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Proceeding Paper

Nanotechnology-Based Strategies for Hair Follicle Regeneration in Androgenetic Alopecia †

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† Presented at 4th International Online Conference on Nanomaterials, 5–19 May 2023; Available online: https://iocn2023.sciforum.net.

Abstract: A frequent type of hair loss that affects both men and women, androgenetic alopecia is indicated by the gradual miniaturization of hair follicles, which results in thinner and shorter hair growth cycles. Despite the availability of various treatment options, a definitive cure for androgenetic alopecia is yet to be found. Nanotechnology has recently become recognized as a promising strategy for treating androgenetic alopecia. This review comprehensively analyzes the present situation and potential nanotechnology applications in managing androgenetic alopecia. The present study highlights various nanomaterials, including nanoparticles, liposomes, and dendrimers, and their potential for the delivery of drugs and growth factors to hair follicles. The possibility of nanomaterials in enhancing the bioavailability and efficacy of existing treatments for androgenetic alopecia, such as minoxidil and finasteride. Additionally, the study discusses the potential of nanotechnology in developing new therapeutic strategies, including gene therapy and tissue engineering approaches for hair follicle regeneration. Furthermore, the challenges associated with the clinical translation of a nanotechnology-based approach to androgenetic alopecia include the need for targeted delivery systems and long-term safety studies. In conclusion, nanotechnology holds great promise for developing effective and safe treatments for androgenetic alopecia. The targeted delivery and improved efficacy of existing drugs and the development of new therapeutic approaches using nanotechnology offer new possibilities for treating androgenetic alopecia.

Keywords: androgenetic alopecia; hair loss; nanotechnology; nanomaterials; nanoparticles; liposomes; gene therapy; Minoxidil

Citation: Shaikh, Z.S.A.; Patel, B.A.A.; Patil, S.G.; Maniyar, A.R.S. Nanotechnology-Based Strategies for Hair Follicle Regeneration in Androgenetic Alopecia. *Mater. Proc.* **2023**, *14*, x. https://doi.org/10.3390/xxxxx
Published: 5 May 2023

1. Introduction

AGA, or androgenetic alopecia, is a common hair-related condition that affects genetically predisposed men and women to dihydrotestosterone (DHT), a hormone that inhibits follicular development. [1,2] Gradual hair loss patterns define AGA. Age is a recognized factor in the development of AGA, which affects 58% of men at the age of 50 and 73% of men and 57% of women over the age of 80 [3]. Although AGA is a non-lethal condition, it usually raises worrying psychological and social issues.[4]

AGA's pathogenic mechanism is still not completely identified. Still, it is evident that it encourages the miniaturization of hair follicles, reduces hair density, and, as a result, favors the growth of vellus hair. This process results from the anagen phase shortening, which also reduces the number of hair follicles and hair density as well as the size of the hair follicles (decreased thickness) and diameter of the hair follicle [5].

Four key therapeutic categories may be described when considering AGA treatment: growth factors, inhibitors of 5-reductase (the hormone responsible for converting testosterone into DHT), ATP-sensitive potassium channel agonists of androgen receptor antagonists [3].

2. Current Treatment Options

The shrinkage of hair follicles characterizes androgenetic alopecia due to changes in the capillary cycle and elevated levels of the hormone dihydrotestosterone. One of the primary medications used in treatment, finasteride, targets the enzyme 5'-reductase [6], which reduces this hormone from testosterone. Along with finasteride, dutasteride belongs to the family of 4-azasteroids. However, although finasteride blocks only one isoform of the 5-reductase enzyme selectively and permanently, dutasteride inhibits both isoforms 1 and 2, reducing dihydrotestosterone levels by around 90% [7]. Importantly, systemic adverse effects such as depression, erectile dysfunction, teratogenicity, gynecomastia infertility, and prostate and breast cancer are linked to using enzyme 5- reductase inhibitors [8,9].

The safest therapeutic solution on the market, minoxidil, is used topically and is known to be a vasodilator that prolongs the anagen phase and contributes to the control of prostaglandin levels; however, the whole mechanism of action is yet unknown [10]. While minoxidil has positive outcomes, most commercial formulations include a significant quantity of ethyl alcohol or propylene glycol, which may cause irritation, burning, allergic dermatitis, redness, and scalp dryness, which can be made worse by frequent use. Moreover, an elevated heart rate, hypertrichosis, and salt and water retention have been shown [11]. Just minoxidil 2 and 5% solution or foam—administered twice daily—are now the pharmaceutical therapies permitted in the USA for both men and women. In contrast, the US FDA has only approved oral finasteride (tablets, 1 mg/day) for males [12]. The accessibility of pharmaceutical treatments, however, may differ globally. Dutasteride (0.5 mg daily) is authorized for treating androgenetic alopecia in males in various nations, such as Korea and Mexico.

Spironolactone has been extensively utilized as a therapy for female pattern hair loss owing to its antiandrogenic effects, despite being prescribed for managing cardiovascular problems. Its mechanism of action involves interfering with the 17a-hydroxylase, desmolase, and competitive inhibitor of the androgen receptor, which decreases the adrenal gland's ability to produce testosterone. The most popular antiandrogen for female pattern hair loss (FPHL) is spironolactone, and the recommended dosage is 100–200 mg per day [13] despite being well-tolerated and available for years. Spironolactone's adverse effects include electrolyte imbalance, decreased renal function, and hypotension.

Flutamide is an oral antiandrogen that's only occasionally used in clinical settings. Oral flutamide was first discovered as a suitable treatment for hyperandrogenic alopecia [14] In a 55-year-old female with FPHL that was resistant to topical minoxidil and oral spironolactone, oral flutamide 250 mg daily was shown to be helpful [15]. AGA treatment by oral flutamide was examined in large-population research. The Alopecia score was significantly reduced, and 4% of the patients withdrew from the research in the first phase due to liver damage[16]. Hepatic damage and hepatic failure are potential side effects of flutamide.

An antiandrogen drug called bicilutamide is non-steroidal. While managing prostate cancer, it offers a better safety profile than flutamide. A recent retrospective review study of 17 women who received oral bicalutamide (OB) with or without adjuvant therapies revealed that OB is a beneficial therapeutic option for female pattern hair loss, particularly for patients with other comorbid conditions polycystic ovarian syndrome or hirsutism [17]. Bicalutamide's most frequent adverse effect is a temporary, slight increase in liver enzymes.

Cyproterone acetate (CA) decreases androgen receptor function, cutaneous 5-alpha-reductase activity, and gonadotropin secretion. While CA is not marketed in the US, it has

been utilized in other countries. Weight gain, breast tenderness, and reduced libido are all effects of cyproterone acetate [18,19].

Current treatments for AGA, such as Minoxidil, Finasteride, Spironolactone, etc., are ineffective and often provide only temporary relief. These treatments also have potential side effects, which may limit their long-term use. Given the limitations of current treatments, there is a critical need to develop a definitive cure for AGA that can provide long-term and safe solutions to hair loss. Nanotechnology-based strategies offer a promising avenue for hair follicle regeneration in AGA, providing a potential cure that can target the underlying cellular and molecular causes of hair loss. These innovative approaches can potentially revolutionize the treatment of AGA and improve the quality of life for individuals affected by this condition. Therefore, further research is necessary to explore the full potential of nanotechnology-based strategies for hair follicle regeneration in AGA and to develop safe and effective treatments for this condition.

Nanosystems, including liposomes, ethosomes, niosomes, lipid nanoparticles, and polymeric nanoparticles, have proposed promising strategies for treating hair loss [20,21]. These systems offer advantages over conventional formulations, such as improved patient compliance, controlled drug release, and reduced systemic adverse effects. Furthermore, nanosystems can mitigate irritation associated with traditional formulations and utilize biocompatible materials. Nanotechnology is particularly advantageous for treating hair follicle disorders as these systems naturally accumulate in follicle casts, increasing local drug concentration and reducing systemic side effects. The present study highlights the latest advancements in nanotechnology-based strategies for treating the most common types of alopecia, highlighting the potential of these approaches to revolutionize hair loss treatment.

3. Nanomaterials for Drug Delivery in Androgenetic Alopecia

3.1. Lipid Nanoparticles

Drugs may be absorbed via the skin through the intact epidermis (transepidermal route) or cutaneous appendages (by transappendageal) [22]. One of these appendages, the hair follicle, serves as an entrance site for drugs administered topically and also aids in the passage of medications through the skin [23]. The focused therapy increases medication bioavailability, resulting in the intended impact with low drug concentrations [24]. Some of the most researched lipid nanosystems are solid lipid nanoparticles or a solid matrix containing a combination of liquid, amorphous, or unsaturated lipids (nanostructured lipid carriers) [25]. The size ranges below 100 nm are shown to be essential for the start of action on dermal drug release.

Moreover, drug release along the isthmus portion of the hair follicles has been favoured by diameter ranges around 200 nm. Compared to marketed products, solid lipid nanoparticles containing minoxidil with a diameter of 190 nm showed superior accumulation in porcine skin layers. While solid lipid nanoparticles have shown excellent penetration findings, stability is a persistent concern because solid lipids may form crystalline networks [26], which can cause drug ejection during storage, particularly when the solid lipid matrix is made up of a highly pure lipid [27]. As a result, nanostructured lipid carriers were created as a new class of lipid particles.

Finasteride and minoxidil may be encapsulated in nanostructured lipid carriers, exhibiting high physical and chemical stability during storage [28]. Minoxidil-containing nanostructured lipid carriers showed excellent entrapment efficiency (92.5 0.3%) and were more stable over three months than solid lipid nanoparticles. Also, compared to solid lipid nanoparticles containing minoxidil, minoxidil encapsulated in nanostructured lipid carriers offered a 10.7-times better skin permeability. The composition contains oleic acid, which may be a permeation enhancer [29]. Notably, the effectiveness of trapping is closely correlated with lipid content. With the more oleic acid present, clobetasol propionate was

more effectively trapped within nanostructured lipid carriers, with an entrapment efficiency of more than 70%. More oleic acid (a liquid lipid) in the mixture has been shown to encourage an amorphous form in the solid lipid matrix, reducing the particles' crystallinity and increasing encapsulation effectiveness [30]. This was attributed to either the presence of the unentrapped drug in the dispersion of the nanostructured lipid carriers or to the localization of lipids in the outer shell containing clobetasol propionate in the dissolved form [49]. Clobetasol propionate was present in nanostructured lipid carriers of glyceryl behenate (compritol 888 ATO, solid lipid) and oleic acid (liquid lipid).

A similar release profile was seen with nanostructured lipid carriers that contained minoxidil. Oleic acid reduced the size of the lipid particles, increasing their surface area and perhaps causing an initial increase in release rate. Compared to controls containing free medicines, the follicular deposition of a different particle system made of tallow-derived lipids (squalene and fatty esters), known as squarticles, encapsulates diphenylcyclopropenone and minoxidil was two to seven times greater, respectively. Confocal pictures verified these results [31]. The polymeric coating is another factor affecting nanosystems' effectiveness in targeting medications through hair. The bioavailability of the medicine at the action site and the drug's release profile may be impacted by coating. Compared to nanostructured lipid carriers coated with 5% stearic acid-chitosan, uncoated nanostructured lipid carriers carrying dutasteride delivered a quicker drug release (72% over 36 h), which had an impact on the drug's availability at the site of action. As compared to coated particles (2.8 ± 0.4 g/cm^2 with a diameter of 220.1 ± 11.9 nm), the uncoated particles had a more excellent permeability for dutasteride (6.1 ± 1.1 g/cm^2 with a diameter of 187.6 ± 7.0 nm) [32,33].

3.2. Liposomes

The phospholipid bilayer structures known as liposomes have aqueous cores and can contain either lipophilic or hydrophilic drugs trapped within the phospholipid bilayers [34]. This system works well to enter the lipid-filled hair follicles because liposomes are lipophilic. As a result, their convenience in preparation and ability to boost the skin's absorption of active chemicals make them appropriate for cosmetic and medical purposes [35]. Because of their phospholipid composition, liposomes can interact with the lipids in the stratum corneum to enable MXD to penetrate the skin or to pass through the hair follicles to form MXD depots [36]. Using liposomes to administer MXD topically has been investigated. Liposomes are biocompatible and biodegradable and can stay in the bloodstream long. However, their usefulness is limited because of stability problems such as aggregation, drug leakage, hydrolysis, and altered particle size [37]. The disruption of the skin's tight connections brought on by the presence of positively charged polymers may help improve MXD skin permeation. Liposomes containing finasteride were integrated into 2%*w*/*w* methylcellulose gel, and the results demonstrated much greater penetration in abdominal mice skin compared to finasteride hydroalcoholic solution and conventional gel containing finasteride [35]. Liposomal phospholipids can mix and change how intercellular lipids are arranged, allowing drugs to accumulate and improving skin delivery.

3.3. Polymeric Nanoparticles

Using biodegradable and biocompatible polymers or monomers, such as chitosan, cellulose, polystyrene, PLA, PLGA, polyvinyl alcohol, and polyethyleneimine, polymeric nanoparticles in the nanometer range are developed [38]. Through different bodily barriers, NPs with a diameter of around 1 nm and 1000 nm are more likely to reach their target organs or tissues [39]. NPs can be deeply entrapped within the hair follicle even though they are unable to cross the skin barrier fully. Furthermore, the large surface area to volume ratio improves particle-target cell contact. Time-dependent NPs systems preferentially enter the follicle, but optimal-size NPs show higher follicular accumulation. As a

result, in the last ten years, polymer-based synthetic nanotechnology-based formulations have attracted increasing attention as a follicular drug delivery treatment.

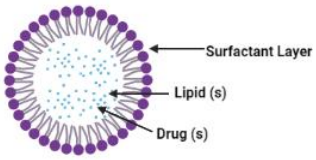
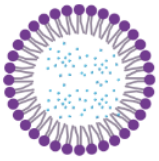
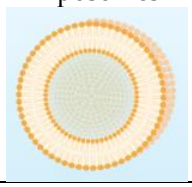
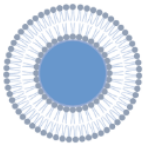
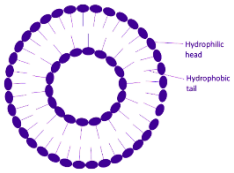
Finasteride-containing poly(lactide-co-glycolide) copolymer nanoparticles were developed and characterized. Tests on the Saccharomyces cerevisiae model demonstrated that the polymer was not toxic, demonstrating these systems' biocompatibility and a high potential for treating alopecia [40].

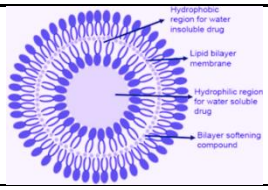
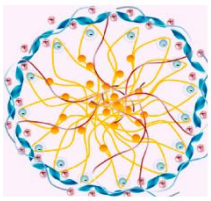
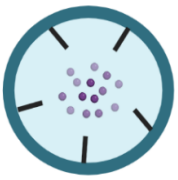
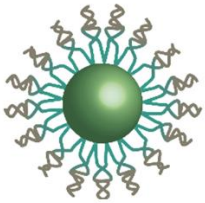
Moreover, polymeric nanoparticles can encapsulate medications in shells from deterioration, extending shelf life and regulating drug release. Lecithin/chitosan nanoparticles containing clobetasol propionate remain stable for three months at room temperature [41]. In another investigation, polymeric finasteride microspheres have demonstrated continued drug release for up to 5–6 weeks following an initial burst release [42].

The use of polymers for drug loading and administration in hair follicles is a potent non-invasive mode of administration by promoting homogenous, stable systems that release in a controlled manner.

3.4. Table 1: Important Roles for Nanosystems in Hair Follicle Regeneration in Androgenetic Alopecia: [43,44]

Table 1. Describes various nanoparticles, drugs in incorporated into it, diameter and their advantages used to treat Androgenetic Alopecia.

Nanoparticle	Drugs	Diameter	Advantages
Solid lipid nanoparticles 	Minoxidil	190 nm	Enhanced development of new hair follicles and targeted medication administration to the hair follicles
Nanostructured lipid carriers 	Minoxidil Finasteride Clobetasol Propionate Dudasteride	120–280 nm	Increased medication bioavailability, enhanced encapsulation effectiveness, and high chemical and physical stability in storage.
Liposomes 	Minoxidil Finasteride	1–5 µm 3.66 µm	Phospholipid film is formed on the skin and interacts with sebum to facilitate follicular penetration and accumulation.
Ethosomes 	Finasteride	92 nm	Higher permeation flux
Niosomes 	Minoxidil	-	An increased concentration of drugs in the skin's layers
Transfersomes	Minoxidil	-	Boosts hair growth

			
Chitosan/lecithin nanoparticles 	Minoxidil Clobetasol Propionate	271 nm 246.6 nm	Higher medication concentration and more excellent drug stability in hair follicles
Chitosan microparticles 	Minoxidil	2.9–4.2 μm	The retention of particles in the upper portion enabled controlled medication release.
PLGA/microspheres/effervescent Granules 	Finasteride Minoxidil	300 nm; 0.2 mm	High drug absorption and controlled release
Hydroxypropyl-β-cyclodextrin Nanostructures 	Dutasteride	160 nm	Enhanced bioavailability and high drug solubility
Nanosuspension 	Finasteride	200 nm	Higher solubility and dissolution

4. New Therapeutic Strategies for Hair Follicle Regeneration

Gene Delivery to the Hair Follicle

Genes are inserted in hair follicles for therapeutic purposes for two leading causes. First, single-gene alterations that affect the development of the hair shaft must be treated. The second is the treatment of polygenic hair follicle cycle abnormalities that cause hair loss. Hair follicle abnormalities caused by single-gene deficiencies must be phenotypically corrected well, which will need both long-term and widespread gene expression in the hair follicles. Moreover, most keratinocytes in every hair follicle must express their genes usually to restore a normal hair phenotype. To accomplish these aims, it is necessary to efficiently and consistently transduce the relevant genes into the keratinocyte stem cells. After a gene or genes have been selected to provide a therapeutic effect, they must be

effectively achieved to hair follicle keratinocytes directly in vivo or ex vivo during tissue culture. By using techniques like topical application of lipoplexed DNA or a liposome mixture containing the vectors, direct intradermal injection of the vectors, or gene gun introduction of the vectors into the hair follicle, plasmid or viral vectors containing the gene of interest are directly delivered into follicular keratinocytes in an in vivo approach [45].

5. Challenges and Considerations for Clinical Translation

Targeted drug delivery systems can potentially improve the efficacy and safety of drug delivery for various diseases; several challenges and considerations must be addressed for successful clinical translation. These include targeting specificity, stability and storage, manufacturing complexity, regulatory approval, cost-effectiveness, clinical trial design, and efficacy and safety. Due to the unique physicochemical characteristics of such formulations, They should be thoroughly evaluated concerning their safety profile as nanoscale-tailored materials. Interaction between the nanosized carrier and the biological systems is amplified by the nanosized dimension, which causes the increased surface area and, consequently, the surface contact area. As a result, due to increased exposure, there should be vigilance regarding the reactivity and toxicity when in contact with the human body. Therefore, an evaluation of their pharmacological and toxicological profiles is necessary to develop and continue using nanotechnology-based formulations for hair treatment in androgenetic alopecia, along with their analytical and characterization evaluation, in order to understand better and predict their suitability and potential degradation products [46].

6. Regulatory Consideration

Creating clear and simple guidelines and regulations surrounding the production and evaluation of pharmacokinetic, pharmacodynamic, and toxicological profiles is necessary to ensure the ultimate safety and effectiveness of formulations based on nanotechnology. A material with exterior dimensions in the nanoscale or an internal or surface structure in the nanoscale, with particle sizes ranging from 1 to 100 nm, is called a "nanomaterial", according to the IOS. However, not all regulating parties agreed with this concept, and they came up with different definitions based on their viewpoints. The toxicity assessment of the nanotechnology-based formulation, which offers the necessary safety and efficacy outcomes, is critical for accepting or rejecting regulatory approval [47,48].

7. Conclusions and Future Prospective

Nanotechnology holds great promise for the treatment of androgenetic alopecia. The use of nanosystems can improve the performance of currently available medications and enable the efficient delivery of new therapeutic options, overcoming the drawbacks of current medicines. The available research demonstrates that nanotechnological-based therapies can improve treatment outcomes, but further study is required to optimize delivery mechanisms and understand specific skin interaction mechanisms. The potential of nanosystems in treating androgenetic alopecia has been demonstrated by recent research. For example, it has been demonstrated that using lipid-based nanoparticles to deliver minoxidil increases treatment efficacy and minimizes side effects. Similarly, it has been demonstrated that using solid lipid nanoparticles to deliver finasteride improves therapeutic results and increases drug permeability. Other research investigated the delivery of novel therapeutics, including dutasteride and clobetasol propionate.

The prospects are promising for enhancing the efficacy of existing therapies for Hair Follicle Regeneration in Androgenetic Alopecia. Targeted medication delivery, controlled drug release, enhanced bioavailability, and biocompatibility are only a few benefits lipid nanosystems offer. However, several challenges are associated with nanomedicines' reg-

ulatory and commercial approval, including reproducible scale-up, manufacturing processes, quality concerns, and safety implications. These additional development and regulatory considerations can elevate product costs, which must be compensated by the pharmacological advantages of the nanosystems to enable successful commercialization. In conclusion, the successful translation of nanotechnology-based therapies for androgenetic alopecia from the laboratory to the bedside will require the collaboration of developers and health authorities to solve these regulatory and commercial challenges. With further research and development, nanotechnology has the potential to revolutionize Hair Follicle Regeneration in Androgenetic Alopecia, providing safe and effective solutions for individuals affected by this condition.

Author Contributions: Conceptualization, Z.S.A.S. and S.G.P.; data curation, Z.S.A.S. and B.A.A.P.; writing—original draft preparation, Z.S.A.S., B.A.A.P. and A.R.S.M.; writing—review and editing, Z.S.A.S., B.A.A.P. and A.R.S.M.; supervision, S.G.P. All authors have read and agreed to the published version of the manuscript.

Funding: This review received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We would like to convey our obligation to the Management and Principal of P.S.G.V.P.M's College of Pharmacy Shahada, Maharashtra. Additionally, to the colleagues & friends for their constant support and motivation.

Conflicts of Interest: The authors declare no conflict of interest.

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