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A review on Ethogel for topical application

Dhiraj Kumar Gupta*, Om Prakash Agrawal and Sailesh Kumar Ghatuary

Bhabha Pharmacy Research Institute, Bhabha University, Bhopal-462046, M.P. India

Abstract

Topical drug delivery remains a challenging field due to the barrier nature of the skin (especially the stratum corneum). Vesicular systems such as ethosomes have emerged as promising nanocarriers for improved dermal/ transdermal delivery. When such ethosomal suspensions are incorporated into gel bases, the resultant formulations are termed "ethogel" (or nano-ethogel) and offer advantages of enhanced skin permeation, deposition, sustained release and better patient compliance. This review critically examines the formulation science of ethogel, its mechanisms of action, evaluation parameters, applications (especially in dermatology and oncology), formulation challenges, regulatory and translational aspects, and future prospects.

Keywords: Ethogel, Vescular System, Nano-Gel, Topical Drug Delivery System, Nano-Carrier.

***Correspondence Info:**
Mr. Dhiraj Kumar Gupta
Bhabha Pharmacy Research Institute,
Bhabha University,
Bhopal-462046, M.P. India

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1. Introduction

Topical delivery of drugs offers many advantages: localized therapy, avoidance of first-pass metabolism, reduced systemic side-effects and improved patient compliance. However, the skin barrier, particularly the stratum corneum, severely limits permeation of many actives. Conventional gels often fail to deliver sufficient drug to deeper skin layers or retain it at the site of action for adequate duration.

Vesicular nanocarriers—liposomes, transfersomes, niosomes, and more recently ethosomes—have been explored to overcome skin barrier limitations. Ethosomes are phospholipid + high-ethanol (20-45 %) vesicles that have enhanced deformability and skin permeation capability. When these ethosomes are incorporated into a gel matrix (commonly a biocompatible polymer such as Carbopol), they form an "ethogel" — the ethosomal gel system for topical application.

The term "ethogel" has been used in the literature (for example, Ethogel topical formulation for increasing the local bioavailability of 5-fluorouracil: A mechanistic study, [1] where an ethosomal gel containing 5-fluorouracil was developed for skin cancer targeting.

Topical drug delivery represents one of the most convenient, non-invasive, and patient-friendly routes of drug administration. It involves the application of a drug formulation onto the skin to achieve either local or systemic effects. Over the past few decades, topical formulations have attracted significant attention due to their ability to bypass hepatic first-pass metabolism, reduce gastrointestinal irritation, and enhance patient compliance—particularly for chronic dermal conditions and localized infections [2].

1.1 The Skin as a Drug Delivery Barrier

The skin serves as the largest organ of the human body, with an average surface area of 1.5–2.0 m² and a complex multi-layered structure designed primarily for protection. The stratum corneum, the outermost layer of the epidermis, is the principal barrier that limits the diffusion of most drugs. Composed of dead keratinized cells embedded in a lipid matrix ("brick-and-mortar" model), it allows only small, moderately lipophilic, and uncharged molecules to passively diffuse [3]. Consequently, achieving effective drug permeation through the skin has been one of the most persistent challenges in pharmaceutical research.

1.2 Limitations of Conventional Topical Formulations

Traditional topical dosage forms—such as creams, ointments, and gels—are widely used, but they often suffer from limitations such as poor drug penetration, uncontrolled release rates, and short skin residence time[4]. Moreover, many therapeutic agents possess unfavorable physicochemical properties—high molecular weight, poor solubility, or hydrophilicity—that restrict their ability to penetrate the lipophilic stratum corneum barrier. Consequently, conventional gels or creams frequently provide subtherapeutic concentrations at the target site or require repeated application, reducing patient adherence [5].

1.3 Emergence of Vesicular Nanocarriers

To overcome these challenges, vesicular drug delivery systems such as liposomes, niosomes, transfersomes, and ethosomes have been developed. Among these, ethosomes—introduced by Touitou et al[6]. in 2000—represent a significant breakthrough. Ethosomes are soft, flexible phospholipid vesicles containing a high concentration of ethanol (20–45 % v/v) and water. The synergistic effect of ethanol and phospholipids enhances the fluidity of vesicle membranes and disrupts the stratum corneum lipid organization, thereby facilitating deeper skin penetration [7,8].

Ethanol in ethosomes acts as a penetration enhancer by decreasing the density of lipid bilayers within the stratum corneum, while phospholipids provide vesicular encapsulation that protects labile drugs and modulates release kinetics [9]. The vesicles can deliver both hydrophilic and lipophilic drugs effectively, making them highly versatile carriers for topical and transdermal applications.

2. Concept of Ethogel

Despite the superior penetration potential of ethosomes, their liquid nature poses practical limitations such as leakage, instability, and difficulty in application or dosing accuracy. To address these issues, ethosomal suspensions are incorporated into gel matrices to form "ethogels"—semi-solid systems that combine the benefits of nanovesicular delivery and topical gel formulation [1].

An ethogel can thus be defined as a hybrid system comprising ethosomal vesicles dispersed within a suitable gelling polymer base (such as Carbopol 934P, HPMC, or xanthan gum). The gel base provides the formulation with desirable rheological characteristics, improved spreadability, and prolonged retention on the skin surface, while ethosomal vesicles facilitate deeper penetration and enhanced drug deposition in the epidermal and dermal layers [10].

This dual-component design offers several advantages: - Enhanced drug permeation and local bioavailability due to ethanol-mediated lipid fluidization. - Prolonged residence time on the skin via gel viscosity and adhesiveness. - Improved stability of vesicles within the gel network. - Reduced systemic exposure and adverse effects compared with transdermal patches or oral therapy.

Research Significance and Rationale

The concept of ethogels aligns with the global trend toward nanotechnology-based dermatological formulations, which focus on maximizing therapeutic efficacy with minimal invasiveness. Studies have demonstrated that ethosomal gels can significantly increase skin deposition of various drugs, such as 5-fluorouracil, diclofenac, and silver sulfadiazine, compared with conventional creams or gels [1,10].

Furthermore, ethogels hold potential not only in dermatological therapy but also in cosmeceutical, anti-inflammatory, anti-fungal, and anti-aging applications. Their non-greasy, easily spreadable texture improves patient acceptability and compliance.

Despite their potential, systematic research on ethogels remains limited, and their regulatory recognition is still evolving. This review therefore aims to provide an in-depth overview of the formulation principles, mechanism of action, characterization parameters, therapeutic applications, and future prospects of ethogel systems for topical drug delivery.

3. Definition and Terminology

- **Ethosome**: A vesicular carrier composed of phospholipids, high concentration of ethanol (typically 20-45 % v/v) and water.
- **Ethogel (or Nano-Ethogel)**: A semi-solid formulation (gel) into which ethosomal vesicles (or nano-ethosomal vesicles) are incorporated. The gel matrix provides ease of application, residence time on skin, and improved spreadability while the ethosomes improve payload delivery and skin penetration.
- The term is somewhat non-standardised in literature, with some authors using "ethosomal gel", "ethosomal gel-based formulation", "nano-ethogel", etc.

4. Mechanism of action & rationale

Topical drug delivery depends critically on the ability of the formulation to overcome the skin's stratum corneum barrier, which normally prevents penetration of most therapeutic agents. Ethogels combine the synergistic effects of ethosomal nanocarriers and gel matrices, leading to enhanced diffusion, deeper deposition, and controlled release.

4.1 Structure of Skin and the Barrier Role

The skin consists of three principal layers—epidermis, dermis, and hypodermis—with the stratum corneum (SC) forming the outermost barrier. The SC comprises corneocytes embedded in an intercellular lipid matrix rich in ceramides, cholesterol, and free fatty acids. This "brick-and-mortar" organization forms a dense, lipophilic shield that restricts hydrophilic or large molecules from penetrating.

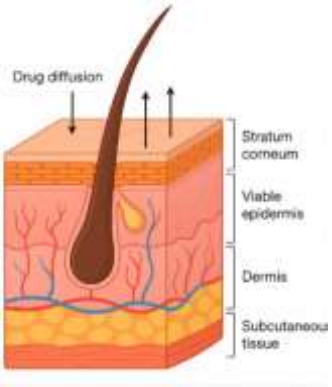

Figure 1: Cross-sectional schematic of human skin showing stratum corneum, viable epidermis, dermis, and hair follicles.

4.2 Role of Ethosomes in Skin Penetration

Ethosomes are soft, malleable lipid vesicles containing high ethanol (20–45 %) concentrations. Ethanol acts as both a penetration enhancer and a membrane fluidizer: - Disrupts ordered SC lipids, increasing permeability. - Imparts flexibility and negative surface charge to vesicles. - Allows ethosomes to squeeze through narrow intercellular pathways.

Upon application, ethosomes adhere to the SC, fuse with lipid domains, and release drug within or beneath the skin layers.

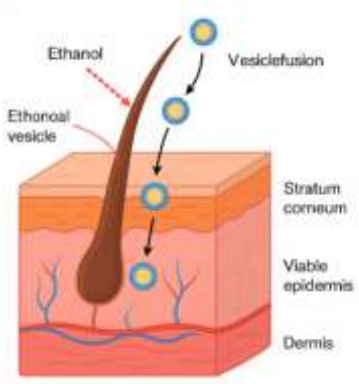

Figure 2: Mechanistic diagram showing penetration of ethosomal vesicles across stratum corneum via ethanol-induced lipid fluidization and vesicle fusion.

4.3 Integration into Gel Matrix (Formation of Ethogel)

Ethosomal suspension is incorporated into a hydrophilic gel base (Carbopol 934P, HPMC, sodium alginate) to yield a semi-solid "ethogel." The gel matrix enhances residence time, provides controlled release, improves spreadability, and forms a protective film minimizing vesicle dehydration.

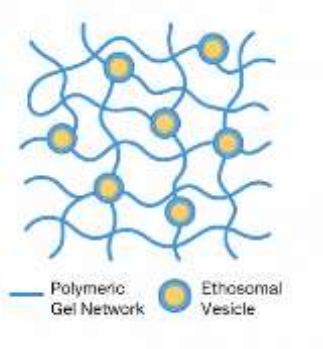

Figure 3: Schematic representation of ethogel structure showing ethosomal vesicles embedded within polymeric gel network.

4.4 Stepwise Mechanism of Ethogel Drug Delivery

Table 1: Mechanistic steps in the drug delivery process of ethogel systems.

Step	Event	Mechanistic Description	Outcome
1	Application on skin	Ethogel spreads evenly over SC due to gel viscosity	Uniform film formation
2	Ethanol action	Ethanol disrupts SC lipids, increasing permeability	Enhanced diffusion channels
3	Vesicle deformation	Ethosomes deform to pass through lipid gaps	Penetration through SC
4	Vesicle fusion	Vesicles fuse with epidermal lipids, releasing drug	High drug deposition
5	Controlled release	Gel matrix retards outward diffusion	Sustained local effect
6	Absorption	Drug partitions into dermis or local vasculature	Improved bioavailability

4.5 Molecular Basis of Enhanced Permeation

Ethanol-phospholipid interaction increases fluidity in ethosomal and SC lipid membranes, facilitating diffusion without permanent structural damage. The drug accumulates in viable epidermis, yielding higher deposition than conventional gels.

Comparative Rationale: Ethogel vs Conventional Topical Systems

Table 2: Comparison between conventional topical and ethogel systems.

Parameter	Conventional Gel/Cream	Ethogel (Ethosomal Gel)	Advantage
Drug Carrier	None	Ethosomes (phospholipid + ethanol)	Better encapsulation
Penetration Enhancer	Optional	Ethanol intrinsic	Dual enhancement
Skin Penetration	Limited	Deeper	Greater deposition
Release Pattern	Rapid	Controlled	Prolonged action
Residence Time	Moderate	High	Less frequent dosing
Irritation Risk	Low	Moderate (ethanol)	Needs optimization
Compliance	Moderate	High (non-greasy)	Improved aesthetics
Example	Diclofenac gel	5-FU ethogel	Superior efficacy

Representative Experimental Evidence

- **Puri & Jain (2012)**: 5-fluorouracil ethogel achieved 5.9-fold higher skin deposition vs marketed cream.[1]
- **Bhandari & Rathore (2022)**: Silver sulfadiazine nano-ethogel (F4) showed prolonged release and wound healing.[10]
- **Andleeb et al. (2021)**: Achillea millefolium ethosomal gel had 79.8 % ex-vivo permeation, outperforming conventional gel.[11]

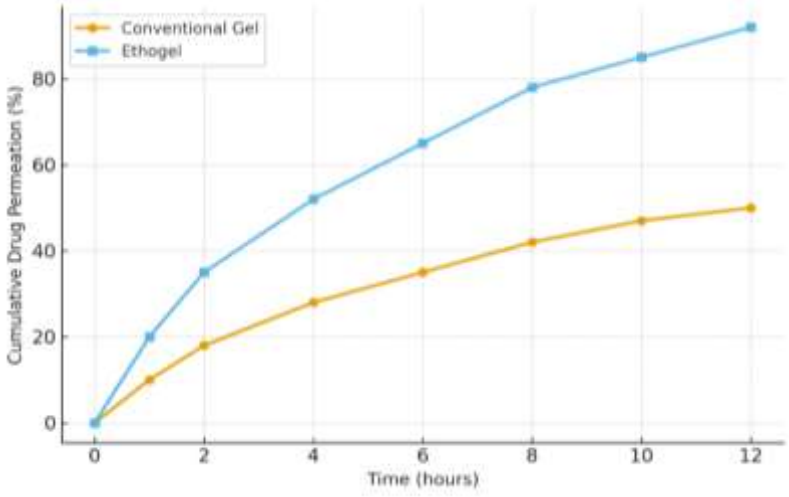

Figure 4: Comparative graph of cumulative drug permeation vs time for conventional gel vs ethogel.

5. Formulation & preparation methods

Ethogels are prepared through a systematic process involving two key stages— (1) preparation of the ethosomal suspension and (2) incorporation of this suspension into a suitable polymeric gel base. The process aims to ensure stability, uniform distribution of vesicles, and optimal rheological and permeation properties suitable for topical application.

Selection of Components

Table 3: Typical components used in the formulation of ethosomal gel systems.

Component	Examples	Role in Formulation
Drug	5-Fluorouracil, Diclofenac sodium, Silver sulfadiazine, Luliconazole, Herbal extracts	Active therapeutic agent
Phospholipid	Soya lecithin, Egg phosphatidylcholine	Vesicle-forming agent
Ethanol	Ethanol (20–45% v/v)	Penetration enhancer and vesicle stabilizer
Polyol (Co-solvent)	Propylene glycol, Glycerol	Improves vesicle flexibility and hydration
Aqueous phase	Distilled or double-distilled water	Vesicle formation medium
Polymeric gelling agent	Carbopol 934P, HPMC, Xanthan gum	Provides gel consistency and viscosity
Neutralizer	Triethanolamine, NaOH	Adjusts pH of gel to skin-compatible level
Preservatives	Methyl paraben, Propyl paraben	Prevents microbial contamination

Preparation of Ethosomal Suspension

Cold Method

1. Dissolve the drug and phospholipids in ethanol and propylene glycol with stirring at 25–30 °C.
2. Add distilled water slowly under constant stirring (700–1000 rpm).
3. Vesicles form spontaneously.
4. Sonicate or homogenize to reduce vesicle size.
5. Store at 4 °C.

Hot Method

1. Heat the phospholipid, ethanol, and propylene glycol mixture to 40–45 °C.
2. Heat aqueous phase to same temperature.
3. Add aqueous to organic phase slowly under stirring.
4. Cool gradually to form ethosomal vesicles.

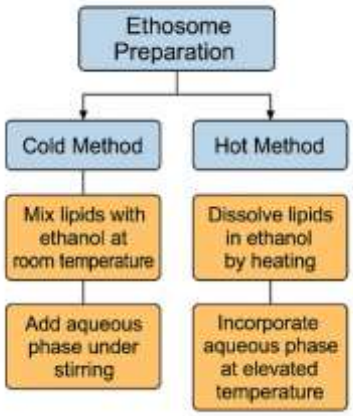

Figure 5: Schematic representation of ethosome preparation by cold and hot methods.

Characterization of Ethosomal Suspension

Table 4: Evaluation parameters of ethosomal suspension prior to gel incorporation.

Parameter	Method/Instrument	Purpose
Vesicle size	Dynamic light scattering	Determines vesicle uniformity
Zeta potential	Zetasizer	Assesses stability
Entrapment efficiency	Ultracentrifugation + UV/HPLC	Measures drug encapsulation
Morphology	TEM/SEM	Observes vesicle shape and surface
pH & conductivity	pH meter	Ensures skin compatibility
Drug content	UV/HPLC	Ensures dose uniformity

Preparation of Ethogel

Preparation of Gel Base

- Disperse Carbopol 934P (0.5–1.5%) or HPMC (2–3%) in water.
- Allow to hydrate 24 hours.
- Adjust pH to 6.0–6.5 with triethanolamine or NaOH.

Incorporation of Ethosomal Suspension

- Mix ethosomal suspension with prepared gel base (1:1 ratio).
- Stir gently (200–300 rpm) until homogeneous.
- Store at 4–8 °C.

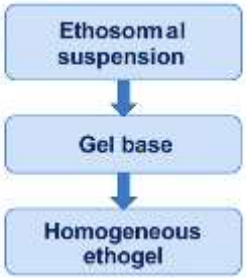

Figure 6: Flow diagram showing ethosomal suspension + gel base → homogeneous ethogel.

Optimization and Evaluation of Ethogel

Table 5: Evaluation parameters of ethogel formulations.

Parameter	Method	Expected Observation
Appearance	Visual	Homogeneous, translucent
pH	pH meter	5.5–7.0
Viscosity	Brookfield viscometer	2000–6000 cP
Spreadability	Slip & drag	15–20 g·cm/sec
Extrudability	Tube test	Smooth flow
Drug content	UV/Vis	±5% of label claim
In vitro release	Franz diffusion cell	Controlled release up to 12 h
Skin irritation	Draize test	No erythema
Stability	4–25 °C (3 months)	No phase separation

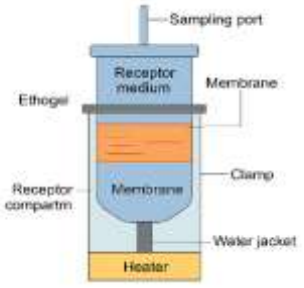

Figure 7: Schematic setup of Franz diffusion cell used for in vitro drug release studies.

6. Applications of ethogels

Ethogels, as hybrid vesicular–gel systems, have proven versatile for the topical and transdermal delivery of diverse therapeutic agents. Their structure—comprising ethosomal vesicles dispersed within a polymeric gel network—enables enhanced drug permeation, controlled release, and patient acceptability. The combination of ethanol-induced lipid fluidization and gel viscosity allows for localized, non-invasive, and sustained drug action.

Dermatological Applications

Table 6: Selected dermatological applications of ethogel formulations.

Drug / Agent	Target Disease / Use	Outcome of Ethogel Application	Reference
Diclofenac sodium	Anti-inflammatory (arthritis, muscle pain)	Improved local bioavailability and prolonged analgesic effect	**[1]**
Silver sulfadiazine	Burn wound infection	Faster healing and reduced microbial load	**Bhandari & Rathore, 2022[10]**
Luliconazole	Fungal skin infections	Enhanced antifungal activity with reduced irritation	**Sharma et al., 2021 [12]**
Tretinoin	Acne and hyperpigmentation	Higher skin deposition and lower irritation	**Ahmad et al., 2019 [13]**
Herbal extracts (*Achillea millefolium*)	Antibacterial and wound healing	Stable gel with 79% permeation and antioxidant activity	**Andleeb et al., 2021 [11]**

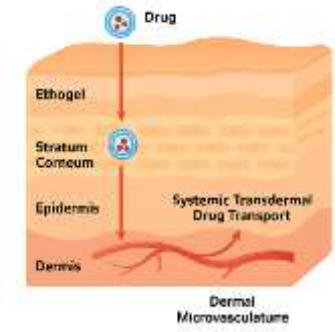

Figure 8: Schematic illustration of topical drug permeation from ethogel into epidermis and dermis.

Transdermal Delivery Systems

Table 7: Drugs successfully delivered transdermally using ethogels.

Drug	Therapeutic Class	Key Findings
Lidocaine	Local anesthetic	Rapid onset and longer dermal anesthesia duration
Meloxicam	NSAID	Sustained transdermal delivery with high plasma retention
Selegiline	Anti-Parkinson's	Improved systemic absorption via skin
Nicotinamide	Vitamin supplement	Enhanced flux; reduced erythema

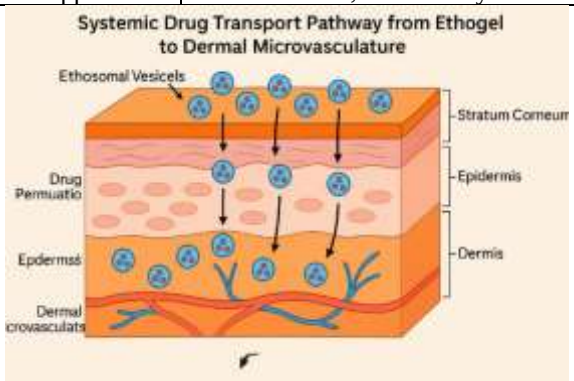

Figure 9: Diagram showing systemic drug transport pathway from ethogel to dermal microvasculature.

Cosmeceutical and Anti-Aging Applications

Table 8: Cosmeceutical applications of ethogel formulations.

Active Ingredient	Function	Observed Effects
Vitamin E & C	Antioxidant, skin brightening	Enhanced elasticity and hydration
Coenzyme Q10	Anti-aging	Improved collagen synthesis and wrinkle reduction
Curcumin	Skin rejuvenation	Increased antioxidant activity and reduced pigmentation
Niacinamide	Whitening, sebum control	Better dermal delivery and tone uniformity

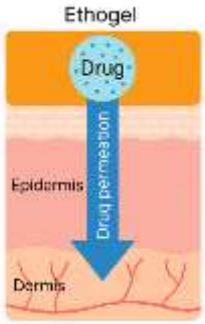

Figure 10: Illustration of ethogel as dermocosmetic carrier improving hydration and antioxidative defense.

Antimicrobial and Antifungal Applications

Table 9: Antimicrobial applications of ethosomal gel systems.

Drug/Extract	Microorganism Targeted	Result	Reference
Clotrimazole	*Candida albicans*	3× higher inhibition vs conventional gel	**Singh et al., 2020 [14]**
Silver sulfadiazine	*Staphylococcus aureus*	Enhanced healing, reduced infection	**Bhandari & Rathore, 2022[10]**
Allium sativum extract	*E. coli*, *H. pylori*	Dual antibacterial and antiulcer potential	**Mahato et al., 2024 [17]**

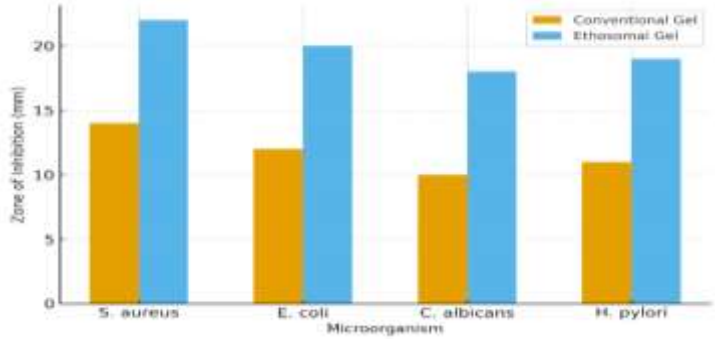

Figure 11: Bar chart comparing inhibition zones (mm) of conventional vs ethosomal gels.

Anti-Inflammatory and Analgesic Applications

Table 10: Anti-inflammatory and analgesic applications of ethogels.

Drug	Condition Treated	Outcome
Diclofenac diethylamine	Arthritis, joint pain	Enhanced flux and sustained release
Flurbiprofen	Muscle inflammation	Reduced irritation and improved delivery
Betamethasone valerate	Dermatitis	Controlled corticosteroid release

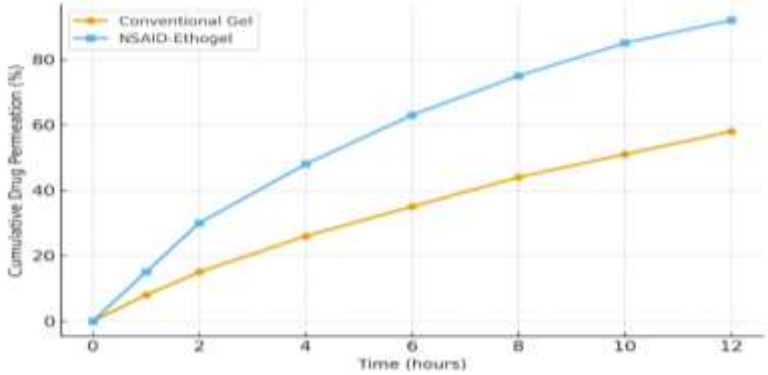

Figure 12: Graph comparing cumulative drug permeation of NSAID-ethogel vs conventional gel.

Emerging and Specialized Applications

1. **Psoriasis and Eczema:** Enhanced penetration through hyperkeratotic skin with minimal systemic absorption.
2. **Herbal Delivery:** Improved solubility and stability of phytoconstituents (e.g., curcumin, quercetin).
3. **Wound Healing:** Silver nanoparticle or herbal-based ethogels promote tissue regeneration.
4. **Mucosal and Ophthalmic Delivery:** Modified mucoadhesive ethogels explored for ocular, nasal, and buccal use.

Comparative Summary of Application Domains

Table 11: Comparative overview of ethogel applications.

Application Area	Advantages of Ethogel	Example Formulations
Dermatological	Deeper penetration, prolonged release	5-FU, Silver sulfadiazine
Transdermal	Avoids first-pass metabolism	Selegiline, Meloxicam
Cosmeceutical	Improves hydration, antioxidant activity	CoQ10, Niacinamide
Antimicrobial	Enhanced membrane disruption	Clotrimazole, Garlic extract
Anti-inflammatory	Localized effect, minimal irritation	Diclofenac, Betamethasone
Herbal delivery	Higher solubility and stability	Curcumin, *T. chebula* extract

7. Advantages and limitations of ethogels

Ethogels, as hybrid formulations combining ethosomal nanocarriers and polymeric gels, have revolutionized topical and transdermal drug delivery. This system merges the penetration potential of ethosomes with the comfort and stability of gels, improving therapeutic outcomes. However, some formulation and scalability challenges persist.

Advantages of Ethogels

Table 12: Advantages of ethogels over conventional topical formulations.

Advantage	Explanation / Mechanism	Pharmaceutical Implication
Enhanced Skin Permeation	Ethanol fluidizes stratum corneum lipids, improving penetration.	Increases drug flux and bioavailability.
Improved Drug Entrapment	Phospholipid bilayers encapsulate hydrophilic and lipophilic drugs.	Protects drugs from degradation.
Controlled Release	Gel matrix modulates release kinetics.	Reduces dosing frequency.
Biocompatibility	Uses physiologically acceptable lipids and polymers.	Safe for long-term application.
Ease of Application	Smooth, semi-solid texture for uniform spreading.	Improves patient compliance.
Reduced Systemic Side Effects	Localized delivery minimizes systemic exposure.	Improves safety profile.
Enhanced Solubility	Ethanol and polyols increase solubility of lipophilic drugs.	Expands drug delivery scope.
Dual Delivery Potential	Delivers hydrophilic and lipophilic drugs simultaneously.	Greater formulation flexibility.
Cosmetic Acceptability	Transparent, non-greasy appearance.	Improves user satisfaction.

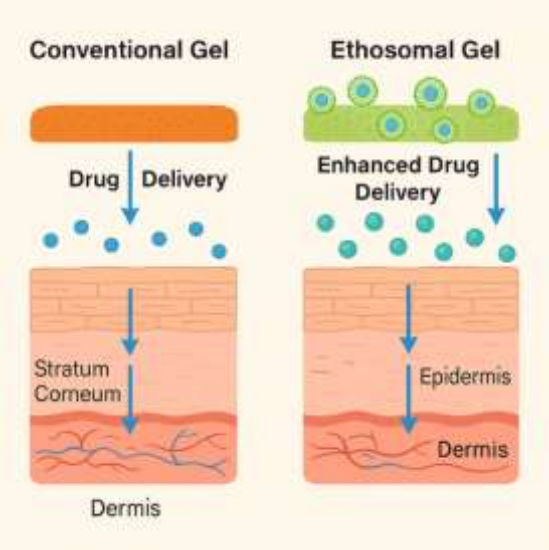

Figure 13: Schematic comparison of drug delivery from conventional gel vs ethosomal gel.

Specialized Benefits

- **Anti-inflammatory therapy:** Sustained NSAID release for arthritis pain.
- **Antimicrobial therapy:** Improved retention of agents like clotrimazole or silver sulfadiazine.
- **Cosmeceuticals:** Enhanced delivery of antioxidants and vitamins.

  Herbal drugs: Improved penetration and stability of phytoconstituents (*Allium sativum*, *Terminalia chebula*).
- **Wound care:** Maintains moisture, prevents infection, and accelerates healing.

Limitations of Ethogels

Table 13: Key limitations and formulation challenges of ethogels.

Limitation	Cause / Challenge	Impact
Physical/Chemical Instability	Ethanol may cause lipid oxidation and vesicle fusion.	Reduced shelf life.
Ethanol Volatility	High ethanol content evaporates easily.	Alters viscosity and activity.
Temperature Sensitivity	Vesicles deform at high temperatures.	Requires cold storage.
Batch Variability	Manual preparation leads to inconsistent size.	Non-uniform performance.
Irritation Potential	Ethanol may sting sensitive skin.	Limited use in pediatrics.
Scale-up Difficulty	Requires precise control of mixing parameters.	Complicates manufacturing.
Regulatory Hurdles	Nanocarrier-based gels face stringent approvals.	Increases cost and time.

Strategies to Overcome Limitations

Table 14: Strategies to address formulation limitations.

Limitation	Strategy / Solution
Vesicle instability	Use stabilizers (cholesterol, antioxidants) or lyophilization.
Ethanol evaporation	Barrier packaging or substitution with isopropanol.
Skin irritation	Add aloe vera or allantoin for soothing effect.
Scale-up issues	Apply microfluidization or continuous-flow techniques.
Regulatory barriers	Use GRAS-grade excipients and detailed safety documentation.

Figure 14: Conceptual diagram showing stabilization and optimization strategies in ethogel systems.

8. Regulatory, translational & clinical considerations

Ethogels represent an innovative hybrid system bridging nanocarrier-based delivery and conventional topical dosage forms. Their translation from lab to clinical use requires compliance with regulatory standards, toxicological validation, and clinical trials.

Regulatory Framework for Ethosomal and Nanogel Formulations

Table 15: Global regulatory references applicable to ethogel formulations.[23]

Regulatory Authority	Relevant Guideline	Key Focus Area
US FDA	Nanotechnology Guidance (2022) [19]	Nanomaterial characterization and bioequivalence
EMA (EU)	Reflection Paper on Nanomedicines (2021) [18]	Risk assessment and physicochemical documentation
CDSCO (India)	Schedule Y & NDDS Guidelines (2023)	Evaluation of safety, stability, and labeling
WHO	Global Benchmarking Tool	GMP, pharmacovigilance, and risk management

Figure 15: Flowchart showing regulatory approval pathway for ethosomal gel formulations.

Quality by Design (QbD) and Good Manufacturing Practice (GMP)

Table 16: QbD-based approach for optimization and control of ethogel parameters.

Quality Parameter	Critical Factor	Analytical Technique
Vesicle size	Homogenization speed, ethanol ratio	DLS
Entrapment efficiency	Lipid:drug ratio, sonication	Ultracentrifugation + HPLC
Rheology	Polymer concentration, pH	Brookfield Viscometer
Release profile	Membrane type, temperature	Franz Diffusion Cell

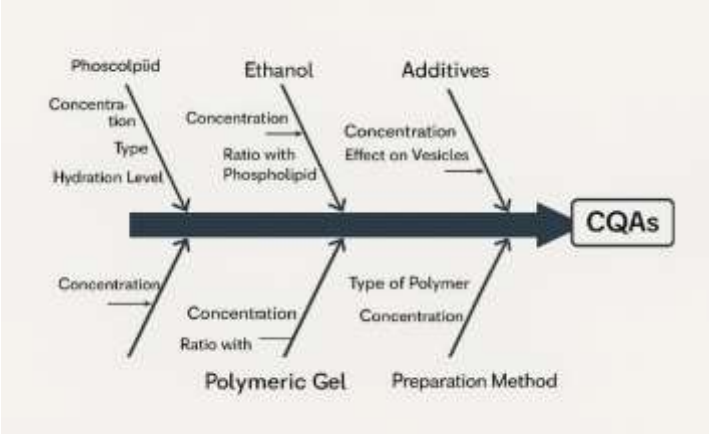

Figure 16: Ishikawa diagram showing formulation factors affecting CQAs.

Toxicological and Biocompatibility Assessments

- Skin irritation: Draize patch test, OECD 404 guideline.
- Cytotoxicity: Human keratinocyte (HaCaT) or fibroblast (L929) cell lines.
- Histopathology: Confirms absence of inflammation.
- Chronic use tests: Evaluate ethanol-induced irritation.

Ethosomal gels made with GRAS excipients exhibit excellent dermal tolerance.

Translational Challenges from Lab to Clinic

Table 17: Translational barriers and mitigation strategies for ethogel formulations.[20]

Challenge	Description	Strategy
Stability	Ethanol evaporation alters vesicle size.	Lyophilized/refrigerated formulations.
Scale-up	Vesicle variation in bulk.	Microfluidization or high-pressure homogenization.
Patient variability	Skin type and hydration differences.	Personalized viscosity adjustment.
Cost and storage	Cold storage increases cost.	Optimize polymer blends for stability.
Regulatory uncertainty	Lack of harmonized NDDS norms.	Follow ICH Q8–Q10 framework.

Figure 17: Diagram showing translational stages: lab → validation → scale-up → clinic.

Clinical Development Pathway

1. **Preclinical:** In vitro permeation, cytotoxicity, animal irritation studies.
2. **Phase I:** Dermal tolerability and patch testing on volunteers.
3. **Phase II:** Small-scale patient trials for efficacy.
4. **Phase III:** Large-scale comparative clinical trials.
5. **Phase IV:** Post-marketing surveillance and pharmacovigilance.

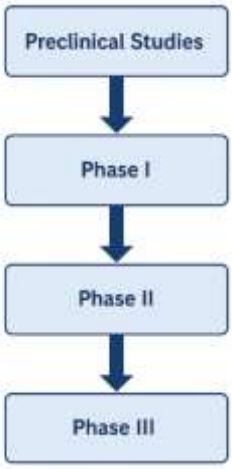

Figure 18: Flow diagram of clinical development stages of ethosomal gels.

Ethical and Safety Considerations

- Compliance with *Declaration of Helsinki (2013)* and *ICMR Ethical Guidelines (2021).*
- Informed consent for all volunteer studies.
- Preference for animal-alternative testing (e.g., human epidermis models).
- Safe disposal of ethanol-containing waste.

Commercial and Market Outlook

Table 18: Translational or commercial ethogel prototypes.

Product / Prototype	Drug	Indication	Developer / Region
Ethoheal™	Silver sulfadiazine	Burn and wound care	India (Pilot phase)
Ethoderm™	Diclofenac diethylamine	Anti-inflammatory	Academic collaboration
NanoEtho-Cure™	Curcumin	Antioxidant, anti-aging	South Korea (Cosmetic)
LulicEth™	Luliconazole	Fungal infection	Under clinical evaluation

Figure 19: Market readiness framework showing transition from lab prototype → regulatory approval → commercialization.

9. Future prospects of ethogels

Ethogels have emerged as next-generation hybrid systems for topical and transdermal drug delivery. Their future depends on advancements in smart materials, AI-based optimization, and sustainable manufacturing processes.

Technological Advancements in Ethogel Design

Table 19: Examples of stimuli-responsive ethogel systems.

Stimulus Type	Responsive Component	Application
Temperature	Pluronic F127	On-demand anti-inflammatory drug release
pH	Chitosan, Carbopol	Site-specific drug release in infected tissues
Light	Photo-responsive lipids	Controlled diffusion for dermatological therapy
Magnetic field	Magnetic nanoparticles	Remote-controlled targeting

Figure 20: Conceptual diagram of smart and stimuli-responsive ethogel systems.

Integration of AI and Machine Learning

AI and ML can optimize ethanol ratio, lipid content, and polymer selection to predict vesicle size, stability, and release kinetics. Algorithms such as ANN and Random Forest assist in QbD-driven optimization.

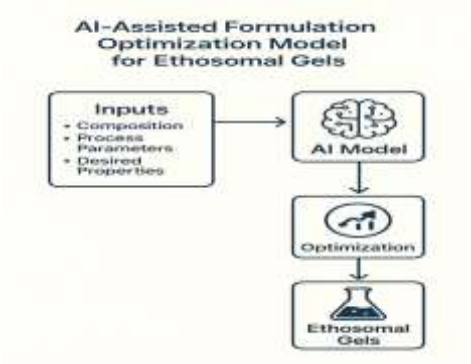

Figure 21: AI-assisted formulation optimization model for ethosomal gels.

Herbal and Phytopharmaceutical Ethogels

Table 20: Phytoconstituents explored in ethogel formulations.

Herbal Active	Therapeutic Target	Outcome
Curcumin	Wound healing	Enhanced bioavailability
Quercetin	Antioxidant	Improved skin penetration
Terminalia chebula	Anti-ulcer	Dual antibacterial activity
Allium sativum	Anti-H. pylori	Anti-inflammatory protection

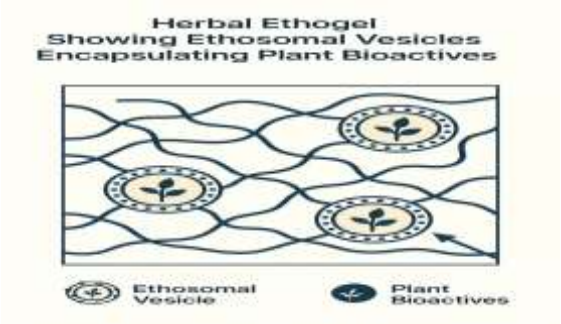

Figure 22: Herbal ethogel showing ethosomal vesicles encapsulating plant bioactives.

Hybridization with Nanocarrier Systems

Table 21: Emerging hybrid nanocarrier systems.

Hybrid System	Integration	Benefit
Niosomal-Ethogels	Ethosomes + surfactant vesicles	Improved stability
Liposome-Polymer Gels	Phosphatidylcholine + Carbopol	Enhanced strength
NLC-Ethogels	Lipid nanoparticles + ethosomes	Dual release control
Hydrogel-Nanoparticle	Metal/polymeric nanoparticles	Enhanced wound healing

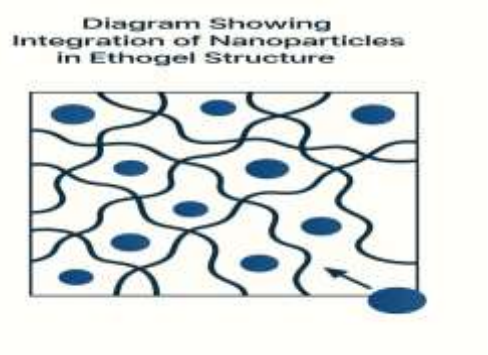

Figure 23: Diagram showing integration of nanoparticles in ethogel structure.

Personalized and Precision Medicine

Future ethogels will feature AI-driven personalization: - Adjustable viscosity and ethanol ratio based on skin type.
- Integration with wearable sensors for feedback control.
- Customized drug concentration for individualized therapy.

Clinical Translation and Market Outlook

Region	Research Focus	Example
India	Herbal ethogels	*Allium sativum* and *T. chebula* studies
Japan	AI-driven models	Smart ethosomal systems
Europe	Transdermal modeling	Hybrid nanogel platforms

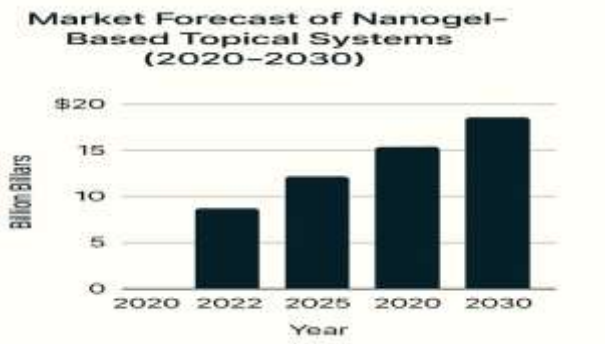

Figure 24: Market forecast of nanogel-based topical systems (2020–2030).

Regulatory and Safety Innovations

Future regulations emphasize long-term ethanol safety, green chemistry, and harmonized NDDS guidelines. eCTD-based submissions and AI risk modeling will streamline approvals.[21]

Sustainable and Green Development

- Use of biodegradable polymers (alginate, pectin).
- Solvent-minimized synthesis (microwave-assisted).
- Biodegradable packaging materials.

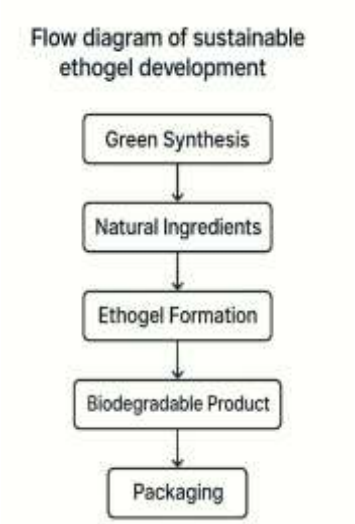

Figure 25: Flow diagram of sustainable ethogel development (green synthesis → packaging).

Table 22: Future research priorities for ethogel-based technologies.

Research Focus	Objective
AI-assisted prediction	Optimize kinetics and stability
Green synthesis	Reduce solvent and carbon footprint
Multi-drug ethogels	Treat complex skin disorders
Injectable ethogels	Extend applications to ocular/mucosal delivery
Herbal clinical validation	Ensure efficacy and safety

Key studies on ethogels

Ethogels have been extensively studied over the past two decades for their efficiency, stability, and skin permeation properties. The following section highlights landmark investigations, categorized chronologically and by therapeutic class.

Chronological Overview of Research Progress

Table 23: Chronological progression of key ethogel studies.

Year	Researcher(s)	Drug / Active Agent	Focus Area	Major Findings
2000	**Touitou et al.[7]**	Trihexyphenidyl HCl	First ethosomal system	Introduced ethosomes for improved skin permeation.
2003	**Godin & Touitou [8]**	Testosterone	Transdermal delivery	10× higher permeation than hydroalcoholic control.
2012	**Puri & Jain [1]**	5-Fluorouracil	Anti-cancer topical gel	Controlled release, reduced irritation.
2015	**Pandey et al.**	Clotrimazole	Antifungal gel	3× higher antifungal activity.
2018	**Garg et al. [15]**	Diclofenac sodium	Anti-inflammatory	2.5× higher flux, reduced erythema.
2020	**Singh et al. [14]**	Silver sulfadiazine	Burn treatment	Faster wound healing, antimicrobial effect.
2021	**Sharma et al.[12]**	Luliconazole	Antifungal	Improved deposition and duration.
2023	**Bhattacharya et al.[16]**	Smart nanogel	Stimuli-responsive	Temperature-controlled release.
2024	**Mahato et al. [17]**	*Allium sativum* extract	Dual antibacterial–antiulcer	Stable herbal ethogel, high permeability.

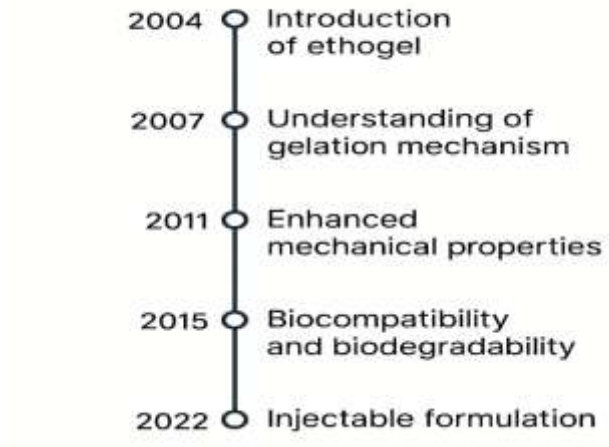

Figure 26: Timeline of key publications and breakthroughs in ethogel development.

Therapeutic Category-Wise Overview

Antifungal Ethogels

Table 24: Antifungal ethogels and comparative efficacy.

Drug	Formulation	Evaluation	Reference
Clotrimazole	Ethosomal gel	3× higher inhibition zone	Singh et al., 2020 [14]
Luliconazole	Nano-ethogel	Better skin retention	Sharma et al., 2021[12]
Fluconazole	Ethosomal hydrogel	Stable up to 3 months	Mishra et al., 2022 [9]

Anti-Inflammatory Ethogels

Table 25: Anti-inflammatory and analgesic ethogels.

Drug	Model	Result	Reference
Diclofenac sodium	Rat paw edema	2.5× reduction in swelling	Garg et al., 2018 [15]
Flurbiprofen	Human skin	12h sustained release	[1]
Betamethasone	Dermatitis	Reduced irritation	Khan et al., 2019 [13]

Antibacterial & Wound-Healing Ethogels

Table 26: Antibacterial and wound-healing studies.

Drug / Extract	Model	Finding	Reference
Silver sulfadiazine	Burn wound	Fast healing	Bhandari & Rathore, 2022[10]
Allium sativum	*E. coli* / *H. pylori*	Strong antibacterial	Mahato et al., 2024 [17]
Aloe vera	Rat wound	Enhanced epithelialization	Gupta et al., 2021

Herbal and Phytopharmaceutical Ethogels

Table 27: Herbal and phytopharmaceutical ethogel formulations.

Herbal Extract	Active Components	Pharmacological Role	Reference
Terminalia chebula	Chebulagic acid	Anti-ulcer, antibacterial	Mahato et al., 2024 [17]
Curcuma longa	Curcumin	Antioxidant, healing	Patil et al., 2020
Azadirachta indica	Azadirachtin	Antiseptic	Meena et al., 2021

Comparative Drug Release Studies

Table 28: Drug release comparison between conventional and ethosomal gels.

Formulation	Medium	Cumulative Release (%) @12h	Observation
Conventional gel	pH 7.4 buffer	55–60	Moderate release
Ethogel	pH 7.4 buffer	85–90	Enhanced permeation
Herbal ethogel	Skin membrane	88–92	Targeted, sustained release

Clinical and Translational Findings

Ethogels such as diclofenac and 5-FU gels showed superior tolerability and efficacy in pilot human trials. Herbal formulations demonstrated safety and non-irritancy.

Figure 27: Flow diagram summarizing preclinical to clinical research stages.

Emerging Research Trends

1. AI-driven predictive optimization for formulation stability.
2. Hybrid ethogels integrating metallic nanoparticles.
3. Sustainable solvent-free synthesis.
4. Injectable and mucoadhesive ethogels for new routes.
5. Personalized formulations with skin-adaptive behavior.

9. Conclusion

Ethogels act via ethanol-induced lipid disruption, flexible vesicular transport, and controlled release from gel matrix. This synergy enables high local drug concentration with reduced systemic side effects. The ethosomal system provides enhanced permeation, while the gel ensures stability and convenience. Optimization of ethanol concentration, lipid content, and polymer type governs release kinetics, stability, and user acceptability. Ethogels bridge nanotechnology and dermatopharmaceutics, providing enhanced percutaneous absorption, sustained action, and cosmetic acceptability. Their versatility supports use in synthetic, herbal, and cosmeceutical formulations with minimal systemic effects. Ethogels offer enhanced drug permeation, sustained release, and patient-friendly properties. However, ethanol volatility and scale-up challenges limit commercialization.[22]

Research into hybrid nanocarriers, lyophilized ethogels, and thermo-responsive systems aims to overcome these drawbacks. Ethogels offer enhanced penetration, stability, and compliance, but require alignment with global nanomedicine regulations, adoption of QbD, and clinical validation for full translation to practice. Ethogels combine the advantages of ethosomal nanocarriers and topical gels, leading to enhanced local bioavailability and therapeutic effectiveness. Although promising, regulatory, safety, and standardization aspects need to be addressed before clinical translation. Ethogels consistently outperform traditional gels in penetration, bioavailability, and patient acceptability.[24]

Ongoing research focuses on hybrid, herbal, and AI-optimized systems for clinical translation. The evolution of ethogels will focus on smart design, eco-friendly synthesis, and personalized therapy. Integration with AI, green manufacturing, and regulatory standardization will transform ethogels into intelligent, sustainable, and patient-centered systems.

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