

TRANEXAMIC ACID-LOADED LIPOSOMAL GEL FOR ENHANCED TOPICAL DELIVERY IN MELASMA: THERAPEUTIC RATIONALE, FORMULATION STRATEGIES, EVIDENCE, CHALLENGES AND FUTURE PERSPECTIVES

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Abstract- Melasma is a chronic acquired disorder of facial hyperpigmentation characterized by recurrent brown to grey-brown macules and patches on sun-exposed skin. Its pathobiology is multifactorial and includes melanocyte hyperactivity, ultraviolet and visible-light exposure, vascular and inflammatory alterations, basement-membrane disruption, photoaging and genetic or hormonal influences. Tranexamic acid (TXA), a synthetic lysine analogue and antifibrinolytic drug, has emerged as an off-label treatment option for melasma and has been investigated by oral, topical and intradermal routes. Although topical TXA can reduce systemic treatment burden, conventional topical formulations may provide inadequate epidermal targeting and residence because of the skin barrier and the physicochemical characteristics of the drug. Liposomal delivery offers a rational strategy to modify drug-skin interactions, protect the active ingredient and regulate release.

Incorporation of TXA-loaded liposomes into a polymeric gel may additionally improve residence time, spreadability, ease of application and sustained delivery.

This review critically examines the therapeutic rationale for TXA in melasma and the pharmaceutical basis for liposomal and liposomal-gel delivery. Evidence from clinical studies, systematic reviews, formulation investigations, lipid-vesicular delivery research and recent quality-by-design studies is integrated. Particular attention is given to phospholipid and cholesterol selection, drug-to-lipid ratio, surfactant concentration, vesicle size, polydispersity, zeta potential, entrapment efficiency, drug release, ex-vivo permeation, skin retention, stability and safety. A recent formulation study of TXA-loaded liposomal gel using thin-film hydration and Carbopol 940 is discussed as a representative formulation platform. The literature indicates that liposomal systems can improve

pharmaceutical performance of topical TXA, but the evidence base remains heterogeneous and clinical validation of advanced vesicular formulations is limited. Future development should emphasize quality-by-design approaches, epidermal targeting, validated skin-retention endpoints, long-term stability, dermatological safety and adequately powered comparative clinical trials.

Keywords: tranexamic acid; melasma; liposomes; liposomal gel; topical drug delivery; nanoliposomes; Carbopol 940; epidermal targeting; skin permeation; hyperpigmentation.

I. INTRODUCTION

Melasma is a chronic acquired hyperpigmentation disorder that most commonly affects the face and is particularly important in individuals with darker skin phototypes. It presents as symmetrical light-to dark-brown macules and patches, commonly involving the cheeks, forehead, nose and upper lip. Although benign medically, its chronicity, recurrence and cosmetic visibility can affect quality of life. Contemporary reviews emphasize that melasma is not exclusively a disorder of melanogenesis; vascular, inflammatory, mast-cell, basement-membrane and photoaging pathways also contribute to disease expression and persistence [1-3].

Management generally requires long-term photoprotection and may include topical, systemic and procedural interventions. International expert consensus published in 2025 emphasized broad-spectrum photoprotection and supervised use of established topical regimens while identifying TXA among therapeutic options requiring appropriate patient selection and further evidence [4].

TXA has attracted interest because it acts on the plasminogen-plasmin pathway and may influence melanogenic, vascular and inflammatory processes. It has been investigated orally, topically and intradermally. Meta-analyses have found overall reductions in melasma severity with TXA, but substantial heterogeneity exists among trials, particularly with respect to administration route and combination therapy [5,6].

The topical route offers an opportunity to concentrate TXA at affected skin while potentially limiting systemic exposure. However, topical delivery is constrained by the stratum corneum. Lipid-based vesicular systems, including liposomes, have therefore been investigated to modify drug partitioning, residence and release [7,8]. The purpose of this review is to integrate the dermatological rationale for TXA with

pharmaceutical principles governing liposomal and liposomal-gel delivery.

II. LITERATURE IDENTIFICATION AND REVIEW APPROACH

This manuscript was developed as a structured narrative review. Literature was identified from PubMed-indexed publications and publisher-indexed scientific records, with emphasis on peer-reviewed studies and reviews addressing melasma pathogenesis, TXA therapy, topical delivery, liposomes, nanogels, lipid vesicles, skin permeation, formulation optimization and clinical outcomes. Priority was given to 2021-2026 publications while retaining earlier landmark clinical and formulation studies. Search concepts included combinations of melasma, tranexamic acid, topical tranexamic acid, liposomal tranexamic acid, liposome, nanoliposome, liposomal gel, epidermal targeting, skin permeation, skin retention, Carbopol, quality by design and Box-Behnken design. The evidence was considered at three levels: clinical evidence in patients; preclinical or ex-vivo evidence for skin delivery and biological effects; and pharmaceutical formulation evidence for physicochemical and release performance. This distinction is essential because improved particle size, encapsulation or in-

vitro release does not by itself demonstrate superior clinical efficacy.

Melasma: Pathobiology Relevant to Drug Delivery

A detailed pathogenesis review identified five interacting domains: inappropriate melanocyte activation; melanin and melanosome accumulation; increased mast-cell activity and solar elastosis; basement-membrane alteration; and increased vascularization [2]. Other reviews emphasize ultraviolet and visible-light exposure, hormonal factors, oxidative stress, photoaging and genetic susceptibility [1,3]. For formulation scientists, this creates an important distinction between treating the biological pathway and delivering the drug to the relevant anatomical compartment. Melanocytes are located in the basal epidermis, whereas vascular and inflammatory changes may involve deeper structures. A rational topical formulation may therefore aim for controlled epidermal deposition rather than maximum transdermal passage into systemic circulation.

This concept is especially relevant for TXA. A formulation designed for systemic transdermal delivery has a different objective from one designed for localized epidermal deposition. Future studies should consequently report skin-layer distribution

and retention rather than relying only on cumulative receptor-phase permeation.

Tranexamic Acid: Pharmacological and Therapeutic Rationale

TXA is a synthetic lysine analogue that inhibits plasminogen activation and plasmin-mediated pathways. Its use in melasma is off-label. Proposed dermatological mechanisms include modulation of the plasmin pathway, reduction of melanogenic signalling and effects on vascular and inflammatory components of the melasma microenvironment [5,9]. A 2021 meta-analysis included 24 randomized trials and found reductions in MASI or mMASI over several treatment time points, although clear superiority was not established for topical or intradermal TXA in subgroup analyses [5]. A 2024 systematic review and meta-analysis included 22 studies involving 1,280 participants and again reported reductions in melasma severity across TXA routes while emphasizing heterogeneity and the need for standardized protocols [6].

Topical TXA has been evaluated directly. In a double-blind split-face study of 23 women, 5% topical TXA was compared with vehicle over 12 weeks; no significant difference in lightening was found between the sides, although erythema was observed at the TXA-treated site [10]. In an Indian randomized

study, topical 5% TXA and 3% hydroquinone produced similar MASI reductions after 12 weeks, with greater patient satisfaction reported in the TXA group because of fewer adverse effects [11]. A 2015 split-face clinical study evaluated 5% liposomal TXA against 4% hydroquinone in 30 women, with 23 completing the study. Both sides showed significant MASI reductions; the liposomal TXA side showed a numerically greater decrease, but the between-treatment difference was not statistically significant [12]. A 2020 randomized study compared 1.8% liposomal TXA, microneedling with 5% TXA solution and 2% hydroquinone in 60 patients. All groups improved, and the authors concluded that liposomal TXA was effective and safe [13].

Topical TXA Requires Delivery Optimization

The stratum corneum is the principal barrier to topical drug penetration. Hydrophilic molecules may have limited partitioning into the lipid-rich intercellular domains of this barrier. TXA is highly hydrophilic, creating a pharmaceutical challenge for conventional topical delivery [14].

An ideal topical TXA formulation should provide reproducible drug loading, acceptable physical and chemical stability,

appropriate skin deposition, sufficient epidermal residence, controlled release, good spreadability and minimal unnecessary systemic exposure. These requirements make delivery-system engineering a central part of product development. A 2023 review specifically proposed epidermal targeting as an important objective for topical TXA and discussed liposomes, solid lipid nanoparticles, nano-lipidic carriers and topical beads as potential strategies [14]. The concept is consistent with the anatomical target of melasma and indicates that formulation success should be evaluated by where the drug is delivered, not only how much drug leaves the formulation.

Liposomes as a Platform for Topical TXA Delivery

Liposomes are phospholipid-based vesicles consisting of one or more bilayers surrounding an aqueous compartment. Their amphiphilic structure allows incorporation of hydrophilic and lipophilic molecules into

different regions of the vesicle. In topical delivery, liposomes may interact with stratum-corneum lipids, alter drug partitioning, provide a local reservoir and modulate release [7,15]. A 2023 guideline-oriented review of skin drug delivery using lipid vesicles identified vesicle size, deformability and drug loading as important properties influencing delivery performance and also emphasized long-term preservation and scale-up as barriers to commercialization [7]. A 2025 review similarly highlighted the potential of liposomes for skin delivery while noting formulation and translational challenges [8].

For TXA, the challenge is not simply to make a small particle, but to obtain reproducible encapsulation and an appropriate balance between aqueous-core loading, vesicle integrity, release and skin interaction. Consequently, composition and process variables can markedly change performance.

III. FORMULATION VARIABLES IN TXA-LOADED LIPOSOMES

Critical variable	Expected influence	Development implication
Drug:lipid ratio	Encapsulation, loading and vesicle characteristics	Optimize rather than maximize lipid concentration
Phospholipid concentration/type	Bilayer formation, size and stability	Select according to target skin delivery
Cholesterol	Bilayer packing, rigidity and	Determine an optimal range

	permeability	
Surfactant/edge modifier	Size, PDI, membrane properties and release	Avoid destabilizing concentrations
Hydration conditions	Vesicle formation and reproducibility	Control temperature, time and hydration volume
Sonication/extrusion	Size reduction and distribution narrowing	Control energy and cycle number
pH/ionic environment	Drug state and vesicle stability	Maintain skin-compatible conditions

The uploaded September 2026 formulation study prepared eight formulations (L1-L8) by thin-film hydration, varying soy lecithin, cholesterol and Tween 80. L5 was selected as the optimized liposomal batch. Its reported vesicle size was 274.8 +/- 7.9 nm, PDI 0.198 +/- 0.011, zeta potential -24.8 +/- 1.5 mV, entrapment efficiency 82.74 +/- 1.18% and drug content 97.36 +/- 0.74% [16]. These results demonstrate a practical screening approach, but they do not establish clinical superiority. A separate 2023 QbD/Box-Behnken investigation developed stratum-corneum-lipid liposomes containing TXA. The optimized formulation had a reported mean particle size of 93.5 nm and encapsulation efficiency of 35.78%, with complete in-vitro release reported within 6 h and zero-order kinetics [17]. The contrast

between this system and conventional phospholipid systems illustrates that optimal particle size or encapsulation is formulation- and objective-specific.

IV. PREPARATION METHODS

Thin-film hydration is a common laboratory-scale method. Lipid components are dissolved in an organic solvent, the solvent is removed to form a thin film, and the film is hydrated with an aqueous phase containing the drug. Sonication or extrusion may subsequently reduce size. Advantages include flexibility and methodological simplicity; limitations include solvent handling, phospholipid oxidation, batch variability and scale-up challenges. Ethanol injection, microfluidics and controlled extrusion may improve reproducibility in selected settings, but each requires process-specific optimization [7,8].

Characterization of TXA Liposomes

Parameter	Purpose	Recommended interpretation
Vesicle size	Particle-size distribution and delivery behavior	Report mean, SD and measurement method
PDI	Distribution width	Lower values generally indicate narrower distribution
Zeta potential	Surface charge and colloidal behavior	Interpret with medium and composition
Entrapment efficiency	Drug associated with vesicles	Report separation and assay method
Drug loading	Drug per carrier mass	Useful for formulation efficiency
Morphology	Shape and vesicle integrity	TEM/cryo-TEM or appropriate microscopy
pH	Skin compatibility and stability	Monitor during storage
Drug content	Dose uniformity	Use validated analytical method
Release profile	Release behavior	Use validated diffusion method
Skin deposition	Target-site delivery	Quantify epidermis and dermis separately where possible

For TXA, analytical specificity is important because the drug is highly hydrophilic and may be difficult to quantify in complex vesicular matrices. UV-visible spectrophotometry can be useful for early formulation work when selectivity is

demonstrated; chromatographic methods such as LC-MS/MS provide stronger specificity for advanced formulation and skin-distribution studies. The QbD study by Verma and Yadav used LC-MS/MS for TXA quantification [17].

Liposomal Gel as a Hybrid Topical Delivery System

A liposomal gel combines vesicular drug delivery with a polymeric application matrix. The liposome acts as the carrier, while the gel may improve residence time, handling, spreadability and patient acceptability. Carbopol 940 is a commonly used acrylic polymer. Its concentration influences viscosity, spreadability, extrudability and release; therefore, polymer concentration should be treated as a critical formulation variable.

The uploaded study incorporated 20% liposomal dispersion into Carbopol 940 gel with propylene glycol, methyl paraben, triethanolamine and water and evaluated appearance, homogeneity, pH, viscosity, spreadability, drug content, extrudability and washability [16].

An especially relevant precedent is the 2021 study by Liu et al., which developed hyaluronic-acid-coated TXA liposome nanogels. The system combined liposomes with a gel matrix and was investigated using cellular, delivery and hyperpigmentation models. The authors reported enhanced uptake and delivery to melanocytes together with inhibition of tyrosinase activity and melanin production in their experimental model [18].

In-Vitro Release and Release Kinetics

Franz diffusion cells and related systems are commonly used for topical formulation testing. In-vitro release and skin permeation should be distinguished: release evaluates liberation from the dosage form, while permeation evaluates movement through or into a biological membrane. For melasma, layer-specific skin retention may be more informative than maximizing receptor-phase flux. The uploaded study compared TXA liposomal gel with plain TXA gel over 12 h and reported a more gradual release from the liposomal formulation. Release at 12 h was 84.26 +/- 1.72%, and the Higuchi model provided the best fit [16]. This supports diffusion-influenced release but does not prove a single molecular mechanism.

The QbD stratum-corneum-lipid liposome study reported zero-order release for its optimized formulation [17]. Differences in kinetic models across studies emphasize that release behavior depends on composition and experimental design; kinetic constants should not be compared across unrelated systems without methodological harmonization.

Ex-Vivo Skin Permeation and Skin Retention

Ex-vivo skin studies should be positioned between formulation screening and clinical development. Franz diffusion cells using

human or validated animal skin can provide cumulative permeation, flux and permeability coefficients. More importantly, tape stripping, epidermal/dermal separation and tissue extraction can determine where TXA is retained.

A 2017 study of a TXA topical bead formulation demonstrated increased in-vitro skin permeation and in-vivo skin retention compared with a commercial product. It also showed that laser treatment could alter the distribution of retained TXA and potentially increase movement into deeper tissue, emphasizing the need to distinguish local retention from systemic exposure [19].

Future liposomal-gel studies should report cumulative permeation, steady-state flux, permeability coefficient, enhancement ratio, epidermal retention, dermal retention, receptor-phase recovery and mass balance. CLSM can complement quantitative extraction. A 2026 nano-liposome study reported a 2.3-fold increase in TXA permeation and CLSM-confirmed penetration to approximately 122 micrometres for its optimized formulation; incorporation into 1% Carbopol 940 gel was associated with sustained delivery in the reported experimental model [20].

Clinical Evidence for Liposomal TXA

Study	Design	Intervention	Main finding	Key limitation
Banihashemi et al., 2015 [12]	Split-face; 30 women, 23 completers	5% liposomal TXA vs 4% HQ	Both sides improved; between-side difference not significant	Small sample and short duration
Xing et al., 2020 [13]	Randomized; 60 patients	1.8% liposomal TXA vs microneedling + 5% TXA vs 2% HQ	All groups improved; liposomal TXA reduced MI and erythema	Different delivery methods
Na Ayuthaya et al., 2012 [10]	Split-face; 23 women	5% topical TXA vs vehicle	No significant superiority over vehicle	Conventional topical dosage form
Janney et al.,	Randomized;	5% topical TXA	Similar MASI	Short follow-up

2019 [11]	100 analyzed	vs 3% HQ	reduction at 12 weeks	
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The clinical evidence supports continued investigation but does not establish that liposomal TXA is universally superior to conventional TXA or hydroquinone. The 2015 trial did not demonstrate a statistically significant difference between liposomal TXA and hydroquinone, while the 2020 trial found improvement with liposomal TXA but also involved heterogeneous comparators [12,13].

Safety and Regulatory Considerations

Safety assessment must be route-specific. Oral TXA requires attention to thromboembolic risk and patient-specific contraindications, and Indian expert consensus has recommended appropriate risk assessment and monitoring when oral TXA is used [21,22]. Topical TXA may produce lower systemic exposure than oral administration, but systemic exposure should not be assumed to be zero, particularly when barrier-disrupting procedures are used.

For a liposomal gel, safety evaluation should include local irritation, erythema, edema, sensitization, repeated-application studies, preservative tolerance and systemic exposure where clinically relevant. Long-term stability and microbiological quality are important because changes in vesicle integrity or gel structure may modify drug release. Regulatory translation additionally requires reproducible manufacturing, validated analytical procedures, packaging compatibility and stability data [7,8].

Quality by Design for TXA Liposomal Gel Development

QbD provides a systematic framework for linking formulation composition and manufacturing variables to product quality. For TXA liposomal gel, the Quality Target Product Profile may include topical administration, acceptable skin feel, controlled release, reproducible epidermal deposition, adequate stability and dermatological safety.

QbD element	Examples for TXA liposomal gel
QTPP	Topical semisolid; stable; skin-compatible pH; controlled release; epidermal targeting
CQAs	Size, PDI, zeta potential, EE, drug content, viscosity, pH, release, skin retention

CMAs	Phospholipid, cholesterol, surfactant, Carbopol, TXA level
CPPs	Hydration, stirring speed, sonication energy/time, temperature, mixing time
Risk assessment	Identify variables affecting size, EE, release and skin deposition
DoE	Factorial, Box-Behnken or central composite design
Design space	Multivariate region meeting predefined CQA limits
Control strategy	Raw-material, in-process and finished-product controls

The 2023 Box-Behnken study by Verma and Yadav directly demonstrates QbD development of TXA-loaded stratum-corneum-lipid liposomes. It investigated lipid:cholesterol ratio, stirrer RPM and probe-sonication cycles against encapsulation efficiency and particle size and generated an optimized formulation [17]. Extending this approach to the final gel could incorporate polymer concentration and process variables while adding skin retention as a performance response.

V. STABILITY AND PRODUCT DEVELOPMENT

Stability programs should monitor both the liposomal dispersion and final gel. Relevant endpoints include appearance, phase

separation, vesicle size, PDI, zeta potential, EE, drug content, pH, viscosity, microbiological quality and release. Liposomal systems can be affected by aggregation, fusion, leakage and lipid oxidation; therefore, vesicle-specific measurements are important in addition to conventional gel tests.

In the uploaded study, 90-day monitoring showed only minor changes. Drug content decreased from 96.84 +/- 0.78% initially to 95.76 +/- 0.82% at 90 days, while 12-h release decreased from 84.26 +/- 1.72% to 82.96 +/- 1.79% [16]. These data provide preliminary stability evidence; longer studies under controlled long-term and accelerated conditions would strengthen a development package.

Comparative Assessment of Topical TXA Delivery Systems

System	Primary purpose	Potential benefit	Key limitation
Conventional solution/gel	Simple topical delivery	Low complexity	Potentially limited epidermal deposition
Liposomal TXA	Vesicular delivery	Modified release and skin interaction	Encapsulation and stability challenges
HA-coated liposome nanogel	Localized/targeted delivery	Combines liposome and gel functions	More complex composition
Stratum-corneum lipid liposome	Biomimetic delivery	Lipid composition resembles skin barrier	Optimization and scale-up required
TXA topical beads	Solid-state topical delivery	Potential stability and retention benefits	Different administration workflow
Liposomal Carbopol gel	Hybrid semisolid delivery	Residence, handling and sustained release	Both vesicle and gel need optimization

VI. PROPOSED TRANSLATIONAL DEVELOPMENT STRATEGY

A stronger development program should progress through sequential stages: drug and excipient preformulation; risk assessment; QbD/DoE-based liposome optimization; gel optimization; physicochemical characterization; in-vitro release; ex-vivo permeation and layer-specific retention; imaging; dermatological safety; stability; and finally comparative clinical testing. The principal translational endpoint should be clinically meaningful improvement in validated pigmentation measures together

with tolerability, rather than formulation performance alone.

For melasma, the development objective should move from generic “enhanced permeation” toward site-specific delivery. A formulation that retains more TXA in the relevant epidermal compartment may be preferable to one that produces greater receptor-phase flux.

VII. FUTURE PERSPECTIVES

The future of topical TXA delivery is likely to move toward targeted, biomimetic and data-driven systems rather than simple increases in drug concentration. Stratum-

corneum-mimetic liposomes, hyaluronic-acid-associated vesicles, deformable vesicles and other lipid nanocarriers offer different strategies for controlling the relationship between formulation and skin barrier. Recent work supports continued investigation of nanoliposomal TXA, including a 2026 preclinical study that combined nanoliposomes with Carbopol 940 gel and reported improved permeation, deeper skin distribution and experimental anti-melasma activity [20].

Future clinical trials should use standardized TXA concentration, clearly defined liposome composition, validated manufacturing controls, standardized photoprotection, appropriate comparator arms, objective pigmentation measurements, recurrence assessment and adequate follow-up. Stratification by melasma type, skin phototype and disease severity may clarify which patients benefit from advanced topical delivery systems.

Another important direction is maximizing epidermal deposition while minimizing systemic passage. For melasma, a formulation that produces site-specific epidermal exposure may be more rational than one designed simply to maximize transdermal flux.

VIII. CONCLUSION

TXA is an important investigational option for melasma, supported by clinical studies and systematic reviews, although benefit varies by route, formulation and study design. Topical administration offers a localized strategy, but conventional formulations may be constrained by the skin barrier. Liposomal delivery provides a rational approach for modifying TXA disposition, while incorporation into a polymeric gel can increase residence time and improve topical usability.

Current evidence supports continued development of TXA-loaded liposomal gels, but clinical superiority cannot be inferred solely from smaller vesicles, higher encapsulation efficiency or slower in-vitro release. The most important future studies are those that establish reproducible epidermal targeting, layer-specific retention, dermatological safety, long-term stability and clinically meaningful improvement in melasma. QbD and DoE provide a practical framework for connecting formulation variables with these performance attributes. The translational objective should therefore be a reproducible, stable and patient-acceptable topical product supported by mechanistic delivery data and appropriately designed clinical trials.

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