cosmetics

MDPI

Review

Overview of Hydrogels and the Use of Hyaluronic Acid-Based Hydrogels in Pharmaceutical Transdermal Delivery Systems and Topical Cosmetic Skin Applications

Fatimah Rashid *, Paul Carter and Stephen Childs *

Faculty of Health Sciences and Wellbeing, University of Sunderland, Sunderland SR1 3SD, UK
* Correspondence: bg82xh@research.sunderland.ac.uk (F.R.); stephen.childs-1@sunderland.ac.uk (S.C.)

Abstract

Hydrogels have gained significant attention as effective vehicles for transdermal applications offering significant advantages in pharmaceutical and cosmetic applications. Their unique polymeric network structure enables efficient encapsulation and controlled release of active ingredients, making them ideal for therapeutic drug delivery systems (TDDs) and topical skincare formulations. In pharmaceutical approaches, hydrogels facilitate the transdermal transport of therapeutic agents into systemic circulation, improving bioavailability and patient compliance. In cosmetics, they enhance skin hydration and support the delivery of bioactive compounds, contributing to improved product performance and user satisfaction. Among various hydrogel-forming polymers, Hyaluronic Acid (HA) stands out as the most often used polymer in this field due to its biocompatibility, moisture-retention properties, and ability to penetrate the skin. This review explores the dual role of HA-based hydrogels in pharmaceutical and cosmetic application, detailing their structural characteristics, preparation methods, and mechanisms of active ingredient loading and release. Furthermore, the review presents the details on hydrogels and how they are used as TDDs. Special attention is given to hyaluronic acid (HA) in this field, and this review discusses the properties, preparation methods, and applications of HA-based hydrogels as a delivery system, including methods of loading the actives and the releasing of these actives from them.

Keywords: hydrogels; TDD; hyaluronic acid; dermatology; cosmetics; skin; loading; release

Academic Editor: Enzo Berardesca

Received: 5 October 2025
Revised: 6 November 2025
Accepted: 13 November 2025
Published: 20 November 2025

Citation: Rashid, F.; Carter, P.; Childs, S. Overview of Hydrogels and the Use of Hyaluronic Acid-Based Hydrogels in Pharmaceutical Transdermal Delivery Systems and Topical Cosmetic Skin Applications. *Cosmetics* **2025**, *12*, 265. https://doi.org/10.3390/cosmetics12060265

1. Introduction

Hyaluronic acid (HA) is a naturally occurring biopolymer that plays a significant role in maintaining skin hydration, elasticity, and structural integrity. It has unique physicochemical properties such as an ability to retain water and interact with the body's extracellular matrix components that have allowed it to be a cornerstone in both pharmaceutical and cosmetic formulations. Among its many delivery systems, HA-based hydrogels have gained vital attention as the most skin-targeted therapeutical systems [1].

Despite the growing research and literature on HA-based hydrogels, most studies tend to focus on the discussion of either pharmaceutical or cosmetic applications, without bridging the two domains. The aim of this review is to uniquely fill that gap by providing a comprehensive analysis of their dual functionality in transdermal drug delivery and topical skin applications.

The review discusses hydrogel properties, preparations, and applications in the pharmaceutical and cosmetic sectors. In addition, it delves into skin physiology, the transdermal

delivery system revolution, and integrative analysis of HA-based hydrogels used in transdermal drug delivery systems (TDDs) and topical cosmetic skin applications. Particular attention is placed on the HA polymer, which is considered a key ingredient nowadays in transdermal and topical skin applications.

1.1. Overview of Skin Physiology

The skin is the interface between the internal and external environment of the body, providing a physical barrier against trauma, harsh weather conditions, hazardous chemicals, microorganisms, and UV radiation such as the sun (or artificial radiation) [2]. It also plays essential physiological functions, including excretion of wastes, thermoregulation, and sensation. The skin is a large, complex organ composed of the epidermis, dermis, and hypodermis [2]. The epidermis is the first outer layer. It is a vascular multilamellar multi-layered epithelial tissue consisting mainly of epidermal cells known as keratinocytes. The stratum corneum (SC) is the outer layer of the epidermis. It functions as an epidermal permeability barrier, preventing the loss of water and electrolytes from the skin [3,4]. The SC is a heterogeneous tissue consisting of non-nucleated, flat, protein-enriched corneocytes and lipid-enriched intercellular areas [2–4]. The lipid-rich domain playing the barrier function is formed by the synthesis of lipids in the keratinocytes of the nucleated epidermal layers and subsequent storage in the lamellar bodies of these cells. During the transition, the contents of lamellar bodies are excreted through the exocytosis process into the intercellular spaces between the corneum and stratum granulosum (SG) to the SC, forming continuous membrane bilayers [3].

Other skin components, including melanins, structural proteins in the SC and epidermis, free amino acids, and many other small molecules, have essential roles in the skin's protective barrier function [3–5].

The skin plays a significant role in pharmaceutical transdermal delivery of the drugs, whether it is for local or systemic treatment. On the hand, topical cosmetic treatments are used directly on the skin surface. This organ's layered architecture, hydration mechanisms, and permeability directly influence how a HA-based hydrogel systems interact with the skin—affecting absorption, retention, and therapeutic efficacy. This section outlines the key physiological features of the skin that underpin the performance of HA hydrogel systems in dermatological applications [6].

1.1.1. Dermatological Conditions and Skin Diseases

Due to its extensive surface area for external exposure, the skin is susceptible to various dermatological conditions and diseases. Common skin conditions and diseases include eczema and inflammatory conditions, such as atopic dermatitis, psoriasis, and seborrheic dermatitis, which can occur at any age [7–9].

These skin pathologies arise due to many factors, including genetic disorders, environmental exposure, immune system dysfunction, and infections. They vary in symptoms, severity, and treatment choices. The treatment of these conditions often involves the use of various topical and systemic medications [10]. These skin conditions can be treated through various methods, including medical treatments and cosmetic approaches. Depending on the severity of these conditions, dermatologists can determine if a specific condition needs a personalised treatment plan, such as medical treatment in combination with cosmetic products, or if the condition could require continuous use of specific cosmetic products. Overall, cosmetic products may be approached in any manner and prescribed for dermatological purposes [7,10].

Hydrogels usually used and been promise in treating acne.

From the other side, the skin itself needs special care, for example, skin wrinkles form as a normal part of the skin ageing process. Skin ageing is a progressive process in which environmental damage combined with aged skin determines the final skin appearance. There are two different types of ageing. Chronological or intrinsic ageing is due to the genes we inherit and the passage of time. Extrinsic ageing is due to environmental factors, including sun (UV) exposure and chemical irritants. While environmental variables significantly impact skin ageing, age does not determine the condition of mature skin. For example, skin tone, elasticity, and epidermal regeneration capacity do not deteriorate until advanced age in skin areas not exposed to sunlight. However, this occurs early in exposed skin areas [11–13].

1.1.2. Role of Skin Hydration and Cosmetic Formulations Used for Skin Hydration

Most of the skin conditions are characterised by loss of skin moisture, causing skin dryness. Topical products containing skin-hydrating properties are essential in treating and manageing various skin conditions. Topical formulations with skin hydration benefits can be divided into four categories: moisturising agents, protective agents, anti-inflammatory agents, and itchiness-soothing agents. The type of skin condition and anatomical location determine the formulation choice. For example, creams, lotions, and drying pastes work better in wet or sticky skin conditions.

On the other hand, ointments and oils are more suitable for dry and scaly conditions. Gels and foams are more appropriate for scalp or other hairy skin areas because they penetrate easily and leave little residue following their generous or frequent application. Moisturisers, or emollients, are essential in manageing dry skin conditions; they assist in restoring the skin barrier to prevent water loss from the skin. Therefore, formulations that hold water in their structure are more efficient in such skin conditions such as hydrogels [14,15].

2. Overview of Hydrogels

Hydrogels, composed mainly of water-absorbing polymers, have gained attention in cosmetology and dermatology due to their superior hydration and skin regenerative properties [15]. They can retain a large quantity of water within their network and provide a moist environment, helping to replenish and maintain skin moisture [16]. Hydrogels may be used in skin care products and transdermal applications, offering a potential solution to skin conditions characterised by severe skin dryness and wrinkles. Furthermore, hydrogels are effective delivery systems for various substances, including skincare ingredients and medications. They are ideal for immediate and controlled release applications. In skincare, hydrogels can deliver hydrating compounds, antioxidants, or other active ingredients to the skin, promoting better absorption and targeted delivery [16]. This makes hydrogels valuable in enhancing the efficacy of skincare products and ensuring a more sustained impact on skin hydration and health.

2.1. Introduction to Hydrogels

Hydrogels are networks of hydrophilic polymers that swell in water and retain it within their structure without dissolving [17,18]. Hydrogels may comprise one or more polymers, which are cross-linked three-dimensional (3D) chains [19]. The spaces between the macromolecules fill with water, swelling the compound to form a hydrogel. Covalent cross-links prevent the dissolution of the hydrogel in water [19] (Figure 1).

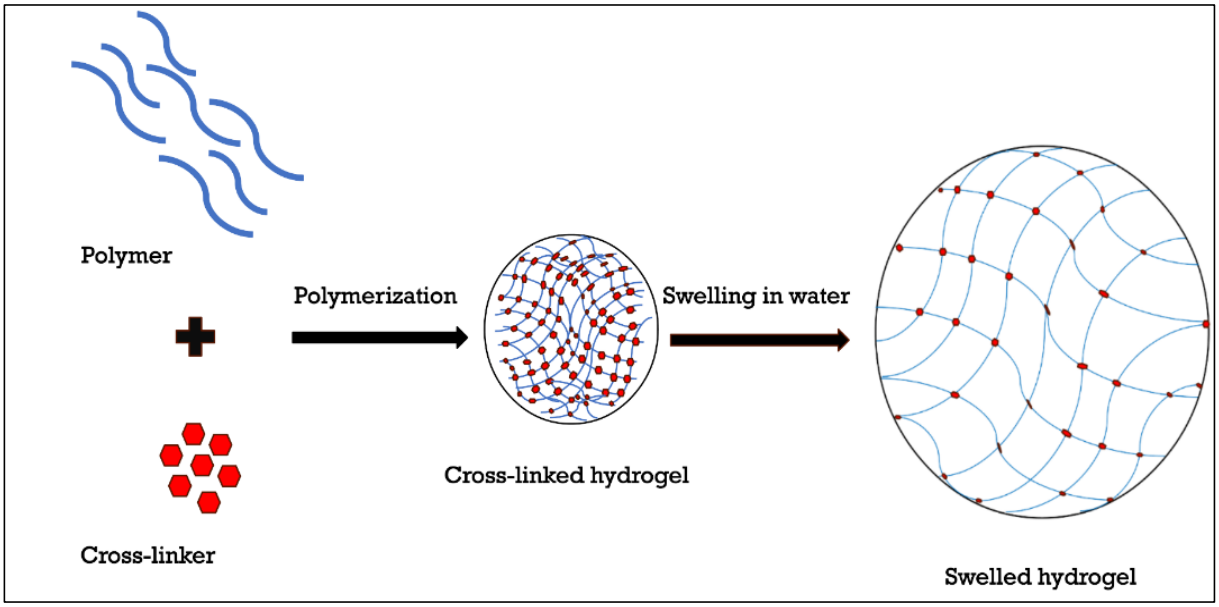


Figure 1. Figure Schematic representation of hydrogel synthesis illustrating the three-dimensional cross-linked polymer network responsible for water intake and swelling behaviour.

2.2. Classifications of Hydrogels

Hydrogels are classified based on their origin (natural versus synthetic), polymer composition (e.g., copolymer and homopolymeric hydrogels), biodegradability (biodegradable hydrogels versus non-biodegradable hydrogels), and configuration (crystalline, non-crystalline, hydrocolloid aggregates, and semi-crystalline) [20,21]. Hydrogels can also be classified according to their type of cross-linking (chemically and physically cross-linked hydrogels), physical appearance (matrix and microsphere), as well as the network's electrical charge (neutral, anionic, cationic) [20,21]. Hydrogels can also be classified according to their method of preparation (e.g., irradiation, UV radiation) [20].

2.3. Rheological Properties of Hydrogels

The mechanical strength of hydrogels is fundamental for pharmaceutical, cosmetic, and biomedical applications. Hydrogels should have the necessary mechanical strength to be suitable for these applications. Several biomedical applications such as tissue engineering, tendon and ligament repairs, wound healing, and drug delivery systems require hydrogels to have specific mechanical strength and rheological properties. However, hydrogel mechanical strength depends on the incorporated polymer structure and the crosslinker used for the cross-linking mechanism. In addition, the crosslinking degree determines the rheological properties of the hydrogel [22].

The term rheology refers to the viscoelastic behaviour of materials which can be investigated by a rheometer. Rheology is also defined as the science that studies the deformability and flowability of materials under stress or strain. A material is considered elastic when it undergoes changes in shape upon applying force and causes an elastic strain but returns to the original shape after removing the force. Conversely, viscous materials shape irreversibly changes after the force is removed because the force causes irreversible strain and allows the viscous material to flow. Furthermore, most hydrogels are neither fully viscous nor completely elastic but show a viscoelastic nature. While most rheological studies are conducted within the linear viscoelastic region (LVR) of the hydrogels, the deformation in viscoelasticity is small because it is more related to the polymer molecular arrangement within the hydrogel [22]. Therefore, the rheological behaviour of hydrogels is mostly dependent on the molecular structure of its polymers [23]. According to Di

Giuseppe et al. [24], the consistency and the elasticity of hydrogel improve when polymer concentration increases. While a higher shear-thinning behaviour is indicated with a decrease in polymer concentration. Snetkov et al. mentioned the rheological properties of four hyaluronic acid (HA) solutions with concentrations of 20 mg/mL and with different molecular weights (77 kDa, 640 kDa, 1060 kDa, 2010 kDa). They found that HA solutions exhibit non-Newtonian shear-thinning behaviour, and the solution with 2010 kDa HA has the most significant decrease in viscosity with increasing shear rate. Meanwhile, the shear-thinning effect was much less pronounced in the solution with 77 kDa HA solution [25].

2.4. Characterisation of the Physical and Chemical Properties of the Hydrogels

The characterisation of hydrogels depends on the gel bonding type. Physical or reversible hydrogels are formed by molecular entanglements or secondary bonds (e.g., ionic, H-bonding, stereo-complexation, and hydrophobic forces). In contrast, chemical hydrogels are irreversible and formed by covalent cross-linking (chemical functionalisation), which are stronger and have higher mechanical properties [26]. The chemical composition also influences the response of the hydrogel to stimuli, such as pH, temperature, and light [27]. Due to the unique properties of hydrogels, they are an excellent choice for transdermal drug delivery systems, offering improved efficacy, patient comfort, and versatility compared to many traditional approaches. Table 1 represents common actives and drugs loaded for pharmaceutical and topical cosmetic application.

Table 1. Overview of application of hydrogel-based formulation in different pharmaceutical and cosmeceutical skin applications. The table represents how different polymers enable controlled drug release, improved bioavailability, enhanced skin permeation, and improved therapeutic or cosmetic outcomes.

Hydrogel Polymer	Drug/Active Ingredient	Therapeutic Application (Pharmaceutical or Cosmetic Use)	Main Outcome/Benefit	References
HPMC	Etofenamate, Ibuprofen	Anti-inflammatory-Analgesic	Provided controlled drug release with improved skin permeation; reduced systemic adverse reaction and enhanced local anti-inflammatory action.	Labie et al., Mancini et al. [28,29]
	Chlorphenesin	Antifungal	Enhanced local drug delivery with minimised the irritation; enabled drug retention at infection site and improved antifungal efficacy.	Mohammed et al. [30]

Table 1. *Cont.*

Hydrogel Polymer	Drug/Active Ingredient	Therapeutic Application (Pharmaceutical or Cosmetic Use)	Main Outcome/Benefit	References
Carbopol 940	Terbinafine	Antifungal	Improved drug stability and skin adherence; facilitated prolonged antifungal activity with reduced dosing frequency.	Sheikh et al. [31]
	Diclofenac, Mefenamic acid	Anti-inflammatory-Analgesic	Enhanced transdermal penetration and controlled drug release; reduced gastrointestinal side effects that associate oral NSAIDs.	Rajalakshm et al. [32]
	Betamethasone, salicylic acid	Psoriasis	Enabled dual-action delivery—anti-inflammatory and keratolytic; enhanced lesion clearance and reduced recurrence.	Zagorska et al. [15]
Polyacrylamide	Platensimycin	Antibacterial	Provided targeted antibacterial action with reduced cytotoxicity; hydrogel matrix enhanced drug stability and skin compatibility.	Wang et al. [33]
Chitosan	Silver sulfadiazine	Burns	Accelerated wound healing and antimicrobial effect	Almoshari et al. [34]
Pluronic F-127	Platelet lysate	Wound healing	Accelerated wound healing and tissue regeneration; offered antimicrobial protection and moisture retention at burn sites.	Bernal et al. [35]
HA	Vitamin B_3	Antioxidant, brightening, skin hydrating, reduce fine wrinkles (Cosmetic applications)	Enhanced skin hydration and barrier repair; reduced fine lines and improved skin tone through deep dermal delivery.	Rashid et al. [16]
	Baicalin	Antioxidant, anti-inflammatory	Enhanced transdermal absorption and bioavailability; reduced inflammation and oxidative stress in skin tissues.	Wei et al. [36]

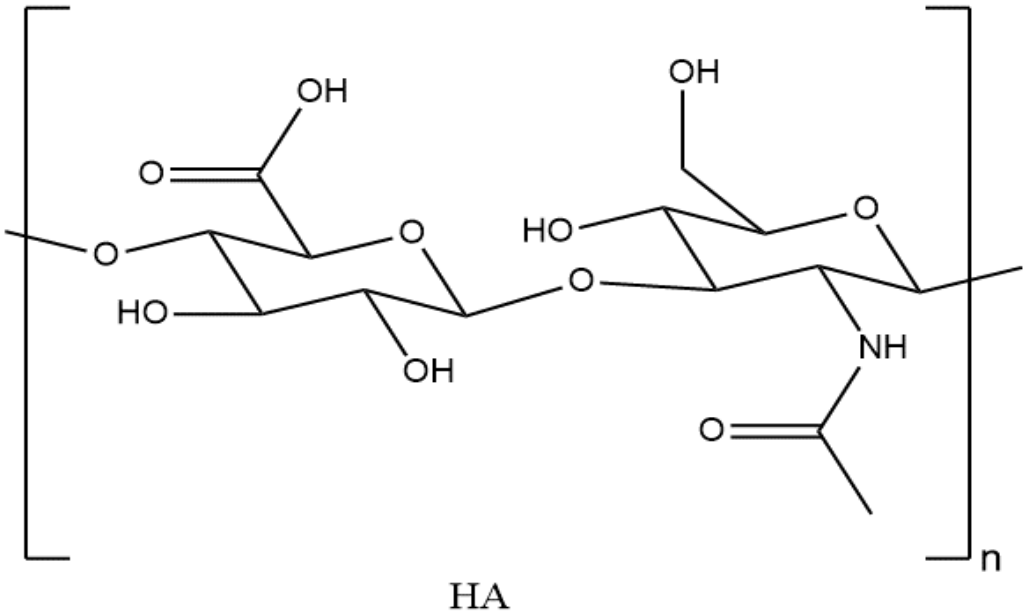
Table 1. *Cont.*

Hydrogel Polymer	Drug/Active Ingredient	Therapeutic Application (Pharmaceutical or Cosmetic Use)	Main Outcome/Benefit	References
HA	Tannic acid	Antioxidant, anti UV, suncream (Cosmetic applications)	Enhanced delivery and supported multifunctional performance—-UV protection, antioxidant activity, cooling effect, and skin hydration—all in a stable, biocompatible formulation.	Gawak et al. [37]
Xanthan gum	Quercetin	Antioxidant, antibacterial	Enhanced delivery of quercetin and stabilised it; improved the solubility and functional performance.	Yazidi et al. [38]
	Salicylic acid	Skin exfoliating agent (Cosmetic application)	Provided controlled skin exfoliation with reduced irritation; improved skin clarity and reduced pore congestion.	Rashid et al. [16]
Hydroxyethyl cellulose	Rosmarinic acid	Anti-ageing skin products (Cosmetic application)	Delivered antioxidant with high skin compatibility; reduced oxidative damage and improved elasticity and hydration.	Marafon et al. [39]
PVP (polyvinylpyrroli-done) and chitosan	Vitamin C	Antioxidant, whitening agent, reduce dark spots (Cosmetic applications)	Improved skin brightening and collagen synthesis; stabilised vitamin C and enhanced its penetration and efficacy.	Kedzierska at al. [40]

3. Hyaluronic Acid-Based Hydrogels: Properties and Preparation

3.1. Introduction to Hyaluronic Acid

Hyaluronic acid (HA) is a non-sulphated glycosaminoglycan comprising repeating polymeric disaccharides of N-acetyl-D-glucosamine and D-glucuronic acid [1,18]. These are linked together by alternative beta-1, 3, and beta-1,4 glycosidic bonds [41]. It is a naturally occurring biopolymer identical in molecular and chemical form in all tissues and has significant biological functions in all living cells. It is found in the body's connective tissues, joints, and skin. HA contributes to tissue hydration, lubrication, and cellular signalling. In the skin, it helps maintain moisture and elasticity. Additionally, HA is involved in wound healing, inflammation regulation, and other physiological processes across different cell types, making it a versatile and significant component of the body (Figure 2) [42].



HA

Figure 2. Chemical structure of HA showing repeating disaccharide units: N-acetyl-D-glucosamine and D-glucuronic acid (drawn using ChemDraw i16).

3.2. Classification of HA

HA can be classified into low and high MW based on HA molecular size. High MW HA has a molecular mass of more than 1000 kDa [43]. Low molecular weight HA is HA with a molecular mass of less than 500 kDa [43]. The MW of HA is dependent primarily on its source. For example, the weight of HA in rabbit vitreous is generally high, in the range of 2000–3000 kDa [44]. The biological effects of HA may differ depending on the molecular weight [25]. Different molecular weights may influence how HA interacts with cells and tissues. Generally, high molecular weight (HMW) HA is known for its hydrating and lubricating properties. It forms a protective barrier on the skin's surface, helping to retain moisture and maintain elasticity. Meanwhile, low molecular weight (LMW) HA is believed to penetrate the skin more easily. It may have anti-inflammatory effects that can influence cellular processes, such as promoting wound healing and modulating inflammation [45].

3.3. Physical and Chemical Properties of HA

HA has hydroxyl and carboxyl groups and can form a hydrogel under mild conditions, such as mixing it with water [46]. The degree of cross-linking and modification determines its physical and chemical properties. Hydrogen atoms around the axis of the structure are non-polar and hydrophobic, while the side chains are more polar and hydrophilic [46]. Hydrogen bonding stabilises the conformation of HA in solution. However, temperature and pH can easily disrupt these bonds. HA behaves like most other polymers at intermediate pH levels, with no remarkable intermolecular interactions. Still, as pH reduces towards 2.5, HA forms a gel due to decreasing carboxylate dissociation and increased intermolecular interaction [47]. HA must be chemically modified into a less degradable gel to be practically useful in biomedical applications [47].

3.4. Preparation of HA-Based Hydrogels

3.4.1. Effect of Temperature on Preparation and Gelation Mechanism of HA-Based Hydrogel

Gelation of HA is temperature-sensitive, a typical characteristic of thermo-reversible (sol–gel-sol) hydrogels. They have a gelation temperature and a gelation concentration. HA is non-gelling, but Fujiwara et al. found it can form hydrogels if annealed in the sol state [48]. The authors studied the effect of annealing on the gelation of HA in an aqueous

solution. They found that HA solutions of higher concentration (3% *w*/*w*) formed a gel at 60 °C if given more than 6 h, but not at lower concentrations (1% *w*/*w* and 2% *w*/*w*) [48].

Qiao et al. developed a novel technique for inducing gelation in (HA) solutions using alternate compression–decompression cycles. However, this method was using mechanical pressure on HA solutions instead of relying on chemical cross-linkers or thermal annealing, which triggered rapid gelation within minutes. The method enhanced intermolecular hydrogen bonding and chain entanglement, resulting in hydrogels with improved mechanical strength and elasticity. Their approach provides a rapid and reversible route to HA hydrogel formation, useful for biomedical applications [49].

Additionally, other researchers reported the temperature influence on the formation of temperature-sensitive HA hydrogels. HA has a low critical solution temperature above which it becomes less soluble or insoluble in water [20]. For example, a thermo-responsive hydrogel comprising HA and poly (N-isopropyl acrylamide) (PNIPAAm) phase transition occurred at around 30–33 °C [48]. Above 35 °C, the viscosity of the hydrogel increased [48]. HA hydrogels (cross-linked with thiol end-capped Pluronic F127 copolymer) were solid at room temperature but transitioned to a gel state at body temperature [50]. Such materials have numerous applications in drug and cell delivery [50].

3.4.2. Effect of pH on Preparation and Gelation Mechanism of HA-Based Hydrogel

The gelation mechanism of HA hydrogels' formation and behaviour is highly dependent on pH. It has a significant impact on the polymer's charge density, intermolecular interactions, and structural conformation. At neutral pH, HA typically remains in solution due to strong electrostatic repulsion between negatively charged carboxylate groups. While, in acidic pH levels—particularly around pH 2.5—these carboxylate groups become protonated, reducing the net charge and leading to more polymeric chains interaction. This results in hydrogen bonding and physical entanglement, forming a gel-like structure without the need for chemical cross-linkers [51]. Conversely, at extremely low pH (<1.6) or high pH (>12), HA undergoes hydrolysis and depolymerization, compromising its molecular integrity and reducing viscosity. Such behaviour will help in designing HA hydrogels with tailored mechanical properties and stability for biomedical applications. However, pH alteration by reducing or raising has been employed in numerous studies to induce the cross-linking reaction between HA and cross-linkers, such as divinyl sulfone (DVS), glutaraldehyde, methacrylate, and 1,4-butanediol diglycidyl ether (BDDE) [52,53].

The pH of the medium partly influences the uptake of water and, thus, the swelling of the HA hydrogel. Preparation methods for HA hydrogels in mediums of different pH levels should be carefully performed because the behaviour of the gel changes with pH. Larraneta et al. prepared HA hydrogels using 5% *w*/*w* of HA and varying concentrations of Gantrez S97 (cross-linker). The polymer with a lower cross-linker concentration had a higher water swelling capacity than PBS. In contrast, those with higher concentrations of the cross-linker had a lower swelling capacity in water than PBS. The cross-linker comprises poly-acids (pKa_1 = 3.47 and pKa_2 = 6.47), but only a few groups can react with the HA to form the hydrogel [54]. The remaining functional groups are ionised depending on the pH of the medium. Deionised water is slightly acidic compared to PBS, which explains the different swelling behaviour [54].

3.4.3. Effect of HA Molecular Weight on Preparation and Gelation Mechanism of HA-Based Hydrogel

The molecular weight (MW) of HA is one of the factors that determines the viscosity and elasticity of the gel formed. HA of high MW can preferably be used as a gelling agent. These gels can be reversible (pH or temperature-induced gelation) or irreversible (covalent cross-links using cross-linking agents). In contrast, HA of low MW is used as an active

ingredient. The preparation of HA hydrogels using HA of different molecular weights differs depending on the material produced and the gelling agent used. In a study by Chun et al., HA hydrogels of various MWs were prepared. The concentration of the solutions was 0.5% *w*/*v*; the molecular weights were low (69 kDa) and high (1058 kDa) [55]. The sodium hyaluronate for the two compounds of different molecular weights is dissolved in sodium hydroxide, and the pH is adjusted. A cross-linker was added, and the hydrogels dried at 60 °C for two hours. The cross-linked HA microspheres of the lower molecular HA were larger than those of the higher molecular weight HA [55].

The molecular weight (MW) HA is one of the factors that determine the rheological properties, mechanical strength, and biological performance of HA-based hydrogels. High molecular weight HA (HMW-HA) is widely favoured as a gelling agent due to its ability to form more viscous and elastic networks in the hydrogel structure, especially when covalently cross-linked using agents such as 1,4-butanediol diglycidyl ether (BDDE). In contrast, low molecular weight HA (LMW-HA) is often incorporated for its bioactivity and ease of diffusion. Xue et al. prepared hydrogels by mixing HMW-HA and LMW-HA at various ratios and cross-linking with BDDE. The authors found that a 4:1 ratio of HMW to LMW HA resulted in hydrogels with improved mechanical integrity and reduced cytotoxicity, making them suitable for biomedical applications [56]. Luo et al. highlighted that the choice of HA molecular weight influences not only the gelation behaviour but also the degradation rate and tissue compatibility, with different crosslinking methods yielding reversible or irreversible hydrogels depending on the intended use [47].

3.5. Preparation of HA-Based Hydrogels Using Cross-Linking Agents

Preparation of HA hydrogels typically involves the addition of cross-linking agents to form a stable three-dimensional polymer network structure. HA itself can be a gelling agent. However, other gelling agents that facilitate the cross-linking of polymers into viscoelasticity and give a gel its structure for different applications have been reported [57–59]. In our previous work [42], we explored the use of pentaerythritol tetra-acrylate (PT) as a chemical cross-linker to prepare injectable HA-based hydrogels, demonstrating that effective gelation occurred under alkaline conditions, with oven heating yielding partially crosslinked hydrogels that vary in their rheological behaviour and are useful for different applications. Luo et al. highlighted the importance of modifying HA's hydroxyl, carboxyl, and N-acetyl groups to enhance its reactivity and cross-linking [47]. The resulting hydrogels exhibit improved mechanical strength and biological compatibility, particularly when they covalently cross-linked. These chemically modified hydrogels have a stabilised matrix and act as injectable formulations with self-healing properties, as discussed by Yadav et al., enabling them highly suitable for tissue engineering and regenerative medicine [60].

Another cross-linking agent that is used to form HA-based hydrogels is boronic acid. Pérez et al. highlighted the boronic acid-based cross-linking strategies, especially phenylboronic acid derivatives, used to form a covalent cross-linking through the formation of boronated ester bonds between boronic acid groups and the cis-diols present on the HA backbone. However, this was considered a physical interaction that is reversible and pH sensitive. The resulting hydrogel exhibited self-healing, injectability, and stimuli-responsive behaviour under physiological conditions useful for biomedical applications such as drug delivery, wound healing, and tissue engineering [46].

4. Hydrogels Applications in Pharmaceutical Transdermal Delivery Systems

4.1. Uses of HA in Pharmaceutical and Biomedical Applications

HA is used as a drug delivery system due to its biocompatibility, non-immunogenicity, and biodegradability [1]. it has been used in numerous pharmaceutical applications, such

as osteoarthritis treatments providing joint lubrication, in ophthalmology for many eye dryness conditions, and as a drug delivery system by targeting the drug to the tumour cells in cancer treatment. In addition to its use in wound healing and tissue engineering applications, HA can interact with receptors, such as CD44 (cluster of differentiation 44) antigen, a cell-surface glycoprotein expressed in many types of tumour cells. Thus, it is a candidate for the delivery of imageing and anticancer agents [61]. HA can embed the fibroblast growth factor and be used to make scaffolds that can be used to promote wound healing [61].

4.2. Overview of Transdermal Delivery Systems

The most common drug or active pharmaceutical ingredient (API) delivery routes are via oral and parenteral routes, with oral delivery being the most common route for small molecule drugs [62,63]. The main pros of the oral route are pre-determined doses, portability, and patient self-administration, which explains why the oral route is the most convenient for delivering medications [62]. In other cases, some APIs, such as therapeutic peptides and proteins, are unsuitable for oral route delivery because they rapidly degrade in the stomach and have size-limited transport across the epithelium [63]. Therefore, the parenteral route could efficiently deliver these macromolecules [64]. However, the parenteral route also has some limitations, notably lower compliance by patients due to the invasive nature of injections and the associated pain. Additionally, parenteral administration requires officially trained medical personnel, which can increase treatment costs [64]. Reasonably, to overcome these disadvantages, other advanced API delivery methods have been developed, such as transdermal drug delivery (TDD) [65].

Transdermal drug delivery (TDD) delivers API to the body system by applying an API formulation onto an appropriate intact and healthy skin site, thereby mitigating painful injection [66,67]. Firstly, the API will penetrate the outer layer of skin through the SC and pass through the deeper layers without accumulation of the API in any of the dermal layers of skin. Once the API reaches the dermal layer, it will be absorbed systemically via the dermal microcirculation [65–67].

Furthermore, the transdermal delivery route has many benefits over other routes. Being a non-invasive technique, it is a suitable alternative to parenteral routes, which addresses patient compliance issues related to trypanophobia (needle phobia) [65,67]. The large surface area of the human skin provides multiple skin sites for transdermal delivery of API [66]. Looking at the pharmacokinetic aspects of API, TDD provides a lower risk of toxic side effects due to more stable and consistent drug release and absorption. Other advantages of the TDD method are enhanced patient compliance because it minimises dose frequencies and is suitable for administering to unconscious patients or those who cannot swallow and rely on self-administration [65]. The transdermal drug delivery system avoids pre-systemic metabolism (first-pass hepatic metabolism), improving the drug bioavailability [67].

Transdermal patches are now considered potential pharmaceutical, topical, and therapeutical delivery systems, with significant consideration given to the diffusion area and skin hydration level [68]. The transdermal delivery system transfers API through the skin to the body depending on the dose, skin area, and drug delivery vehicle or device [65,68]. The transdermal drug delivery system has undergone significant evolution and market growth since its early stages in the 1990s. They have evolved from the growth in skin science, technology, and development trials [68–70]. Figure 3 represents the evolution of the TDD system over the years.

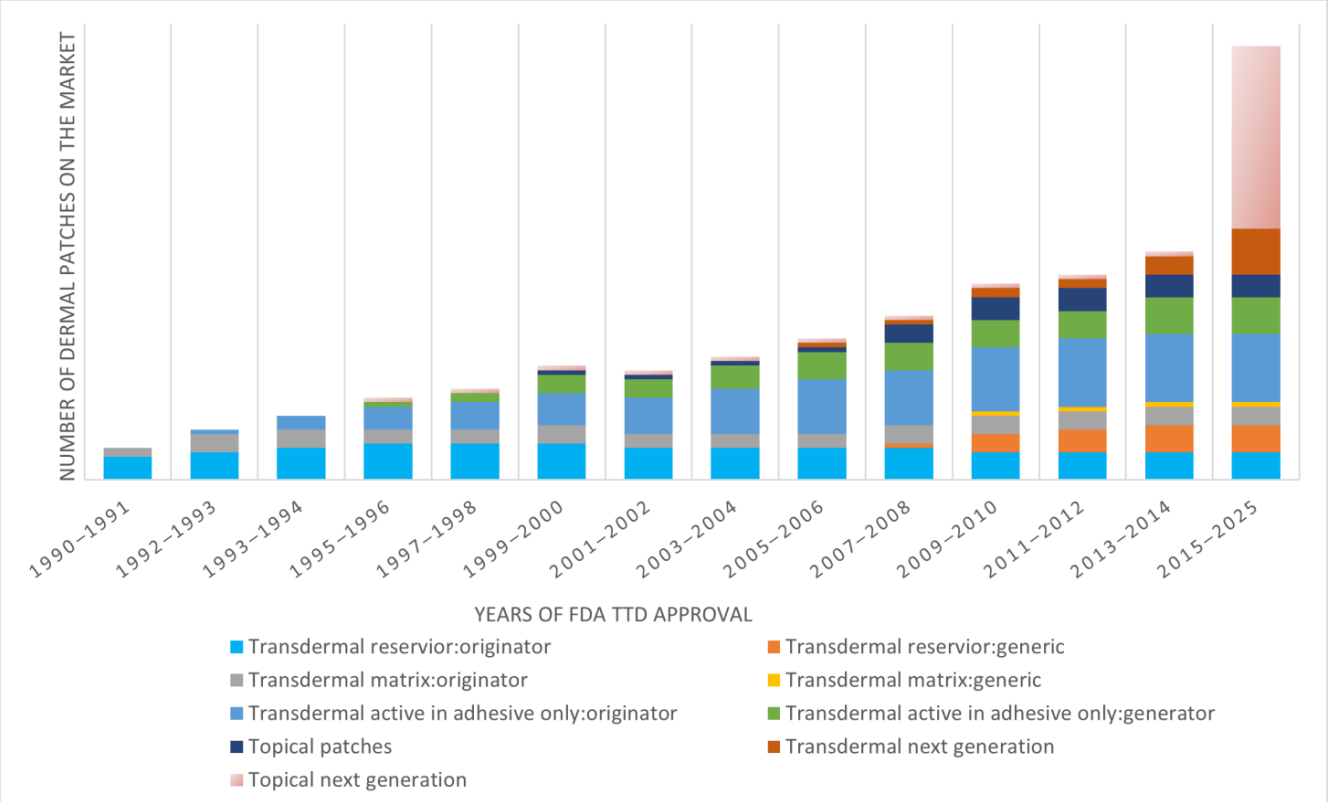


Figure 3. Evolution of transdermal delivery systems. Adapted and modified from Pastor et al. [69] and Grand View Research [70].

4.2.1. API Delivery via Transdermal Patches

Transdermal patches are a dosage form that adheres to the skin and delivers API through the skin and into the bloodstream [69]. Not all APIs may be suitable for loading in the patches due to incompatibilities and physicochemical properties. For example, APIs with large peptides, certain lipophilic drugs, and susceptibility to degradation in the patch matrix due to pH instability are unsuitable for this delivery mode. Clinical potency and safety requirements are among the main points that regulatory authorities consider when approving a drug for transdermal application before releasing it to the market. Many parameters of the APIs, such as the molecular weight (MW) and solubility, determine the skin penetration, diffusion and flux from the SC to the dermis and hypodermis layers [67]. The molecular size of any API is critical for its transdermal penetration efficiency. High MW drugs, such as large proteins, are difficult to administer Via transdermal patches [65]. Drugs with low MW (<500 Da), balanced lipophilicity, and partition coefficient (log P) of preferably 1–3 are suitable for transdermal delivery.

Furthermore, a high rate of transdermal penetration of an API may depend on a two-pathway (polar and lipid) model for API transportation through the SC layer of the skin [69]. In addition, for an API candidate to be feasible for transdermal delivery, it must be of high pharmacological potency. This helps minimise the amount of the API required to be loaded on the patch, reducing the risk of skin irritation and enhancing patient compliance. Examples of such drugs are fentanyl and nitroglycerin, which have high potency and are commonly delivered via transdermal patches [69].

4.2.2. API Loading in Hydrogel Patches as TDD System

Hydrogel patches are considered an innovative form of transdermal drug delivery system that provides API delivery through specific skin sites of the body at a more controlled rate. The API distribution within a hydrogel structure can be manipulated and, therefore, modified for immediate drug release [71]. The API entrapment is directly connected with the process of swelling/deswelling mechanisms of the hydrogel films [72]. Thus, swelling governs the uptake of the drug into the hydrogel and influences the release of the API from the same hydrogel matrix to the skin site. The API in the hydrogel film matrices can be loaded through post-loading and in situ loading methods [73].

4.2.3. Post-Loading (Osmosis Dependent Loading) Method in the Hydrogel Patches

Commonly, with the post-loading method, the drug-loading process is performed by immersing the hydrogel films in the dry state into the API solution (usually aqueous), depending on their swelling behaviour [73]. The API molecules diffuse and incorporate into the hydrogel structure via the osmosis process, which depends on the hydrogel swelling rate and the time it takes to reach equilibrium [72,73]. Hence, many factors affect the amount of drug incorporated into the hydrogel, such as the MW of the desired API and the physicochemical properties. The disadvantages of this method appear particularly in high MW drug molecules. When the drug molecules are too large, they will not efficiently move through the hydrogel polymer network, resulting in drug loading failure.

Moreover, hydrophobic drugs that solubilise only in organic solvents, such as ethanol, methanol, and dimethyl sulfoxide (DMSO), require additional detoxification steps. Most organic solvents are potentially toxic and must be removed to minimise their harmful effects and ensure the biocompatibility of the loaded drug [74]. Therefore, it is crucial to optimise the drug-loading method of hydrogels to maximise the drug-loading capacity to enhance matrix swelling and drug release [71].

4.2.4. In Situ Loading Method in the Hydrogel Patches

The in situ loading method involves initially adding the drug or API to the solution during transdermal patch preparation. During in situ loading, a polymer precursor solution is mixed with a drug or drug-polymer conjugated solution with or without a cross-linker and allowed to polymerise. Incorporating the drug within the matrix allows simultaneous hydrogel network formation and drug or API encapsulation as shown in Figure 4 [75]. Similarly to Pastor et al., who used in situ loading of dimenhydrinate (DMH) to form a DMH transdermal patch, this method has the advantage of overcoming many limitations of osmosis loading. The in situ loading method allows the loading and incorporation of higher amounts of drugs and API than the post-loading method. Thus, in situ loading achieves a higher drug delivery efficiency than the post-loading method. Additionally, it overcomes the physicochemical incompatibilities, such as pH associated with osmotic uptake [75]. Furthermore, this method enables drug delivery in controlled or modified release due to the entrapment of the loaded drug in the hydrogel polymer network, leading to slower drug diffusion from the hydrogel structure to the skin site [71].

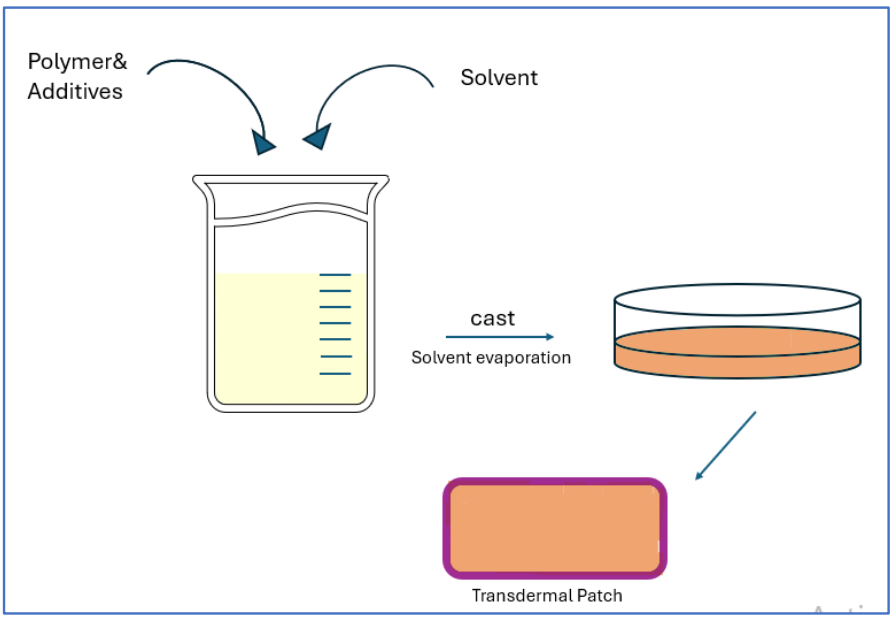


Figure 4. Schematic of in situ drug loading during hydrogel patch preparation, using solvent casting method.

4.2.5. API Release from the Hydrogel Patch

There are three primary API delivery or release mechanisms: diffusion, erosion, and swelling [76]. Hydrogels have various characteristics, such as water absorption, swelling, and degradation aspects, and these properties can significantly improve the utilisation rate of API and help control their release as desired [77]. An example of the advantages of hydrogels based on drug-controlled release systems has been demonstrated in tissue engineering [77]. Many studies describe the connection between the duration and release rate of an API from a hydrogel matrix with some of the structural properties of the hydrogel network, such as (crystallinity of the substances, swelling degree, molecular weight (MW) between the cross-linking points, cross-link density, and chemical structure of polymer chains inside the hydrogel) [76,78,79]. The influence of one or more of the hydrogel polymer network parameters upon the release of the drug, such as network structure made up of meshes of different sizes as a result of a cross-linking process (for example, cross-linking copolymerisation or irradiation) and chains with functional groups that distribute randomly, are also reported [76,78,80].

Generally, API release studies are carried out in vitro, followed by in vivo and human trials. In vitro drug release studies test a range of mathematical equations to model the release kinetics of drugs from polymeric carriers. The drug release follows Fick's first or second law of diffusion [79]. According to Fick's first law of diffusion, the diffusion from a reservoir environment of the hydrogel has a direct relationship with time without depending on the drug concentration. This is now well known as the zero-order release kinetics, characterised by a constant release rate from a drug delivery system or device [76,78,79]. According to Fick's second law, diffusion from a matrix-style and swellable system immediately reaches the swelling equilibrium when the rapid uptake from surrounding media happens. In addition, the dispersed drug will then diffuse through the swollen network [76,78,79]. Numerous models were developed to estimate API release from multi-layered hydrogel composites such as multi-layer devices to produce dual active release. For this model, Fick's second law of diffusion was employed to predict the drug release profiles. Furthermore, the diffusion equations were derived to account for constant or non-constant diffusivities. Multi-layer matrices can also be utilised to reduce the cause of burst release, which is a prevalent problem in API delivery from the system that is

associated with protein delivery. Lastly, since more advanced release devices are produced, such as (affinity hydrogels, microparticle systems, and in situ forming gels), additional mathematical modelling strategies are required to describe the associated mechanisms controlling API release from these systems [76].

Overall, many types of polymers are used to synthesise the hydrogels for TDD and topical skin applications, which may be natural or synthetic in composition. Synthetic polymers that are used commonly to graft the hydrogel matrix include poly (vinyl pyrrolidone) (PVP), poly (vinyl alcohol) (PVA), poly (lactic acid) (PLA), poly (ethylene oxide) (PEO), poly (ethylene glycol) (PEG), and polycaprolactone. Natural polymers include polysaccharides, polynucleotides, and polypeptides. These polymers are considered non-toxic and biodegradable and have other beneficial biological properties. In addition, they are accessible, numerous, and inexpensive. Polysaccharides are the most naturally occurring polymers that are extensively used in hydrogel synthesis. They possess exceptional structural characteristics; they are formed from long-chain carbohydrate molecules of repeated monomers connected by glycosidic bonds. Hyaluronic acid, cellulose, starch, chitin, chitosan, carrageenan, alginates, dextran, and pectin are natural polysaccharides that are extensively used for industrial, medical, tissue engineering, pharmaceutical, and cosmetic applications [76,78,79].

4.3. Recent Advances in Transdermal Delivery Systems

Microneedles (MNs) are one of the recent advances in the delivery system through the skin. They are designed to physically bypass the dermal barrier, enhancing drug permeability [81]. MNs consist of needle arrays and base, are minimally invasive, and elicit the lowest pain and discomfort [81]. Thereby, the local administration of MNs transdermally provides patients with a convenient and pain-free approach to self-medication by allowing them to overcome the intravenous route [82]. This is especially valuable for individuals requiring prolonged drug administration [83]. The system allows the penetration of the arrays through the stratum corneum while ensuring to minimise contact with nerve endings and blood vessels, which results in reduced pain during microneedle application [84]. Array designs depend on their application and possess specific properties. For instance, the length of MN arrays is dependent on their specific function and intended application. Usually, they range from 250 to 1500 μm in size [85]. The largest advantage of the MNs is the formation of micropores on the skin's surface, which thus enhances the penetration of macromolecular actives into the stratum corneum and facilitates the direct delivery of active molecules to the dermis [84]. In addition, it enhances a more controlled release of actives, with the tip design playing a significant role in controlling the kinetics of the actives' release. However, the large difference between individuals' SC thickness and the skin layers can cause inconsistent penetration and drug delivery. In general, microneedles are categorised as solid, coated, dissolving, hollow, and hydrogel-forming depending on their composition with various materials and preparation methods [84]. All these types are useful to deliver actives for therapeutic and cosmetic applications. Du et al. fabricated a HA hydrogel microneedle loaded with methotrexate for psoriasis management. The authors aimed to decrease its systemic toxicity compared to oral administration [86]. Miura et al. designed a new HA microneedle system for biomedical application; however, they found the MW of HA significantly influenced its solubility and permeability, highlighting the potential effectiveness of MNPs as actives delivery systems. It was also represented that the material's MW directly effects the MNP's mechanical strength [81,86]. Snetkov et al. highlighted the materials with HMW hold stronger intermolecular interactions and form higher mechanical structuring, ensuring better puncture properties in areas of hard skin [25,81], in contract to the LMW of a polymer that is less useful for MN skin application [81].

Nano-carrier-based transdermal delivery systems are a recent advance and development in skin applications [14,87,88]. Nanocarriers are nano-scaled delivery systems consisting of nano-sized active ingredient particles encapsulated with lipids or polymers [87,89]. The most common types are vesicular nanocarriers (liposomes, niosomes, and transferosomes), lipid-based nanocarriers (solid lipid nanoparticles, nanostructured lipid carriers), emulsion-based nanocarriers, polymeric nanocarriers, inorganic nanoparticles, and inclusion complexes, which are utilised extensively in topical dermal application to deliver various actives [87].

Incorporating nanocarriers in HA hydrogels provides a platform with synergistic action for enhanced therapeutic efficacy and patient compliance. Due to HA's specific characteristics such as biocompatibility and hydrophilicity, it serves as an ideal matrix for embedding nanocarriers providing excellent skin permeability and moisture-retaining properties [90,91]. Liposomal nanocarriers, solid lipid nanoparticles, and polymeric nanoparticles, when combined together, facilitate controlled and sustained actives release, improved dermal penetration, and minimised systemic adverse reactions [87].

Extensive reviews by Trombino et al. and Fu et al. provide a valuable insight of HA-based hydrogel drug delivery systems developed for targeted cancer treatment [90,91].

Kang et al. highlighted the importance of the hybrid systems that leverage the deformability and tunable surface charge of nanocarriers to disrupt the SC and enhance drug penetration, making them powerful and effective for treating dermatological conditions and delivering high molecular weight biologics [87].

Furthermore, researchers highlighted the role of HA-based hydrogels in minimising immunogenicity and enabling targeted delivery, allowing them to be the most advanced solutions in the TDD applications [88].

4.4. HA-Based Hydrogels in Transdermal Delivery

HA-based hydrogels are increasingly used in transdermal drug delivery systems for pharmaceutical and biomedical applications due to their excellent biocompatibility, hydration capacity, and ability to enhance controlled release of therapeutic molecules [92]. These hydrogels with HA bases enhance skin permeability by using advanced formulation techniques and are suitable for delivering anti-inflammatory agents, peptides, and other drug molecules. Their rheological behaviour and swelling properties can be tailored to optimise drug release kinetics, making them ideal for treating chronic skin conditions and systemic diseases [34].

Recent innovations in TDDs include conjugating HA in microneedle-based systems that improve transdermal penetration and target delivery to specific skin layers, especially for bio-ingredients. For instance, HA-based microneedle systems have been used for antibody delivery and non-invasive vaccination, demonstrating improved bioavailability and reduced systemic side effects [93]. In addition, HA has been introduced to nanotechnologies. HA-coated nanoparticles and liposomes have demonstrated promise in enhancing drug stability and targeting CD44 receptors on skin cells, further improving therapeutic outcomes [93].

Furthermore, crosslinking strategies for hydrogels, such as acrylation of HA-based hydrogels and the use of agents like BDDE that act as a crosslinker, allow improving the hydrogel properties, reducing degradation rate, and enhancing mechanical strength, which are essential for tailoring drug release profiles [25]. These characteristics make HA-based hydrogels highly effective for treating chronic dermatological conditions, localised pain, and systemic diseases via transdermal routes.

Salih et al. has introduced HA-modified liposomes as advanced carriers for the controlled release of vitamin E in skin wound therapy. The formulation structured not

only extends the half-life of the active ingredient but also reduces its toxicity, making the treatment safer and more effective. Furthermore, HA incorporation in liposome enhances the permeability of the skin barrier, allowing for deeper penetration of vitamin E and improved therapeutic outcomes [93].

4.5. HA-Based Hydrogel Phase Transition by Changing the pH for Full Absorption via the Skin

Some HA hydrogel formulations for use on the skin are made to change phase when applied to the skin after or during the application by pH or temperature (thermo-responsive) [35]. Hydrogels with thermo-induced gelation systems consist of interpenetrating networks of polymer chains that transition into a gel-sol state due to temperature change. The drugs are loaded at room temperature, but once the formulation is injected into the body, the gel shrinks, traps the other contents, and facilitates drug release [94]. Other mechanisms include pH change, solvent exchange or crystallisation, UV light exposure, thickening after removal of injection shear, and ionic cross-linking [95]. Ionic cross-linking of hydrogels is cross-linking under mild conditions, such as physiological pH and room temperature [96]. This can be easily reversed with a slight change in the conditions, leading to the release of the loaded materials. HA hydrogels have specific behaviour in low, high, and intermediate pH. This can be exploited to facilitate the release of drugs, for example, in the stomach where the pH is low. Electro-sensitive hydrogels respond to changes in the electric field and may shrink or swell when the surface of the hydrogel is in contact with the electric field [97]. Light-sensitive hydrogels change phases due to changes in light and have applications in ophthalmic drug delivery systems [97].

Some of the limitations and problems associated with the use of HA are rapid degradation and clearance and a short half-life of about 12 h, as it undergoes rapid degradation by the hyaluronidase enzymes present in body tissues [6]. Therefore, cross-linking of HA in the formulations was approached to overcome the above limitation and achieve lower enzymatic degradation rates and lower swelling ratios compared to linear HA polymers due to the presence of covalent bridges and intermolecular bonds between the HA polymer chains and the chemical cross-linker, which allows the applications to last longer [53,98]. Other limitations are allergic reactions from individuals; although they are rare, Bhojani-Lynchet et al. represented clinical cases of a late-onset inflammatory response toward HA that occurred 3 months after an uneventful injection of HA dermal [99].

5. Hydrogels Applications in Cosmetic Skin Topical Applications

5.1. Uses of HA in the Cosmetic Field

HA in the cosmetic industry has gained widespread usage in limiting or reducing skin ageing [100]. HA is coupled with the modern cosmetic world. Due to its specific characteristics, it has become one of the most significant moisturisers and humectant ingredients in skincare products. HA is employed as an effective anti-ageing agent. It restores skin hydration and elasticity, potentially reducing the appearance of wrinkles and fine lines. Injectable HA dermal fillers are widely used to volumize the lips, lift cheeks, soften lines, and enhance the skin. HA formulations of different molecular weights (50, 130, 300, 800, and 2000 kDa) are used in products promoting wound healing and wrinkle reduction. Low molecular weight HA (50, 130 kDa) significantly improved wrinkle reduction. It is also used as filler to shape lips, model cheeks, and correct facial lines [53,101].

Usually, the range of HA concentrations in cosmetic formulations is 0.01% to 2%, with serums and creams having the highest concentrations (0.1–1%) [102]. The effectiveness of HA is supported by clinical research, which showed that a thermosensitive hydrogel mask greatly improved skin moisture after only one application and even more after four

applications [103]. Furthermore, over a 56-day period, wrinkle elasticity and depth were enhanced by a combination of topical and oral HA treatments [104].

5.2. HA-Based Hydrogels in Cosmetic Applications

In cosmetic and topical applications, HA, specifically hydrogel formulations, serve as powerful moisturisers and delivery systems for active ingredients such as vitamins, antioxidants, and botanical extracts. Their ability to bind with water molecules and retain it to form a protective barrier improves skin elasticity and reduces the appearance of fine lines and wrinkles. HA hydrogels are commonly used in facial masks, under-eye patches, and anti-ageing products, offering both immediate and long-term skin benefits [93,102]. The molecular weight of HA significantly influences its performance within hydrogel formulation that is intended for cosmetic performance. High molecular weight HA forms a protective hydrogel film on the skin surface, providing immediate plumping and hydration, which is widely employed in products as under eye patches and facial masks, while low molecular weight HA penetrates deeper layers, stimulating collagen synthesis and cellular regeneration [25]. However, they can either be made in serums and dermal fillers or incorporated into facial masks and under-eye patches for the same purposes [25].

Advanced formulations such as HA-based microneedles offer targeted delivery and enhanced skin absorption of antioxidants, contributing to improved skin barrier function and protection against environmental stressors such as UV radiation [93]. Due to HA's adaptability and proven safety, it remains a foundational ingredient in modern cosmetic and dermatological products, especially in hydrogels.

A study by Xue et al. [56] developed five different HA-based hydrogel formulations using high molecular weight (HMW, 2000 kDa) and low molecular weight (LMW, 200 kDa) HA. They used 1,4-butanediol diglycidyl ether (BDDE) to produce the hydrogels were chemically crosslinked and evaluated for their enzymatic degradation behaviour in the presence of hyaluronidase enzyme. They found the hydrogels with a 4:1 ratio of HMW to LMW HA had the highest resistance to enzymatic hydrolysis, which suggested more stable structural integrity, while hydrogels with higher proportions of LMW HA degraded more rapidly. This was attributed to the cooperative entanglement of HA chains, which reinforced the hydrogel network and slowed enzymatic breakdown. Such findings highlighted the importance of molecular weight composition in designing HA- based hydrogels with better mechanical strength for biomedical applications [56].

6. Conclusions

Hyaluronic acid (HA)-based hydrogels represent a transformative advancement in skin applications for both pharmaceutical and cosmetic applications. Their ability to absorb water and maintain it in their structure made them superior to many conventional formulations for skin applications. In addition, HA hydrogels can provide more hydration to the skin, which allows them to be ideal for skin cosmetic product applications ranging from facial masks to injectable fillers and in pharmaceutical sectors as effective transdermal delivery systems for localised and systemic treatment.

This review has highlighted the strategic design considerations, cross-linking techniques, and functional enhancements that overcome many limitations such as fast enzymatic degradation and difficult transdermal permeation for biological actives.

The future research developments should focus on smart hydrogel systems that can respond to physiological stimuli including pH, temperature, or electric fields to allow more personalised and accurate drug delivery. Biodegradable and eco-friendly hydrogels are designed to assist with sustainability concerns, and combining them with nanotechnology, microneedles, and bioactive carriers will make them more effective for both medical and

cosmetic purposes. These improvements will make HA-based hydrogels an important part of the next generation of drug delivery and skin care systems.

Author Contributions: Conceptualization, F.R.; Investigation, F.R. and S.C.; Supervision, S.C. and P.C.; Validation, F.R.; visualisation, F.R.; Writing—original draft, F.R.; Writing—review and editing, F.R., S.C. and P.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Gholamali, I.; Vu, T.T.; Jo, S.-H.; Park, S.-H.; Lim, K.T. Exploring the Progress of Hyaluronic Acid Hydrogels: Synthesis, Characteristics, and Wide-Ranging Applications. *Materials* **2024**, *17*, 2439. [CrossRef] [PubMed]
2. Lotfollahi, Z. The Anatomy, Physiology and Function of All Skin Layers and the Impact of Ageing on the Skin. *Wound Pract. Res.* **2024**, *32*, 6–10. [CrossRef]
3. Hatta, I. Stratum Corneum Structure and Function Studied by X-ray Diffraction. *Dermato* **2022**, *2*, 79–108. [CrossRef]
4. Tharakan, M.; Lonczak, L. Supporting Skin Structure and Its Barrier Functions with Evidence-Based Skin Care Ingredients. *J. Cosmet. Dermatol. Sci. Appl.* **2024**, *14*, 200–210. [CrossRef]
5. Sparr, E.; Wennerström, H.; Engblom, J.; Norlén, L. The Stratum Corneum Barrier—From Molecular Scale to Macroscopic Properties. *Curr. Opin. Colloid Interface Sci.* **2023**, *67*, 101725. [CrossRef]
6. Chylińska, N.; Maciejczyk, M. Hyaluronic Acid and Skin: Its Role in Aging and Wound-Healing Processes. *Gels* **2025**, *11*, 281. [CrossRef]
7. Rostkowska, E.; Gromadzka, M.; Sławińska, M.; Górska, A.; Górska, R. Dermatological Management of Aged Skin. *Cosmetics* **2023**, *10*, 55. [CrossRef]
8. Abdo, J.M.; Sopko, N.A.; Milner, S.M. The Applied Anatomy of Human Skin: A Model for Regeneration. *Wound Med.* **2020**, *28*, 100179. [CrossRef]
9. Fargnoli, M.C.; De Simone, C.; Gisondi, P.; Pellacani, G.; Calzavara-Pinton, P. Topical Treatment for the Management of Mild-to-Moderate Psoriasis: A Critical Appraisal of the Current Literature. *Dermatol. Ther.* **2023**, *13*, 1249–1268. [CrossRef]
10. Guo, J.-W.; Jee, S.-H. Strategies to Develop a Suitable Formulation for Inflammatory Skin Disease Treatment. *Int. J. Mol. Sci.* **2021**, *22*, 6078. [CrossRef]
11. Cao, H.; Wang, M.; Ding, J.; Lin, Y. Hydrogels: A Promising Therapeutic Platform for Inflammatory Skin Diseases Treatment. *J. Mater. Chem. B* **2024**, *12*, 8007–8032. [CrossRef] [PubMed]
12. Song, L.; Qiu, H.; Chen, Z.; Zhang, Y.; Liu, J.; Wang, Y. Injectable Hyaluronate/Collagen Hydrogel with Enhanced Safety and Efficacy for Facial Rejuvenation. *Collagen Leather* **2024**, *6*, 21. [CrossRef]
13. Waggett, S.; Lyles, E.; Schlesinger, T. Update on Low-Molecular Weight Hyaluronic Acid in Dermatology: A Scoping Review. *EMJ Dermatol.* **2024**, *12*, 134–146. [CrossRef]
14. Jain, A.K.; Jain, S.; Abourehab, M.A.S.; Mehta, P.; Kesharwani, P. An Insight on Topically Applied Formulations for Management of Various Skin Disorders. *J. Drug Target.* **2022**, *30*, 919–934. [CrossRef]
15. Zagórska-Dziok, M.; Sobczak, M. Hydrogel-Based Active Substance Release Systems for Cosmetology and Dermatology Application: A Review. *Pharmaceutics* **2020**, *12*, 396. [CrossRef]
16. Rashid, F.; Albayati, M.; Dodou, K. Novel Crosslinked HA Hydrogel Films for the Immediate Release of Active Ingredients. *Cosmetics* **2023**, *10*, 6. [CrossRef]
17. Ahmed, E.M. Hydrogel: Preparation, Characterization, and Applications—A Review. *J. Adv. Res.* **2015**, *6*, 105–121. [CrossRef]
18. Rashid, F.; Albayati, M.; Dodou, K. Studies on Novel Methods for Formulating Novel Cross-Linked Hydrogel Films of Hyaluronic Acid. *Cosmetics* **2019**, *6*, 59. [CrossRef]
19. Akhtar, M.F.; Hanif, M.; Ranjha, N.M. Methods of Synthesis of Hydrogels: A Review. *Saudi Pharm. J.* **2016**, *24*, 554–559. [CrossRef]
20. Ahmad, Z.; Salman, S.; Khan, S.A.; Amin, A.; Rahman, Z.U.; Al-Ghamdi, Y.O.; Akhtar, K.; Bakhsh, E.M.; Khan, S.B. Versatility of Hydrogels: From Synthetic Strategies, Classification, and Properties to Biomedical Applications. *Gels* **2022**, *8*, 167. [CrossRef]
21. Mansuri, A.; Gupta, D.; Pawar, R.; Tanwar, S.S. A Comprehensive Review of Hydrogel Classification, Fabrication, and Utility. *Int. J. Res. Publ. Rev.* **2025**, *6*, 521–530.

22. Kim, J.; Lee, H.; Park, S.; Choi, Y. The Role of Rheology in Cosmetics Research: A Review. *Korea-Aust. Rheol. J.* **2024**, *36*, 271–282. [CrossRef]
23. Tang, G.; Du, B.; Stadler, F.J. A Novel Approach to Analyze the Rheological Properties of Hydrogels with Network Structure Simulation. *J. Polym. Res.* **2018**, *25*, 4. [CrossRef]
24. Di Giuseppe, E.; Billi, A.; Spagnuolo, E.; Scuderi, M.M.; Collettini, C. Characterization of Carbopol® Hydrogel Rheology for Experimental Tectonics and Geodynamics. *Tectonophysics* **2015**, *642*, 29–45. [CrossRef]
25. Snetkov, P.; Zakharova, K.; Morozkina, S.; Olekhnovich, R.; Uspenskaya, M. Hyaluronic acid: The influence of molecular weight on structural, physical, physico-chemical, and degradable properties of biopolymer. *Polymers* **2020**, *12*, 1800. [CrossRef]
26. Protsak, I.S.; Morozov, Y.M. Fundamentals and Advances in Stimuli-Responsive Hydrogels and Their Applications: A Review. *Gels* **2025**, *11*, 30. [CrossRef]
27. Hameed, H.; Faheem, S.; Paiva-Santos, A.C.; Sarwar, H.S.; Jamshaid, M. A Comprehensive Review of Hydrogel-Based Drug Delivery Systems: Classification, Properties, Recent Trends, and Applications. *AAPS PharmSciTech* **2024**, *25*, 64. [CrossRef] [PubMed]
28. Labie, H.; Blanzat, M. Hydrogels for Dermal and Transdermal Drug Delivery. *Biomater. Sci.* **2023**, *11*, 4073–4093. [CrossRef] [PubMed]
29. Mancini, G.; Gonçalves, L.M.D.; Marto, J.; Carvalho, F.A.; Simões, S.; Ribeiro, H.M.; Almeida, A.J. Increased Therapeutic Efficacy of SLN Containing Etofenamate and Ibuprofen in Topical Treatment of Inflammation. *Pharmaceutics* **2021**, *13*, 328. [CrossRef]
30. Mohamed, M. Optimization of Chlorphenesin Emulgel Formulation. *AAPS J.* **2004**, *6*, 26. [CrossRef] [PubMed]
31. Sheikh, U.; Dhote, V.; Dhote, K.; Jain, S. Formulation and Evaluation of Topical Hydrogel of Terbinafine HCL for Effective Management of Dermatophyte. *J. Emerg. Technol. Innov. Res.* **2023**, *10*, 555–562.
32. Rajalakshmi, P.; Rani, S.; Kumar, S. Formulation and Evaluation of Diclofenac Sodium Gel Using Carbopol 934 and 940. *Int. J. Pharm. Res. Allied Sci.* **2020**, *9*, 65–68.
33. Wang, Z.; Liu, Y.; Li, Y.; Wang, J.; Zhang, Y.; Liu, Y.; Wang, X.; Liu, Y.; Wang, Y.; Liu, Y. Nanoparticle-Hydrogel Systems Containing Platensimycin for Local Treatment of MRSA. *Mol. Pharm.* **2021**, *18*, 3456–3468. [CrossRef]
34. Almoshari, Y. Novel Hydrogels for Topical Applications: An Updated Comprehensive Review Based on Source. *Gels* **2022**, *8*, 174. [CrossRef]
35. Bernal-Chávez, S.A.; Alcalá-Alcalá, S.; Cerecedo, D.; Ganem-Rondero, A. Platelet Lysate-Loaded PLGA Nanoparticles in a Thermo-Responsive Hydrogel Intended for the Treatment of Wounds. *Eur. J. Pharm. Sci.* **2020**, *146*, 105231. [CrossRef] [PubMed]
36. Wei, S.; Xie, J.; Luo, Y.; Ma, Y.; Tang, S.; Yue, P.; Yang, M. Hyaluronic Acid Based Nanocrystals Hydrogels for Enhanced Topical Delivery of Drug: A Case Study. *Carbohydr. Polym.* **2018**, *202*, 64–71. [CrossRef] [PubMed]
37. Gwak, M.A.; Hong, B.M.; Park, W.H. Hyaluronic Acid/Tannic Acid Hydrogel Sunscreen with Excellent Anti-UV, Antioxidant, and Cooling Effects. *Int. J. Biol. Macromol.* **2021**, *191*, 918–924. [CrossRef]
38. Yazidi, R.; Hammami, M.; Ghadhoumi, H.; Ben Abdennebi, A.; Selmi, S.; Zayani, K.; Horchani-Naifer, K.; Bettaieb Rebey, I.; Saidani Tounsi, M. Development and Optimization of a Quercetin-Loaded Chitosan Lactate Nanoparticle Hydrogel with Antioxidant and Antibacterial Properties for Topical Skin Applications. *Cosmetics* **2025**, *12*, 141. [CrossRef]
39. Marafon, P.; Fachel, F.N.S.; Dal Prá, M.; Bassani, V.L.; Koester, L.S.; Henriques, A.T.; Braganhol, E.; Teixeira, H.F. Development, Physico-Chemical Characterization and In-Vitro Studies of Hydrogels Containing Rosmarinic Acid-Loaded Nanoemulsion for Topical Application. *J. Pharm. Pharmacol.* **2019**, *71*, 1199–1208. [CrossRef]
40. Kędzierska, M.; Sala, K.; Bańkosz, M.; Grzela, K.; Potemski, P.; Miernik, K.; Tyliszczak, B. Enhanced Hydrogel Materials: Incorporating Vitamin C and Plant Extracts for Biomedical Applications. *Molecules* **2024**, *29*, 2633. [CrossRef]
41. Rashid, F.; Childs, S.; Dodou, K. Comparison of Analytical Methods for the Detection of Residual Crosslinker in Hyaluronic Acid Hydrogel Films. *Cosmetics* **2023**, *10*, 70. [CrossRef]
42. Rashid, F.; Carter, P.; Childs, S. Novel Injectable Hydrogel Formulations and Gas Chromatography Analysis of the Residual Crosslinker in Formulations Intended for Pharmaceutical and Cosmetic Applications. *Gels* **2024**, *10*, 280. [CrossRef]
43. Albano, G.D.; Bonanno, A.; Giacomazza, D.; Cavalieri, L.; Sammarco, M.; Ingrassia, E.; Gagliardo, R.; Riccobono, L.; Moscato, M.; Anzalone, G.; et al. A 3D "In Vitro" Model to Study Hyaluronan Effect in Nasal Epithelial Cell Line Exposed to Double-Stranded RNA Poly(I:C). *Biomol. Ther.* **2020**, *28*, 272–281. [CrossRef]
44. Cowman, M.K.; Lee, H.G.; Schwertfeger, K.L.; McCarthy, J.B.; Turley, E.A. The Content and Size of Hyaluronan in Biological Fluids and Tissues. *Front. Immunol.* **2015**, *6*, 261. [CrossRef] [PubMed]
45. Jabbari, F.; Babaeipour, V.; Saharkhiz, S. Comprehensive Review on Biosynthesis of Hyaluronic Acid with Different Molecular Weights and Its Biomedical Applications. *Int. J. Biol. Macromol.* **2023**, *240*, 124484. [CrossRef] [PubMed]
46. Pérez, L.A.; Hernández, R.; Alonso, J.M.; Pérez-González, R.; Sáez-Martínez, V. Hyaluronic Acid Hydrogels Crosslinked in Physiological Conditions: Synthesis and Biomedical Applications. *Biomedicines* **2021**, *9*, 1113. [CrossRef]
47. Luo, Z.; Wang, Y.; Xu, Y.; Wang, J.; Yu, Y. Modification and Crosslinking Strategies for Hyaluronic Acid-Based Hydrogel Biomaterials. *Smart Med.* **2023**, *2*, e20230029. [CrossRef]

48. Fujiwara, J.; Takahashi, M.; Hatakeyama, T.; Hatakeyama, H. Gelation of hyaluronic acid through annealing. *Polym. Int.* **2000**, *49*, 1604–1608. [CrossRef]
49. Qiao, P.; Shi, K.; Wang, Y.; Li, B.; Su, L.; Zhang, K.; Nishinari, K.; Yang, G. Ultrafast Gelation of Hyaluronan Hydrogels via Alternate Compression–Decompression. *Food Hydrocoll.* **2023**, *141*, 108732. [CrossRef]
50. Lee, Y.; Lee, H.; Kim, Y.B.; Kim, J.; Park, H.; Park, T.G. Thermo-Sensitive, Injectable, and Tissue Adhesive Sol–Gel Transition Hyaluronic Acid/Pluronic Composite Hydrogels Prepared from Bio-Inspired Catechol-Thiol Reaction. *Soft Matter* **2010**, *6*, 977–983. [CrossRef]
51. Maleki, A.; Kjøniksen, A.-L.; Nyström, B. Effect of pH on the Behavior of Hyaluronic Acid in Dilute and Semidilute Aqueous Solutions. *Macromol. Symp.* **2008**, *274*, 131–140. [CrossRef]
52. Alonso, J.M.; Andrade Del Olmo, J.; Domínguez-Arca, V.; Pérez-González, R.; Pérez-González, R.; Pérez-González, R. Injectable Hydrogels: From Laboratory to Industrialization. *Polymers* **2021**, *13*, 650. [CrossRef] [PubMed]
53. Andrade Del Olmo, J.; Alonso, J.M.; Pérez-González, R.; Domínguez-Arca, V. Drug Delivery from Hyaluronic Acid-BDDE Injectable Hydrogels for Antibacterial and Anti-Inflammatory Applications. *Gels* **2022**, *8*, 223. [CrossRef]
54. Larrañeta, E.; Henry, M.; Irwin, N.J.; Trotter, J.; Perminova, A.A.; Donnelly, R.F. Synthesis and Characterization of Hyaluronic Acid Hydrogels Crosslinked Using a Solvent-Free Process for Potential Biomedical Applications. *Carbohydr. Polym.* **2018**, *181*, 1194–1205. [CrossRef]
55. Chun, C.; Lee, H.; Kim, J.; Kim, Y.; Park, Y.; Kim, M. Effect of Molecular Weight of Hyaluronic Acid (HA) on Viscoelasticity and Particle Texturing Feel of HA Dermal Biphasic Fillers. *Biomater. Res.* **2016**, *20*, 10. [CrossRef] [PubMed]
56. Zhang, Q.; Wei, X.; Ji, Y.; Yin, L.; Dong, Z.; Chen, F.; Zhong, M.; Shen, J.; Liu, Z.; Chang, L. Adjustable and ultrafast light-cured hyaluronic acid hydrogel: Promoting biocompatibility and cell growth. *J. Mater. Chem. B* **2020**, *8*, 3437–3445. [CrossRef]
57. Zhao, L.; Zhou, Y.; Zhang, J.; Liang, H.; Chen, X.; Tan, H. Natural Polymer-Based Hydrogels: From Polymer to Biomedical Applications. *Pharmaceutics* **2023**, *15*, 2514. [CrossRef]
58. Sapuła, P.; Bialik-Wąs, K.; Malarz, K. Are Natural Compounds a Promising Alternative to Synthetic Cross-Linking Agents in the Preparation of Hydrogels. *Pharmaceutics* **2023**, *15*, 253. [CrossRef]
59. Mengyuan, H.; Changlin, W.; Tong, X.; Ping, D.; Xiaojun, Y.; Huaying, S.; Congying, L.; Peng, G.; Zhufeng, C. Modification and Preparation of Four Natural Hydrogels and Their Application in Biopharmaceutical Delivery. *Polym. Bull.* **2023**, *80*, 7101–7144. [CrossRef]
60. Vasvani, S.; Kulkarni, P.; Rawtani, D. Hyaluronic acid: A review on its biology, aspects of drug delivery, route of administrations and a special emphasis on its approved marketed products and recent clinical studies. *Int. J. Biol. Macromol.* **2020**, *152*, 437–446. [CrossRef] [PubMed]
61. Pashkina, E.; Bykova, M.; Berishvili, M.; Lazarev, Y.; Kozlov, V. Hyaluronic Acid-Based Drug Delivery Systems for Cancer Therapy. *Cells* **2025**, *14*, 61. [CrossRef]
62. Alqahtani, M.S.; Kazi, M.; Alsenaidy, M.A.; Ahmad, M.Z. Advances in Oral Drug Delivery. *Front. Pharmacol.* **2021**, *12*, 618411. [CrossRef]
63. Baral, K.C.; Choi, K.Y. Barriers and Strategies for Oral Peptide and Protein Therapeutics Delivery: Update on Clinical Advances. *Pharmaceutics* **2025**, *17*, 397. [CrossRef] [PubMed]
64. Giram, R.; Bhagwat, D.; Kakad, A.; Nimse, A. A Comprehensive Review on Parenterals. *Int. J. Pharm. Sci.* **2024**, *2*, 2318–2336.
65. Liu, S.; Deng, T.; Cheng, H.; Lu, J.; Wu, J. Advances in Transdermal Drug Delivery Systems and Clinical Applications in Inflammatory Skin Diseases. *Pharmaceutics* **2025**, *17*, 746. [CrossRef]
66. Kushwaha, R.; Palei, N.N. Transdermal Drug Delivery Systems: Different Generations and Dermatokinetic Assessment of Drug Concentration in Skin. *Pharm. Med.* **2024**, *38*, 407–427. [CrossRef] [PubMed]
67. Jeong, W.Y.; Kwon, M.; Choi, H.E.; Kim, K.S. Recent Advances in Transdermal Drug Delivery Systems: A Review. *Biomater. Res.* **2021**, *25*, 24. [CrossRef]
68. Al Hanbali, O.A.; Khan, H.M.S.; Sarfraz, M.; Arafat, M.; Ijaz, S.; Hameed, A. Transdermal Patches: Design and Current Approaches to Painless Drug Delivery. *Acta Pol. Pharm.* **2019**, *76*, 377–386. [CrossRef]
69. Pastore, M.N.; Kalia, Y.N.; Horstmann, M.; Roberts, M.S. Transdermal Patches: History, Development and Pharmacology. *Br. J. Pharmacol.* **2015**, *172*, 2179–2209. [CrossRef]
70. *Transdermal Skin Patches Market Size, Share & Trends Analysis Report by Type (Matrix, Reservoir, Drug-in-Adhesive), by Application (Pain Relief, Smoking Cessation, Hormone Replacement Therapy), by Region, and Segment Forecasts, 2024–2030*; Grand View Research: San Francisco, CA, USA, 2024; Available online: https://www.grandviewresearch.com/industry-analysis/transdermal-skin-patches-market-report (accessed on 2 November 2025).
71. Penn, M.; Hennessy, M. Optimal Loading of Hydrogel-Based Drug-Delivery Systems. *Appl. Math. Model.* **2022**, *112*, 649–668. [CrossRef]
72. Rumon, M.M.H.; Rahman, M.; Hasan, M.M.; Islam, M.S. Advances in Cellulose-Based Hydrogels: Tunable Swelling Dynamics and Their Versatile Real-Time Applications. *RSC Adv.* **2025**, *15*, 11688–11712. [CrossRef]

73. Raeisi, A.; Farjadian, F. Commercial Hydrogel Products for Drug Delivery Based on Route of Administration. *Front. Chem.* **2024**, *12*, 1336717. [CrossRef]
74. Moshikur, R.M.; Carrier, R.L.; Moniruzzaman, M.; Goto, M. Recent Advances in Biocompatible Ionic Liquids in Drug Formulation and Delivery. *Pharmaceutics* **2023**, *15*, 1179. [CrossRef]
75. Hu, X.; Zhang, C.; Xiong, Y.; Ma, S.; Sun, C.; Xu, W. A Review of Recent Advances in Drug Loading, Mathematical Modeling, and Applications of Hydrogel Drug Delivery Systems. *J. Mater. Sci.* **2024**, *59*, 15077–15116. [CrossRef]
76. Nizam El-Din, H.M.; El-Naggar, A.W.M.; Abu-El Fadle, F.I. Characterization and Drug Release Kinetics of Polyacrylamide/Sodium Alginate Blend Hydrogels Synthesized by Gamma Irradiation. *Polym. Bull.* **2024**, *81*, 6149–6171. [CrossRef]
77. Kesharwani, P.; Jain, H.; Jain, S.; Rajput, S.; Tiwari, R.; Choudhury, H.; Tekade, R.K. Biomedical Applications of Hydrogels in Drug Delivery System: An Update. *J. Drug Deliv. Sci. Technol.* **2021**, *66*, 102914. [CrossRef]
78. Manghnani, P.N.; Nelson, A.Z.; Wong, K.; Lee, Y.W.; Khan, S.A.; Doyle, P.S. From Burst to Controlled Release: Using Hydrogel Crosslinking Chemistry to Tune Release of Micro-Crystalline Active Pharmaceutical Ingredients. *RSC Pharm.* **2025**, *2*, 94–101. [CrossRef]
79. Nawrotek, K.; Zarzycki, R.; Modrzejewska, Z. Drug Release from Hydrogel Matrices: Mathematical Modeling and Structural Influence. *Pol. J. Chem. Technol.* **2024**, *26*, 45–52.
80. Reddy, O.S.; Rao, K.M.; Subha, M.C.; Reddy, C.S.; Reddy, B.S. Fabrication and Characterization of Smart Karaya Gum/Sodium Alginate Semi-IPN Microbeads for Controlled Release of D-Penicillamine Drug. *Polym. Polym. Compos.* **2021**, *29*, 163–175. [CrossRef]
81. Miura, S.; Yamagishi, R.; Ando, M.; Hachikubo, Y.; Ibrahim, N.A.; Md Fadilah, N.I.; Maarof, M.; Oshima, M.; Goo, S.L.; Hayashi, H.; et al. Fabrication and Evaluation of Dissolving Hyaluronic Acid Microneedle Patches for Minimally Invasive Transdermal Drug Delivery by Nanoimprinting. *Gels* **2025**, *11*, 89. [CrossRef] [PubMed]
82. Kim, Y.-C.; Park, J.-H.; Prausnitz, M.R. Microneedles for Drug and Vaccine Delivery. *Adv. Drug Deliv. Rev.* **2012**, *64*, 1547–1568. [CrossRef]
83. Lee, G.; Ma, Y.; Lee, Y.-H.; Jung, H. Clinical Evaluation of a Low-Pain Long Microneedle for Subcutaneous Insulin Injection. *BioChip J.* **2018**, *12*, 309–316. [CrossRef]
84. Oliveira, C.; Teixeira, J.A.; Oliveira, N.; Ferreira, S.; Botelho, C.M. Microneedles' Device: Design, Fabrication, and Applications. *Macromol* **2024**, *4*, 320–355. [CrossRef]
85. Pettis, R.J.; Harvey, A.J.; Ham, A.S.; Buckheit, R.W.; Singla, S.K.; Sachdeva, V.; Shin, C.I.; Jeong, S.D.; Rejinold, N.S.; Kim, Y.-C.; et al. Microneedle Delivery: Clinical Studies and Emerging Medical Applications. *Ther. Deliv.* **2012**, *3*, 357–371. [CrossRef] [PubMed]
86. Du, H.; Liu, P.; Zhu, J.; Lan, J.; Li, Y.; Zhang, L.; Zhu, J.; Tao, J. Hyaluronic Acid-Based Dissolving Microneedle Patch Loaded with Methotrexate for Improved Treatment of Psoriasis. *ACS Appl. Mater. Interfaces* **2019**, *11*, 43588–43598. [CrossRef]
87. Kang, H.; Lee, J.; Park, S. Hyaluronic Acid-Based Hydrogels for Enhanced Transdermal Delivery: Recent Progress and Future Perspectives. *Pharmaceutics* **2024**, *16*, 1384. [CrossRef]
88. Kim, M.-H.; Nguyen, D.-T.; Kim, D.-D. Recent Studies on Modulating Hyaluronic Acid-Based Hydrogels for Controlled Drug Delivery. *J. Pharm. Investig.* **2022**, *52*, 397–413. [CrossRef]
89. Mauri, E.; Scialla, S. Nanogels Based on Hyaluronic Acid as Potential Active Carriers for Dermatological and Cosmetic Applications. *Cosmetics* **2023**, *10*, 113. [CrossRef]
90. Fu, C.-P.; Cai, X.-Y.; Chen, S.-L.; Yu, H.-W.; Fang, Y.; Feng, X.-C.; Zhang, L.-M.; Li, C.-Y. Hyaluronic Acid-Based Nanocarriers for Anticancer Drug Delivery. *Polymers* **2023**, *15*, 2317. [CrossRef]
91. Rathore, K.S.; Jain, M. Nanocarriers Revolutionizing Transdermal Drug Delivery: A Comprehensive Review of Recent Advances. *Int. J. Pharm. Sci.* **2024**, *14*, 112–125. [CrossRef]
92. Trombino, S.; Servidio, C.; Curcio, F.; Cassano, R. Strategies for Hyaluronic Acid-Based Hydrogel Design in Drug Delivery. *Pharmaceutics* **2019**, *11*, 407. [CrossRef]
93. Rahim, A.; Hafiz, A.; Amin, H.; Karn, P.R.; Meghani, N.; Nagendran, S. Hyaluronic Acid: Comprehensive Review of a Multifunctional Biopolymer. *Future J. Pharm. Sci.* **2024**, *10*, 1. [CrossRef]
94. Kondiah, P.J.; Choonara, Y.E.; Kondiah, P.P.D.; Marimuthu, P.; Kumar, P.; Du Toit, L.C.; Pillay, V. A Review of Injectable Polymeric Hydrogel Systems for Application in Bone Tissue Engineering. *Molecules* **2016**, *21*, 1580. [CrossRef]
95. Ha, D.I.; Lee, S.B.; Chong, M.S.; Lee, Y.M.; Kim, S.Y.; Park, Y.H. Preparation of thermo-responsive and injectable hydrogels based on hyaluronic acid and poly(N-isopropylacrylamide) and their drug release behaviors. *Macromol. Res.* **2006**, *14*, 87–93. [CrossRef]
96. Maitra, J.; Shukla, V. Cross-Linking in Hydrogels—A Review. *Am. J. Polym. Sci.* **2014**, *4*, 25–31. [CrossRef]
97. Liaqat, H.; Badshah, S.F.; Minhas, M.U.; Barkat, K.; Khan, S.A.; Hussain, M.D.; Kazi, M. pH-Sensitive Hydrogels Fabricated with Hyaluronic Acid as a Polymer for Site-Specific Delivery of Mesalamine. *ACS Omega* **2024**, *9*, 28827–28840. [CrossRef] [PubMed]
98. Hong, G.-W.; Wan, J.; Park, Y.; Yoo, J.; Cartier, H.; Garson, S.; Haykal, D.; Yi, K.-H. Manufacturing Process of Hyaluronic Acid Dermal Fillers. *Polymers* **2024**, *16*, 2739. [CrossRef]

99. Chen, L.H.; Xue, J.F.; Zheng, Z.Y.; Shuhaidi, M.; Thu, H.E.; Hussain, Z. Hyaluronic Acid, an Efficient Biomacromolecule for Treatment of Inflammatory Skin and Joint Diseases: A Review of Recent Developments and Critical Appraisal of Preclinical and Clinical Investigations. *Int. J. Biol. Macromol.* **2018**, *116*, 572–584. [CrossRef] [PubMed]
100. Galvez-Martin, P.; García-Martínez, O.; Ruiz, C.; De Luna-Bertos, E.; Ramos-Torrecillas, J. A Novel Hyaluronic Acid Matrix Ingredient with Regenerative, Anti-Aging and Antioxidant Capacity. *Int. J. Mol. Sci.* **2023**, *24*, 4774. [CrossRef]
101. Gosiya, M.; Hafiz, A.; Karn, P.R.; Meghani, N.; Nagendran, S. Hyaluronic Acid in Modern Cosmeceuticals: A Review of Skin Health and Anti-Aging Innovations. *J. Dermatol. Cosmetol.* **2025**, *9*, 3. [CrossRef]
102. Juncan, A.M.; Moisă, D.G.; Santini, A.; Morgovan, C.; Rus, L.L.; Vonica-Țincu, A.L.; Loghin, F. Advantages of Hyaluronic Acid and Its Combination with Other Bioactive Ingredients in Cosmeceuticals. *Molecules* **2021**, *26*, 4429. [CrossRef] [PubMed]
103. Quattrone, A.; Czajka, A.; Sibilla, S. Thermosensitive Hydrogel Mask Significantly Improves Skin Moisture and Skin Tone; Bilateral Clinical Trial. *Cosmetics* **2017**, *4*, 17. [CrossRef]
104. Nobile, V.; Roveda, G.; Spartà, E.; Tursi, F. Oral Intake and Topical Application of Hyaluronic Acid Ameliorates Skin Aging Signs: Efficacy Results of a Placebo-Controlled In&Out Trial. *Cosmetics* **2025**, *12*, 52. [CrossRef]