-sized emulsions loaded with Minoxidil and Clove oil. Journal of Drug Delivery Science and Technology. 2020;59:1-10.
105. Upadhyay DK, Sharma A, Kaur N, Narang RK, Gupta GD, Rai VK. Nanoemulgel for Efficient Topical Delivery of Finasteride Against Androgenic Alopecia. Journal of pharmaceutical innovation. 2020;1-12.
106. Kumar R, Singh B, Bakshi G, Katare OP. Development of liposomal systems of finasteride for topical applications:design, characterization, and in vitro evaluation. Pharm Dev Technol. 2007;12(6):591-601.
107. Jain B, Singh B, Katare OP, Vyas SP. Development and characterization of minoxidil-loaded liposomal system for delivery to pilosebaceous units. Journal of Liposome Research. 2010;20(2):105–114.
108. Kochar P, Nayak K, Thakkar S, Polaka S, Khunt D, Misra M. Exploring the Potential of Minoxidil Tretinoin Liposomal Based Hydrogel for Topical Delivery in the Treatment of Androgenic Alopecia. Cutaneous and Ocular Toxicology. 2019;1-31.
109. Ahmed OAA, Rizg WY. Finasteride nano-transferosomal gel formula for management of androgenetic alopecia:ex vivo investigational approach. Drug Des DevelTher. 2018;12:2259-2265.
110. Ramezani V, Honarvar M,Seyedabadi M, Karimollah A, Ranjbar AM, Hashemi M. Formulation and Optimization of transferosomes containing minoxidil and caffeine. Journal of Drug Delivery Science and Technology. 2018;1-26.
111. Mali N, Darandale S, Vavia P. Niosomes as a vesicular carrier for topical administration of minoxidil:formulation and *in vitro* assessment. Drug Deliv. and Transl. Res. 2013;3:587–592.
112. Khatereh Z, Payam K, Abbas P, Mehdi R. Preparation and Physicochemical Characterization of Topical Niosomal Formulation of Minoxidil and Tretinoin. Glob J Pharmaceu Sci. 2017;3(2):555606.
113. Wilson V, siram k, Rajendran S, Sankar V. Development and evaluation of finasteride loaded ethosomes for targeting to the

pilosebaceous units. Artif Cells Nanomed Biotechnol. 2018;46(8):1892-1901.
114. Pravalika G, Chandhana P, Chiranjitha I, Dhurke R. Minoxidilethosomes for treatment of alopecia. International Journal of Recent Scientific Research. 2020; 11(1):37112-37117.
115. Kwon TK, Kim JC. *In-vitro* skin permeation of monoolein nanoparticles containing β-cyclodextrins/minoxidil complex. International Journal of Pharmaceutical Sciences. 2010;392:268-273.
116. Boca S, Berce C, Jurj A, Petrushev B, Pop L, Gafencu GA, Selicean S, Moisoiu V, Temian D, Micu WT, Astilean S, Braicu C, Tomuleasa C, Berindan-Neagoe I. Ruxolitinib-conjugated gold nanoparticles for topical administration: An alternative for treating alopecia? Med Hypotheses. 2017 Nov;109:42-45.
117. Nagai N, Iwai Y, Sakamoto A, Otake H, Oaku Y, Abe A, Nagahama T. Drug Delivery System Based On Minoxidil Nanoparticles Promotes Hair Growth In C57BL/6 Mice. Int J Nanomedicine. 2019; 14:7921-7931.
118. Madheswaran T, Baskaran R, Thapa RK, et al. Design and in vitro evaluation of finasteride-loaded liquid crystalline nanoparticles for topical delivery. AAPS Pharm Sci Tech. 2013;14(1): 45-52.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/71885