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PRECISION-RESPONSIVE HYDROGEL THERAPEUTICS FOR CUTANEOUS DISORDERS: FROM PATHOPHYSIOLOGY-DRIVEN DESIGN TO PERSONALIZED DERMATOLOGY

Rajaganapathy kaliyaperumal*[1], Puniparthi Sunitha[1], Pratheeba G.[1], Pratheep N.[1], Rahul M.[1], Dhanush Kumar S.[1], Srinivasan R.[1], Kalaivanan Seeni[1],Vignesh S.[1]

[1]Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Selaiyur, Chennai-600073, Tamil Nadu, India.

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***Corresponding Author: Rajaganapathy kaliyaperumal**
Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Selaiyur, Chennai-600073, Tamil Nadu, India.

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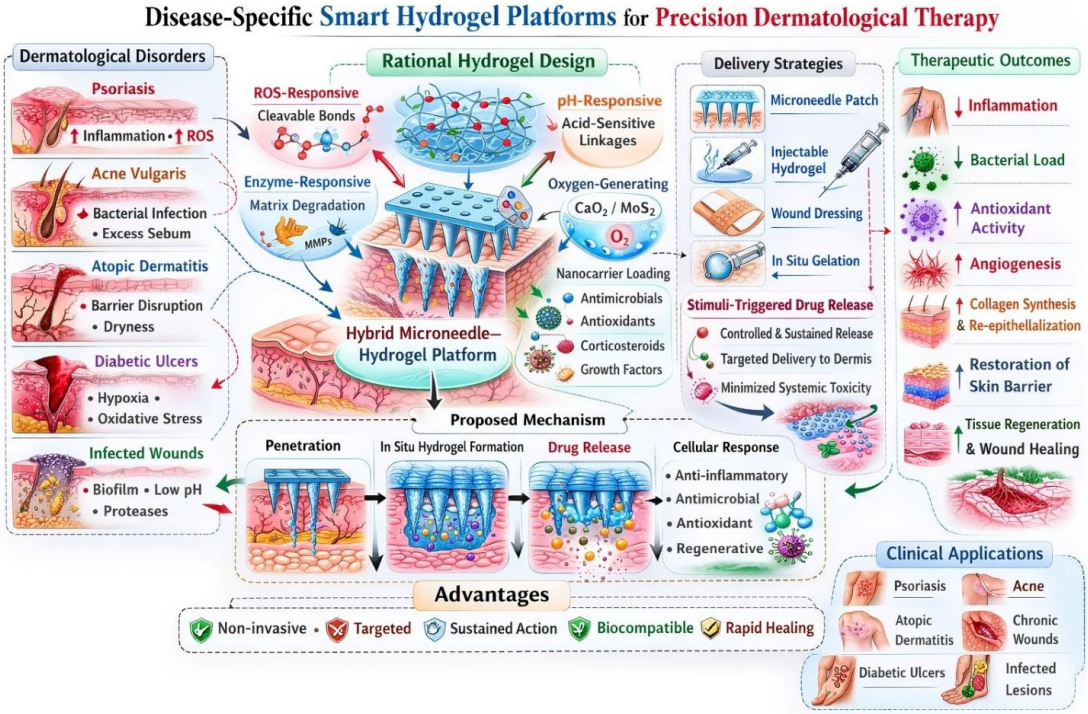
ABSTRACT

Because hydrogel-based systems offer special structural, physicochemical, and biological characteristics, they have become cutting-edge platforms for the treatment of dermatological illnesses. These three-dimensional, crosslinked polymeric networks allow for the controlled and prolonged administration of therapeutic drugs across the epidermal barrier because of their high water content, customisable mesh architecture, and tunable mechanical strength. The design of hydrogels has changed recently from traditional sustained-release matrices to disease-driven, microenvironment-responsive systems that may adjust to pathological triggers such microbial dysbiosis, oxidative stress, enzyme overexpression, and pH imbalance. Contemporary hydrogels can offer targeted, localised, and stimuli-sensitive drug release that is suited to inflammatory dermatoses, acne, chronic wounds, and diabetic ulcers by combining natural and synthetic polymers, dynamic crosslinking chemistries, nanocarriers, and multifunctional bioactive components. New approaches that broaden their therapeutic scope toward precision dermatology include follicular targeting, living bioactive hydrogels, hybrid microneedle–hydrogel systems, multi-therapeutic co-delivery platforms, and digitally integrated smart dressings. Translational hurdles, such as sterility assurance, regulatory classification, microbiome safety, and scalable manufacturing, persist despite encouraging preclinical results. Clinical progress depends on overcoming these obstacles by integrating biomaterials science, dermatology, and regulatory frameworks in an interdisciplinary manner. All things considered, precision-responsive hydrogel therapies offer flexible, multipurpose,

and patient-centered treatments for intricate skin conditions, marking a revolutionary advancement in dermatological drug delivery.

KEYWORDS: Hydrogels; Cutaneous disorders; Stimuli-responsive delivery; Nanocomposite systems; Precision dermatology; Transdermal therapy.



Graphical Abstract: Schematic representation of disease-specific smart hydrogel engineering strategies for precision dermatological therapy. The illustration highlights stimuli-responsive hydrogel design (ROS-, pH-, and enzyme-sensitive systems), nanocarrier integration, microneedle-assisted delivery, and oxygen-generating platforms enabling controlled, targeted, and regenerative treatment of inflammatory, infectious, and chronic skin disorders.

1.INTRODUCTION

One of the most common types of human diseases, cutaneous problems afflict people of all ages and geographical locations [1,2]. Inflammation, oxidative stress, microbial imbalance, immunological dysregulation, and compromised barrier function are some of the complex and frequently overlapping pathogenic mechanisms that define conditions like psoriasis, acne vulgaris, atopic dermatitis, chronic wounds, and diabetic ulcers. As the biggest organ in the body and its principal barrier of defence, the skin is essential to preserving physiological

equilibrium. But efficient medication penetration is severely hampered by its highly ordered stratified structure, especially the stratum corneum [3, 4]. Conventional creams, ointments, and gels often have limited skin retention, poor penetration efficiency, variable drug release, and suboptimal patient adherence, despite topical therapies' localised action and decreased systemic side effects, which continue to make them the cornerstone of dermatological treatment [5,6]. These restrictions have prompted ongoing research into cutting-edge biomaterial-based delivery systems that can get past the biological and structural obstacles found in sick skin [7].

Hydrogel-based technologies have drawn a lot of interest as flexible and biocompatible cutaneous drug delivery methods [8]. Three-dimensional networks of crosslinked polymers called hydrogels are able to absorb and hold onto huge amounts of water while preserving their structural integrity [9]. They are especially well suited for cutaneous applications due to their high hydration level, adjustable mechanical characteristics, and structural resemblance to the extracellular matrix [10,11]. Hydrogel technologies have developed over the past few decades from straightforward sustained-release matrices to multipurpose platforms that include bioactive compounds, nanocarriers, and stimuli-responsive components. The changed microenvironment seen in many dermatological conditions is closely aligned with the characteristics of modern hydrogels, which can be designed to react to environmental stimuli such pH changes, reactive oxygen species, enzyme activity, and temperature variations [12,13]. Furthermore, their therapeutic scope has been extended beyond passive drug administration into interactive and adaptive treatment systems through integration with nanotechnology, microneedle arrays, microbiome-modulating components, and digital sensing elements [14,15].

Important research gaps still exist in the transition of hydrogel systems from laboratory invention to clinically optimised dermatological therapy, despite notable advancements [16,17]. The design of many current formulations is material-centric, focusing on drug release kinetics and polymer composition without adequately incorporating disease-specific pathophysiology into design principles. Many hydrogel systems fail to effectively utilise pathogenic triggers including increased oxidative stress, abnormal enzyme expression, follicular involvement, or microbiome imbalance, despite the fact that cutaneous illnesses are physiologically diverse and constantly changing [18,19]. Additionally, the integration of patient-centric usability considerations, regulatory translation problems, and multi-therapeutic co-delivery strategies inside a single conceptual framework has received little

attention. In order to guarantee that hydrogel design is directly influenced by the biological mechanisms behind particular skin disorders, a thorough methodology that connects biomaterial engineering with disease-driven therapeutic reasoning is still required [20,21].

Given these factors, the current study intends to offer a comprehensive and integrated analysis of precision-responsive hydrogel systems for cutaneous conditions, highlighting the shift from traditional drug carriers to therapeutic platforms with biological intelligence. In order to improve treatment specificity, safety, and efficacy, the goal is to investigate how polymer composition, crosslinking techniques, nanocomposite integration, and stimuli-responsive mechanisms can be logically matched with disease microenvironment features [22]. While critically addressing translational and regulatory considerations, this work also aims to highlight new approaches such as follicular targeting, hybrid microneedle–hydrogel systems, living bioactive hydrogels, multi-therapeutic co-delivery approaches, and digitally integrated platforms [23]. This manuscript seeks to establish a conceptual foundation for precision dermatology in which hydrogel engineering is methodically guided by pathophysiological insight, ultimately supporting the development of safer, smarter, and more patient-centered treatments for a wide range of skin diseases. It does this by synthesising existing knowledge and identifying future research directions [24].

2.HYDROGEL: INGREDIENTS AND PREPARATION TECHNIQUES

One of the most flexible and biocompatible methods for obtaining prolonged, regulated, and stimuli-responsive release of medicinal chemicals is hydrogel-based drug delivery systems [25]. A three-dimensional, crosslinked polymeric structure that can absorb significant volumes of water or biological fluids without losing structural integrity is what gives them their functionality [26]. Aqueous channels are created as a result of this hydration, and the size of these channels, or the mesh size (ξ), as well as the interactions between the drug and the polymer matrix, dictate how molecules diffuse across the network [27].

The physicochemical characteristics of the polymer and the encapsulating agent both affect the drug release mechanism from hydrogels. Diffusion typically occurs in accordance with Fick's rule, in which a concentration gradient propels the drug through the hydrated matrix [28]. In other systems, the polymer's swelling is a major factor; drug transport is dependent on the polymer's rate of water absorption and relaxation, which frequently leads to non-Fickian or unusual diffusion behaviour [29]. Furthermore, drug release in biodegradable or erodable hydrogels is facilitated by surface erosion or polymer degradation [30]. Such

degradation-driven systems can attain zero-order or pseudo-zero-order kinetics, offering a steady and predictable release rate over time, with careful network architecture design [31].

In addition to diffusion-based release, hydrogel matrices' efficacy for topical and transdermal treatments is greatly influenced by their interactions with skin tissues [32]. Hydrogen bonds and ionic interactions between the polymer chains and the lipid or keratin proteins of the stratum corneum give hydrogels their sticky qualities [33]. The formulation will remain at the application site for an extended period of time thanks to this strong adherence, which improves localised medication bioavailability. Furthermore, hydrogels can dynamically change their structure in response to changes in the local skin environment by incorporating stimuli-responsive functional groups, such as temperature-responsive polymer segments, pH-sensitive Schiff base bonds, or thioketal linkages that are cleavable by reactive oxygen species (ROS) [34]. These chemical moieties, for instance, can cause controlled changes in the mesh size or network architecture in inflammatory or diseased tissues where ROS levels or pH values differ from normal, enabling precise, time-dependent medication release. Because of their responsiveness, these smart hydrogels may adaptively modulate drug delivery in response to pathological conditions, making them particularly well-suited for treating wounds, infections, and chronic inflammatory illnesses [35].

A hydrogel's mechanical strength, physicochemical qualities, biocompatibility, and drug release features are all significantly influenced by its composition [36] shown **Figure 1.** The hydrogel structure's core is made up of the polymeric framework. Because of their biocompatibility, biodegradability, and similarity to the extracellular matrix (ECM), natural polymers such as hyaluronic acid, chitosan, gelatin, alginate, and cellulose derivatives are frequently used [37]. These polymers frequently have natural bioadhesive and bioactive qualities that can trigger cellular reactions and aid in tissue regeneration and wound healing. The mechanical stiffness, crosslink density, and swelling capacity of the hydrogel, on the other hand, can be precisely controlled by synthetic polymers like polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG and PEG diacrylate), polyacrylates (like Carbopol), Pluronics (especially F127), and poly(N-isopropylacrylamide) (PNIPAM) [38]. By combining natural and synthetic polymers, hybrid hydrogels have been created that offer the best possible balance of flexibility, strength, and performance by combining the biocompatibility and functional benefits of natural polymers with the structural integrity and tunability provided by synthetic ones [39].

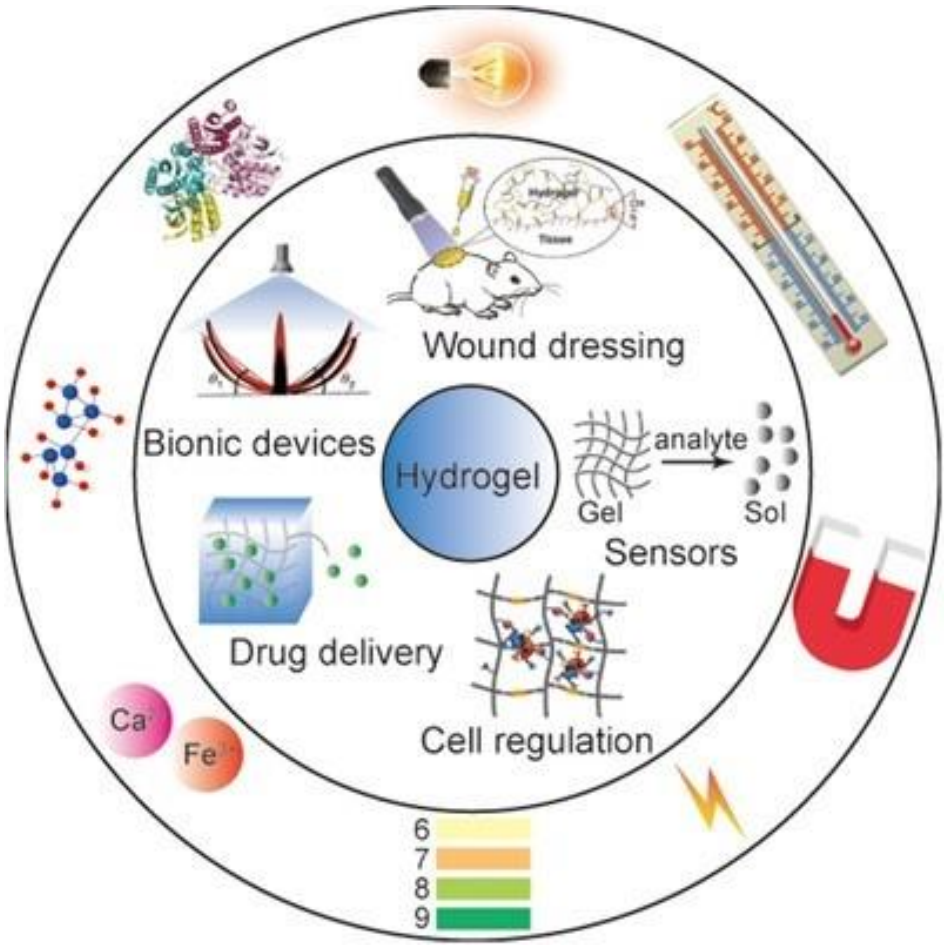


Figure 1. Hydrogel systems' structural design and functional elements for cutaneous conditions: A three-dimensional crosslinked polymer network composed of natural and synthetic polymers forms a hydrated matrix with defined mesh size (ξ). The structure is stabilised by a variety of crosslinking processes, including ionic, covalent, dynamic, and ROS-cleavable. Drug molecules, nanocarriers, antioxidants, antimicrobials, and bioactive biomolecules are examples of embedded functional components that allow for prolonged and stimuli-responsive release. The hydrogel provides focused therapy for inflammatory, viral, and chronic wound disorders by adhering to the skin's surface and promoting localised diffusion through the stratum corneum and follicular channels when applied topically.

In order to define the structural framework that stabilises hydrogel matrices, crosslinking agents are essential. Ionic, covalent, or dynamic reversible interactions can all contribute to the process of crosslinking, each of which has unique mechanical and functional characteristics [40]. Ionic crosslinkers, like calcium ions in alginate-based hydrogels, cause mild gelation, which makes them perfect for encasing living cells or delicate biomolecules

without sacrificing viability [41]. Covalent crosslinkers, on the other hand, such as ethylene glycol dimethacrylate (EGDMA), N,N′-methylenebisacrylamide (MBAA), and genipin, create robust, long-lasting bonds that greatly increase the hydrogel's structural strength and prolong its degradation period, which qualifies them for long-term therapeutic uses [42, 43]. The hydrogel can recover from mechanical strain or modify its structure in response to environmental cues like pH changes or oxidative stress thanks to dynamic covalent linkages like boronate ester or Schiff base bonds, which bring self-healing and stimuli-responsive behaviours shown **Table 1**.

Table 1. Major materials used in dermatological hydrogel systems and their functional roles.

Component Type	Examples	Functional Contribution	Clinical Dermatology Applications
Natural polymers	Hyaluronic acid, chitosan, gelatin, alginate, cellulose	ECM-mimicking structure, biodegradability, bioadhesion	Chronic wounds, regenerative therapy[44].
Synthetic polymers	PVA, PEG, Carbopol, PNIPAM, Pluronic F127, PVP	Mechanical strength, controlled swelling, tunable release	Sustained topical systems, patches[45].
Hybrid polymer blends	Natural–synthetic combinations	Balanced flexibility and structural stability	Precision dermal delivery[46].
Ionic crosslinkers	Ca^{2+}, Mg^{2+}	Mild gelation, cell-compatible encapsulation	Living bioactive hydrogels[47].
Covalent crosslinkers	MBAA, EGDMA, genipin	Strong structural stability, long-term durability	Chronic therapy hydrogels[48].
Dynamic crosslinkers	Schiff-base, boronate ester	Self-healing and stimuli responsiveness	Smart responsive dermal systems[49].
Penetration enhancers	Terpenes, menthol	Improve drug diffusion across stratum corneum	Acne, anti-inflammatory therapy[50].
Humectants	Glycerol	Maintain hydration and flexibility	Skin repair formulations[51].
Bioactive additives	Honey, curcumin, antioxidants	Antimicrobial and tissue healing action	Diabetic ulcers, infected wounds[52].
Nanocarriers	Liposomes, SLNs, polymeric nanoparticles, MOFs	Multi-stage release, improved drug stability	Precision dermatology platforms[53]

Hydrogels frequently contain functional additives suited to certain therapeutic requirements in order to further maximise their efficacy. While humectants like glycerol aid in retaining moisture and preventing dryness, preserving comfort and flexibility, penetration enhancers

like menthol and terpenes boost medication absorption across the epidermal or mucosal barriers [54]. Ascorbic acid, or vitamin C, is an antioxidant that prevents oxidative damage to the polymeric matrix and the medicine that is encapsulated [55]. While antimicrobial ingredients like zinc oxide and silver nanoparticles offer infection resistance, which is especially useful in formulations for wound care, natural bioactive ingredients like honey or curcumin have anti-inflammatory and tissue-healing properties. To maintain the stability of medications that are sensitive to pH and to guarantee physiological compatibility with skin or mucosal tissues, buffering agents are added in some formulations [56].

The development of nanocomposite hydrogels, which include nanoscale elements or carriers into the polymer network, represents a significant advancement in hydrogel engineering [57]. Liposomes, niosomes, ethosomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, metal–organic frameworks (MOFs), nanoclays, and graphene derivatives are a few examples of the structures that are frequently found in these hybrid systems [58]. By adding these nanoparticles, hydrogel performance is improved in a number of areas, such as responsiveness to external stimuli, controlled release kinetics, drug encapsulation effectiveness, and mechanical durability [50]. For example, encapsulating liposome- or NLC-based formulations in hydrogels allows for a two-phase release pattern: a sustained, continuous release from the enclosed nanocarriers after an initial burst release from the polymer matrix. The therapeutic benefits are prolonged and the frequency of administration is decreased by this multi-stage delivery [59].

Small-molecule medications like corticosteroids and retinoids, bioactive peptides and proteins like the antimicrobial peptide LL-37, growth factors, and even live biotherapeutics like Lactobacillus species that alter the skin microbiome are all among the remarkably wide range of therapeutics that can be delivered through hydrogel systems [60]. Because of their great degree of adaptability, hydrogels are now at the forefront of biomedical innovation, finding use in fields as diverse as oncology, tissue regeneration, and personalised medicine in addition to traditional dermatology and wound healing [61].

Hydrogels can be made using a wide range of techniques, each of which is carefully chosen to produce certain structural properties and functional behaviour [62]. Non-covalent interactions between polymer chains, such as ionic complexation, hydrophobic associations, or hydrogen bonds, are necessary for physical gelation. One well-known example is the thermosensitive behaviour of polymers such as poly(N-isopropylacrylamide) (PNIPAM) and

Pluronic F127, which gel at physiological temperatures but remain liquid at low temperatures [62]. In a similar vein, polyvinyl alcohol (PVA) freeze-thaw cycling creates cryogels with linked porosity networks that improve water retention and flexibility [63]. Ionic crosslinking techniques, like the electrostatic interactions between chitosan and polyacrylate or the reaction between alginate and calcium ions, produce stable hydrogels without the need of harsh chemicals, which makes them perfect for encasing living cells and delicate biomolecules [63].

On the other hand, chemical crosslinking creates hydrogel networks that are more mechanically robust and stable. Durability and structural integrity are guaranteed by the irreversible covalent connections created when acrylate or methacrylate monomers undergo free-radical polymerisation [64]. On the other hand, at mild, biocompatible circumstances, click chemistry processes like thiol–ene or azide–alkyne coupling allow for quick and extremely precise crosslinking. An environmentally friendly and gentle technique for creating in situ hydrogels that solidify in physiological environments and are appropriate for drug delivery or tissue repair applications is enzymatic crosslinking, which uses systems like horseradish peroxidase (HRP) with hydrogen peroxide or naturally occurring agents like genipin [65].

Interpenetrating polymer networks (IPNs) and semi-IPNs are examples of more complex designs that are created by crosslinking two different polymer networks either sequentially or simultaneously [66]. The hydrogel's mechanical strength and diffusional characteristics can be independently controlled thanks to its dual-network structure, which also provides adjustable elasticity, swelling behaviour, and permeability. These IPN hydrogels are especially useful for tissue engineering scaffolds and controlled drug administration, where both flexibility and robustness are needed [66].

Another significant invention are in situ gelling systems. Usually administered as liquids (sols), these compositions gel when exposed to environmental stimuli including body temperature, pH shifts, or ionic concentrations. They are perfect for injectable or topical therapy because of their ability to conform to uneven wound surfaces or produce homogenous films over the skin following application [67,68].

By dispersing prefabricated drug-loaded nanocarriers, such as liposomes, polymeric nanoparticles, or lipid-based vesicles, within the hydrogel matrix, nanocomposite embedding

allows for even more sophistication [69]. This combination creates a multi-phase drug delivery system in which the embedded nanocarriers maintain release over extended periods of time, boosting stability and therapeutic accuracy, while the hydrogel controls initial diffusion [69].

Lastly, the creation of hydrogel has been transformed by contemporary fabrication methods including micro-molding and 3D printing. These methods make it possible to produce hydrogels with precise structures, distinct gradients in drug concentration, and sculptable forms suited to particular application locations [70]. Additionally, they aid in the creation of transdermal patches with microneedles integrated, which can administer medications in a patient-friendly, programmed way. Researchers can optimise hydrogel characteristics for optimal drug delivery, mechanical resilience, and biocompatibility in a variety of biomedical applications by combining these various production techniques [71].

3.FORMULATION METHODS FOR HYDROGEL PREPARATION

1. Physical gelation methods include hydrogen-bonded or ionic complexation (alginate–Ca^{2+}, chitosan–polyacrylate), freeze–thaw (PVA cryogels), and thermogelation (Pluronic, PNIPAM).
2. Chemical crosslinking includes enzymatic crosslinking (HRP/H_2O_2), click reactions (thiol–ene, azide–alkyne), free-radical polymerisation (acrylates, methacrylates), and natural crosslinkers (genipin).
3. Interpenetrating networks (IPN/Semi-IPN): When two networks are crosslinked sequentially or simultaneously, the mechanics and diffusion are separated.
4. In situ gelling technologies include injectable or spreadable sols that set on skin and sol–gel transitions based on temperature, pH, or ionic trigger after administration.
5. Drug-loaded nanocarriers are dispersed within gels by nanocomposite embedding, which provides multi-stage release and enhanced stability.
6. 3D printing/casting: Accurate medication gradients on microneedle-backed patches and patterned dressings were shown **Table 2**

Table 2. Preparation techniques and structural outcomes of dermatological hydrogels.

Preparation Strategy	Principle	Structural Outcome	Typical Dermatology Use
Physical gelation	Hydrogen bonding / ionic complexation	Soft, reversible hydrogel network	Injectable and topical gels[72].
Freeze–thaw cryogelation	Repeated freezing cycles of PVA	Porous elastic cryogels	Long-duration wound dressings[73].
Thermo-responsive gelation	Temperature-dependent polymer phase transition	In-situ forming gels	Injectable dermal therapy[74].
Ionic crosslinking	Electrostatic polymer interaction	Mildly crosslinked biocompatible gels	Probiotic or protein delivery[75].
Free-radical polymerisation	Covalent bond formation	Strong permanent hydrogel matrix	Controlled long-term drug release[76].
Click chemistry reactions	Highly specific molecular coupling	Uniform reproducible network	Precision therapeutic hydrogels[77].
Enzymatic crosslinking	HRP/genipin mediated reactions	Mild biofriendly gel formation	Living bioactive hydrogels[78].
Interpenetrating polymer networks (IPN)	Dual polymer networks	Enhanced strength and diffusion control	Tissue regeneration scaffolds[79].
Nanocomposite embedding	Dispersion of drug-loaded nanoparticles	Multi-phase release system	Advanced dermatological therapy[80].
3D printing / micro-molding	Structured fabrication methods	Custom architecture and gradients	Microneedle-integrated systems[81].

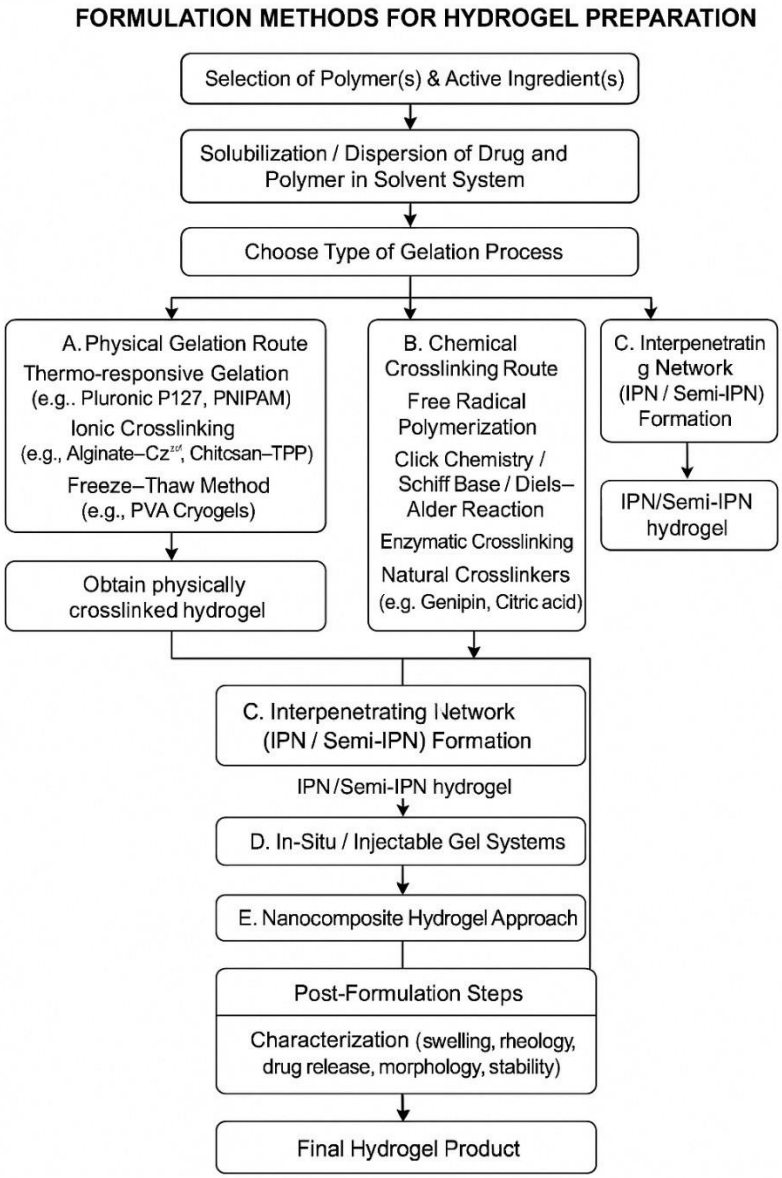


Figure 2: A structured flowchart showing different hydrogel preparation formulation techniques. The selection of the medication and polymer comes first, then the choice of the solubilisation and gelation techniques. Physical gelation (thermo-responsive, ionic, and freeze-thaw), chemical crosslinking (free radical, click/Schiff-base, enzymatic, natural), interpenetrating network (IPN/Semi-IPN) generation, in-situ/injectable systems, and nanocomposite hydrogel techniques are some of the methods. After further characterisation (swelling, rheology, release, morphology, and stability), the hydrogel product is ready for use in cutaneous drug delivery.

4.Hydrogels' Characterisation for Drug Delivery Uses

When creating hydrogel-based drug delivery systems, characterisation is essential because it confirms that the formulation has the right strength, structure, release profile, and biological

safety required for clinical efficacy [82]. Physicochemical, rheological, mechanical, microstructural, and biological criteria are all included in the thorough study; these factors together determine the hydrogel's overall quality and performance. Essential details regarding the hydrogel's behaviour during formulation, storage, and contact with biological tissues are provided by each of these attributes [83].

Properties including swelling ratio, equilibrium water content, gel fraction, and porosity are important markers of a hydrogel's ability to absorb liquids and deliver medications from a physicochemical standpoint [84]. The swelling ratio, which is directly impacted by the density of crosslinking and the hydrophilicity of the polymer, quantifies how much the network of polymers swells in an aqueous environment. For instance, because polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) hydrogels have hydroxyl and carbonyl functional groups that easily form hydrogen bonds with water molecules, they show notable swelling behaviour [71]. Drug diffusion rates are significantly impacted by the equilibrium water content, which is the hydration level at which the hydrogel attain stability. The percentage of polymer chains that are successfully crosslinked into an insoluble network is indicated by the gel fraction; systems with greater gel fractions are often more resilient and degrade more slowly. Porosity analysis, on the other hand, sheds light on the interior pore structure, which controls mechanical integrity and diffusion paths [84,85].

Techniques like nuclear magnetic resonance (NMR) spectroscopy and Fourier-transform infrared spectroscopy (FTIR) are frequently employed to confirm crosslinking and chemical composition. For example, the production of Schiff base linkages in pH-responsive hydrogels is confirmed by the presence of imine (C=N) stretching bands in an FTIR spectrum [86]. In order to determine melting points, glass transition temperatures, and thermal stability and guarantee that the hydrogel retains its integrity under physiological or storage settings, thermal characterisation techniques such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) are used [87]. Furthermore, X-ray diffraction (XRD) examination separates the polymer network's crystalline and amorphous areas, offering vital information about how structural organization affects drug release kinetics and material performance in general [87].

The ease of handling, application behaviour, and overall performance of hydrogels are significantly influenced by their mechanical and rheological characteristics. Rheology provides information about the viscoelastic properties of hydrogels by examining how they

flow and change under stress or strain [88]. Viscosity, storage modulus (G′), and loss modulus (G′) are important markers of the hydrogel's behaviour in dynamic situations. Shear-thinning hydrogels, for instance, which are frequently applied topically, show a reduction in viscosity during spreading, allowing for easy application, and then restore their viscosity when the shear force is eliminated, guaranteeing strong skin adherence [89]. For wound dressings or injectable hydrogels, thixotropic behavior—viscosity that diminishes under stress but recovers upon rest—is also preferred because it makes administration simple and preserves structural integrity after application. When assessing the resilience, elasticity, and durability of hydrogels, mechanical tests like compressive and tensile strength measures are crucial, especially when it comes to microneedle arrays or transdermal patches, where both flexibility and robustness are needed [90]. In order to determine how effectively the hydrogel attaches during use and separates after treatment, tests that measure adhesiveness, tack, and peel strength are particularly crucial since they mimic the interaction between the hydrogel and skin. Strong bioadhesive qualities are a hallmark of hydrogels made with carbopol or hyaluronic acid. This is mainly because of hydrogen bonding interactions with keratin in the stratum corneum, which improves skin retention and promotes extended drug release [91].

Gaining knowledge of hydrogels' microstructure helps one better understand how they work, especially in relation to mechanical and diffusion behaviour. Techniques for morphological characterisation and imaging are frequently employed for this [91]. A common technique for examining the internal pore structure and surface texture of dried hydrogels is scanning electron microscopy (SEM), which provides a fine-grained picture of the size and distribution of pores. For the analysis of nanocomposite hydrogels with embedded nanoparticles, liposomes, or other nanocarriers, transmission electron microscopy (TEM) and cryogenic scanning electron microscopy (cryo-SEM) offer high-resolution images of nanoscale features and hydrated states [92]. A chitosan–alginate hydrogel, for example, may exhibit a honeycomb-like porosity network under cryo-SEM that is appropriate for encasing medicinal compounds. Additionally, by adding fluorescent probes or dyes, confocal laser scanning microscopy (CLSM) can be used to monitor the spatial distribution of medications within the hydrogel [93]. This method aids in determining whether the drug is aggregated or uniformly distributed, which has an immediate effect on bioavailability and release uniformity. These findings are further supported by quantitative image-based pore size analysis, which calculates the average pore dimensions, which are factors strongly linked to the mechanical stability, swelling behaviour, and diffusion rate of the hydrogel [94].

Hydrogels' efficacy as regulated drug delivery systems is largely dependent on their drug release and penetration properties. Dialysis membranes or Franz diffusion cells, which mimic physiological circumstances, are frequently used in in vitro release experiments to examine how medicines diffuse from the hydrogel matrix [95]. To determine the underlying mechanism—whether the release is largely driven by diffusion, polymer erosion, or a combination of both—the ensuing release data are frequently examined using mathematical models such the Higuchi, Korsmeyer–Peppas, or zero-order kinetic equations. A polyethylene glycol (PEG)–Carbopol hydrogel loaded with diclofenac sodium, for example, may exhibit a two-phase release profile, which is defined by a slower, prolonged release time after an initial burst of drug diffusion [96]. Additionally, Franz diffusion setups using excised human or pig skin are used in in vitro skin permeation investigations that shed light on the effectiveness of transdermal medication penetration. Complementary methods such as cutaneous microdialysis and tape stripping enable depth profiling to measure the quantity of medication dispersed throughout different skin layers [97]. In order to ensure that the hydrogel delivers therapeutic concentrations at the target region while minimising systemic exposure and associated side effects, these tests are crucial for forecasting in vivo absorption behaviour [98].

For hydrogel formulations to be safe and therapeutically relevant, bioactivity and biocompatibility evaluations are equally important. The effectiveness of hydrogels containing antibacterial agents, such as silver nanoparticles or plant-derived extracts, is assessed using biological assays such antimicrobial activity tests [99]. Cell viability experiments using fibroblast (3T3-L1) or keratinocyte (HaCaT) cell lines are frequently carried out to evaluate cytotoxicity. Cell survival after exposure to hydrogel materials or their extracts is assessed using quantitative assays such as MTT or resazurin reduction tests, which quantify cellular metabolic activity [100]. When loaded with natural bioactives like curcumin or honey, which support tissue regeneration, hydrogels intended for wound healing applications frequently show increased cell migration and proliferation. In order to verify biocompatibility, cytokine analysis can also be used to evaluate the inflammatory response by detecting the levels of biomarkers such tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [101].

Standardised tests such as OECD 404 (acute dermal irritation) and OECD 439 (reconstructed human epidermis model) are used to assess possible irritation or corrosive effects in order to

guarantee skin safety [102]. Another well-recognized technique for assessing a formulation's tendency to cause allergies or sensitisation is the Local Lymph Node Assay (LLNA). Furthermore, physiological tests like skin hydration measurements and transepidermal water loss (TEWL) are used to evaluate hydrogels' capacity to preserve or restore the skin's barrier function, which is crucial for formulations meant to treat ailments like dermatitis, eczema, or chronic wounds. These assessments collectively demonstrate that hydrogels are safe, compatible with biological tissues, and efficient carriers for long-term drug release [103,104]. Last but not least, stability and quality evaluations are necessary to verify that hydrogel formulations continue to function and be safe for the duration of their shelf life. Both accelerated and real-time stability investigations shed light on possible alterations in the formulation's appearance, pH, viscosity, and drug content over time. For example, for a hydrogel to be deemed stable, it must maintain its pH and viscosity within ±10% of its initial values after three months of storage at 40°C and 75% relative humidity. To ensure that any added antimicrobial agents or preservatives stay effective and able to stop microbiological contamination while being stored, preservative efficacy testing is carried out [105,106].

Furthermore, sterility and bioburden tests are essential because they guarantee the absence of harmful microorganisms, especially for hydrogels used in wound care or ophthalmic applications [107]. In order to ensure dependable dosage and therapeutic efficacy, content uniformity testing is performed to verify that each batch or individual unit of the product contains a constant quantity of the active pharmaceutical ingredient [108, 109]. Additionally, tests for leachables and extractables are carried out to ensure that no potentially hazardous or reactive materials move from the packaging material into the formulation while it is being stored, particularly when hydrogels are packaged in polymer-based containers. Together, these quality control procedures ensure that hydrogel products maintain their chemical stability, microbiologic safety, and therapeutic consistency during the course of their intended use shown **Table 3.**

Table 3. Evaluation parameters and regulatory considerations for dermatological hydrogel systems

Evaluation Domain	Analytical Method	Purpose	Translational Importance
Swelling behaviour	Gravimetric hydration studies	Determines mesh expansion	Controls release rate[110].
Crosslinking confirmation	FTIR / NMR	Validates chemical structure	Ensures formulation reproducibility[111].
Thermal stability	DSC / TGA	Storage stability analysis	Required for shelf-life approval[112].
Mechanical properties	Compression / tensile testing	Determines elasticity and durability	Required for patches/microneedles[113].
Rheology	Rotational rheometer	Spreadability and adhesion	Patient usability factor[114].
Morphology	SEM / TEM / Cryo-SEM	Pore distribution and structure	Predicts drug diffusion[115].
Drug release kinetics	Dialysis / Franz diffusion	Determines release mechanism	Essential regulatory data[116].
Skin permeation	Ex-vivo permeation testing	Measures penetration depth	Predicts clinical efficacy[117].
Cytotoxicity	MTT / cell viability assays	Safety validation	Mandatory for clinical use[118].
Dermal irritation	OECD 404 / reconstructed epidermis	Skin compatibility	Regulatory requirement[119].
Stability testing	Accelerated storage study	Shelf-life prediction	Commercial viability[120].
Sterility testing	Microbial limit / bioburden tests	Ensures absence of contamination	Required for wound applications[121].

5.Designing Skin Hydrogels Based on Disease

A disease-driven design philosophy is gradually replacing the material-centric approach in the development of hydrogel-based dermal delivery systems nowadays. In this approach, the hydrogel's structural and functional properties are customised in accordance with the underlying biological mechanisms of particular cutaneous disorders. The main goals of early hydrogel systems and even conventional topical formulations were enhanced skin retention or prolonged drug release [122, 123]. Modern dermatological treatment, however, necessitates a more complex approach where the hydrogel actively engages with the skin's diseased milieu. In addition to delivering therapeutic molecules, these disease-responsive systems are made to synchronise drug release, degradation behaviour, and physicochemical reactions with the

biological signals found in diseased tissues. This paradigm highlights that the system's capacity to address disease-specific triggers like inflammation, oxidative stress, microbial imbalance, enzymatic activity, and impaired vascularization is just as important to the success of hydrogel therapy as the polymer composition or crosslinking density shown **Table 4**.

Table 4. Pathophysiology-guided hydrogel design strategies for major cutaneous disorders.

Disease Condition	Key Pathophysiological Features	Hydrogel Design Strategy	Therapeutic Goal
Psoriasis	Cytokine overexpression, oxidative stress, keratinocyte hyperproliferation	ROS-responsive linkages + sustained corticosteroid delivery	Reduce inflammation and immune activation[124].
Acne vulgaris	Follicular blockage, sebum excess, microbial colonisation	Follicular-targeting nanocarrier hydrogels + antimicrobial agents	Suppress bacteria and reduce inflammation[125].
Atopic dermatitis	Barrier dysfunction, immune dysregulation	Moisture-retaining bioadhesive hydrogels with immunomodulators	Restore barrier and reduce irritation[126].
Chronic wounds	Persistent inflammation, bacterial infection	Antimicrobial hydrogels + growth factor release	Promote tissue regeneration[127].
Diabetic ulcers	Hypoxia, ROS excess, impaired angiogenesis	Oxygen-generating + antioxidant hydrogels	Accelerate healing and vascular repair[128].
Infected lesions	High protease activity, acidic microenvironment	Enzyme-responsive and pH-triggered drug release	Target infection and inflammation locally[129].

The pathogenic environment of inflammatory diseases like psoriasis is marked by increased levels of pro-inflammatory cytokines like interleukin-17, interleukin-23, and tumour necrosis factor-α, as well as dysregulated immunological signalling and excessive keratinocyte proliferation. A hostile milieu created by psoriatic lesions' elevated oxidative stress and aberrant epidermal turnover necessitates tailored immunomodulation as opposed to topical medication exposure alone. Reactive oxygen species-responsive linkages, anti-inflammatory polymer backbones, or controlled-release compartments that can sustain therapeutic corticosteroid or biologic concentrations in the epidermis for prolonged periods of time are therefore advantageous additions to hydrogels intended for the treatment of psoriasis. These methods can minimise systemic exposure, decrease dose frequency, and enhance therapeutic accuracy by coordinating polymer degradation or drug releases with inflammatory flare-ups. The hydrogel is changed from a passive carrier to an adaptive therapeutic matrix by this

disease-guided design, which can react to changes in the immune activity in psoriatic tissue [130].

Another condition where disease-specific biological processes determine the hydrogel delivery platform design specifications is acne vulgaris. The pilosebaceous unit is the primary site of acne pathology, which includes follicular hyperkeratinization, excessive sebum production, Cutibacterium acnes colonisation, and localised inflammatory reactions. Hydrogel systems designed for acne treatment must put transappendageal targeting and microbiota modification ahead of straightforward surface delivery because the main disease locus is located within hair follicles and sebaceous glands. Preferential follicular penetration and prolonged drug deposition within sebaceous reservoirs can be facilitated by advanced hydrogels that contain lipid vesicles, nanoparticle carriers, or size-optimized polymeric structures. Additionally, adding probiotic strains, antimicrobial peptides, or microbiome-modulating compounds to hydrogel matrix provides a way to lower inflammatory signalling and restore microbial balance. By addressing both the inflammatory and infectious aspects of acne, these biologically informed designs demonstrate how disease-driven hydrogel engineering might produce better therapeutic results than traditional topical gels or creams [131].

The pathogenic environment of chronic diabetes wounds is significantly diverse, which emphasises the need for disease-specific hydrogel design. In contrast to inflammatory dermatoses, diabetic ulcers are typified by aberrant overexpression of matrix metalloproteinases that break down extracellular matrix components necessary for tissue healing, excessive accumulation of reactive oxygen species, poor angiogenesis, and persistent hypoxia. These multifactorial deficits are frequently not resolved by passive hydrogels or conventional wound dressings because they do not actively interact with the wound bed's metabolic environment. On the other hand, oxygen-generating particles, antioxidant polymer segments, or enzyme-cleavable peptide crosslinkers that break down selectively in response to increased protease activity are increasingly being incorporated into hydrogels designed for diabetic wound care. The release of growth hormones, antibiotics, or regeneration biomolecules in accordance with the stage of wound healing is made possible by such responsive breakdown. Furthermore, rather than only serving as a protective dressing, the highly hydrated network of these hydrogels can sustain cellular migration and angiogenic

signalling while maintaining an ideal moist environment, actively promoting tissue regeneration [132].

When taken as a whole, these examples show that the shift from generic drug carriers to biologically intelligent therapeutic systems that are especially designed to align with disease pathophysiology is where dermal hydrogel technology is headed. The formulation can take advantage of endogenous pathological signals, such as oxidative stress, inflammatory cytokines, enzymatic activity, or microbiota imbalance, as triggers for therapeutic action by designing hydrogels based on disease biology. This method allows for adaptive treatment that is in line with the dynamic course of skin problems, improves medication localisation, and minimises needless exposure to healthy tissue. The foundation for precision dermatology, where biomaterial design is directly influenced by clinical pathophysiology rather than just pharmaceutical release kinetics, is thus established by disease-driven hydrogel engineering, which constitutes a crucial conceptual shift in dermatological drug delivery [133].

6.Microenvironment-Responsive Hydrogel Systems

The development of microenvironment-responsive systems that can dynamically interact with harmful biochemical signals seen in sick skin is becoming more and more important in modern hydrogel engineering for dermatological therapy. Microenvironment-responsive hydrogels are intended to detect local physiological changes, such as oxidative stress, aberrant enzymatic activity, or pH variations, and convert these signals into regulated structural changes that control therapeutic release, in contrast to traditional topical carriers that release medications in accordance with predetermined diffusion kinetics. This adaptive behaviour enhances treatment precision for inflammatory dermatoses, infected lesions, and chronic wounds, permits spatially selective drug distribution, and minimises exposure of healthy tissue to needless drug concentrations. Researchers can develop biomaterials that react directly to disease-associated molecular cues by adding chemically labile linkages, degradable peptide sequences, or ionisable polymer segments to the hydrogel network. This turns hydrogels from passive matrices into biologically interactive therapeutic systems [134].

7.ROS-Responsive Hydrogels

Since increased oxidative stress is a defining feature of many skin conditions, such as psoriasis, chronic wounds, diabetic ulcers, and inflammatory dermatitis, reactive oxygen species (ROS)-responsive hydrogels are among the most researched classes of microenvironment-sensitive dermal delivery systems. Excessive hydrogen peroxide,

superoxide radical, and hydroxyl species production in these pathological situations leads to lipid peroxidation, delayed tissue regeneration, and cellular damage. By introducing ROS-cleavable chemical motifs—such as thioketal linkages, boronic ester bonds, selenium-containing groups, or oxidation-sensitive sulphide bridges—into the polymer backbone or crosslinking structure, ROS-responsive hydrogels take advantage of this oxidative imbalance. These chemical linkages undergo selective breaking when exposed to severe oxidative stress in inflammatory tissue, which might result in localised polymer degradation, hydrogel mesh network enlargement, or faster drug diffusion. This method guarantees the preferential release of therapeutic medicines, such as growth factors, antioxidants, corticosteroids, and antibacterial medications, at locations where oxidative damage is most severe. In addition to releasing drugs, some ROS-responsive hydrogels are designed to have inherent antioxidant components that can scavenge free radicals, lowering oxidative damage while delivering therapeutic payloads at the same time. When the trigger and the therapeutic response come from the same disease process, such dual-function materials offer a physiologically synchronised treatment approach [135].

8.Enzyme-Responsive Hydrogels

Another extremely advanced class of disease-adaptive biomaterials are enzyme-responsive hydrogels, which are made to react to aberrant enzymatic profiles linked to skin inflammation, infection, or poor wound healing. Proteolytic enzymes, especially matrix metalloproteinases (MMPs), hyaluronidase, and elastase, are found in high concentrations in many pathological skin situations. These enzymes work together to degrade extracellular matrix and cause tissue instability. This pathogenic activity can be used as a biological trigger for medication release in hydrogels designed with peptide-based crosslinkers or biodegradable polymer segments that these enzymes can selectively cleave. Excessive MMP production, for example, might break down peptide-linked hydrogel networks in chronic wounds, allowing for the local release of antibiotics, anti-inflammatory drugs, or regenerative growth factors in direct proportion to the concentration of the enzyme. Similar to this, hyaluronidase-sensitive hydrogels made from modified hyaluronic acid matrices gradually break down enzymatically in inflammatory or infected tissues, releasing encapsulated medicines in stages and producing low-molecular-weight hyaluronan fragments that could aid in tissue repair and cellular migration. Drug release can be synchronised with the intensity of inflammation by programming elastase-responsive systems, which are especially important in neutrophil-rich inflammatory lesions, to degrade in response to excessive immune activation. These

hydrogels provide a degree of therapeutic precision not possible with traditional topical formulations by achieving biologically regulated breakdown kinetics that match the dynamic course of disease through such enzyme-triggered processes [136].

9.pH-Adaptive Hydrogel Systems

A similar type of microenvironment-responsive materials, pH-adaptive hydrogels use localised variations in acidity or alkalinity as cues to modify their structure and regulate drug delivery. The pH of the surface of healthy human skin is normally slightly acidic, around 5.5, which supports the integrity of the barrier and microbiological defence. Significant departures from this physiological range are brought on by a number of dermatological diseases, though. For instance, inflammatory activity and microbial metabolism within follicles can lower the local pH toward more acidic values around 4.5 in acne vulgaris, and anaerobic bacterial growth and lactic acid accumulation often result in even stronger acidic microenvironments in infected wounds and necrotic lesions. Therefore, polymers with ionisable functional groups—such as amines, carboxylates, or imine bonds—that undergo protonation or deprotonation in response to environmental pH changes are used to create pH-responsive hydrogels. Drug diffusion rates are modulated by these ionisation processes, which also change polymer hydration, swelling behaviour, electrostatic interactions, and network permeability. Such hydrogels may swell more or experience quicker bond cleavage in the acidic environment found in infected or inflammatory skin, facilitating the precise release of antibiotics, antifungal medicines, or anti-inflammatory medications at diseased areas. On the other hand, in systems that use boronate or Schiff-base connections, acidic conditions might cause hydrogel disintegration and destabilise crosslinking bonds, which would result in quick therapeutic release. By maintaining relative inactivity in healthy areas and automatically intensifying treatment in sick tissue, this pH-regulated release technique improves therapeutic efficacy and safety [137].

10.Follicular and Appendageal Targeting Hydrogels

A very promising method for improving the therapeutic efficacy of hydrogel-based dermal delivery systems is to target the skin's appendageal structures, specifically the sebaceous glands and hair follicles. The follicular channel offers a natural anatomical shunt that circumvents the stratum corneum, the main diffusion barrier preventing medication penetration, and grants direct access to deeper epidermal and dermal compartments. Since hair follicles are dynamic, highly vascularised microstructures that extend deep into the

dermis and are encircled by sebaceous glands, immune cells, and stem cell niches, they are important targets for the treatment of a variety of dermatological conditions, such as inflammatory dermatoses, folliculitis, acne vulgaris, and alopecia. In order to provide extended local drug retention and controlled release at disease-relevant locations, modern hydrogel systems are increasingly designed not only for surface adherence but also for preferential deposition into follicular reservoirs [138].

This targeting method is based on the idea of the follicular reservoir. Nanoscale transporters, lipophilic medications, and topically applied particles can all be stored in hair follicles for extended periods of time—often much longer than retention on the skin's surface. The follicular canal's special design, which includes keratinised cells, sebum, and a comparatively protected microenvironment that inhibits outward clearance, gives rise to this storage capacity. In order to take advantage of this reservoir function, hydrogels are usually manufactured with viscoelastic qualities that permit embedded nanocarriers to gradually penetrate follicular holes while retaining enough cohesiveness to inhibit quick removal through washing or mechanical friction. The hydrogel matrix can sustain hydration and release therapeutic chemicals gradually once it has been localised within the follicle, keeping therapeutic concentrations around pilosebaceous units. Because it minimises irritation from repeated high-dose topical treatment and decreases systemic absorption, this localised retention is especially beneficial for chronic inflammatory diseases [139].

Another crucial aspect of appendage-focused hydrogel design is sebaceous gland targeting, especially for acne treatment and other conditions affecting the pilosebaceous unit. Lipid-rich discharges from sebaceous glands affect inflammatory signalling, microbial colonisation, and medication solubility. Therefore, rather of relying solely on epidermal diffusion, effective treatment frequently necessitates drug delivery directly into this lipid-dominated milieu. Lipid-compatible nanocarriers, deformable vesicles, or amphiphilic polymeric components that can pass through the follicular canal and accumulate in sebaceous secretions are increasingly being included into advanced hydrogels. These systems are more successful than traditional topical formulations at suppressing the growth of Cutibacterium acnes, controlling sebum production, and reducing follicular inflammation by delivering antimicrobial agents, retinoids, or anti-inflammatory compounds straight into the sebaceous compartment. Additionally, by preserving moisture balance and minimising mechanical irritation, the

hydrated hydrogel matrix itself can assist in modifying the follicular microclimate, promoting barrier regeneration while therapeutic action takes place within the glandular structure [139].

For hydrogel-embedded delivery systems to enable effective follicular targeting, nanoparticle size optimisation is essential. Particle size has a significant impact on penetration depth and retention within hair follicles, as experimental and clinical observations have repeatedly shown. While very small molecules may diffuse quickly through follicular openings and into the systemic circulation, decreasing the localised therapeutic benefit, too-large particles have a tendency to stay on the skin's surface. Because they can enter follicular ducts while remaining trapped in the intricate keratin–sebum matrix, nanocarriers that are roughly a few hundred nanometres in size have been demonstrated to achieve optimum follicular accumulation. Because hydrogels offer a stabilising three-dimensional network that inhibits aggregation, regulates diffusion velocity, and preserves uniform particle dispersion during topical application, they are especially useful carriers for such optimised nanoparticles. Additionally, shear-thinning hydrogels' rheological properties enable easy spreading and structural recovery, guaranteeing that populations of nanoparticles stay in extended contact with follicular openings and increasing the likelihood of penetration through repeated micro-movement of hair shafts, which can function as mechanical pumps to facilitate particle transport into deeper follicular compartments [140].

Appendage-targeted hydrogel systems have significant prospects for precision dermatology by facilitating spatially selective treatment of disease-localized components, in addition to their efficacy in drug delivery. Targeted hydrogel formulations can deliver therapeutic payloads precisely where needed while preserving surrounding healthy tissue because many dermatological problems start primarily within follicular or sebaceous environments rather than throughout the entire skin surface. Strong therapeutic drugs can be used at lower total doses thanks to this spatial specificity, which can also greatly lessen local discomfort and increase patient tolerance. Recent studies are also investigating the incorporation of stimuli-responsive components into follicular-targeting hydrogels, which would enable medication release to be further controlled by biochemical alterations within the follicular milieu, microbial metabolites, or inflammatory signals. These ideas go from passive deposition to physiologically interactive appendage-responsive systems that can modify therapeutic output according on disease activity [140].

Follicle and appendageal targeting taken together constitute a revolutionary development in dermal hydrogel technology, changing the paradigm of delivery from surface-level application to anatomically guided therapeutic localisation. Advanced hydrogel systems can provide highly effective, long-lasting, and site-specific drug delivery for a variety of cutaneous conditions by utilising the reservoir capacity of hair follicles, the lipid dynamics of sebaceous glands, and the penetration behaviour controlled by nanoparticle size optimisation. In addition to improving therapeutic results, this approach creates a crucial foundation for customised dermatological therapies in the future, where biomaterial design is in line with the anatomical cause and biological course of illness [140].

11.Living Bioactive Hydrogel Platforms

A rapidly developing field in dermatological biomaterials, living bioactive hydrogel platforms go beyond traditional drug-loaded matrices to actively contain biological components that can alter the environment of the skin. Living bioactive hydrogels are designed to hold live microorganisms, bioactive cellular derivatives, or physiologically generated metabolites that directly contribute to therapeutic processes, in contrast to conventional hydrogels that mainly serve as passive carriers for proteins or small chemicals. Since many chronic skin conditions, such as acne, atopic dermatitis, chronic wounds, and inflammatory dermatoses, are significantly impacted by microbial imbalance rather than just inflammatory signalling or barrier dysfunction, this approach reflects a larger trend in dermatology toward microbiome-aware treatment strategies. These sophisticated hydrogels produce safe microenvironments that can sustain biological activity while permitting controlled interaction with the skin surface by incorporating live or biologically active molecules into hydrated polymer networks that replicate the conditions of the extracellular matrix [141].

Probiotic-loaded hydrogels, in which advantageous microbial strains are encased within biocompatible polymeric matrices intended to sustain vitality and progressive release, are among the most inventive instances of this concept. Probiotic cells are protected from dehydration, oxidative stress, and temperature changes by the highly hydrated, nutrient-permissive conditions offered by hydrogels made of alginate, gelatin, hyaluronic acid, cellulose derivatives, or hybrid natural–synthetic networks. Microorganisms like Lactobacillus species can continue to be metabolically active within these matrices and, after application, slowly colonise or briefly interact with the skin surface. The hydrogel network's

regulated diffusion characteristics enable gradual microbial exposure as opposed to instantaneous release, lowering the possibility of instability while permitting long-lasting therapeutic impact. Probiotic hydrogels can enhance barrier repair by producing beneficial metabolites, reducing inflammatory cytokine signalling, restoring commensal microbial balance, and suppressing pathogenic organisms in dermatological settings. By using this method, the hydrogel is changed from a static drug payload to a dynamic ecological delivery system where living things serve as therapeutic producers [142].

The more general idea of microbiome engineering, which seeks to purposefully alter the skin's microbial ecosystem by delivering advantageous strains, microbial consortia, or microbiota-modulating substances, is closely associated with probiotic encapsulation. Because their hydrated three-dimensional structure mimics natural biological niches and can be adjusted to control oxygen transport, moisture content, and nutrient exchange—factors that significantly impact microbial survival and activity—hydrogels are specially suited for this function. Researchers can develop hydrogels with protective microdomains and selective permeability to prevent opportunistic pathogens and promote the persistence of beneficial species. Microbiome-engineered hydrogels have the potential to offer long-lasting microbial stabilisation instead of transient antimicrobial suppression in disorders like acne or atopic dermatitis, where dysbiosis plays a substantial role in the course of the disease. By conceptually shifting from pathogen removal to the restoration of microbiological balance, this ecological therapeutic approach brings treatment into line with our growing knowledge of host–microbiome interactions in skin health [143].

Postbiotic-based hydrogel systems, which employ non-viable microbial components or metabolites produced from beneficial bacteria, are receiving increasing interest in addition to live-cell administration. Short-chain fatty acids, antimicrobial peptides, enzymes, cell wall fragments, and other bioactive compounds that maintain their therapeutic effect without needing live microbial life are examples of postbiotics. By incorporating these compounds into hydrogel matrices, microbiome-derived bioactives can be released in a controlled and sustained manner without encountering the stability and regulatory issues that come with preserving living organisms. By interacting with skin receptors and innate immune cells, postbiotic-loaded hydrogels can reduce inflammation, improve the function of the epithelial barrier, and alter immune signalling pathways. These systems may offer a more readily scalable and clinically flexible path for microbiome-inspired dermatological therapy while

maintaining many of the biological advantages linked to probiotic approaches, as they remove worries about microbial overgrowth or environmental sensitivity [144].

The regulated release of bacteriocins, which are naturally occurring antimicrobial peptides produced by beneficial bacteria, is another extremely promising mechanism made possible by living or microbiome-derived hydrogel systems. Bacteriocins are particularly appealing for treating infections linked to acne, wound colonisation, or resistant skin pathogens because of their highly selective antibacterial activity and ability to inhibit pathogenic germs without significantly altering commensal microbial populations. Probiotic organisms can produce and secrete bacteriocins in situ over time when encased in hydrogel matrix, enabling localised antibacterial action that changes dynamically in response to microbial competition. As an alternative, hydrogel networks can directly include pure bacteriocins for regulated diffusion. While preserving concentrations above their minimum inhibitory levels in the local skin environment, the hydrated polymeric structure shields these peptides from quick breakdown. Unlike traditional topical antibiotics, which frequently disturb the larger microbiome and aid in the development of resistance, such biologically produced antimicrobial administration provides a very tailored approach to infection treatment [144].

Combining the fields of microbiology, immunology, regenerative medicine, and biomaterials science, living bioactive hydrogel platforms mark a revolutionary advancement in the development of cutaneous drug delivery. These systems expand the therapeutic role of hydrogels well beyond traditional controlled release by making it possible to encapsulate viable probiotics, engineer microbiome-supportive environments, deliver postbiotic metabolites, and produce or release bacteriocins continuously. Living bioactive hydrogels serve as biologically interactive therapeutic ecosystems that may continually regulate inflammation, microbial balance, and tissue repair processes rather than merely acting as drug carriers. In addition to creating novel therapeutic options for complicated dermatological conditions, this paradigm lays the groundwork for precision dermatology in the future, where host biology and microbiome dynamics will inform treatment approaches [144].

12.Smart Hybrid Microneedle–Hydrogel Systems

One of the most revolutionary developments in cutaneous drug administration is smart hybrid microneedle–hydrogel systems, which combine the sustained release and hydration characteristics of polymeric hydrogel matrices with the minimally invasive penetration capacity of microneedle arrays. Because of the stratum corneum's strong barrier, conventional

topical formulations frequently fall short of achieving sufficient therapeutic concentrations into deeper epidermal or dermal layers. This restriction is addressed by microneedle-assisted hydrogel platforms, which generate controlled-release depots that govern drug diffusion into viable skin tissues and tiny, painless conduits across the outer barrier. Precision delivery of small-molecule medications, biologics, peptides, vaccines, and regeneration factors with enhanced bioavailability and decreased systemic exposure is made possible by this dual-purpose approach, which combines mechanical barrier bypass with biologically adjustable release kinetics. In order to treat inflammatory dermatoses, chronic wounds, psoriasis, localised infections, and transdermal systemic medicines, hybrid microneedle–hydrogel systems are being studied more and more [145].

Within this class, hydrogel-forming microneedles are among the most clinically promising designs. These devices are usually made of crosslinked hydrophilic polymers, like modified polysaccharides, polyvinyl alcohol, or polyvinylpyrrolidone, which have a high mechanical stiffness while dry but quickly absorb interstitial fluid once they are inserted into the skin. After being applied, the solid microneedles pierce the stratum corneum and swell as they hydrate, becoming soft hydrogel conduits that link the viable epidermis to an external drug reservoir. Therapeutic compounds can move from the attached hydrogel patch into the underlying tissues in a controlled fashion thanks to the continuous diffusion channel created by this swelling behaviour. Hydrogel-forming microneedles reduce the possibility of polymer residue deposition in the skin while enabling sustained administration over long periods of time since the swollen needles are removed after treatment and remain structurally intact. They are especially well-suited for chronic dermatological disorders that necessitate frequent or extended therapy because of their capacity to preserve structural stability and hydration while in use [146].

Another significant hybrid approach is the use of dissolving microneedle reservoir systems, in which the microneedle tips are made of biodegradable hydrogel polymers that contain therapeutic chemicals that have been encapsulated. Following implantation, these microneedles release their payload straight into the dermal or epidermal compartment as they progressively dissolve in the interstitial fluid. The dissolving ingredients can serve as initial loading dosages or principal drug carriers, and an external hydrogel patch offers secondary continuous release at the same time. Programmable biphasic kinetics, in which a lengthy maintenance dose is administered after an initial quick therapeutic pulse, are made possible

by this layered delivery method. Delivering immunomodulatory medications, anti-inflammatory agents, or antibacterial compounds—where an early high local concentration is favourable for quick symptom relief and a constant release to avoid relapse—benefits greatly from such designs. Dissolving microneedles are appealing candidates for self-administered home therapies because of their biodegradable nature, which also removes worries about disposing of sharp waste and improves patient convenience [147].

Swelling microchannel systems provide regulated dermal distribution and serve as a supplementary mechanism in hybrid microneedle–hydrogel platforms. Microscopic aqueous channels are formed when microneedles pierce the skin, and these channels may remain momentarily after being removed. These microchannels can be stabilised and used as regulated diffusion paths for therapeutic transport in hydrogel-integrated systems. These microchannels can be penetrated by hydrogels injected right after microneedle insertion, creating hydrated conduits that increase permeability and enable deeper penetration of encapsulated molecules. In highly sophisticated designs, the microneedles themselves enlarge the microchannels and guarantee continuous communication between the living epidermis and the external hydrogel matrix by swelling and expanding radially upon fluid absorption. While minimising systemic leakage and maintaining localised delivery, this swelling-driven channel enlargement improves drug flux. This technique offers a short-term but extremely effective pathway for targeted therapy without irreversibly disrupting the structure of the skin barrier since the microchannels progressively reseal as the skin heals [148].

Because they combine safety, patient comfort, and therapeutic accuracy, smart hybrid microneedle–hydrogel devices have substantial clinical value in addition to their mechanistic benefits. Compared to hypodermic injections, the needles' micron-scale diameters usually prevent stimulation of deep skin nerves, making administration mainly painless and increasing patient compliance [149]. Even in sensitive or irritated skin, the incorporated hydrogel component minimises irritation and improves tolerance by preserving local hydration, lowering transepidermal water loss, and promoting barrier recovery throughout treatment. Crucially, stimuli-responsive polymers that further control drug release in response to temperature, pH, enzyme activity, or inflammatory signals within the tissue can be integrated into these systems, allowing for adaptive treatment that is in line with the course of the disease. In chronic inflammatory skin disorders, where treatment demand varies over time

and geographic localisation is crucial for reducing side effects, such programmable delivery behaviour is particularly beneficial [150].

Precision dermatological treatment, polymer science, and mechanical microengineering all come together in smart hybrid microneedle–hydrogel systems. These platforms combine swelling-mediated microchannel transport mechanisms, dissolving reservoir structures, and hydrogel-forming needles to administer extremely effective transdermal therapy in a minimally invasive, patient-friendly manner. They are among the most clinically transferable technologies in next-generation dermal therapeutics due to their ability to deliver a variety of therapeutic classes and their programmable release capability. They have the potential to completely change the way that drugs are administered locally and systemically through the skin in the future [151].

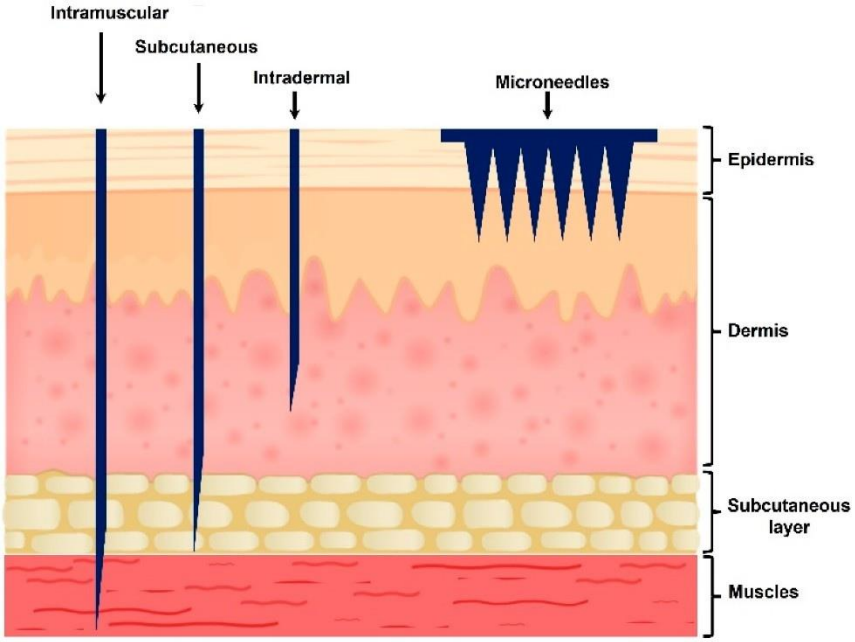


Figure 3: Schematic illustration depicting hydrogel-forming microneedle arrays penetrating the stratum corneum to create transient microchannels, followed by in situ swelling of the hydrogel matrix within the dermal layer. The system enables controlled, stimuli-responsive release of encapsulated therapeutics (e.g., corticosteroids, antimicrobials, antioxidants, growth factors) directly into the pathological microenvironment. This platform enhances dermal bioavailability while minimizing systemic exposure, offering a minimally invasive strategy for targeted dermatological therapy.

13.Multi-Therapeutic Co-Delivery Hydrogel Systems

A sophisticated development in dermal biomaterial design, multi-therapeutic co-delivery hydrogel systems reflect the increasing understanding that the majority of cutaneous illnesses result from a combination of overlapping pathogenic pathways rather than a single genetic flaw. Complex interactions between immunological dysregulation, oxidative stress, microbial colonisation, poor tissue regeneration, and barrier disruption are present in conditions such psoriasis, chronic wounds, acne, infected ulcers, and inflammatory dermatitis. This complex disease is frequently not addressed by traditional topical medicines that only use one active ingredient, which leads to insufficient therapeutic responses or repeated relapse. As a result, contemporary hydrogel platforms are being designed more and more to co-encapsulate complementary therapeutic agents with different but complementary modes of action. This allows for the simultaneous control of oxidative damage, inflammation, microbial burden, and tissue repair processes in a single localised delivery system. Researchers can spatially arrange various therapeutic components, control their individual release kinetics, and sustain extended retention at the disease site by taking advantage of the three-dimensional polymer network and adjustable mesh architecture of hydrogels. This turns hydrogels into integrated multifunctional treatment platforms as opposed to straightforward drug carriers [152].

Combining the administration of antioxidant and anti-inflammatory drugs is a significant use of this approach, especially for chronic inflammatory dermatoses that are marked by high reactive oxygen species and excessive cytokine signalling. Because it damages cellular membranes, activates transcription pathways, and hinders barrier healing, chronic oxidative stress intensifies inflammatory cascades. Corticosteroids, non-steroidal anti-inflammatory medications, or immunosuppressive substances can be combined with free-radical scavengers such polyphenols, flavonoids, or enzymatic antioxidants in hydrogels intended for dual anti-inflammatory and antioxidant delivery. These components can be released in a controlled manner thanks to the hydrogel matrix. Antioxidants initially lessen oxidative damage and stabilise the tissue microenvironment, which increases the efficiency of the accompanying anti-inflammatory medication and lowers the dosage needed. In addition to improving symptom management, this coordinated therapeutic approach reduces the long-term damage linked to continuous high-dose anti-inflammatory medication [153].

Antimicrobial medicines are combined with growth factors or regenerative biomolecules in another extremely important co-delivery paradigm, which is especially well-suited for post-

surgical lesions, diabetic ulcers, and infected wounds. In these diseased settings, extracellular matrix degradation, delayed epithelial migration, and decreased angiogenesis often occur alongside microbial colonisation and biofilm development. While growth factor therapy alone might not work in the midst of ongoing microbial contamination, antimicrobial medication delivery alone may reduce infection but may not always restore the damaged tissue's ability to regenerate. In order to lower the bacterial load, hydrogel-based co-delivery systems can be designed to release antimicrobial compounds early in the course of treatment. This is followed by a sustained release of growth factors, peptides, or biomolecules that support the extracellular matrix and promote angiogenesis, collagen deposition, and cell proliferation. By integrating the various therapeutic ingredients into discrete microdomains, nanocarriers, or layered polymer compartments inside the hydrogel network, this staged or overlapping release pattern can be accomplished, guaranteeing that each agent operates at the most suitable point in the healing process. These multifunctional hydrogels improve healing outcomes while shortening treatment times by accurately mimicking the natural temporal sequence of wound repair [153].

Co-delivery of immunomodulators with biologic or molecularly targeted medicines is another significant aspect of multi-therapeutic hydrogel design that has great potential for treating inflammatory and autoimmune skin conditions. Topical anti-inflammatory drugs cannot completely manage conditions like psoriasis or severe atopic dermatitis because they include dysregulated immune cell activation, aberrant cytokine generation, and persistent inflammatory feedback loops. Hydrogels that can transport physiologically active peptides, monoclonal antibody fragments, nucleic acid-based therapies, and small-molecule immunosuppressants all at once provide a potent way to target several regulatory sites in the inflammatory cascade. The local delivery reduces systemic exposure usually linked to injectable biologic therapy, and the polymeric network can shield delicate biologic molecules from deterioration while permitting slow diffusion into the epidermis. These integrated systems provide as an example of how hydrogel-mediated co-delivery might be used in dermatology to support next-generation precision immunotherapy techniques in addition to traditional drug combinations [154].

A prime example of this contemporary co-delivery approach is the creation of hydrogels that include quercetin and tacrolimus. While quercetin is a naturally occurring flavonoid with significant antioxidant, anti-inflammatory, and membrane-stabilizing effects, tacrolimus is a

powerful calcineurin inhibitor that inhibits T-cell activation and lowers the generation of inflammatory cytokines. When combined in a hydrogel matrix, tacrolimus exhibits targeted immunosuppressive action while quercetin reduces oxidative stress and improves tissue tolerance, resulting in a more potent therapeutic combination than either substance alone. Both chemicals are further stabilised by the hydrogel vehicle, which further enhances local retention and permits prolonged diffusion into areas of inflammatory skin. These combinations show how pharmacological and natural bioactive substances can be judiciously paired in a controlled hydrogel environment to improve efficacy and lessen the requirement for high dosages of powerful immunosuppressive medications [155].

All things considered, multi-therapeutic co-delivery hydrogel systems mark a significant advancement toward integrated dermatological treatment platforms that can handle the complex nature of skin conditions. These systems offer a degree of therapeutic versatility and precision that is not possible with single-agent topical formulations by facilitating the coordinated administration of anti-inflammatory and antioxidant agents, antimicrobial and regenerative factors, immunomodulators, and biologic therapies. Advanced control over the timing, location, and sequence of drug release is made possible by the variable structural characteristics of hydrogels, which include stimuli-responsive degradation, layered structures, nanoparticle embedding, and adjustable mesh size. This feature makes multi-therapeutic hydrogel platforms a key component of precision dermatology in the future, as treatment plans aim to simultaneously address several pathological factors that contribute to the development of the illness in addition to symptom suppression [156].

14.Patient-Centric Engineering of Dermatological Hydrogels

A strong patient-centric engineering approach has started to be included into the development of dermatological hydrogel systems in recent years, realising that clinical success depends not only on pharmacological efficacy but also on user comfort, cosmetic acceptance, and real-world adherence. Modern translational dermatology is placing more emphasis on how patients perceive, tolerate, and consistently use topical therapies over extended treatment periods, whereas traditional biomaterial research has mostly concentrated on drug release kinetics, mechanical strength, and biological compatibility. Therapeutic formulations must be applied repeatedly or over an extended period of time for many chronic skin conditions, including psoriasis, eczema, acne, and diabetic wounds. Even very effective medications may not work as intended in clinical settings if the delivery system is uncomfortable, leaves

visible residue, detaches easily, or interferes with everyday activities. In order to ensure that therapeutic platforms are designed for both biological performance and practical usability in a variety of real-life environments, patient-centric hydrogel engineering aims to optimise the physical, sensory, and behavioural interaction between the formulation and the user [157].

The hydrogel's sensory feel both during and after application is one of the most crucial factors in this situation. Particularly in areas of the body that are visible, dermatological formulations that cause significant stickiness, greasiness, or uneven distribution frequently result in poor patient adherence. Because of their high water content and tissue-like softness, hydrogels have intrinsic benefits that can produce a cooling and calming sensation when applied to irritated or inflamed skin. Because of this, contemporary hydrogel formulations are designed with precisely calibrated rheological characteristics, such as shear-thinning behaviour that permits smooth spreading under light pressure and quick viscosity recovery that stops runoff after application. Researchers can create formulations that feel light, non-greasy, and quickly comfortable by modifying the polymer composition, hydration level, and crosslink density. This increases acceptance in both therapeutic and cosmetic dermatology contexts. For illnesses requiring hypersensitive or injured skin, where even slight discomfort can deter ongoing therapy, such tactile optimisation is especially crucial [158].

Transparency and aesthetic appeal are also important factors in patient acceptance, especially when it comes to treatments used on exposed areas like the hands, face, or neck. Topical systems that are opaque or highly coloured may not be aesthetically pleasing, which could deter daytime use and compromise therapeutic consistency. When treating socially sensitive dermatological disorders like acne, post-inflammatory lesions, or persistent dermatitis, transparent or nearly invisible hydrogel films let patients keep their natural appearance. Precise control over the hydration uniformity, polymer compatibility, and nanoscale dispersion of implanted therapeutic particles are necessary to achieve optical clarity. Thanks to developments in polymer blending and nanocarrier stabilisation, active substances may now be added without sacrificing visual transparency, resulting in the production of discrete therapeutic films that work well without being unsightly [159].

Adhesion durability, which establishes how consistently the hydrogel maintains contact with the skin during mobility, daily activities, and environmental exposure, is another crucial element of patient-centric design. While excessively strong adhesion may result in discomfort or skin irritation during removal, insufficient adhesion might cause premature detachment,

uneven drug exposure, and wasted medication. Thus, bioadhesive polymers, hydrogen-bonding interactions, and dynamic reversible crosslinking mechanisms are used in modern dermal hydrogels to give a strong yet flexible adhesion to the skin's surface. Even in highly dynamic places like joints or face regions, these materials can maintain touch and adjust to uneven anatomical features. Crucially, reversible adhesive interactions enable painless removal without endangering sensitive or irritated skin, which is crucial for long-term dermatological treatments that call for frequent cycles of application [160].

The ability of dermatological hydrogels to remain functional in the presence of perspiration and ambient moisture is closely linked to adhesion performance. Because sweat can dilute topical formulations, disrupt adhesive contacts, and accelerate medication loss from the application site, sweat resistance has emerged as a key design concern. In order to permit controlled vapour transmission while avoiding excessive hydration or structural breakdown, advanced hydrogels are increasingly being designed with moisture-tolerant adhesive chemistries and semi-permeable network topologies. In order to provide consistent medication administration during physical activity or in warm regions, many methods use dynamic bonding motifs or amphiphilic polymer domains that sustain adherence even on damp or oily skin surfaces. For long-wearing therapeutic patches and wound dressings, where continuous skin contact is necessary to achieve long-lasting therapeutic benefits, this stability is especially crucial [160].

Given that children with dermatological conditions frequently have increased skin sensitivity, behavioural resistance to treatment, and trouble tolerating uncomfortable or visually noticeable formulations, paediatric compliance is another crucial aspect of patient-centric hydrogel engineering. Therefore, hypoallergenic composition, gentle adherence, quick comfort, and ease of application must be given top priority in hydrogels designed for paediatric usage. Younger patients' acceptance of therapy can be greatly increased by lightweight, flexible hydrogel films that easily adapt to the skin without needing intense pressure or intricate fixing. Furthermore, the lack of harsh solvents, irritating preservatives, or potent perfumes lessens the possibility of pain or an allergic reaction. In order to promote regular use and lessen treatment anxiety in paediatric populations, hydrogels should be designed with aesthetically pleasing yet medically relevant features, such as a smooth surface, soft texture, and unobtrusive look [161].

All things considered, patient-centric engineering is an essential but traditionally overlooked component of dermatological hydrogel design that has a direct impact on treatment success outside of laboratory performance measurements. Modern hydrogel technologies can greatly improve real-world treatment adherence and long-term therapeutic outcomes by optimising sensory feel, visual transparency, adhesive durability, resistance to perspiration, and usability in sensitive populations like youngsters. This all-encompassing strategy acknowledges that the best dermatological biomaterials must not only work well with biological tissue but also blend nicely with patients' everyday routines. Transforming cutting-edge hydrogel technologies from experimental prototypes into extensively used therapeutic medicines would need taking patient-experience factors into account in addition to pharmacological and material science considerations as precision dermatology develops [161].

15.Digital Dermatology-Integrated Hydrogel Systems

One of the most innovative approaches to biomaterial-enabled skin therapy is represented by digital dermatology-integrated hydrogel systems, which combine soft hydrogel matrices with wireless communication technologies, sensing electronics, and responsive indicators to produce intelligent therapeutic platforms. The major purpose of conventional hydrogel dressings and topical drug delivery systems is to release medications or keep patients hydrated; however, they usually don't offer real-time data regarding the course of the disease, the presence of infections, or the efficacy of treatment. By serving as both therapeutic carriers and diagnostic interfaces that may directly monitor physiological factors at the skin's surface, digitally integrated hydrogels seek to get over this restriction. These cutting-edge solutions allow for the continuous evaluation of wound environment parameters like temperature, pH, moisture content, mechanical strain, or biochemical markers by enclosing micro-sensors, responsive dyes, conductive polymers, or flexible electronic circuits within hydrated polymer networks. Hydrogels become interactive clinical platforms that can allow individualised, data-driven dermatological care when such monitoring features are incorporated [162].

Hydrogel systems with wearable sensors integrated into them are an essential part of this new paradigm. Hydrogels offer the perfect interface for connecting flexible electrical components with the skin while preserving comfort and reducing irritation because of their high water content, mechanical softness, and tissue-like flexibility. Both drug delivery reservoirs and sensing substrates that can identify changes in electrical impedance, temperature, or hydration in the underlying tissue can be found in conductive hydrogel formulations that

contain materials like metallic nanowire networks, ionic polymers, or graphene derivatives. These signals may indicate aberrant wound moisture balance, impaired circulation, or early inflammatory activity—all of which are important markers in the treatment of inflammatory skin conditions and chronic wounds. By using such hydrogel-sensor hybrids for continuous physiological monitoring, physicians can identify issues early, modify treatment plans quickly, and prevent needless dressing removal that could otherwise damage delicate healing tissue [163].

Another very creative method for including diagnostic capabilities in hydrogel dressings is the use of colorimetric healing feedback systems. pH-sensitive dyes, enzyme-responsive chromophores, or nanoparticle-based optical indicators that alter colour in response to biochemical changes linked to infection, inflammation, or tissue healing are incorporated into the hydrogel matrix in these designs. Visually discernible colour transitions can offer instantaneous, non-invasive information on wound health without the requirement for laboratory testing because many pathological wound settings show distinctive acidity changes, protease increase, or microbial metabolite synthesis. By merely looking at the dressing surface, patients and professionals can evaluate the healing process or identify the development of an infection thanks to this real-time visual feedback. This feature is especially helpful for wound care at home, as early problem discovery can drastically lower the risk of hospitalisation and treatment expenses. Crucially, contemporary colorimetric hydrogels are designed to preserve mechanical integrity and drug release performance while maintaining optical stability, guaranteeing that therapeutic efficacy is not jeopardised by diagnostic function [163].

This idea is further developed by smart wound patches, which combine automated therapeutic responsiveness with regulated medication delivery. These systems could include temperature-responsive polymer segments, hydrogel reservoirs with embedded microfluidic channels, or electronically controlled release modules that can modify drug flux based on physiological parameters that are monitored. For instance, a hydrogel patch that detects rising local temperature or infection-related protease levels may be programmed to boost the release of antimicrobial drugs, while a drop in inflammatory markers could cause the therapeutic administration to gradually taper down. An important step toward adaptive dermatological therapy, where treatment intensity is automatically matched with disease activity, is represented by such closed-loop systems. Hydrogels are particularly well-suited platforms for

the implementation of such self-regulating therapeutic structures because they can be built with programmable swelling behaviour, conductive responsiveness, or stimulus-triggered permeability alterations [164].

An extra degree of connectivity is provided via Bluetooth-enabled therapy monitoring, which facilitates remote clinical supervision and individualised treatment optimisation. Flexible electronic modules built inside hydrogel patches can wirelessly send sensor data to wearable receivers, smartphones, or hospital monitoring systems. This enables medical professionals to monitor environmental exposure conditions, therapy compliance, and wound healing metrics in real time. For the treatment of long-term dermatological disorders such diabetic ulcers, pressure injuries, and inflammatory autoimmune dermatoses, such wireless communication capabilities are especially helpful. By reducing the need for frequent in-person visits and enabling early clinical intervention when healing trajectories vary from expected patterns, remote data transmission improves patient convenience while preserving medical monitoring. The expansion of teledermatology and digital health ecosystems, where treatment devices actively engage in clinical data networks instead of operating as standalone therapeutic materials, is further supported by the integration of Bluetooth connectivity with soft hydrogel interfaces [165].

Together, wearable electronics, responsive chemistry, biomaterials science, and data-driven healthcare technology are represented by digital dermatology-integrated hydrogel systems. These platforms redefine the functional role of hydrogels in clinical dermatology by integrating wearable sensors for physiological monitoring, colorimetric indicators for visual healing assessment, adaptive smart wound patch architectures, and Bluetooth-enabled communication for remote therapeutic supervision. Digitally integrated hydrogels serve as intelligent therapeutic interfaces that can sense, react, and communicate within the treatment environment rather than just serving as passive drug delivery matrix. Through continuous real-time feedback and adaptive therapeutic control, these systems, though still in the early translational stages, hold extraordinary potential for enabling precision dermatology, enhancing long-term treatment adherence, and supporting personalised management of chronic skin disorders [166].

16.Translational Barriers and Regulatory Science

Dermatological hydrogel systems have shown impressive success in the lab, but a number of significant translational and regulatory obstacles still stand in the way of their development

into clinically approved and economically viable therapies. The conventional distinctions between medicines, biologics, and medical devices have become less clear due to the increasing sophistication of contemporary hydrogels, especially those that incorporate nanocarriers, biologics, responsive polymers, or microbiome-modulating components. As a result, regulatory review today encompasses more than just traditional drug-release performance; it also includes ecological effects on the skin microbiome, formulation stability, microbiological safety, manufacturing sterility assurance, and accurate product classification. To avoid expensive redesign, postponed approval dates, and possible safety difficulties during clinical deployment, these challenges must be addressed early in the development cycle [167].

One of the most important but technically challenging prerequisites for dermatological hydrogel translation is ensuring sterility. If contamination happens during production or storage, hydrogels, which are networks of highly hydrated polymers, can offer ideal conditions for microbial survival and growth. Nevertheless, a lot of hydrogels contain biologically active compounds, thermosensitive polymers, or live medicinal agents that are incompatible with common sterilisation techniques such steam autoclaving. Although alternative sterilisation techniques like gamma irradiation, electron beam exposure, or sterile filtration of precursor solutions followed by aseptic gelation can be used, there are risks associated with each of these techniques, such as decreased mechanical strength, changed crosslink density, polymer degradation, or chemical modification of active ingredients. Clinical dependability may be jeopardised by even minute structural changes that affect swelling behaviour, drug diffusion kinetics, or adhesion performance. To guarantee long-term sterility assurance, developers must thus rigorously verify sterilisation compatibility, show that physicochemical integrity is preserved following sterilisation, and establish regulated aseptic manufacturing conditions with strict microbiological monitoring [168].

The problem of preservative compatibility in hydrogel formulations meant for multiple doses or prolonged usage in dermatological applications is closely related to sterility control. Preservative inclusion is required in many formulations due to the high water content and organic polymer composition of hydrogels, which can foster microbial growth during storage or repetitive handling. Preservatives themselves, however, have the potential to destabilise the system through interactions with the hydrogel matrix or the encapsulated medicinal ingredient. Some antimicrobial preservatives can break down nanocarrier membranes, change

the ionic crosslinking equilibrium, bind to polymer chains, or hasten the breakdown of delicate biologic medications. Furthermore, preservatives can occasionally trigger allergic responses or local skin irritation, especially in patients with weakened epidermal barriers like those with eczema or chronic wounds. Therefore, thorough compatibility testing, preservative efficacy validation, and long-term stability investigations under both accelerated and real-time storage circumstances are necessary to achieve the best possible balance between antimicrobial protection, formulation stability, and skin tolerability [169].

The growing use of dermatological treatments that target the microbiota adds another level of regulatory complexity, which is still a developing area of international pharmaceutical supervision. It is now necessary to assess hydrogels intended to modify microbial populations—whether by probiotic colonisation, selective antimicrobial release, or microbiome-supportive biomaterials—not only for their pharmacological safety but also for their ecological impact on the commensal microbial community of the skin. Regulatory bodies are becoming more aware that indiscriminate microbial suppression might damage beneficial flora, which may result in long-term barrier failure, opportunistic infections, or changes in immunological signalling. Therefore, manufacturers of hydrogels that interact with the microbiome may need to prove regulated selectivity, the lack of detrimental ecological disruption, and long-term microbial balance. One major translational challenge that has not yet been completely harmonised across regulatory jurisdictions is the establishment of standardised experimental frameworks for microbiome safety assessment, including genomic profiling, microbial diversity monitoring, and long-term ecological follow-up [170].

Classifying probiotic-containing hydrogels, which can be classified into several regulatory categories based on their composition, mode of action, and proposed therapeutic claims, is a very complex regulatory challenge. Formulations containing live microbial strains can be categorised as combination drug-device systems, biologic medications, topical pharmaceuticals, or live biotherapeutic treatments. Specific documentation is needed for each categorisation route, such as thorough strain characterisation, confirmation of genomic stability, confirmation of contamination management, and reproducibility of microbial viability during production and storage. Evidence that integrated microbes do not develop antibiotic resistance, show pathogenic characteristics, or remain safe for use even in immunocompromised people is also needed by regulatory bodies. Hydrogels that deliver non-

viable microbial derivatives, like pure bacteriocins or postbiotic metabolites, on the other hand, could adhere to different regulatory circuits that prioritise pharmacological safety and biochemical consistency over microbial viability. Such microbiome-based treatments lack globally accepted classification standards, which makes international product development strategies more difficult and may call for region-specific regulatory submissions [171].

The requirement to scale hydrogel manufacture while upholding rigorous quality repeatability presents broader translational hurdles in addition to microbiological and categorisation issues. Small-batch polymer mixing, manually regulated crosslinking, and experimental encapsulation techniques are frequently used in laboratory-scale synthesis, which may not be directly applicable to industrial production. Proving batch-to-batch homogeneity in viscosity, polymer network design, drug loading distribution, mechanical strength, and release kinetics is becoming more and more important for regulatory approval. Implementing established quality-by-design techniques, automated mixing systems, inline rheological monitoring, and standardised analytical characterisation processes that can identify even minute formulation changes are necessary to achieve this degree of consistency. Despite excellent laboratory performance, potentially intriguing hydrogel technologies may face regulatory rejection in the absence of such industrial-scale process control [172].

The complicated process that advanced dermatological hydrogels must go through before entering clinical practice is demonstrated by the combined difficulties of sterilisation compatibility, preservative interaction, microbiome safety evaluation, probiotic regulatory classification, and scalable manufacturing reproducibility. In order to overcome these obstacles, regulatory science ideas must be incorporated into biomaterial design early on. This will guarantee that innovation advances concurrently with safety validation, manufacturability, and adherence to changing international standards. In order to turn promising experimental systems into authorised, widely available, and clinically effective dermatological treatments, proactive coordination between scientific research and regulatory strategy will be crucial as hydrogel technologies continue to advance toward more complex, biologically interactive therapeutic platforms [173].

17.Future Perspective

Hydrogel-based treatments for dermatological conditions are on the verge of evolving from traditional sustained-release platforms to extremely intelligent, customised, and adaptable therapy regimens. It is anticipated that next-generation hydrogels will be created with a

deeper integration of molecular pathology, immunological profiling, microbiome dynamics, and patient-specific biological markers as dermatological research continues to acknowledge the complexity and heterogeneity of skin diseases. Future hydrogel systems will probably act as biointeractive matrices that can sense local biochemical changes, such as spikes in inflammatory cytokines, oxidative stress, enzymatic activity, or microbial metabolites, and dynamically modify drug release profiles in real time, rather than just acting as passive carriers. In addition to minimising overtreatment and reducing long-term negative consequences linked to chronic dermatological drug usage, this shift toward feedback-regulated and microenvironment-synchronized therapy will allow for more accurate control over disease flares.

Multifunctional and hybrid hydrogel structures will be developed more quickly thanks to developments in materials science. Through the use of self-healing dynamic crosslinking chemistries, stimuli-responsive polymers, and nanotechnology, hydrogels will be able to combine mechanical robustness with programmed degradation and sequential drug release. Spatial patterns in drug distribution, gradient-controlled release zones, and anatomically tailored dressings for particular lesion geometries will all be made possible by emerging fabrication technologies like additive manufacturing, 3D bioprinting, and microfluidic structuring. Simultaneously, it is anticipated that the combination of hydrogel matrices and microneedle arrays will increase the number of minimally invasive transdermal delivery options for immunomodulators, biologics, and nucleic acid therapeutics. This will help to close the gap between topical therapy and systemic treatment while preserving localised precision.

The combination of hydrogel platforms with regenerative medicine and microbiome engineering is another revolutionary path. In order to actively restore microbial balance and influence immune responses, future systems might include cell-derived exosomes, postbiotic metabolites, live probiotic consortia, or artificial bacteriocins. By targeting the underlying ecological and immunological dysregulation rather than just reducing symptoms, such biologically interacting hydrogels may be crucial in the treatment of chronic inflammatory dermatoses, stubborn acne, and non-healing wounds. Furthermore, hydrogels may be able to directly contribute to tissue remodelling and long-term disease modification by integration with stem cell-derived growth factors or gene-editing techniques, creating opportunities for long-lasting remission in illnesses that were previously only treated symptomatically.

The functional range of dermatological hydrogels is anticipated to be redefined by digital integration as well. Flexible sensors, colorimetric markers, or wireless communication modules integrated with smart hydrogel dressings may enable ongoing tracking of the course of wound healing, the level of inflammation, or the danger of infection. When combined with teledermatology platforms and analytics powered by artificial intelligence, these technologies could support personalised therapy optimisation, adaptive dosing, and remote clinical decision-making. Dermatological care would shift from episodic intervention to continuous, data-informed management with the use of such closed-loop therapeutic platforms. These platforms would be especially helpful for chronic wounds and autoimmune skin illnesses that need long-term monitoring.

From a translational standpoint, future development will rely on cost-effective production techniques, scalable manufacturing strategies, regulatory harmonisation, and technical sophistication. Accelerating clinical approval routes will require the establishment of standardised evaluation frameworks for stimuli-responsive performance, nanocomposite stability, and microbiome safety. Batch consistency and economic feasibility will be enhanced by the use of automated production methods, reproducible crosslinking techniques, and quality-by-design approaches. Furthermore, modern hydrogel technologies will successfully transition into practical dermatological treatment if more focus is placed on patient-centric design, which includes sensory optimisation, cosmetic transparency, and ease of application.

In the end, the intersection of precision medicine, digital health, molecular dermatology, and biomaterials engineering will determine the future of hydrogel treatments for cutaneous conditions. Hydrogels are anticipated to evolve from sophisticated drug delivery systems into intelligent therapeutic ecosystems that can sense, react, and adapt to dynamic disease situations as knowledge of skin pathophysiology grows and material technologies advance. This paradigm shift has great potential to improve patient quality of life, increase treatment efficacy, and usher in a new era of precision-responsive dermatological therapy.

18.CONCLUSION

In summary, hydrogel-based systems offer a revolutionary transition from traditional topical formulations to precision-responsive therapeutic technologies, making them one of the most promising and adaptable platforms for the treatment of dermatological illnesses. Controlled, sustained, and stimuli-responsive drug administration that is suited to the intricate biological

landscape of sick skin is made possible by their special three-dimensional polymeric architecture, high water content, variable mechanical properties, and ability to be functionally modified. It is possible to design hydrogels to address important pathological drivers like inflammation, oxidative stress, enzymatic imbalance, microbial dysbiosis, and impaired tissue regeneration by combining natural and synthetic polymers, dynamic crosslinking techniques, nanocomposite embedding, and microenvironment-sensitive linkages.

One significant development in dermatological biomaterials is the shift from material-centric design to disease-driven engineering. Therapeutic release that is biologically adaptable, temporally regulated, and geographically localised is made possible by matching the structure and activity of hydrogels with certain pathophysiological triggers. New developments like digitally integrated smart dressings, hybrid microneedle–hydrogel platforms, follicular targeting systems, living bioactive hydrogels, and multi-therapeutic co-delivery matrices increase the therapeutic potential of these systems beyond passive drug carriers into interactive, multipurpose treatment platforms. All of these developments contribute to the development of precision medicine in dermatology, where treatment plans are influenced by patient-specific factors, disease microenvironment dynamics, and pharmacology.

Notwithstanding these noteworthy technology advancements, regulatory science, manufacturing reproducibility, sterility assurance, microbiome safety assessment, and patient-centric usability must all be carefully considered for clinical translation to be successful. Innovative hydrogel technologies must effectively transition from laboratory development to bedside application, which will require interdisciplinary collaboration among material scientists, doctors, microbiologists, and regulatory specialists to overcome these translational challenges.

All things considered, precision-responsive hydrogel treatments are a potent combination of modern drug delivery engineering, dermatological pathophysiology, and biomaterials science. These technologies have great potential to increase therapeutic efficacy, decrease side effects, improve patient adherence, and redefine the future of managing cutaneous disorders by facilitating adaptive, targeted, and multifunctional treatment approaches.

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