A Review on an Evaluation of a Liposomal Hydrogel for Combined Minoxidil and Tretinoin Delivery in Androgenetic Alopecia

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ABSTRACT

This critique examines a 2019 investigation by Kochar and colleagues, which engineered a liposomal hydrogel for the concurrent topical administration of Minoxidil (MXD) and Tretinoin (TRET) in addressing androgenetic alopecia (AGA). The foundational research offers a viable option beyond traditional formulations by utilizing liposomes to improve drug stability, encapsulation efficiency, and dermal compatibility, integrated with a hydrogel base to facilitate application and extend release duration. Although the investigation is methodically sound in its design, refinement, and preliminary *ex vivo* assessment, this analysis pinpoints notable shortcomings. These encompass the absence of *in vivo* effectiveness data within an alopecia model, inadequate exploration of the mechanistic interplay between MXD and TRET, and an incomplete stability evaluation. This review suggests specific remedial actions and prospective research avenues to address these deficiencies, promoting dedicated *in vivo* trials, sophisticated analytical methods for interaction analysis, and a more thorough stability-indicating protocol. The engineered system shows substantial promise, yet additional verification is necessary to transform this encouraging ex *vivo* outcomes into a viable clinical treatment.

Keywords: Androgenetic Alopecia, Minoxidil, Tretinoin, Liposomes, Hydrogel, Topical Administration

INTRODUCTION

Androgenetic alopecia (AGA) is a prevalent hereditary condition characterized by the progressive miniaturization of hair follicles, affecting a significant proportion of the global population (Otberg et al., 2007). First-line topical treatment often involves Minoxidil (MXD), a vasodilator believed to prolong the anagen phase and enhance cutaneous blood flow (Suchonwanit et al., 2019). Tretinoin (TRET), a retinoid typically used for its comedolytic effects, is noted for its ability to improve the skin penetration of other compounds, including MXD, potentially allowing for reduced dosing frequency and mitigated side effects (Shin et al., 2009).

Conventional formulations, however, face considerable challenges. MXD is prone to crystallization in aqueous vehicles, while TRET is photolabile and known to cause significant skin irritation (Gupta & Charrette, 2019). Furthermore, patient compliance is often low due to the requirement for twice-daily application of these suboptimal formulations (Adil & Godwin, 2017). Advanced drug delivery systems, particularly nanocarriers like liposomes, offer a promising solution. These phospholipid-based vesicles can encapsulate both hydrophilic (MXD in the aqueous core) and lipophilic (TRET in the lipid bilayer) drugs, enhance follicular targeting, provide a sustained-release depot within the skin, and reduce the irritancy of encapsulated agents (Mura et al., 2007; Desai & Patlolla, 2019).

The study by Kochar et al. (2019) aimed to leverage these advantages by developing a co-loaded liposomal system incorporated into a Carbopol hydrogel. This review provides a critical analysis of their methodology, highlights the strengths of the formulated system, identifies major scientific and methodological gaps, and

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offers targeted recommendations for future research to bridge the divide between promising formulation and proven therapeutic agent.

Advantages

Promotes hair growth

Increase skin cell turnover

Stimulate collagen synthesis

Reduce hyperpigmentation

Enhance penetration of minoxidil

Reboost hair-growth

Synopsis of the investigation

Aim and Rationale

The primary objective of Kochar et al. was to design, optimize, and characterize a stable liposomal hydrogel for the simultaneous topical delivery of MXD and TRET. The rationale was based on the potential synergy between the two drugs and the beneficial properties of liposomes (improved skin penetration, follicular targeting, reduced irritation) combined with the advantages of a hydrogel base (ease of application, sustained release, improved patient compliance).

METHODOLOGY: AN EXEMPLAR OF SYSTEMATIC CREATION

Component Selection: Phospholipids were selected based on partition coefficient and Differential Scanning Calorimetry (DSC) studies to ensure optimal drug-lipid miscibility. Lipoid S100 was chosen for MXD and Phospholipon 90H for TRET.

Refinement: Vital process parameters (rotary evaporation speed/temperature, sonication duration) and formulation variables (drug-lipid ratio, phospholipid-cholesterol ratio) were carefully optimized employing a one-factor-at-a-time method. A hydration medium containing 10% propylene glycol was utilized to boost encapsulation and penetration.

Fabrication: Liposomes (MXD-loaded: ML, TRET-loaded: TL, and co-loaded: MTL) were produced using the thin-film hydration technique followed by probe sonication for size reduction.

Profiling: The liposomes were analyzed for size, Polydispersity Index (PDI), zeta potential, encapsulation efficiency (%EE), and structure (TEM). All preparations exhibited nanoscale sizes (<200 nm), low PDI (<0.4), and outstanding %EE (>99% for single-drug liposomes; 83.5% for MXD and 71.4% for TRET in MTL).

Hydrogel Integration: The refined MTL was incorporated into a 1% Carbopol 974P NF hydrogel. The hydrogel was evaluated for flow properties (shear-thinning behavior), pH (~6.5), spreadability, and drug content.

***Ex Vivo* Assessment:** Permeation tests using rat skin in Franz diffusion cells indicated sustained release from the hydrogel relative to liposomal suspension. Significantly, TRET displayed no permeation but considerable retention in skin layers, which might potentiate MXD absorption. Confocal Laser Scanning Microscopy (CLSM) with fluorescent tags verified the formulation's delivery to hair follicles.

***In Vivo* Irritation Test:** A 3-day study on Sprague Dawley rats applying Draize's scale revealed that the liposomal hydrogel was non-irritating, a crucial finding considering TRET's recognized irritancy.

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Principal Outcomes

The study successfully developed a nanosized, co-loaded liposomal hydrogel with high encapsulation efficiency, desirable physical properties, sustained *ex vivo* release profile, effective follicular targeting, and no signs of irritation in a preliminary animal model.

Appraisal and Detected Shortcomings

3.1 Absence of *In Vivo* Effectiveness Data: The most significant shortcoming is the complete absence of *in vivo* efficacy data. While *ex vivo* permeation and follicular delivery are promising, they are surrogate markers. Demonstrating actual hair growth promotion—through measures such as anagen-to-telogen ratio, hair count, density, and follicle size in a validated animal model of AGA (e.g., testosterone-induced alopecia in mice or C57BL/6 mice)—is imperative to claim therapeutic efficacy. Without this data, the clinical relevance of the formulation remains speculative.

3.2 Unverified Synergy Assertion: The entire rationale for co-encapsulation hinges on the purported synergistic effect between MXD and TRET. However, the study design lacks a critical control group: a formulation containing MXD alone in the liposomal hydrogel. Without a direct comparative assessment of the combination (MTL) against MXD-only liposomes, the claim of enhanced efficacy due to synergy is unfounded and remains a hypothesis rather than a demonstrated result.

3.3 Partial Stability Assessments: Although the study tracked physical stability (size, PDI, zeta potential) for 90 days, it omitted essential chemical stability data. TRET is highly susceptible to oxidation and photodegradation. The failure to monitor the chemical integrity of both active ingredients using a stability-indicating method (e.g., HPLC with detection of degradation products) under ICH-recommended storage conditions (accelerated and long-term) is a major flaw that questions the formulation's shelf-life and real-world viability (Blessy et al., 2014).

3.4 Restricted Mechanistic Insight into Performance: The study provides superficial explanations for key observations. The reduction in EE% for both drugs in the co-loaded system (compared to single-loaded) is not mechanistically investigated (e.g., via FTIR to study drug-lipid interactions). Similarly, the reduction in TRET-induced irritation is attributed to the hydrogel but not proven through objective measures of inflammation (e.g., quantification of cytokines like IL-1α or TNF-α in tissue).

3.5 Debatable Biocompatibility Model: The 3-day irritation study is insufficient to declare the formulation safe for chronic use, as AGA treatment requires long-term, daily application. A longer-term repeated application study (e.g., 4-6 weeks) is necessary to properly assess cutaneous safety, including the potential for delayed irritancy or sensitization.

Suggested Remedies and Future Avenues

4.1 Conduct Rigorous *In Vivo* Efficacy Studies: Future work must include a well-designed *in vivo* study in a relevant alopecia model. The MTL hydrogel should be tested against:

A placebo hydrogel (negative control)

A conventional MXD solution (standard control)

A liposomal hydrogel containing MXD alone (to isolate TRET's contribution) Endpoints should include histopathological analysis of skin biopsies, photographic assessment, and manual hair count.

4.2 Confirm Synergistic Impacts: The experimental design should include a group with MXD-only liposomes to directly examine the hypothesis that TRET augments MXD's efficacy. Statistical comparison between the MXD-alone and MXD+TRET groups is imperative to substantiate synergy.

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4.3 Undertake Extensive Stability Studies: A full stability study following ICH Q1A(R2) guidelines must be conducted. The formulation should be stored under accelerated (40°C ± 2°C / 75% RH ± 5% RH) and long-term (25°C ± 2°C / 60% RH ± 5% RH) conditions for at least 6 months. Stability must be assessed using a validated, stability-indicating HPLC method to track the degradation of both MXD and TRET.

4.4 Augment Mechanistic Comprehension: Advanced analytical techniques (e.g., FTIR, DSC) should be employed to understand drug-phospholipid interactions affecting encapsulation. The irritation study should be expanded to include biomarker analysis (e.g., ELISA for inflammatory cytokines) to objectively quantify the formulation's safety profile.

4.5 Investigate Scale-Up and Sterility: Probe sonication is not a scalable manufacturing technique. Future development should explore scalable alternatives like high-pressure homogenization. Furthermore, the formulation strategy must include a plan for ensuring sterility or incorporating appropriate antimicrobial preservatives for a multi-dose topical product.

CONCLUSION

The investigation by scientist denotes a substantial and praiseworthy advancement in the sophisticated topical delivery of anti-alopecia drugs. The methodical development of a co-loaded liposomal hydrogel is scientifically rigorous, and the findings concerning characterization, *ex vivo* permeation, follicular targeting, and preliminary safety are highly encouraging. The formulation effectively tackles several main challenges of conventional treatments.

Nonetheless, the lack of *in vivo* efficacy data and a direct comparison to confirm synergistic action are vital flaws that leave the core therapeutic assertion unconfirmed. The transition from a well-defined formulation to an established therapeutic agent necessitates closing this divide. By enacting the proposed solutions—specifically, performing robust *in vivo* efficacy studies, validating synergy, and finalizing a comprehensive stability profile—this innovative liposomal hydrogel system holds strong potential to develop into a clinically enhanced treatment alternative for millions suffering from androgenetic alopecia.

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