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DEVELOPMENT AND EVALUATION OF HYDROGEL FOR TOPICAL PAIN RELIEF: A COMPREHENSIVE REVIEW

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ABSTRACT: Hydrogels are semi-solid, three-dimensional polymeric systems capable of holding large amounts of water, making them ideal for topical drug delivery, especially in pain management. This review explores hydrogel formulation and its application in topical pain relief. Hydrogels are classified based on origin, polymer type, cross-linking method, and responsiveness to stimuli. Their advantages include biocompatibility, ease of application, and controlled drug release. However, limitations such as low loading capacity for hydrophobic drugs and risk of microbial contamination are noted. Preparation methods such as physical, chemical, and radiation cross-linking, along with grafting polymerization, are discussed. Each method provides unique properties suited to specific applications. The formulation process is outlined with emphasis on the functional role of each component. These include active pharmaceutical ingredients (e.g., NSAIDs, anesthetics), gelling agents (e.g., Carbopol, HPMC), pH adjusters, penetration enhancers, humectants, preservatives, and solvents. Each contributes to hydrogel performance, stability, and skin compatibility. A sample formulation using diclofenac sodium illustrates how these components combine into an effective gel for localized drug delivery. In conclusion, hydrogels offer a promising, patient-friendly approach to topical pain relief. Continued innovation in hydrogel systems may enhance future pain management strategies.

INTRODUCTION: Pain is a multifaceted physiological response that serves as a protective mechanism, alerting the body to potential or actual tissue damage. It is classified broadly into acute and chronic pain, each with distinct etiologies and treatment strategies. Acute pain typically arises from injury, surgery or inflammation and is often self-limiting, whereas chronic pain, which persists beyond normal healing periods, is associated with conditions such as arthritis, neuropathy, and fibromyalgia.

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Conventional pain management strategies primarily rely on systemic administration of pharmacological agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids and anticonvulsants [1]. While effective in many scenarios, these systemic medications are often linked with significant adverse effects such as gastrointestinal bleeding, hepatotoxicity, nephrotoxicity, cardiovascular risks, and, in the case of opioids, the risk of addiction and tolerance [2].

These concerns have triggered a growing interest in alternative and safer drug delivery methods that can provide targeted relief with minimal systemic exposure. Topical drug delivery systems (TDDS) offer a localized, non-invasive approach to pain management by delivering therapeutic agents

directly to the site of discomfort. Unlike systemic administration, which exposes the entire body to the drug, topical delivery minimizes systemic absorption and associated toxicity [3]. This method is particularly beneficial for treating musculoskeletal pain, joint inflammation, and neuropathic conditions localized near the surface of the skin. Among the various TDDS available, such as creams, ointments, gels, patches, and sprays, hydrogels have garnered considerable attention due to their unique physicochemical and biological properties [4]. Hydrogels are three-dimensional, hydrophilic polymeric networks capable of retaining substantial quantities of water or biological fluids while maintaining their structure. This high-water content not only contributes to their soft and flexible texture making them comfortable and non-irritating for patients but also enhances skin hydration, which in turn promotes the permeation of active pharmaceutical ingredients (APIs) through the stratum corneum, the outermost layer of the skin.

Hydrogels provide numerous advantages over conventional topical formulations. Their non-greasy, transparent, and spreadable nature allows for patient-friendly application and better cosmetic acceptability. They also provide a cooling effect on application, which is soothing in cases of inflammation or skin irritation, adding to their therapeutic value. Furthermore, hydrogels can be engineered to achieve controlled or sustained drug release, thus maintaining therapeutic drug concentrations at the site of application for extended periods and reducing the need for frequent reapplication [5].

This controlled release behavior is influenced by the choice of polymer, cross-linking density, drug-polymer interactions, and environmental factors such as skin pH and temperature. Commonly used polymers in hydrogel formulation include both natural and synthetic types such as polyvinyl alcohol (PVA), carbopol, hydroxypropyl methylcellulose (HPMC), chitosan, alginate and polyethylene glycol (PEG). These polymers are selected based on their biocompatibility, gelling ability, swelling capacity, and interaction with the incorporated drug [6, 7]. A wide array of analgesics and anti-inflammatory drugs have been successfully incorporated into hydrogel systems for topical pain relief. These include synthetic drugs such as diclofenac, ibuprofen, ketoprofen, lidocaine, and prilocaine, as well as natural bioactive agents like menthol, capsaicin, camphor, and eucalyptus oil. The choice of drug depends on the type and severity of pain being targeted. NSAIDs are typically used for inflammatory conditions, whereas local anesthetics are more effective for nerve-related pain [8]. Additionally, natural compounds often offer multifunctional benefits including anti-inflammatory, counter-irritant, and vasodilatory effects, making them suitable for combination therapies. Modern hydrogel systems can also be designed to respond to specific stimuli such as temperature, pH, or enzymatic activity so called “smart hydrogels” which allow on-demand drug release based on the physiological environment of the application site [9].

Despite their immense potential, the successful development of a hydrogel-based pain relief system is a complex process that involves multiple stages of formulation, optimization, and evaluation. Critical formulation parameters such as pH, viscosity, spreadability, drug loading capacity, and bioadhesion must be optimized to ensure therapeutic efficacy and patient compliance. Additionally, in vitro studies including drug release kinetics, diffusion studies, and skin permeation assays are essential to predict the performance of the hydrogel *in-vivo*. Stability studies under different storage conditions are also necessary to ensure the long-term integrity and efficacy of the product. Regulatory considerations, patient safety, and scalability of the manufacturing process further influence the clinical translation of these systems [10].

Given the increasing demand for effective, safe, and user-friendly topical pain relief products, hydrogels represent a versatile and innovative platform that bridges pharmaceutical science and clinical need. Recent advancements in polymer chemistry, nanotechnology and drug delivery systems have further enhanced the functionality of hydrogels, enabling the development of formulations with improved drug release profiles, greater skin permeability, and targeted therapeutic action. This comprehensive review aims to delve into the principles, methodologies, and challenges involved in the development and evaluation of

hydrogel-based topical systems for pain relief [11]. By exploring the current state of the art and future directions in this field, the review seeks to provide valuable insights for researchers, clinicians and pharmaceutical developers aiming to advance the science of topical pain management.

Hydrogels: Hydrogels are three-dimensional networks composed of hydrophilic polymers capable of retaining large quantities of water and biological fluids. This high water-retention ability stems from the presence of functional groups such as amino ($–NH_2$), carboxylic acid (–COOH), hydroxyl (–OH), amide (–CONH), and sulfo ($–SO_3H$) moieties along the polymer chains. The term "hydrogel" was first introduced in scientific literature in 1894, as noted by Lee, Kwon, and Park, marking the early understanding of these water-absorbing materials [12]. A major breakthrough in hydrogel development occurred in 1960 when Wichterle and Lim synthesized the first cross-linked hydrogel using poly (2-hydroxyethyl methacrylate) (pHEMA) for the fabrication of soft contact lenses [13]. This innovation highlighted hydrogels' biocompatibility, elasticity and high moisture content, qualities that have since supported their widespread application in biomedical and pharmaceutical fields [14].

The evolution of hydrogel technology has been categorized into three developmental stages. The first generation consisted of simple, inert hydrogels with high water content but limited responsiveness. The second generation, developed in the 1970s, introduced hydrogels with environmental responsiveness, enabling changes in structure or swelling behavior in response to external stimuli such as pH and temperature [15]. The third generation introduced the concept of "smart hydrogels," which are constructed using supramolecular inclusion complexes that allow dynamic behavior and adaptability to physiological conditions. These advanced hydrogels are more selective, sensitive and suitable for intelligent drug delivery systems and tissue interactions [16].

Since the 1980s, hydrogels have found applications across a broad spectrum of biomedical technologies. They have been employed in the manufacture of soft contact lenses, wound dressings, surgical sutures, and absorbent materials [17]. More recent innovations include their use in drug delivery systems, biosensors, regenerative medicine, 3D cell culture platforms, and cell therapy applications [18, 19]. Due to their versatility, tunable mechanical properties and excellent biocompatibility, hydrogels continue to be a foundational material in both conventional and advanced pharmaceutical formulations.

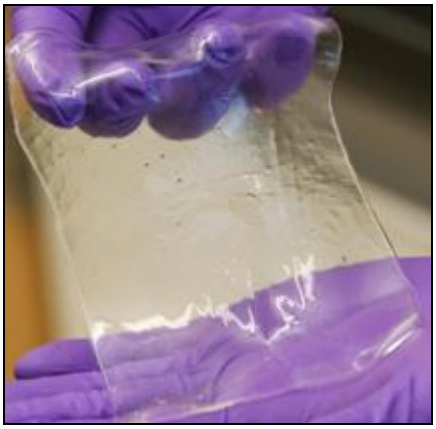

FIG. 1: HYDROGELS

Advantages:

Enhanced Patient Compliance: Hydrogels are soft, cool, and non-greasy, making them more comfortable and aesthetically appealing for topical application compared to ointments or creams.

Localized Drug Delivery: Hydrogels allow targeted delivery of analgesic drugs directly to the site of pain, minimizing systemic side effects and improving therapeutic efficacy.

High Water Content: Their high-water content hydrates the skin, provides a cooling sensation, and promotes skin permeability, enhancing drug absorption.

Controlled Drug Release: Hydrogels can be engineered to provide sustained or controlled release of drugs, maintaining therapeutic concentrations over an extended period.

Biocompatibility and Safety: Many hydrogels, especially those made from natural or biocompatible polymers, are non-toxic, non-irritating, and safe for repeated application.

Ease of Application and Removal: Hydrogels spread easily over the skin and can be removed without leaving residues, making them convenient for both patients and caregivers.

Versatility in Formulation: A wide range of polymers and additives can be used to tailor the mechanical, rheological, and drug release properties of hydrogels for specific clinical needs [20].

Disadvantages:

Limited Drug Penetration: Some analgesic drugs may have poor skin permeability, and even with hydrogel formulations, may not achieve effective concentrations in deeper tissues.

Short Residence Time: Hydrogels may dry out or be wiped off easily from the application site, especially in high-friction areas, reducing their effectiveness unless reapplied frequently.

Stability Issues: Some hydrogel formulations can degrade over time or under environmental conditions (e.g., temperature, humidity), which may affect drug stability and release.

Limited Drug Loading Capacity: Hydrogels are best suited for low to moderate doses; they may not effectively deliver drugs that require high concentrations for pain relief.

Microbial Contamination Risk: The high moisture content can promote microbial growth, necessitating preservatives and careful packaging.

Potential for Skin Irritation or Allergic Reaction: Although generally biocompatible, certain polymers, crosslinking agents, or additives in the hydrogel may cause skin irritation or sensitization in some individuals.

High Production Cost: Advanced hydrogels with controlled-release features or responsive properties may involve complex synthesis and higher manufacturing costs [20, 21].

Applications of Hydrogels for Topical Pain Relief:

Musculoskeletal Pain: Hydrogels are widely used to deliver nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, ibuprofen, and ketoprofen for treating localized muscle and joint pain, including sprains, strains, arthritis, and tendonitis. These formulations provide sustained drug release, reduce inflammation, and offer cooling relief, making them preferable over oral NSAIDs which can cause gastrointestinal side effects.

Post-Surgical and Injury Pain: Hydrogel-based dressings loaded with analgesics or anti-inflammatory agents are often applied to surgical incisions, bruises, or trauma sites. Their moist environment promotes healing while simultaneously providing pain relief without the need for oral medications, which is especially important in post-operative care and elderly patients.

Neuropathic Pain: Some hydrogels are formulated with drugs like lidocaine or capsaicin for managing localized nerve pain in conditions like post-herpetic neuralgia or diabetic neuropathy. These formulations allow for prolonged contact with the skin, improving drug penetration and reducing the frequency of application.

Sports Medicine: In athletes, hydrogel patches and gels are popular for the treatment of acute injuries, such as muscle soreness, ligament sprains, or impact-related trauma. The hydrogels offer rapid, localized relief while avoiding the adverse effects of systemic analgesics, and their cooling effect is an added benefit in acute inflammation.

Burn and Wound-Associated Pain: Hydrogels not only aid in wound healing but also serve as carriers for pain-relieving agents in minor burns, abrasions, and pressure ulcers. Their soothing, cooling nature relieves pain instantly while maintaining a moist wound environment that accelerates tissue repair.

Chronic Pain Conditions: In cases of chronic conditions like osteoarthritis or chronic back pain, hydrogels can provide long-term management by incorporating sustained-release drug delivery systems. This minimizes the need for frequent dosing and enhances patient adherence.

Pediatric and Geriatric Care: Hydrogels are especially beneficial in sensitive populations such as children and elderly patients, where oral medications might be unsuitable or risky. Their non-invasive nature, ease of use, and gentle action make them a safer alternative for managing localized pain [22, 23].

Formulation of Hydrogel:

Active Pharmaceutical Ingredient (API): The active pharmaceutical ingredient is the core therapeutic agent in the hydrogel formulation, responsible for delivering pain relief or anti-inflammatory action. The choice of API depends on the type of pain being treated musculoskeletal, neuropathic, or inflammatory. Commonly used APIs include diclofenac sodium, ketoprofen, and ibuprofen, which are NSAIDs that work by inhibiting prostaglandin synthesis to reduce inflammation and pain. Other drugs like lidocaine and prilocaine serve as local anesthetics that block nerve conduction, offering immediate numbing effects. Additionally, natural compounds such as menthol, camphor, or capsaicin are often included for their counterirritant and vasodilatory effects, promoting a cooling or warming sensation that distracts from pain perception. The API must be stable, skin-compatible, and efficiently released from the gel matrix to achieve effective topical delivery [24].

Gelling Agents / Polymers: Gelling agents are the primary structural components that give hydrogels their semi-solid consistency and capacity to retain water. These polymers form a three-dimensional network that holds the drug in place and allows for its controlled release. Carbopol 934 or 940 is one of the most widely used synthetic polymers due to its excellent gelling ability at low concentrations and clear, smooth texture [25]. Natural polymers like xanthan gum or sodium alginate offer biocompatibility and biodegradability, while semi-synthetic polymers such as HPMC provide a balance of viscosity and skin tolerance. The polymer concentration must be optimized to ensure the gel is neither too runny nor too stiff, which would affect application, spreadability, and drug diffusion [26].

Neutralizers / pH Adjusters: Neutralizers are used to adjust the pH of the hydrogel to be compatible with human skin and to activate gelation in polymers like Carbopol. For example, triethanolamine (TEA) or sodium hydroxide are commonly used to neutralize acidic polymers and promote gel formation. The optimal pH for most topical hydrogels is between 5.5 and 7.0, which is close to the skin's natural pH, reducing the risk of irritation. Neutralization also affects the viscosity of the hydrogel; improper pH adjustment can lead to poor gel formation, phase separation, or instability of the API [24].

Penetration Enhancers: Penetration enhancers are critical in promoting the movement of the drug from the hydrogel through the skin layers to reach the site of action. They work by disrupting the structure of the stratum corneum, the outermost barrier of the skin, or by improving the drug's solubility and partitioning into the skin. Common agents include propylene glycol, ethanol, oleic acid, and dimethyl sulfoxide (DMSO). These substances must be used in optimal amounts because while they enhance drug absorption, excessive use can cause skin irritation or dryness[26]. In topical pain relief formulations, penetration enhancers are particularly important for ensuring rapid and effective analgesia.

Humectants / Moisturizers: Humectants are substances that attract and retain moisture, keeping the hydrogel hydrated and preventing it from drying out upon exposure to air. They also help maintain skin moisture, reducing dryness or cracking, which is especially beneficial in chronic pain conditions involving inflamed or irritated skin. Glycerin, propylene glycol, and sorbitol are commonly used humectants in hydrogel formulations. Apart from their moisturizing effect, they also contribute to the smooth texture of the gel and aid in drug solubilization and delivery [27].

Preservatives: Preservatives are added to the hydrogel formulation to inhibit the growth of bacteria, fungi, and other microorganisms, particularly in aqueous-based gels stored over long periods. Commonly used preservatives include methylparaben, propylparaben, and benzyl alcohol. The selection of preservatives depends on the nature of the hydrogel, the expected shelf life, and whether the product is intended for multiple uses or single-dose application [28]. While they are essential for preventing microbial contamination, care must be taken to ensure the preservatives do not react with the drug or irritate the skin.

Solvents / Co-solvents: Solvents and co-solvents are used to dissolve the drug and other components, creating a uniform and stable formulation. Purified water is the primary solvent in most hydrogel

systems, while co-solvents like ethanol, PEG 400, or propylene glycol are added when the drug is poorly water-soluble [29]. These solvents also influence the evaporation rate, viscosity, and penetration characteristics of the hydrogel [30]. The choice and proportion of solvents are crucial for ensuring complete solubilization of the API and for enhancing the overall performance of the formulation.

Preparation of Hydrogels:

Physical Crosslinking Methods:

Freeze-Thaw Cycling Method: The freeze-thaw method is one of the most widely used physical techniques for hydrogel preparation, especially when using polymers like polyvinyl alcohol (PVA). This method involves repeated cycles of freezing and thawing a polymer solution, typically at -20°C for several hours, followed by thawing at room temperature. These cycles lead to the formation of microcrystalline regions within the polymer matrix due to phase separation and physical entanglement of polymer chains. The number of cycles and the freezing time determine the crosslink density and mechanical strength of the resulting hydrogel. This technique is advantageous because it avoids the use of toxic crosslinking chemicals and is relatively simple and cost-effective [31]. The resulting hydrogels exhibit good elasticity, high water retention capacity, and are biocompatible, making them ideal for use in drug-loaded gels or patches for localized pain relief applications.

Ionic Crosslinking: Ionic crosslinking relies on electrostatic interactions between oppositely charged ions and polymers. It is commonly employed with anionic polysaccharides like sodium alginate, which gel upon exposure to divalent cations such as calcium (Ca^{2+}). The preparation involves dissolving the polymer in water and gradually adding a solution of the crosslinking agent, such as calcium chloride. The ions bridge the polymer chains, forming a three-dimensional network without the need for covalent bonds [32]. This method is particularly suited for thermosensitive drugs and biologics, as it occurs under mild conditions. However, the ionic bonds are reversible and can be disrupted by changes in pH or ionic strength, which may limit the long-term stability of the hydrogel. Still, it remains a valuable approach for formulating hydrogels that provide fast and effective delivery of pain relief agents such as diclofenac or lidocaine [33].

Hydrogen Bonding and Hydrophobic Interaction: This method utilizes weaker non-covalent forces such as hydrogen bonds and hydrophobic interactions to form gel networks. Gelatin and other natural polymers form gels through hydrogen bonding when cooled below their gelation temperature. Similarly, block copolymers like poloxamers (e.g., Pluronic F127) form thermoresponsive hydrogels via hydrophobic interactions. These polymers remain in solution at lower temperatures but rapidly gel at body temperature. The preparation typically involves dissolving the polymer in cold water, mixing with the drug, and storing the formulation at a refrigerated temperature until use. Upon topical application, the formulation warms and solidifies, allowing prolonged contact with the skin. This method is beneficial for making user-friendly, injectable, or spreadable topical gels with quick onset of pain relief. However, these gels may lack the mechanical robustness of chemically crosslinked hydrogels [32].

Chemical Crosslinking Methods:

Crosslinking with Chemical Agents: Chemical crosslinking involves the formation of covalent bonds between polymer chains using chemical crosslinkers, resulting in hydrogels with higher mechanical strength and durability. Common crosslinking agents include glutaraldehyde, genipin (a natural alternative), and epichlorohydrin. The preparation process starts by dissolving the polymer (e.g., chitosan, polyacrylamide, or gelatin) in a suitable solvent, followed by the addition of a crosslinker under controlled conditions of temperature and pH [34]. For example, chitosan can be crosslinked with glutaraldehyde to form a stable, flexible hydrogel matrix capable of holding and slowly releasing pain-relieving agents like ketoprofen or lidocaine. While this method allows precise control over gel properties such as porosity, swelling, and drug release kinetics, it requires careful handling of chemicals to minimize cytotoxicity from residual crosslinkers. Post-synthesis purification steps, like dialysis or washing, are often necessary to ensure biocompatibility before the gel can be used for topical applications [35].

Click Chemistry and "Green" Crosslinking: Click chemistry is a newer, highly specific and efficient approach to chemical crosslinking that involves bio-orthogonal reactions like azide-alkyne cycloaddition. This technique allows for hydrogel formation under mild, aqueous conditions without producing harmful byproducts. Polymers are functionalized with reactive groups and mixed, initiating a rapid and controlled crosslinking reaction. This method is especially useful for preparing hydrogels designed for precision drug delivery systems or sensitive biologics like peptides and proteins used in chronic pain management. Similarly, "green" crosslinking methods using naturally derived agents like genipin offer reduced toxicity and improved safety, especially important for skin applications. These techniques are often more expensive and require advanced synthesis capabilities but offer unmatched control over chemical structure and drug compatibility [35].

Radiation-Induced Crosslinking Methods:

Gamma Radiation Crosslinking: Gamma irradiation is a chemical-free method of hydrogel synthesis that uses high-energy gamma rays (typically from Cobalt-60 sources) to initiate free radical formation within polymer chains, leading to covalent crosslinking. This method is suitable for both synthetic and natural polymers, such as PVA, PEG, and carboxymethyl cellulose. The polymer solution is prepared and sealed in sterile containers, then exposed to a controlled dose of radiation. One major advantage is that this process simultaneously sterilizes the final product, making it ideal for medical applications like hydrogel-based wound dressings or drug delivery films for postoperative pain. Gamma irradiation produces strong, durable hydrogels with long shelf lives. However, it requires expensive equipment and careful dose management, as excessive radiation can degrade the polymer or the drug incorporated [36].

UV or Electron Beam (E-Beam) Crosslinking: In this method, hydrogel formation is achieved through photo-induced or electron beam-initiated reactions. A photoinitiator, such as Irgacure, is added to a polymer solution that contains acrylate or vinyl functional groups. When exposed to UV light or electron beams, the initiator forms free radicals that trigger polymer chain crosslinking. This method is highly efficient and allows spatial and temporal control over the gelation process, making it possible to create hydrogel films, coatings, or patterned patches with drug-loaded zones. It is particularly useful for the preparation of sophisticated hydrogel dressings used in precision topical pain therapy [37]. However, the use of photo initiators must be optimized to minimize toxicity, and the formulation must be protected from premature exposure to light.

Evaluation and Characterization of Hydrogels for Topical Pain Relief: After hydrogel preparation, thorough evaluation and characterization are necessary to confirm the formulation's suitability for topical application and its ability to provide effective pain relief. These evaluations assess both physicochemical and pharmaceutical properties, ensuring consistency, efficacy, and patient acceptability.

Physical Appearance and Homogeneity: One of the first and most basic assessments involves visual inspection of the hydrogel for color, clarity, smoothness, and phase separation. The formulation should be free from air bubbles, gritty particles, or visible drug precipitates. A homogeneous texture indicates proper polymer dispersion and drug incorporation. Uniform consistency is particularly important for ensuring accurate and predictable drug delivery over the application site.

pH Determination: The pH of the hydrogel must be compatible with skin physiology to avoid irritation or damage. Generally, topical hydrogels should have a pH in the range of 5.5 to 7.0. pH is measured using a calibrated digital pH meter, and adjustments are made using suitable agents like sodium hydroxide or citric acid. This step is critical, especially when dealing with pH-sensitive polymers or drugs that degrade in extreme conditions.

Viscosity and Rheology: Viscosity is a key parameter that affects the spreadability, adhesion, and drug release of a hydrogel. It is measured using a Brookfield viscometer or cone and plate rheometer under controlled temperatures. Ideal topical hydrogels should exhibit pseudoplastic or shear-thinning behavior, where viscosity decreases with increased shear (e.g., during spreading on the skin). This property ensures that the gel remains

viscous in the container but spreads easily upon application.

Spreadability: Spreadability determines how easily the hydrogel can be applied to the skin. It is typically assessed by placing a fixed amount of gel between two glass plates and measuring the area covered under a known weight or pressure. Good spreadability is essential for uniform dosing, comfort, and effective absorption of the analgesic agent.

Swelling Index: The swelling capacity of the hydrogel reflects its water absorption ability, which is crucial for drug diffusion and skin hydration. Swelling studies are performed by immersing pre-weighed dried hydrogel samples in distilled water or buffer solutions and measuring the weight increase over time. A higher swelling index generally correlates with enhanced bioadhesion and drug release, although excessive swelling may compromise structural integrity.

Drug Content Uniformity: Uniform drug distribution within the hydrogel matrix is essential for consistent therapeutic action. Drug content is determined by dissolving a measured quantity of hydrogel in a suitable solvent, filtering it, and analyzing it using UV-Vis spectrophotometry, HPLC, or LC-MS. The results should fall within ±5% of the intended drug concentration to be considered acceptable.

***In-vitro* Drug Release Studies:** This is one of the most critical evaluations for topical hydrogels. Drug release is studied using diffusion cells, such as the Franz diffusion cell, where the hydrogel is placed in contact with a semipermeable membrane (e.g., cellophane, dialysis membrane) separating it from a receptor medium. The receptor fluid (usually phosphate buffer) is sampled at regular intervals, and the amount of drug diffused is measured. These studies help determine release kinetics (zero-order, first-order, Higuchi model, etc.) and confirm whether the hydrogel provides sustained or immediate relief.

Bioadhesive Strength: Bioadhesion refers to the hydrogel's ability to stick to the skin or mucosal surface, enhancing the residence time and local drug action. It is evaluated using a modified balance or texture analyzer. Hydrogels with good bioadhesion are particularly useful in treating localized chronic pain conditions like arthritis, where prolonged contact improves drug absorption and efficacy.

Skin Permeation and Retention Studies: To assess the hydrogel's ability to deliver the drug through the skin, ex vivo skin permeation studies are conducted using excised animal or human cadaver skin mounted on Franz diffusion cells. The amount of drug permeated and retained in the skin layers is analyzed over time. High skin retention with minimal systemic absorption is the goal for topical pain relief hydrogels.

Stability Studies: Stability testing ensures that the hydrogel maintains its physicochemical and pharmaceutical properties under various environmental conditions. Formulations are stored at different temperature and humidity conditions (e.g., 25°C/60% RH, 40°C/75% RH) for up to 6 months, and are periodically tested for changes in appearance, pH, viscosity and drug content. These studies are performed according to ICH guidelines [38-42].

TABLE 1: NOVEL FORMULATION FORMULATED WITH HYDROGEL FOR TOPICAL APPLICATIONS [43-50]

API	Novel Formulation	Novel Formulation Method	Gelling Agent for Making Hydrogels	Uses
Vitamin C	Self-double-emulsifying drug delivery system	Two-step emulsification method	Xanthan gum	Penetration enhancement of skin
Pentyl Gallate	Nanoemulsions	Spontaneous emulsification method	Chitosan	Increased skin penetration for herpes labialis
Phenytoin	Nanocapsule / Nanoemulsion	Interfacial deposition / Spontaneous emulsification method	Chitosan	Skin permeation and wound healing activity
Ibuprofen	Microemulsion	NM	Xanthan gum	Enhance percutaneous delivery

Terbinafine hydrochloride	Microemulsion	NM	Chitosan, Natrosol 250	Antifungal activity
Curcumin	Microemulsion	NM	Xanthan and galactomannan	Increase skin penetration and anti-inflammatory activity
Baicalin	Nanocrystals	Coupling homogenization + spray-drying technology	Hyaluronic acid	Improve skin permeation
Silver sulfadiazine	Cubosome	Emulsification method	Chitosan	Increase skin permeation and treat topical burns

CONCLUSION: Hydrogels have emerged as one of the most promising topical drug delivery systems for effective pain relief due to their unique physicochemical properties, biocompatibility, and patient-friendly application. The formulation of hydrogels involves a strategic selection of active pharmaceutical ingredients, gelling agents, penetration enhancers, moisturizers, and other functional excipients to create a stable, efficient, and therapeutically active system. Each component plays a vital rolenot only in determining the consistency and stability of the gel but also in ensuring optimal skin penetration and controlled drug release. Polymers like Carbopol and HPMC form the structural matrix, while substances such as triethanolamine help in achieving the desired pH and gelation. Penetration enhancers like propylene glycol and ethanol significantly improve the bioavailability of the drug across the skin barrier, and humectants such as glycerin maintain skin hydration and gel consistency. Moreover, the non-greasy texture, ease of application, and soothing effect of hydrogels make them highly acceptable to patients, particularly for chronic or localized pain conditions. By optimizing the formulation variables, it is possible to tailor hydrogels for rapid onset, prolonged action, and minimal side effects. Overall, hydrogel-based topical systems offer a versatile and effective platform for pain management, bridging the gap between comfort and therapeutic efficiency. With continued innovation and evaluation, hydrogel formulations are poised to play a critical role in modern dermatological and pharmaceutical care.

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