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REVIEW ARTICLE

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Hydrogels for localized drug delivery: A special emphasis on dermatologic applications

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Abstract

Skin disease treatment is a complex and time-consuming process due to the complex etiology, numerous side effects of conventional therapies, and difficulties in determining primary causes of the disease. Superficial wounds are often easy to treat. However, treatment of severe wounds caused by burn is challenging for clinicians. Optimum therapeutic benefits are based on the site-specific delivery of medicaments at the right time for a prolonged duration. Systemic toxicity and frequent dosing are the major challenges associated with the use of conventional therapeutics. Hydrogels are material of choice for drug delivery because of their high biocompatibility and ability to hold and release therapeutic agents. The number of hydrogels available for use in cosmetology and dermatology continues to grow during the past 1–2 decades. However, new hydrogel materials with high biocompatibility, antibacterial properties, and the ability to stimulate skin regeneration processes are in high demand. These are three-dimensional networks, which absorb a large amount of biological fluids and water. Hydrogels can be used as a biosensor, carrier systems for cells, drug delivery carriers especially for topical applications and in contact lenses. Hydrogels are highly porous carriers containing about 90% water. Stimuli-responsive hydrogels cause a change in network structure that is completely reversible in nature. The present review describes the applications of hydrogels in pharmaceutical formulations with a special emphasis on the treatment of dermatologic conditions such as acne, psoriasis, and mycosis.

KEYWORDS
chemically controlled release, dermatologic applications, diffusion-controlled, hydrogel, swelling controlled, topical delivery

1 | INTRODUCTION

Topical drug delivery systems are used for local delivery of drugs to the ophthalmic, rectal, vaginal, and skin areas of the body or for systemic delivery of drugs via skin.[1] This route avoids hepatic first-pass metabolism.[2] Topical drug delivery systems are generally used to increase the duration of drug action of short half-life drugs.[3] Thus, this route is preferred for the delivery of drugs having poor oral bioavailability.[4] Topical route offers advantages such as better patient compliance, local drug action, the lack of dose proportionality, specific skills are not required to apply, do not cause gastrointestinal irritation or toxicity.[5] Several topical formulations like ointments, creams, gels, patches, films, etc., are available commercially to deliver poorly water-soluble molecules. However, up to a certain extent these formulations also have limitations. The conventional topical formulations cannot release the medicament at the desired rate and extent. Thus, there is a need to develop a delivery system that can easily cross the complex structure of skin and deliver specific amount of drug at a desired rate. Hydrogels have unique chemical and physical properties and thus can be used in the preparation

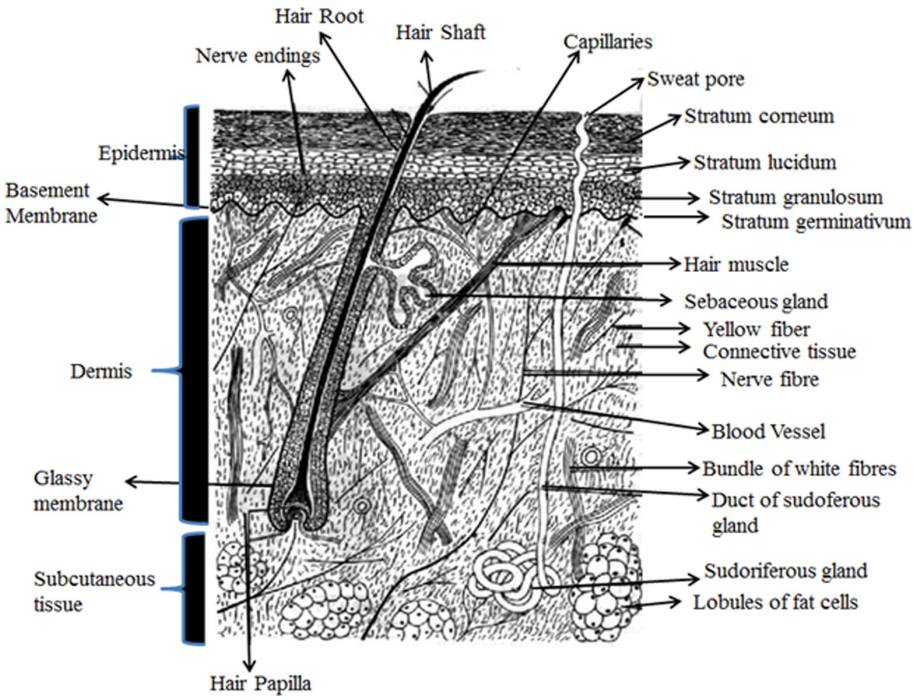

FIGURE 1 Structure of skin.

of topical preparations to overcome limitations of the existing conventional therapeutics.[6,7]

2 | STRUCTURE AND ANATOMY OF SKIN

Skin is the largest organ of human body that restricts the entry of chemicals and pathogens within the body.[8] Skin covers around 2 m^2 average surface area of the body. Skin encompasses three tissue layers namely epidermis, dermis, and subcutaneous layer.[9] The epidermis is composed of five layers, that is, stratum corneum, stratum granulosum, stratum basale, stratum spinosum, and stratum lucidum. Stratum corneum is the outermost horny layer of the skin and is composed of viable and non-viable epidermis. This layer offers a unique barrier due to the presence of an extracellular lipid layer. The main function of this layer is to exchange moisture and oxygen to the external environment. This layer is composed of cholesterol, long-chain fatty acids, and ceramides possessing around 40% water and proteins. Stratum granulosum (granular layer) consists of 3–5 layers of the loose granular cell. Thickness of this layer is 3 μm and composed of keratinocytes and cell organelles like nuclei and mitochondria.[10] Stratum basale (stratum germinosum) is the deepest layer of epidermis that is composed of single layer basal cells, merkel cells, melanocytes, keratinocytes, and stem cells. Stratum spinosum (prickle layer) is present between the stratum basale and stratum granulosum and is composed of 8–10 layers of cells. Stratum lucidum (clear layer) consists of thick skin mostly present on the palms and soles. It is composed of 3–5 layers of cells including packed dead cells[11] (Figure 1).

The dermis layer (1–2 mm thick) has fibrous tissues. It contains blood vessels, sebaceous glands, sweat glands, and hair follicles. The dermis layer is composed of papillary layer and reticular layers.[12] The uppermost dermal layer contains loosely packed connective tissues and is known as papillary layer. Many nerve fibers, fibroblast, capillaries, and water are present in this layer. Reticular layer is a dense and thicker network of collagen and fibers that forms lowermost dermal layer. The third bottom dermis layer is composed of fat cells, known as subcutaneous tissue or hypodermis.[13]

TABLE 1 Pros and cons of hydrogels[22]

Pros	Cons
Hydrogels possess a good degree of flexibility and other properties and possess better transport properties.	Hydrogels are difficult to handle
These are biocompatible and biodegradable.	Hydrogels are costly.
For the preparations of conventional hydrogel micro-valves and fabrication no external power requirement, no integrated electronics required.	Mechanical strength of hydrogel is very low.
Hydrogels sense changes of pH, temperature, and concentration of metabolite. These are sensitive to the environmental conditions.	The loading of drugs and nutrients are difficult.

3 | HYDROGELS

Hydrogels are receiving considerable attention in the formulation of drug delivery systems. These are cross-linked three-dimensional networks containing hydrophilic polymer chains that can swell and retain a substantial amount of water.[12,14,15] Since the body is comprised of

TABLE 2 Classification of hydrogels[23]

Classification	Type of hydrogel	Description
According to method of preparation	Homopolymer hydrogel	Cross-linked network of one type of hydrophilic monomer unit
	Copolymer hydrogel	Crosslinking of chains composed of two common units one should be hydrophilic
	Multipolymer hydrogel	Three or more comonomer units reacting together
	Interpenetrating network hydrogel	Polymerize one monomer with in a different cross-linked hydrogel network
According to ionic charge present on gel	Neutral hydrogel	Unchanged
	Anionic hydrogel	Negative charges
	Cationic hydrogel	Positive charges
	Ampholytic hydrogel	Net negative /positive or neutral charge
According to physicochemical features	Amorphous hydrogel	Covalent cross links macromolecular chains arranged randomly
	Semi crystalline hydrogel	May or may not cross links
Complexation hydrogel according to the specific type of the secondary forces	Heterodimers	Peptide interaction called COIL-COIL
	Biotin/	–
	Antibody/ Antigen,	–
	Glucose	–
	Poly (D-lactic acid)/ poly (L-lactic acid),	–
	Cyclodextrin	Inclusion complexes

70% water, hydrogels can be considered as great potential for various biological and medical purposes.[16–19] Hydrogels are used in development of drug delivery systems like nanocarriers, microparticles, and films.[20] Hydrogels are gaining popularity in the biomedical field as smart drug delivery carriers that satisfy the definite requirements for targeting therapeutics and regulating drug release.[21] Table 1 illustrates various pros and cons of hydrogels in drug delivery systems.

The water-loving polymeric core is probably not preferred to hold incompatible hydrophobic drugs. The tensile strength of hydrogels is weak, and this may cause premature drug release before arrival at its target site. To incorporate into hydrogels, a drug should have optimum hydrophilicity, pH 5–9, and molecular weight < 500 Daltons.

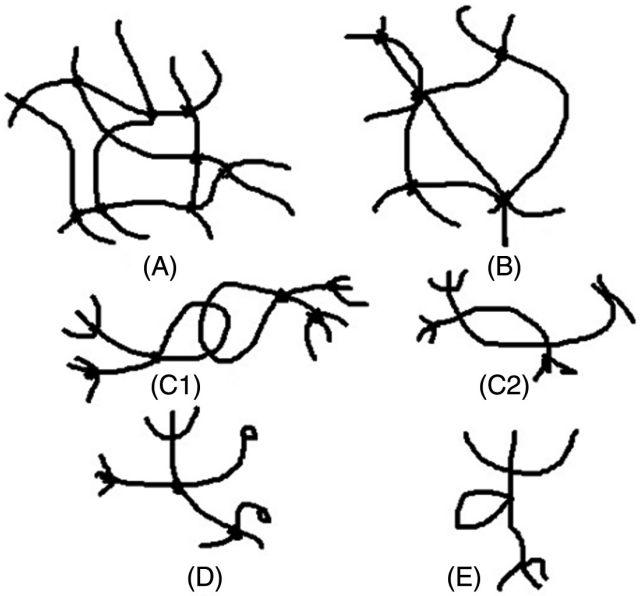

FIGURE 2 Ideal macromolecular network of a hydrogel (A), network with multifunctional junctions(B), physical entanglements in a hydrogel (c1 and c2), unreacted functionality in a hydrogel (d), and chain loops in a hydrogel (E).

3.1 | Classification and structure of hydrogels

Hydrogels are classified based on physical structure, ionic charge, and method of preparation (Table 2).[23] Changing or controlling the density of crosslinking polymer leads to the formation of a highly porous hydrogel structure. Porosity helps in the loading of drugs and allows them to release at a predetermined rate from the gel matrix.[24] Some of the structural networks or types of networks are illustrated in Figure 2.

3.2 | Stimuli-responsive hydrogels and their applications

A fascinating feature of stimuli-responsive hydrogels (smart hydrogels) is that the process producing network structure changes can be completely reversible in nature. These materials have advantageous properties as carriers for the delivery of pharmaceuticals, including peptides and proteins. pH- or temperature-responsive gels have the ability to quickly alter their pore structure and swelling behavior in response to changes in the environment. These materials can deliver the drugs in self-regulating, pulsatile, or oscillating fashion.[25] Smart hydrogels such as temperature responsive hydrogel, pH-responsive hydrogel, light responsive hydrogel, electro-responsive hydrogel, and glucose sensitive hydrogel have been widely used in drug delivery. Smart hydrogels are used in a wide range of biomedical applications,

TABLE 3 Preparation methods for physically cross-linked hydrogels

Cross-linking Methods	Polymers used	Characteristics	Reference
Hydrogen bonding	Polyacrylic acid and polymethacrylic acid complexed with polyethylene glycol	Hydrogen bonds are formed due to the protonation of carboxylic acid groups. This allows pH dependent swelling.	38–40
Amphiphilic graft and block polymer	Polylactic acid or its polymer with glycolic acid and polyethylene glycol	Ability to self-assemble in aqueous media to form hydrogel.	41
	Multiblock polymer of PEG and poly butylene terephthalate		42
	Hydrophobic modifications in polysaccharides like dextran, chitosan, pullulan, etc.		43
	Grafts and block polymers like PEG-poly (γ-benzyl $_{L}$-glutamate), Poly(2-ethyl-2-oxazoline)-PCL and thermosensitive hydrogel from PEG-PNIPAAm		44
Cross linking by crystallization	Polyvinyl alcohol aqueous solution	Crystallization in homopolymer by freeze thaw process.	45
	Homopolymers of L-lactic acid and D-Lactic acid, that is, is PLLA and PDLA	Stereo-complex formation	46
Cross linking by ionic interaction	Synthetic and natural amino acids	Cross linked by protein–protein interactions	47
Cross linking by protein interaction	Additional crosslinking agent's antibody, rabbit IgG grafted to polyacrylamide	Crosslinked by antigen–antibody interactions	48

such as tissue engineering, where self-healing hydrogels are used,[26,27] drug delivery,[28,29] wound healing,[30,31] and 3D bioprinting.[30,32]

To control the liquid flow in microfluidic systems, stimuli-responsive hydrogels can be used to create sensors, micromanipulators, robotics, and optical systems with adjustable focal length.[33,34] These hydrogels can be used as a biosensor. For instance, biomimetic hydrogels have been widely used to create biochemical sensors due to their specific responsiveness to nearby stimuli. Thus, significant progress in the control of numerous illnesses has been made since they may experience phase change mechanics and send biological information to these sensors.[35,36] Other application include targeted drug delivery, tissue engineering of cardiac tissues, neuronal tissues, cornea, tendons and meniscus, bone, and cartilages along with skin wound healing.[37]

3.3 | Preparation of hydrogels

Hydrogels can be prepared by physical and chemical crosslinking methods (Tables 3 and 4). Chemically cross-linked hydrogels contain covalent bonds between polymer chains. Chemically cross-linked hydrogels have good mechanical strength. Physically cross-linked hydrogels possess physical interaction between polymer chains that prevent their premature dissolution.[63]

3.4 | Mechanisms of drug release from hydrogels

Formulations containing hydrogels shows a different drug release profile than the hydrophobic polymer-based formulations.[57–59] Drug release models from hydrogel containing formulations is explained in the below subsections:

3.4.1 | Diffusion controlled

This is the most extensively reported drug release mechanism that follows Fick's law of diffusion. Based on diffusion-controlled drug release mechanism hydrogel systems are classified as reservoir systems and matrix systems. A reservoir or capsular system contains drug as a depot which is bounded by polymeric hydrogel membrane. Drug release from the reservoir systems is best described by Fick's law of diffusion. Drug release from the matrix systems is described by Fick's second law of diffusion.[60]

3.4.2 | Swelling controlled

A swelling-controlled release profile is obtained when drug diffusion is faster than the hydrogel swelling. The drug is released at the interface of glassy and rubbery phases of swollen hydrogel mass. The release of small molecule drugs from the hydroxypropyl methylcellulose hydrogel-based mechanism has been reported earlier.[61]

3.4.3 | Chemically controlled

Chemically controlled release occurs when the drug releases through the matrix reaction. Most of these matrix reactions are due to the cleavage of polymer chains by hydrolytic or enzymatic degradation. A

TABLE 4 Preparation methods for chemically cross-linked hydrogels

Methods	Polymers used	Characteristics	Reference
Cross-linking by complementary groups chemical reaction	Polyvinyl alcohols crosslinked through glutaraldehyde, chitosan-PVA	Cross-linking with aldehydes	[49]
	Polysaccharides crosslinked by means of 1,6-hexamethyllenediisocyanate, divinylsufone, 1-6-hexanedibromide	By addition reactions	[50–52]
	N,*N*-(3-dimethylaminopropyl)-*N*-ethyl carbodiimide (EDC)	By condensation reactions	[53]
Cross-linking by high-energy radiation	–	High energy radiations, for example, gamma rays and electron beam used to polymerize unsaturated substances	[54]
Cross-linking by free radical polymerization	To synthesize gels via this route, natural, synthetic, and semi-synthetic hydrophilic polymers were applied	Using enzymes as catalyst, methacrylic groups have been introduced into the mono and disaccharides, which may be used for the hydrogel synthesis	[55–62]
Cross-linking using enzymes	Glutaminyl groups with tetrahydroxy PEG (PEG-Qa). To aqueous solutions of poly(lysine-co-phenylalanine) and PEG-Qa, addition of transglutaminase resulted in the formation of PEG networks	Transglutaminase catalyzed reaction between the γ-carboxamide group of the PEG-Qa and the ε-amine group of lysine resulted in the formation of an amide bond	[56]

reversible or irreversible reaction controls drug release from the polymer network.[62]

4 | HYDROGELS IN TOPICAL DRUG DELIVERY

Hydrogels have attracted considerable attention for their dermatologic and cosmetology applications. In drug delivery, hydrogels are used for controlled drug release. Application of several active substances is limited in local dermatologic conditions due to their inappropriate pharmacokinetic profile and physicochemical properties. However, this can be overcome by modifying the dosage form characteristics using hydrogels. Applications of hydrogels in the treatment of skin diseases such as acne, psoriasis, and mycosis are presented in Figure 3.[64]

4.1 | Acne vulgaris

Acne vulgaris is a chronic multifactorial disease of the pilosebaceous unit that primarily affects people under the age of 18 years.[65] However, it also affects 20–40 years age group people. Colonization of *Propionibacterium acnes* in the skin, ductal hyperkeratinization, desquamation of follicular keratinocytes and abnormal differentiation, immunologic host reactions, androgen stimulation of sebaceous gland secretion, and inflammatory signaling are associated with the pathogenesis of this disease.[66,67] Lee et al., tested hydrogel adhesive patch of triclosan on female hairless mice skin for its effectiveness in the treatment of acne. A significant increase in triclosan transport with hydrogel was recorded as compared to the conventional formulation. The patches were effective against *Propionibacterium acnes*.[68] Co-delivery of clindamycin (1%) and tretinoin (0.025%) using hydrogel for the management of acne vulgaris showed good tolerance of the fixed combination with significantly improved therapy of acne vulgaris.[69] Fadel et al., evaluated efficacy of liposomal methylene blue hydrogel on mice skin. A significant reduction in the number of inflammatory and noninflammatory acne lesions and moderate to significant improvement in the acne in treated areas with no serious side effects was observed.[70] Resveratrol containing carboxy methylcellulose hydrogel have been reported for the eradication of facial acne vulgaris. A clinical study on 12 males and 8 females revealed reduction in the average area of microcomedones, decreased inflammation, and pustular lesions with no adverse effects. The study reported clinical improvement on resveratrol-treated face.[71]

4.2 | Mycosis

Fungal infection, also known as mycosis, is a common problem that affects people of all ages, genders, and geographical locations.[72] Asthma, cancer, acquired immunodeficiency syndrome (AIDS), organ transplantation, and corticosteroid therapy are common co-existing diseases. Irritated, scaly, dry, red, and flaky skin with itching and swelling are the common signs of fungal skin infection. Dermatophytosis, candida and malassezia infection, tinea capitis, fungal keratitis, and onychomycosis are the common fungal skin infection.[73] Luliconazole containing hydroalcoholic hydrogel was effective in the treatment of *Candida albicans* induced mycosis with the enhanced solubility and high skin retention.[74] Bifonazole hydrogel, prepared by microemulsion-based technique, has shown good stability for 3 months, sustained release of bifonazole, improved drug

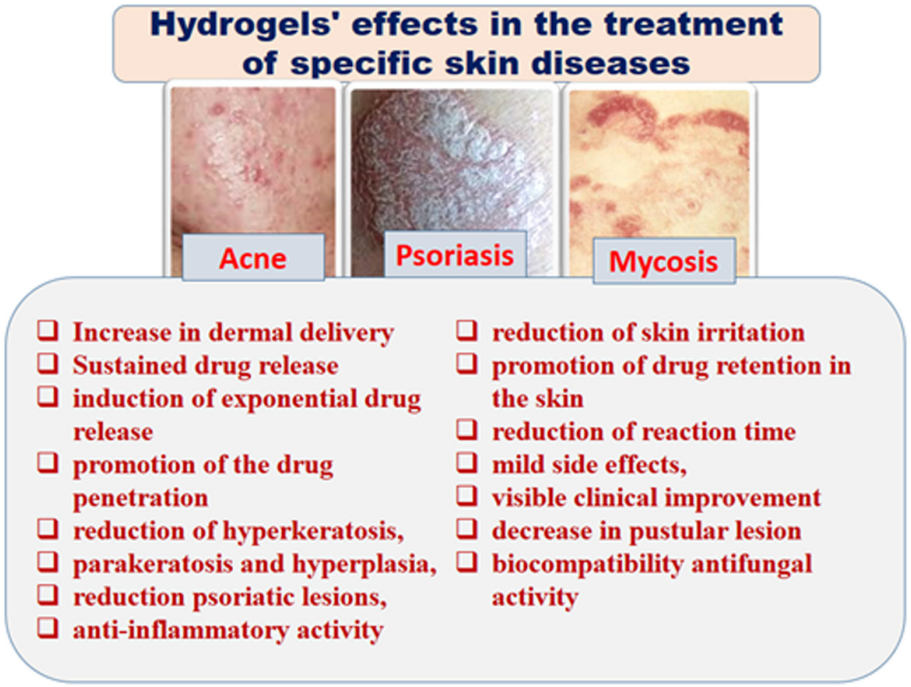

FIGURE 3 Hydrogel effects in the treatment of specific dermatologic conditions.

permeability, and good antifungal activity.[75] Amphotericin B containing hydrogel was found to be effective in the treatment of mycosis.[76,77]

4.3 | Psoriasis

Psoriasis is a chronic inflammatory skin disease marked by whitish scale and sharply demarcated erythematous plaques. It is the most common chronic inflammatory skin diseases. Prevalence of psoriasis can strike at any age implying that the ethnicity, genetic background, and environmental factors plays an important role on the onset of psoriasis.[78] It can cause a negative impact on the physical, emotional, and psychosocial status of the patient. Psoriasis has several clinical cutaneous manifestations, but the most common forms are chronic, symmetrical, erythematous, scaling papules, and plaques. The epidemiologic and clinical characteristics can affect the quality of life.[79]

For the treatment of psoriasis and related skin conditions, hydrogel-based topical drug delivery has been extensively investigated. Hydrogels can improve skin permeability and skin deposition while lowering systemic absorption. This indicates that it could be a good carrier for topical drug delivery.[64] Supramolecular bis-imidazolium-based amphiphile hydrogel containing multiple agents has been reported for the effective treatment of psoriasis. This formulation effectively reduced psoriasis-induced inflammation and hyperplasia.[80] Tripathi et al., developed methotrexate nanostructured hydrogel syetem for the effective treatment of psoriasis. The formulation was effective in Wistar albino rats and rabbits with reduced skin irritation.[81] Kaur et al., studied in vitro and in vivo effect of momentasone furoate hydrogel and found that the hydrogel reduced psoriatic lesions and skin blackening.[82]

TABLE 5 Dimensional description of hydrogel products administered via different routes of administration[12,83–94]

Routes of Administration	Dimensions and shape
Implants	Discs with diameter of 14 mm and thickness of 0.8 mm, Cylinders with diameter of 3 mm and length of 3.5 cm
Transdermal	Dressings of various variable shape and size
Vaginal Torpedo-shaped pessaries	Vaginal tablets with height of 2.3 cm, width of 1.3 cm and thickness of 0.9 cm Length of 30 mm and thickness of 10 mm used
Ocular Drops Suspensions/ ointments Circular inserts	Contact lenses with Conventional dimensions Hydrogel particles present in the eye drops must be smaller than 10 μm N/A Diameter of 2 mm and total weight of 1 mg (round shaped)
Peroral Discs Nanoparticles	Spherical beads 1 μm to 1 mm Diameter of 0.8 cm and thickness of 1 mm 10–1000 nm
Rectal suppositories	Conventional adult suppositories dimensions (length ≈32 mm) with a central cavity of 7 mm and wall thickness of 1.5 mm

5 | MISCELLANEOUS APPLICATION OF HYDROGELS

Hydrogels are used in the development of drug delivery and cosmetic formulations. Table 5 discusses the dimensions of hydrogel products administered via various routes. Several commercially available

TABLE 6 Companies investing in the development of hydrogel-based commercial products[95]

Company	Product	Drug/ ingredient(s)	Main constituent	Formulation	Therapeutic applications
GlaxoSmithKline	Biotene®	Glycerol	Carbomer and hydroxyethyl cellulose	Mouth wash	Relief from dry mouth symptoms
Alliance	Buccastem® M	Prochlorperazine maleate	Xanthan gum	Buccal tablet	Effective in treating nausea (feeling sick) and vomiting (being sick) associated with migraine
Oraldent Ltd.	Gengigel®	Hyaluronic acid	High molecular weight Hyaluronic acid (in the form of sodium hyaluronate)	Buccal drug delivery	Tissue reconstruction. It activates the migration of fibrocytes (cells contributing to tissue healing) and accelerate the healing process of ulcers
Honest O3	Hydrogel15%	Ozone –infused sunflower seed oil	Carbomer	Oral gel	Clean and nourish the mouth for optimal health
Key Pharmaceuticals	Imdur®	Isosorbide mononitrate	Hydroxypropyl cellulose and hydroxypropyl methylcellulose	Buccal drug delivery	Prevent angina
Ashland	Lubrajel™ BA	Clathrate of glyceryl acrylate and glyceryl polyacrylate	Glyceryl acrylate and glyceryl polyacrylate	Oral moisturizing hydrogel	Mouth moisturization
Johnson & Johnson	Nicorette®	Nicotine	hydroxypropyl methylcellulose	Chewing gums	Used for nicotine replacement therapy
GlaxoSmithKline	Nicotinell®	Nicotine	Xanthan gum and gelatin	Spray	Used for Tobacco withdrawal and other conditions
Schali Product	SCHALI®		Cellulose gum and hydrogenated starch	Dental care hydrogel	Promote complete oral hygiene and regeneration. It prevents oral infections caused by bacterial and virus
Zila Pharmaceuticals	Zilactin-B Gel®	Benzocaine	Hydroxypropyl cellulose	Buccal film	Relieve pain from minor mouth problems
Pfizer Inc	Advil®	Ibuprofen	hydroxypropyl methylcellulose	Coated film	Pain relief
Valeant Pharmaceuticals International, Inc.	Aplenzin®	Bupropion hydrobromide	Ethyl cellulose and polyvinyl alcohol	Extended-release tablet	Treatment of major depressive disorder
Eisai Inc.	Belviq XR®	Lorcaserin Hydrochloride	Polyvinyl alcohol, hydroxypropyl methylcellulose, polyethylene glycol	Extended-release tablet	Chronic weight management
Alza Corporation	Concerta®	Methylphenidate	hydroxypropyl methylcellulose (Hypromellose) and polyethylene oxide	Extended-release osmotic tablets	treatment of attention deficit hyperactivity disorder
Reckitt Benckiser Healthcare Ltd.	Gaviscon®	Aluminum hydroxide and magnesium carbonate	Sodium alginate and carbomer 974P	Oral suspension	Used to treat heartburn and upset stomach
AbbVie Ltd	Kaletra®	Opinavir and ritonavir	Croscarmellose sodium	Tablet	Treatment of human immunodeficiency virus-1(HIV-1) infection.
Pfizer Inc	Lopid®	Gemfibrozil	hydroxypropyl methylcellulose	Tablet	Increases high-density lipoprotein (HDL) cholesterol and decreases serum triglycerides and very low-density lipoprotein (VLDL) cholesterol.
Teva Pharmaceutical Industries Ltd.	Portia®	Levonorgestrel and ethinyl estradiol hormones	Hypromellose	Tablet	Contraception
Gilead Sciences	Ranexa®	Ranolazine	Polyvinyl alcohol and hydroxypropyl methylcellulose	Tablet	Treatment of chronic angina
Sanofi Aventis	Suprax®	Cefixime	hydroxypropyl methylcellulose	Tablet	Treatment of bacterial infections
Pfizer Inc	Toviaz®	Fesoterodine	Polyvinyl alcohol and hydroxypropyl methylcellulose	Tablet	Treatment of increased urinary frequency
AbbVie Ltd	Vicoprofen®	Hydrocodone bitartrate and ibuprofen	hydroxypropyl methylcellulose	Tablet	It is used to ease pain
GlaxoSmithKline	Voltaren®	Diclofenac sodium	Hydroxypropyl methylcellulose and polyethylene glycol	Enteric-coated tablets	Relief symptoms of osteoarthritis or rheumatoid arthritis
Mallinckrodt Pharmaceuticals	Xartemis XR®	Oxycodone and acetaminophen	hydroxypropyl cellulose and polyvinyl alcohol	Extended release tablet	It is used to ease pain
Bayer AG	Canesbalance BV Gel	Lactic acid and glycogen	Methyl hydroxypropyl cellulose	Vaginal gel	Neutralizes the unpleasant odor and restores the normal pH of the vagina
Ferring Pharmaceuticals Inc	Cervidil®	Dinoprostone	Polyethylene Oxide	Vaginal insert	Ripening of the cervix in pregnant women who are at or near the time of delivery
Caldwell Consumer Health	Conceptrol®	Nonoxynol-9	Sodium Carboxymethyl Cellulose	Hormones-free contraceptive for vaginal delivery	To prevent pregnancy
Serono	Crinone®	Progesterone	Carbopol	Vaginal gel	For fertility assisted procedures

(Continues)

TABLE 6 (Continued)

Company	Product	Drug/ ingredient(s)	Main constituent	Formulation	Therapeutic applications
Dermofarm S.A.	Deligyn		Carbomer	Vaginal gel	To reduce dryness, irritation and itching of vaginal mucosa.
Grünspecht Naturprodukte GMBH	Elanee Intimate Hydrogel	Panthenol	Hydroxyethyl cellulose	Water-based lubricant	Act as moisturizes and prevent vaginal drying
Blairex Laboratories Inc.	Encare®	Nonoxynol-9	Polyethylene glycol	Vaginal gel	Vaginal contraceptive
Johnson & Johnson	K-Y® jelly		Hydroxyethyl cellulose	Vaginal lubricating jelly	Lubricant for sexual intercourse
3 M Pharmaceuticals	Metrogelvaginal®	Metronidazole	Carbopol	Vaginal gel	Used to treat vaginal infections
Sandoz	Miphil®	Polycarbophil	Hydroxyethyl cellulose	Vaginal gel	To treat bacterial vaginosis
Aurium Pharma Inc.	pHemme® Revive	Aloe, Sodium hyaluronate	Hydroxyethyl cellulose	Vaginal moisturizing gel	Restore natural-like lubrication.
Church & Dwight Co., Inc.	RepHresh™ Vaginal Gel	Metronidazole	Carbopol	Vaginal Gel	Maintaining natural pH
Church & Dwight Co., Inc.	Replens®		Hydroxyethyl cellulose	Vaginal/ topical emollient	Used as vaginal moisturizer and vaginal lubricant
Combe Inc.	Vagisil®	Benzocaine and resorcinol	Hyaluronic acid	Vaginal cream	Used to treat external vaginal itching and irritation
Searchlight Pharma Inc.	Zestica Moisture™		Hyaluronic acid	Vaginal gel	Used to treat vaginal dryness
Gensco Pharma	Astero®	Lidocaine HCl	Polyethylene Glycol (PEG) 400	Topical anesthetic	Applied on painful wounds such as pressure wounds, ulcerations, post-surgical incisions, burns, abrasions and cuts
Skin Republic	Collagen Hydrogel Mask		Collagen and Sodium Hyaluronate	Serum mask	Restores elasticity, moisture and glow the skin
IBSA Farmaceutici Italia	Flector®patch	Diclofenac	Gelatin and carboxymethylcellulose	Transdermal patch	Reduce pain and inflammation
Teikoku Pharma USA	Lidoderm®	Lidocaine	sodium carboxymethylcellulose	Topical, hydrogel patch	Provides analgesia (Without anesthesia). Used treat post-herpetic neuralgia
Johnson & Johnson	Neutrogena®	Coal tar	Hyaluronic Acid	Transdermal gel	Used for topical delivery of drugs in a cosmetic line
Clean & Clear	Persa-Gel®	Benzoyl peroxide	Carbomer, HPMC	Transdermal gel	Used for immediate release of drugs deep into the pores where pimples start. It also has antibacterial effect
GlaxoSmithKline	Voltaren Gel®	Diclofenac	Polyethylene Glycol (PEG)	Transdermal gel	Reduce pain and inflammation
GlaxoSmithKline	Voltadol®	Diclofenac	Polyethylene Glycol (PEG)	Transdermal gel	Reduce pain and inflammation
Altacor	Clinitas Hydrate®		Carbomer	Lubricating eye gel	It enhances layer of tear film and used to relief the dry eye syndrome
Candorpharm Inc.	Hylo® Gel		Hyaluronic acid sodium	Highly viscous eye drops	Provide lubrication of ocular surface and treat dry eyes
Alimera Sciences	Iluvien®	Corticosteroid	Polyvinyl alcohol and silicone adhesives	Injection	Used to treat diabetic macular edema
Surmodics, Inc.	I-vation	Triamcinolone	Poly (methyl methacrylate) (PMMA)	Intravitreal implant	Used to treat various joint conditions
Alza Corporation	Ocusert®	Pilocarpine	Alginic acid	Ocusert	Used for the treatment of glaucoma
Allergan	Ozurdex®	Dexamethasone	poly (D,L-lactide-co-glycolide) (PLGA)	Tiny implant for ophthalmic intravitreal Injection	Used to treat inflammation
Allergan	Restasis®	Cyclosporine	Carbomer	Ophthalmic emulsion	Used to increase tear production
Bausch and Lomb	Retisert®	Fluocinolone acetonide	Silicone elastomer and polyvinyl alcohol membrane	Sterile implant	To prevent the release of substances in the body that cause inflammation
Coloplast Corp.	Comfeel® Plus Contour Dressing		Carboxymethylcellulose	Butterfly shaped hydrocolloid wound dressing	Designed for difficult-to-dress areas due to its good adhesion property
Covalon Technologies, Ltd.	CovaWound™ Hydrocolloid dressing		Hydrocolloids	Wound dressing	It maintains optimal moisture in wounds and maintain a high rate of moisture vapor transmission. It is used in the management of lightly exuding wounds like foot and leg ulcers, superficial partial-thickness burns
Bsn Medical Gmbh	Cutimed® Gel		Carbomer 940	Wound dressing	Used to treat necrotic and sloughy tissues in chronic wounds

TABLE 6 (Continued)

Company	Product	Drug/ ingredient(s)	Main constituent	Formulation	Therapeutic applications
Derma Rite Industries, LLC	DermaFilm®		Hydrocolloids	Wound dressing	Used for closed surgical wounds, minor abrasions, skin grafts and superficial pressure ulcers.
Gentell Corp.	Gentell CMC Fiber Dressing		Carboxymethylcellulose	Wound dressing	Absorptive dressing for wounds with moderate to heavy exudate since gel-like substances support the moist healing process and minimize the risk of leakage and maceration
Systagenix	Helix3-cm®	Bovine collagen	Polyethylene glycol	Thin, semi-transparent wound dressing	Used in the management of burns, sores, blisters, ulcers and other wounds
Convatec	Kaltostat®		Alginate	Soft, sterile, alginate wound dressing	Used on moderate to heavily exuding wounds acute and chronic wounds
Cardinal Health	Kendall™ Hydrogel Dressing		Glycerin formulation	Glycerin containing wound dressing	Used on light- to moderate-draining wounds and burns
Sofar	Sofargel		Carbopol 974P	Self-adhering wound dressing	Used in the healing of cut, abrasions, grazes and burns
3 M Health Care	Tegaderm™ Hydrocolloid Dressing		Hydrocolloids	Wound dressing	Used on superficial wounds and abrasions
Johnson & Johnson	AcuvueOasys®		Siloxane-based materials	Silicone hydrogel contact lens	Stabilizes the tear film promoting comfortable weak
CIBA Vision	Focus Night & Day®		Silicone hydrogel	Silicone hydrogel contact lens	Used to protect the cornea and to relieve corneal pain and post-surgical conditions resulting from cataract extraction and corneal surgery
Menicon	PremiO lenses		Silicone hydrogel	Silicone hydrogel contact lens	Optimizes delivery of oxygen to eye
Baush& Lomb	Purevision®		Silicone hydrogel	Silicone hydrogel contact lens	Used for the correction of nearsightedness (myopia) and farsightedness(hyperopia)

hydrogel-based products have been developed (Table 6). Several applications of hydrogels are discussed below:

5.1 | Cosmetics

Hydrogel-based "beauty masks" synthesized using collagen are marketed by Sephora USA, Inc. Bio collagen cosmeceuticals are another category hydrogel-based product available in the market manufactured by Novostrata UK Ltd. Pecogel is the hydrogel-based product that forms a flexible, non-tacky film produced by Phoenix Chemicals Inc., based on polyvinyl pyrrolidone. Hydrogel face masks produced by Fruit and Passion Boutiques Inc. are also commercially available. All these hydrogels are possessing a Minimum Primary Irritation Index (PII) making them suitable to use as cosmeceuticals.[96]

5.2 | Wound healing

Wound is a rupture of epidermal integrity and anatomical continuity of tissues caused by chemical, thermal or mechanical stress. It is characterized by bleeding, pain, and wound opening. Wound healing is a dynamic process, which involves chemical reactions and physiologically active chemicals. Proper wound care is an essential aspect of rehabilitation since it minimizes the emergence of undesirable infections and other issues, as well as speeds up the healing process with less scarring.[97,98]

Lesions of the skin are caused by various wound healing procedures to varying degrees. To reduce their visibility and avoid ugly scars, the major task is to improve the wound healing process. After each surgery in which tissue is broken and skin is damaged, it is crucial to employ preparations that guarantee the best possible healing circumstances. Modern dermatology and cosmetology have established adequate standards of care, which can effectively enhance wound healing and include the use of hydrogel materials and optimal prevention.[99] Wound healing is slowed down and impeded by a number of coexisting causes (external factor, other coexisting disorders), including skin conditions that result in the development of various types of wounds.

Hydrogels are widely used for the treatment of skin wound caused by burns, diabetic ulcers, or other skin problems. Hydrogel for topical administration gets transformed into a film when applies to the wounds. These hydrogels can easily cover the whole wound.[59] Hydrogels made from cellulose, alginates, chitosan copolymers, chitosan-gelatin-honey copolymer, and new plastic gelatin silk are commonly used in wound healing. Hyaff™ (esterified hyaluronic acid), Autograft, and 3D® are commercially available hydrogels used for wound healing.[100]

Polyvinyl alcohol (PVA)/ß-glucan hydrogel was developed by Muthuramalingam et al. and evaluated in vivo on human keratinocytes (HaCat Cells) and dermal fibroblasts. The author discovered that the developed formulation greatly sped up wound closure, assisted in the

development of capillary vessels, improved granulation and reepithelialization, and significantly improved skin regeneration around the wound site.[101] For the evaluation of fresh skin regeneration in murine and porcine models, Sun (2017) developed a self-crosslinking dextran-isocyanatoethyl methacrylate-ethylamine hydrogel. The formulation showed regeneration of entire skin structures with appendages on both pre-existing scars and acute wounds. The developed formulation promoted full skin regeneration, improved hair development on the existing scars, and allowed new skin to retain the reticulated epithelial layer.[102]

Collagen-hyaluronic acid hydrogel was developed by Ying et al. and evaluated for wound healing and other skin-related issues. Human microvascular endothelial cells (HMECs) were used for in vitro testing, while mice with full-thickness skin were used for in vivo testing. Results showed that the formulation demonstrated an excellent cell differentiation behavior in the hydrogel and good viabilities of HMECs and COS-7 cells. Additionally, up to 7 days of culture, the level of vascular endothelial growth factor (VEGF) increased, and the infiltration of inflammatory cells in the wound model gradually decreased.[103] For the evaluation of cell proliferation and wound healing, Kim et al. created a hydrogel based on human hair keratin. In animal tests, the dose form increased the number of cells migrating into the area between confluent cell colonies and the skin fully recovered without scabs or skin contractions.[104]

5.3 | Transdermal delivery

The transdermal route becomes an important route for the systemic delivery of drugs through the skin. Hydrogel-based formulations with electrical assistance deliver drugs effectively through the skin. Iontophoresis can be used to deliver the drug systemically from a hydrogel system. Several hydrogels are commercially available to deliver drugs such as Luteinizing hormone, sodium nonivamide acetate, nicotine, and evoxacin.[59]

5.4 | Subcutaneous delivery

Implants are used for subcutaneous delivery of drugs for which biocompatibility is the prerequisite feature. Hydrogels are the most encouraging and biocompatible material for subcutaneous drug delivery. Hydrogels have minimum mechanical irritation after implantation due to the elastic properties. These can prevent adsorption of protein and improve cell adhesion. Hydrogels can be used with a wide range of drugs having different hydrophilicity. Crosslinking density and swelling properties of hydrogels control drug release. These can be used to deliver proteins and peptides.[105]

5.5 | Dental applications

Gelatin hydrogel is widely used for the continuous release of biologically fibroblast growth factor-2 (FGF-2) stored in the extracellular matrix. It is used in pulp regeneration therapy. This helps in the controlled release of FGF-2 from the hydrogels.[106]

5.6 | Hydrogel inserts

These inserts are used in the vagina. When placed in a moist environment, these inserts swell and release the medicament at a controlled rate. Cervidil, a vaginal insert, is composed of cross-linked polyethylene oxide/urethane polymer. These are dinoprostone containing rectangular-shaped inserts with 29 mm × 9.5 mm × 0.8 mm in size dimensions.[83]

5.7 | Hydrogel implants

Histrelin acetate (Supprelin LA®, Vantas) prepared usingmethacrylate, 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate trimethylolpropane trimethacrylate, and other nonpolymeric additives are used as hydrogel implants. These implants have been investigated for the treatment of prostate cancer.[83]

5.8 | Rectal delivery

Rectal route offers advantages like avoidance of first-pass metabolism and good systemic circulation of the drug. Drug diffusion out from the body is the common problem associated with conventional rectal dosage forms. Hydrogels exhibit sufficient mucoadhesive property with minimum disadvantage and controlled release of the medicament through the rectal route.[107]

5.9 | Ophthalmic delivery

Major limitations associated with the ocular route are continuous tear drainage, blinking, and lower permeability offered by the cornea. Conventional delivery systems are quickly cleared off from the eye leading to poor ophthalmic bioavailability. Suspensions and ointments can be given for long-term effects. However, these formulations have their limitations. Hydrogels offer resistance against drainage of tear fluid due to their elastic and water-soluble nature. Hydrogels offer a less gritty sensation and thus a good feeling to the patients. In situ hydrogel systems offer great potential in ophthalmic drug delivery.[108]

5.10 | Contact lens

Contact lens material should possess good wettability and permeability in the preparation of hard, soft, and gas permeable lenses. These lenses are made up of cross-linked hydrogel polymeric material. Thus, hydrogels, have wide applications in the manufacturing of contact lenses. Focus night and day (Ciba Vision Company), Acuvne Oasys

(Vistakon a division of Johnson & Johnson Vision Care, Inc.), pure vision (Bausch and Lomb Company) are silicon-based hydrogel lenses available commercially.[21,109]

5.11 | Perfume delivery

Hydrogels can be used for the controlled delivery of perfumes. Due to the swelling and release-controlling nature, hydrogels can control the release of volatile oils from the surface. These devices use the principle of osmotic diffusion to release volatile oils.[110,111]

6 | CONCLUSIONS

Hydrogels have numerous significant properties that distinguish them from other pharmaceutical excipients and enable them to be used as a smart carrier in drug delivery systems. From time to time, significant changes have been made to modify hydrogels for their diverse applications. These are swollen matrix systems holding minimum water solubility and minimum dissolution of natural tissues. These contain high water content and are soft like naturally occurring tissues. The biocompatibility of hydrogels is due to their water content. Hydrogels have great potential in pharmaceutical manufacturing for the development of various drug delivery systems for improved treatment potential. More efforts will be required in future studies to meet specific requirements for the development of advanced hydrogel-based delivery systems. Cross-linked polymer and monomer structures would continue to be the most preferred biomaterials for the synthesis of hydrogel-based systems. Hydrogels are expected to open up new avenues in biomedical science by taking advantage of their structure-specific properties. Thus, many more hydrogel-based pharmaceutical products are expected to enter clinical trials and achieve commercial success in the near future, demonstrating that the future of hydrogels is promising and there is a scope for the further research in this area.

AUTHOR CONTRIBUTIONS

Shammy Jindal contributed to design, resources, data collection, literature search, manuscript writing and final approval of this article. Kamya Goyal contributed to resources, data collection, literature search, and final approval of this article. Rajendra Awasthi contributed to concept, design, data collection, literature search, manuscript writing, analysis and interpretation of data, supervision, critical review and revision of the manuscript, and final approval of this article. Giriraj T. Kulkarni contributed to concept, analysis and interpretation of data, supervision, critical review, and final approval of this article.

CONFLICT OF INTEREST

All the authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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