Chapter 10
Hydrogel Formulation as Efficient Drug Carrier and Delivery for Selected Skin Diseases

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Abstract During the last a few decades, the rapid proliferation in the prevalence of skin diseases has been a major unease for healthcare providers, and it is currently regarded as a global encumbrance and reflected as one of the reasons for rise in health-related spending. Nano-medicine has ascended as the most unique means to break the chain of spreading and eliminating the skin disease altogether. Nano-formulations (NFs) by means of advanced nanotechnology are in great need to address the subject. Lately, hydrogel- and nanogel-based drug delivery approaches have postured new projections to simulate the natural intelligence of many biological systems. Due to their select porous interpenetrating network scheme, hydrophobic drug fusion and stimulus sensitivity, hydrogels are considered as a remarkable potential in the area of targeted drug delivery systems. This chapter gives an outline of an effort to highlight the current trends in hydrogel-based drug carrier cum delivery systems for skin diseases like skin cancer, psoriasis and wound healing. This chapter also covers diverse formulations techniques using hydrogel like topical, subcutaneous, transdermal and comprising its pharmaceutical formulations. Future forecasts and prospects that are accessible for hydrogel-based formulations for various skin disorders are also discussed.

Keywords Polymer · Drug carrier · Formulations · Skin disorder · Topical cream · Diffusion · Swelling · Transdermal · Subcutaneous delivery · Wound healing

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1 Introduction

Hydrogels, water-swollen crosslinked polymer networks have been broadly exploited as wound dressings, therapeutic glue patches, contact lenses and tissue-modifying material during the last 30–40 years [1, 2]. Essentially, hydrogels are considered as perfect vehicles for drug delivery in view of their favorable properties. Hydrogels are fully biocompatible since they hold a close structural similarity to the natural extracellular matrix (ECM). Also, their porous structure is valuable to clench drugs in large quantities. Hydrogels offer an aqueous environment similar to physiological environment that supports to hold drug in their dynamic forms and prevents them from degradation. This property helps hydrogel is being used extensively as tropical care vehicular medicine. Several reports on the application side of hydrogels have pointed out the benefits of hydrogels in the treatment of skin-related diseases, drug delivery medium for a wide variety of skin diseases like skin cancer, skin infection, acne, skin rashes, ringworm and wounds. For instance, dexpanthenol is used for the prevention and treatment of the skin ailments and also used as skin fortification [3, 4].

In recent times, drug delivery has been the most evolving and promising technology in the biomedical field. The physiochemical properties of the drugs are essential for formulation with hydrogels. Once the drug and hydrogels are formulated, it is used for the treatment of diseases by targeted drug delivery system [5–7]. As can be seen from Fig. 1, there are several types of hydrogels that are used for treating skin diseases. In particular, photosensitive hydrogels can be used to release the drugs at the required specific target when it is exposed to specific quantum of light. Reinforced hydrogels can be made by blending specific hydrogel polymers with therapeutically active and biocompatible ingredients to have improved delivery properties. In spite of extensive application in countless disease targets including skin disorders, hydrogels have some shortcomings when it is indecorously formulated or used as drug carrier or delivery medium [8, 9]. A notable problem is that the astonishing permeability of hydrogels makes a swift outflow of the bulk of their drug substances. This occurrence known as “burst release” may have drug concentrations more than the toxic level in vivo, leading to ineffectual drug treatment and objectionable adverse effects [10]. Henceforth, frequent strategies have been tried to comprehend unrelenting drug leaching out from hydrogels with decreased burst effect. These methods encompass the restriction of drugs to gel matrices through a fragmentable spacer and the amalgamation of biodegradable micro- and nanospheres aiding as carriers of drug component [11].

2 Formulation of Hydrogel

The process of formulating the active pharmaceutical ingredient (API) with hydrogel involves mixing of inactive yet biocompatible excipients to afford formulated therapeutic products. This encompasses of preparing the drug, as robust and endurable to

Fig. 1 Pictorial view of hydrogel carriers used for skin delivery

the patients. Suitably formulated therapeutic agents are administered by numerous mode of delivery [12]. For orally administered drugs, the route includes espousing the drug into a tablet or a capsule form. The drug has to be soluble in aqueous medium at a controlled rate, and the particle size and crystal form of the molecule are established. These drugs are scrutinized to guarantee that the encapsulated drug is safe and efficacious [13]. As a drug delivery vehicle, hydrogels are used as a transporter material, which can counteract at the site of gastrointestinal tract, colon, vagina and other body parts thus shielding the API from chemical degradation. It is capable of liberating the drug at the pre-requisite targeted site depending upon the targeted environment like pH or bonding interaction or chemical ionization of drug molecules [14–16]. Hydrogen bonding interactions between polymeric chain of hydrogel and glycoproteins in the mucosalining of the gastrointestinal tract makes the drug intangible of chemical transformation within GI tract. Formulation of drugs using hydrogel can also be prepared in the form of parenteral formulations or injectable formulations. These categories of formulations are used with the intravenous, subcutaneous, intramuscular and intra-articular administration [17]. Hydrogel-based topical formulations are also a vital type of formulation used in the skin-associated problems. In this technique, application of drugs on the required body surface like skin in the form of creams, gels, foams and ointments to treat the skin disorder [18]. Other topical

medication comprises of formulation used as eye and ear drops. Powder form or paste formulation is used in dental application specifically for orthodontic or periodontics diseases [19].

3 Hydrogel as Carrier of Therapeutic Agents

Excruciating pain due to scratched skin conditions present momentous problems and woe to patients and clinicians. One of the main shortcomings with prevailing medication for these types of skin malady is the difficulty of application of medicine for wound dressing at the targeted places. An alternative approach is the use of skin lotions or other gels (hydrogel-loaded drugs) that may cure promptly with an unfailing release [20]. The selection of monomer for loading a therapeutic agent in the hydrogel matrix is an important step in developing hydrogel-API (active pharmaceutical ingredient) formulations. The main starting materials for preparing hydrogel-based formulations are by using suitable monomers which can hold the API till it is carried at the required site [21–23]. The polymers that are used for making hydrogel bio-compatible materials are provided in Table 1.

3.1 Cargo Loading

There are two methods commonly adopted for loading of drugs into hydrogels. In the first method, hydrogel is mixed with active pharmaceutical ingredient, an initiator and a crosslinker (if needed). Then, polymerization is carried out in situ and the drug is embedded within the polymer matrix. In the second method, on the other hand, the hydrogel is conceded to swell in the drug solution (refer Fig. 2). The loading of a drug into a hydrogel is influenced by various aspects viz. contact between polymer and solvent, cross-linking density of polymers, nature of the solvent, etc. These conditions affect the degree of swelling in a large extent [24, 25]. The loading of drug per unit mass of a polymer can be calculated using the following relation (Eq. 1)

$$(\text{Swollen polymer weight} - \text{Dry polymer weight})/(\text{Polymer weight}) \quad (1)$$

3a *Diffusion controlled:* A very few applicable mechanisms are involved in drug delivery releases system. The Fick's law of diffusion is most widely applied in modeling this release. Two types of drug diffusion-controlled systems are used in hydrogel-drug delivery; (a) reservoir system is used in drug loading by an entrapment mechanism within a polymeric hydrogel membrane, and Fick's first law defines the drug delivery via the membrane system, (b) the matrix system is in an unstable state, thus the drug release happens by diffusion in a single-dimensional slap-shaped matrix, described by the second law of Fick's diffusion.

Table 1 Different types of the polymer are used pharma application

S.No.	Drug	Polymer	Application
1	Immobilized Antigen and Antibodies	Polyurethane, poly(ethylene glycol), poly(propyleneglycol) poly(vinyl pyrrolidone), polyethylene glycol and agar	Wound care treatment
2	Dextromethorphan Hydrobromide	Poly(vinyl pyrrolidone) Starch, poly(vinyl pyrrolidone), poly(acrylic acid)	Drug delivery and pharmaceutical formulation
3	Hyaluronic acid-tyramine	Collagen, fibrin, hyaluronic acid	Dental Materials
4	SR-rhGH	Other polymer material Hyaluronan	Tissue engineering, Implants
5	Vinylbenzyltrimethylammonium chloride (VBT) and p- sodium styrene sulphonate (SSS)	poly (vinyl methyl ether) (PVME) and poly (N-isopropyl acrylamide) (PNIPA) gels -	Injectable polymeric system
6	Peptide-based drug	Poly (vinyl methyl ether), poly(N-isopropyl acrylamide)	Technical products (cosmetic, pharmaceutical)
7	Polymer-based Drug	High-acyl gellan gum hydrogel	Rheological investigation
8	5-Fluorouracil	N-succinyl chitosan/Poly (acrylamide-co-acrylic acid) hydrogels	In vitro release of 5-fluorouracil (cancer drug releases)
9	Cellulose membrane	Semi-solid hydrogel ophthalmic, Loratadine-Loaded Thermoresponsive Hydrogel	ocular drug delivery (formulations and in vitro studies)
10	Camptothecin	Hydrogel on chitosan/β-glycerophosphate (β-GP)/β-cyclodextrin	Thermo-sensitive Hydrogel Containing Cyclodextrin

Based on the experimental evidence, it identifies that drug is evenly distributed across the hydrogel matrix used as a drug delivery system [26].

3b *Swelling controlled:* It is a release-controlled phenomenon. The swelling-controlled delivery applies when the diffusion of the drug is quicker than hydrogel bulge. If the polymer chains are soluble in water, erosion might also play a significant rate controlling role for drug release. Upon contact with aqueous media, liquid penetrates into the system, leading to steadily increasing water concentrations. As soon as the water content is high enough, the polymer chains start to disentangle from the network and diffuse through the liquid

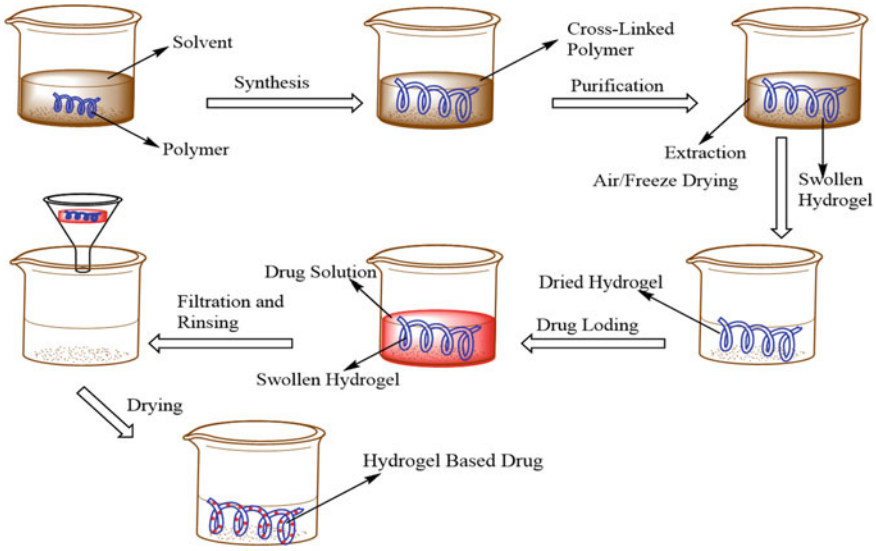


Fig. 2 Mechanism of the hydrogel-based drug delivery systems

unstirred boundary layer surrounding the device into the surrounding fluid [27]. For instance, the delivery of small molecule-based drugs on HPMC (hydroxypropyl methylcellulose) hydrogel tablets happens via swelling-controlled drug release concept [28].

3c *Chemically controlled:* In this method, the molecules are released during the chemical reactions happening inside a delivery matrix. Often times, reaction occurs by fragmentation of polymer chains through water or enzyme-mediated degradation and the released drugs can undergo either reversible or irreversible reactions arising between the polymeric network and releasable drug. It is further classified on the basis of reaction happening while drug release phase is on [29, 30].

1. Complete kinetically driven sustained release: The kinetically controlled and diffusion controlled are further classified into two types: (a) pendent chain (prodrugs) hydrogel network device covalently linked device via fragmentable spacer bonds, and the drug delivery is maneuvered by an approach with which spacer cleavage happens [31, 32]. In certain applications where an additional targeted delivery methodology is anticipated, it is necessary to project further enzymatically cleavable spacer bonds [33]. In surface eroding materials, drug delivery is controlled by the rate of surface erosion of the polymer matrix. In water-resistant polymeric network links, surface attrition happens when the fraction of water carried into the polymer is relatively slower than the rate of bond cleavage due to water molecule [34, 35]. However, the typically high water content of hydrogel, the eroding system was slow due to enzymatic degradation when the rate of the

enzyme reaction into the gel is not faster than the rate of enzymatic degradation systems. Surface eroding models directing at the delivery mechanism are established on hydrolytic degradation polymers [36, 37].

2. Diffusion-controlled system: Diffusion plays a vital part in many controlled drug delivery methods. Diffusion is the mass transport mechanism when other processes do not contribute to the control of drug release. The interactions between enzymes and the drugs, together with polymer degradation, control the diffusion and release of the drugs [38]. Diffusional mass transport is basically important for several processes in the body and nature as a whole. The primary concept is that a solute diffuses in a concentration gradient from region of higher concentration to nearby area of lower concentration. The diffusion equation can be solved when beginning and boundary conditions are given. Analytical approaches to the diffusion equation that are applicable to controlled drug release systems can be explained. The initial condition refers to the initial drug distribution in the system, before the release pathway begins. Boundary conditions imply to the fact that the conditions at the drug delivery system's boundaries during drug release; these specify drug concentrations or concentration gradients at the device's surfaces. The term "analytical solution" refers to an explicit mathematical expression satisfying the diffusion equation, along with the prescribed initial and boundary conditions. The analytical solution is used to calculate drug release from the delivery system as a function of time.

4 Topical Delivery

Topical drug delivery is a restrained drug delivery system which can be applied in the body via ocular, rectal, vaginal and skin as topical means. Skin is the easier stretchable organ on the human body for topical applications and is the central route of topical drug delivery system. This comprises the balanced method to topical formulations, principles of topical permeation and a simple factor of topical drug delivery systems. The scientific confirmation specifies that topical gel is a benign and active management for skin-related problems [39]. Effective components like desonide, a synthetic corticosteroid, are loaded in the hydrogel and used as an anti-inflammatory agent [40]. An antifungal formulation such as clotrimazole also developed by hydrogel formulation for vaginitis, which shows improved absorption than conventional creams [41].

The topical formulations are gel, cream, ointment, paste and lotion. For these types of formulation, drugs are prepared using hydrogel [42]. In this method, hydrogels have a crucial role like suspension agent, viscosity enhancer, thickening the gel as required in ointment or cream. For instance, Adapalene gel is a drug which is used for ACNE [43]; here carbomer 940, a minimally-toxic emulsion stabilizing agent, is added [44] for Adapalene gel drug formulations. Some of the topical drug delivery hydrogels are (i) polyethylene glycol (Lidocaine ointment) [45], (ii) Carbomer 940 (Adapalene gel) [43] and carbomer homopolymer type-C or PEG-400 (Voltaren

gel) [46], and also, Carbopol-910, Carbopol-943, Carbopol-934P, Carbopol-940, Carbopol-941, etc., are used as various topical drug delivery systems [47, 48]. It offers thermodynamic stability to the drug, and it aided to increase topical drug availability, dermal permeation and skin flux with less toxicity [49].

5 Transdermal Drug Delivery

Drug delivery system to the skin disease is commonly directed for topical application of dermatological treatment of skin diseases or improvement of the skin care itself. Nowadays, the hydrogel-based systematic drug delivery path has been considered as a fitting method for the skin diseases. For this, transdermal technique is a right treatment for skin, and it is a systematic delivery of drugs as well [50]. Reasonable advantages of transdermal approach are that all drugs can be transported for the prolonged time at low cost and steady rate. The transdermal-based drug was easy to disconnected whenever it is required to do so by discarding the devices, and it can be a high water content property present in swollen hydrogels. The hydrogels can deliver the better acting ingredients for the skin diseases compare to conventional lotions and patches as shown in Fig. 3 [51]. Advantages of hydrogel-driven devices for transdermal drug delivery were projected by composite membranes of cross-linked polymer of PHEMA with nonwoven fabric polyester supported devices. It was suggested that the formulation-based liposome gel contains phosphatidylcholine liposomes. The liposome gel was considered as skin absorption activity of hydrocortisone, and it was expressed that hydrogels prepared from the copolymerization of bovine serum albumin (BSA) and PEG [52]. It contains over 96% of water which allows the hydrophilic and water-resistant pharmaceutical agents diffuse through polymer network. It was also asserted that it is the most likely application

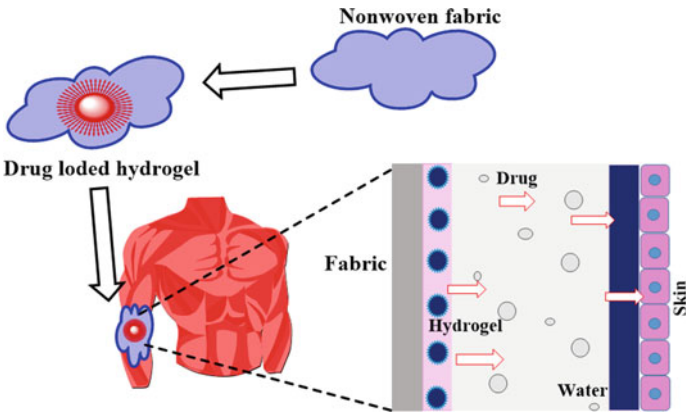


Fig. 3 Drug delivery through the skin epidermis by gel formation

of BSA-PEG hydrogels. Extensive studies on in situ photo-polymerizable hydrogels are synthesized from terminally diacrylate ABA block copolymers of lactic acid oligomers (A) and PEG (B) for barriers and specified drug delivery in a controlled manner. In recent times, studies in transdermal applications focus on electrically operated delivery, using iontophoresis and electroporation. Various hydrogel-oriented formulations have been investigated as a carrier for transdermal delivery to acquire the increased penetration of luteinizing releasing hormone, sodium nonivamide acetate, nicotine and enoxacin. Another method, a methylcellulose-mediated hydrogel was used as a viscous ultrasonic coupling medium for transdermal sonophoresis, resulting in an improved transfer of insulin and vasopressin by in vitro method across human skin [53].

6a *Formulation methods for Transdermal in Hydrogel* Transdermal is one of the methods of administration to deliver the drug across the skin, and it is to be applied as patches on the skin. The drug goes to epidermis and follows microcirculation of dermis [54]. The most common method for transdermal hydrogel formulations is to load the drug within hydrogel using topical drug delivery method [55] with the hydrogel loaded drug to make a shallow compartment from hollow ring-shaped device and drug-impermeable-backing membrane (laminated aluminum foil). A microporous tape of large area is stuck onto the impermeable-backing membrane to bring the transdermal patch in close interaction with the skin. The device is sealed by a release liner on the open side. The drug-loaded hydrogel formulation is tuned as per required ratio of drug and polymer [56]. The formulation for transdermal drug delivery is to load the drug in hydrogel matrix-type transdermal patches. The drug is prepared by solvent casting methodology using different ratio of hydrogels, surfactants or co-surfactants, emulsifier, with required additives, etc.

6 Subcutaneous Delivery

Substantial applications of hydrogel are also found to have in implantable therapeutics. The drug-loaded hydrogels inserted subcutaneously are revealed to arouse less objectionable body reactions, such as inflammation, carcinogenicity and immunogenicity. They are considered as biocompatible polymers due to their high water content and non-interference in the physiological activity in the human body. They also hold several encouraging properties like minimum mechanical irritation resulting to in vivo implantation. Also, their softness, elastic properties, inhibition of protein adsorption, cell adhesion arise from low interfacial tension between water and hydrogels make the subcutaneous delivery an easy method. It has wide suitability for specific drugs with hydrophilicity and molecular dimensions and has typical lotions to exploit, to discharge of incorporated drugs at the required site of action with

time. Histological examination showed that the hydrogel was infused when incorporated subcutaneously into rats. Innumerable hydrogel formulations for subcutaneous delivery of anticancer drugs are also available. Prevalent reports on incorporated hydrogels are concentrated toward the assessment of recyclable systems. Later, two types of novel decomposable PEG hydrogels have been developed for the sustained release of proteins: The first option was developed by poly-condensation of bi-functional PEG and branched PEG polyols then hydrolysis of the ester linkages, the gel decompose into only PEG and PEG derivatives. The second type is PEG-oriented hydrogels with a functional group in which drug covalently linked to the hydrogel by an ester chemical bond [57]. The delivery of the drug is regulated by the hydrolysis of an ester bond between the hydrogel and the protein followed by diffusion of protein out of the hydrogel and by degradation of the gel. These hydrogels are designed on acrylate derivatives of dextran. Through this study, the use of hydrogels and the sustained release of the drug was completely understood.

7 Hydrogel for Melanoma, Psoriasis and Wound Healing

Drug delivery technology is aimed at the product efficiency, safety, convenience of the patient and compliance. The administration of drugs is commonly through the gastrointestinal tract, injections, inhalation, transdermal, topical and oral routes. In this section, we have focused on the drug delivery for the skin diseases. Because skin is the outermost organ and also the largest organ of the human body, it can be easily accessed for drug application. Skin diseases or skin problems are the emanate condition and burden for millions of people every day. Skin problems are due to various pathogens. Researchers in this area unraveled that dermatologic disorders are very less and commonly significance for the populations in many developing countries. There are numerous dermatological treatments that are available for skin-related problems.

A large amount of infectious diseases, associated with skin and hair follicles, might be due to bacteria, fungi and viral infection. These ailments are treated by therapeutic substances such as drugs and vaccines. An immense range of therapeutic indications that are covered by those substances are specially designed for skin or cutaneous administration. Even when the drugs have different molecular structure, they possess some common physicochemical characteristics, such as lipophilicity and poor aqueous solubility. The drugs should retain water partition coefficient value [$\log P$] > 6.0. The drug formulation for delivery is to adequately manage therapeutic concentration in a reasonable time period and afford constant pharmacological action. Destitute drug insertion of skin limits their bioavailability and drugability. Here, hydrogels are used as a carrier molecule for the drug; it received attention owing to their efficiency to stimulate the penetration in the surface of the dermal region. The application of hydrogel-drug carrier system is able to produce effective drugs to the particular site in a proper manner. The drug-loaded hydrogel is based on the pharmacological system, which controls the release of therapeutic agents to

the targeted region at the epidermal layer. Hydrogels show a high equilibrium water content (EWC) which provides the structure the ability to entrap water and subsequently water-soluble drugs. This characteristic makes hydrogels suitable for drug delivery systems [58].

7a ***Skin cancer***

New forms of treatments to aim disease target are essential while concurrently lessening the side effects produced due to foreign agents. To elude side effects, transdermal drug delivery systems seem as an encouraging alternate approach to carry antineoplastic agents. There are numerous benefits from using encapsulated antineoplastic agents; some of them are improved drug solubility, improved bioavailability, increased chemical stability, sustained drug release, extended half-life, non-specific organs or tissue dispersal, and lessening of the total dose required [59]. Altogether, the benefits delineated can help lessen adverse side effects to a dramatic degree. Bulky carrier-based drug delivery systems is a new area that has emerge due to the antagonistic side effects triggered by non-traditional therapies in patients with melanoma. These systems contest the cancerous cells, while destabilizing the adverse side effects. These categories of drug delivery systems hold drug carriers such as nanoparticles, dendrimers, cyclodextrins, liposomes and hydrogels that transport the bioactive antineoplastic drug inside the core/pocket/scaffold. Several types of drug delivery methodologies, such as the development of hydrogels based on natural and synthetic polymers as the drug carriers, have received distinct consideration. These biomaterials offer a stimulating opening for crafting innovative approaches of cancer therapy. Conventionally, paclitaxel (PTX) was administered intravenously to treat skin cancer. Nevertheless, since PTX could not discern among healthy cells and cancer cells, it has created countless undesirable side effects, occasionally resulting in the patient's death. Hence, to minimize the cytotoxicity and reduce side effects, targeted delivery of PTX to the cancerous cells, while not affecting the healthy cells, needs to be developed. Researchers have encapsulated the drug PTX in hydrogels [60]. However, additional efforts are essential to bring out studies on the efficacy of these hydrogel formulations in vitro and in vivo assays in melanoma.

Working on the encapsulation of the bioactive agents in hydrogel scaffolds and successive release, durable retention of 5-fluorouracil (5-Fu), an antineoplastic agent in a hydrogel based on polyethylene glycol, polycaprolactone and poly-L-lactic acid copolymers (MCL), within a tumor is achieved within hydrogel matrix [61]. It was revealed that single injection of 5-Fu-loaded MCL was found to be effective than repeated injections of free 5-Fu. This was confirmed by long-lasting retention of 5-Fu, which induced vital inhibition of tumor growth under in vitro and in vivo assays in melanoma [62]. Moreover, it was established that 5-Fu-loaded hydrogel could act as a biodegradable drug collection capable of offering continual release of 5-Fu after intratumoral injection, hence increasing the chemotherapeutic effect of 5-Fu while decreasing its systemic toxicity [63]. The tumors injected with saline or MCL survived to a great extent and several

blood vessels (yellow arrow) amplified as the implantation time increased. Meanwhile, tumors injected with free 5-Fu (repeat) or 5-Fu-loaded MCL displayed on a surge in areas comprehending necrotic tissue that increased over time. These results designate that it is likely to employ formulations based on hydrogels as a new substitute for drug release platforms [64, 65].

7b ***Psoriasis***:

About 2% population is affected by psoriasis, a common skin disorder, affecting mostly adult population. It is considered as a prolonged inflammation of the skin described by erythematous scaly plaques [66]. Corticosteroid such as betamethasone (BD) is generally used comprehensively in topical medication for the treatment of mild to moderate psoriasis. However, the application of BD has practical shortcomings such as reduced permeability via skin which reduces its medicinal value at the requited site of action [67]. The foremost constraint stands in the hindered function of the skin, which is considered as one of the most impervious epithelia of the human body to exogenous substances. Consequently, the main tasks for a topical formulation are to offer an adequate rise in drug permeation into the skin, without causing any momentous non-reversible adjustment to the skin barrier function. The fabrication of a nano-carrier composite hydrogel formulation for enhanced patient amenability and topical drug delivery to psoriasis lesions was developed using methoxy—poly (ethylene glycol)—hexyl substituted poly (lactic acid) (mPEGhexPLA). mPEGhexPLA is a dual functional polymer which self-assembles to drug-loaded spherical nanostructures in an aqueous medium. These nanostructures have a passive, PEG-based surface with neutral to marginally negative net charge and a particle size <60 nm. Nano-carriers hold a large payload of the hydrophobic tacrolimus (TAC), which is an effective immune suppressive medicine. Prominently, TAC nano-carrier hydrogel composite formulation delivered considerably increased drug levels into inflamed skin permitting next-generation products with reduced drug dose and/or treatment frequency. The composite hydrogel was prepared by concentrated Carbopol® gels (1.2% (w/w)) at a batch size of 40 g. Carbopol® ETD 2020 (480 mg) was measured and spread into water for injectable to get a moderately swollen polymer. The pH was adjusted to 5.5 ± 0.2 with a NaOH solution (10% w/w). The gel was mixed well till the Carbopol® polymer was in its completely swollen state [68]. If essential, weight of the final gel was adjusted to 40 g with sterile water. 0.1% TAC composite hydrogels were prepared at a batch size of 40 g, by slow addition of 0.2% TAC mPEGhexPLA nano-carrier formulation (20 g) to the concentrated Carbopol® gel (20 g) under magnetic stirring. Lipid-, paraffin- or wax-based foundations are commonly used in semi-solid topical formulations of reduced soluble drugs. Further to cosmetic shortcomings, these products generally suffer from suboptimal dermal drug availability, due to an incomplete drug partitioning from the formulation base into the skin. It was validated that topical TAC hydrogel composite formulation carries increased drug doses into the skin, compared to a non-traditional ointment formulation. The inactive surface properties and small size of the nano-carrier system competently aid to overcome the skin barrier. When diluted below the threshold micellar

concentration, the drug is released from the nano-carrier and forms a local depot in the skin. When the therapeutic efficiency of the hydrogel composite formulations was corresponding to commercially obtainable products in the existing in vivo study, product design prospects related with hydrogel-based formulations containing mPEGhexPLA nano-carriers, empower the development of groundbreaking topical composite dosage forms including foams, sprays or gels, with enhanced patient compliance. Increased solubilization and delivery capacity is anticipated to assist the generation of improved drug products with reduced dosing frequency or reduced drug dose [69].

7c ***Infected wound***

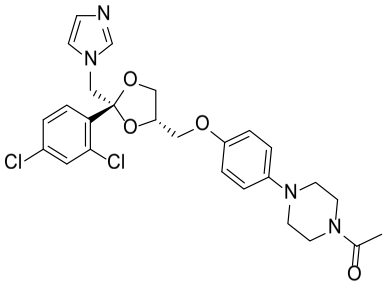
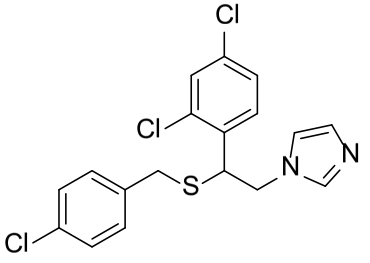
Wound healing method is the evolving new means to heal the impaired skin tissue with improved bio-friendly and bioactive materials. Skin-associated problems such as skin burn, skin ulcer and injured skin are non-affordable to treat for common people. Prosthetic tissue-engineered skin is made, but they are not ready to use due to high cost, and it would not always be matched by the patient. The wound healing applications have a parameter to regulate the wound contraction that can be assessed by this technique, considering that A0 is the original wound area, and A is the wound area at the time of biopsy: wound contraction % A0 − At/A0*100.

Several systems were studied, with or without chemicals to treat the skin alteration. Hyaluronic acid and gelatin are encouraging materials for the treatment due to their natural existence in human ECM of the skin tissues [70]. Other than these two materials, cellulose, alginate chitosan copolymers, chitosan–gelatin-honey copolymers and biphasic gelatin-silk systems are also used in this application [71, 72]. At present, many conventional products are on the market use, as a blend of definite materials and appropriate seeding of cells from innumerable origins, For example, applications of HYAFFTM esterified hyaluronic acid (HA) produced by FIDIA Limited; laser skin auto-graft, made up of an HA-membrane with keratinocytes, and hyalo-graft 3D, made with HA, with added fibroblasts. Table 2 represents some of the drug formulations that are adopted for various skin disorders.

8 Projections for Future Research

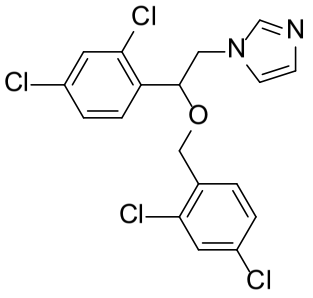
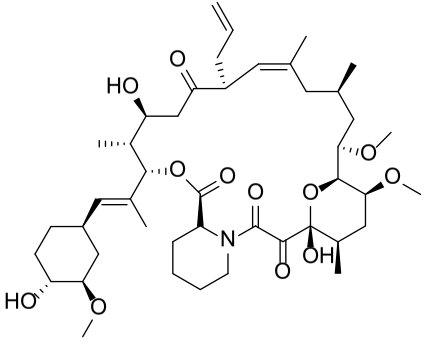
With the advancement in materials construction and engineering, variation of the in vivo efficacy of hydrogel nanoparticles is conceivable. With this groundwork, it is in the offing that, in the future, hydrogel nanoparticles with intended internal structures can be spawned for more adaptable drug delivery uses, including co-administration of multiple drugs. Indeed, a growing level of indication has clearly proposed that multi-drug therapies can provide an increased therapeutic benefit as related to single-drug remedial approach. This is demonstrated by a preceding study, in which double-walled polymeric microspheres are adopted to transport

Table 2 Some of the drugs formulation and its applications

S.no	Drug	Structure	Formulation	Application
1	Ketoconazole		Topical / Transdermal	Antifungal
2	Sulconazole nitrate		Topical / Transdermal/subcutaneous	Cutaneous dermatophytosis

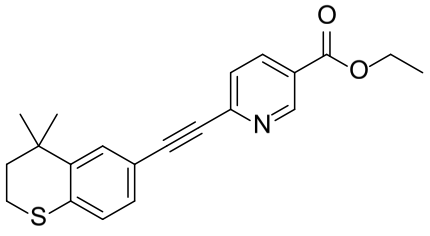
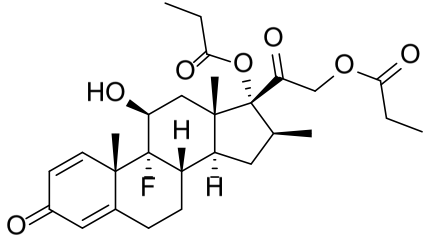
(continued)

Table 2 (continued)

S.no	Drug	Structure	Formulation	Application
3	Miconazole nitrate		Topical / Transdermal/subcutaneous	Cutaneous dermatophytosis
4	Tacrolimus		Topical / Transdermal/subcutaneous	Vitiligo, Atopic keratoconjunctivitis

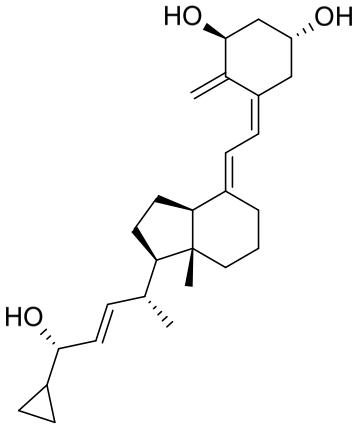
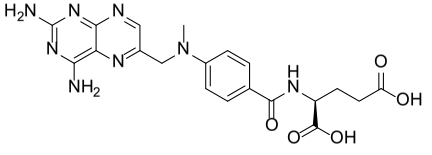
(continued)

Table 2 (continued)

S.no	Drug	Structure	Formulation	Application
5	Tazarotene		Topical / Transdermal	Psoriasis
6	Calcipotriol/betamethasone dipropionate combination		Topical / Transdermal	Psoriasis

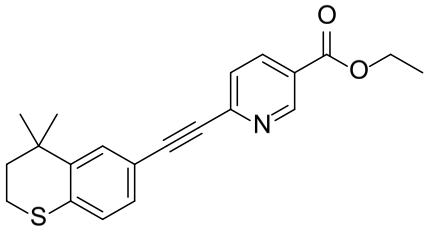
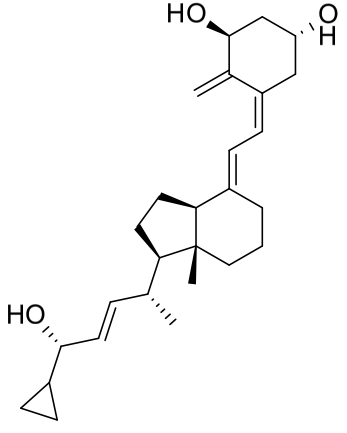
(continued)

Table 2 (continued)

S.no	Drug	Structure	Formulation	Application
7	Calcipotriol		Topical / Transdermal	Psoriasis
8	Methotrexate		Topical / Transdermal/subcutaneous	Psoriasis

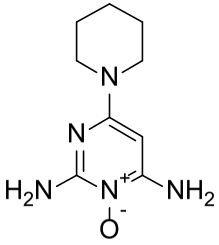
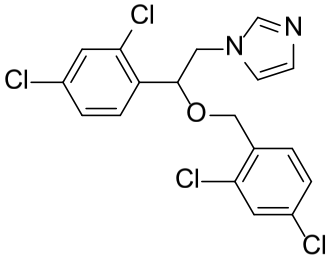
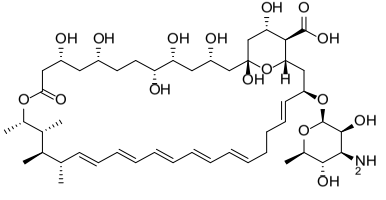
(continued)

Table 2 (continued)

S.no	Drug	Structure	Formulation	Application
9	Tazarotene		Topical / Transdermal/subcutaneous	Psoriasis
10	Calcipotriene		Topical / Transdermal/subcutaneous	Psoriasis

(continued)

Table 2 (continued)

S.no	Drug	Structure	Formulation	Application
11	Minoxidil		Propylene glycol--water-ethanol solutions, Topical / Transdermal	Androgenic alopecia
12	Miconazole		Powders, parenteral, gels, creams, and ointments, Topical / Transdermal/subcutaneous	Candida infections, fungal infections
13	Amphotericin B		Cream, lotion, gels, ointments, Topical / Transdermal/subcutaneous	Fungal skin infections

both doxorubicin and a medicinally active transgene to HepG2 cells. The collective treatment enriches the cytotoxicity when compared to either of the two remedies alone. The increased potential of multi-drug therapies is further sustained recently by the observation that the therapeutic benefits of aerosol cisplatin can be improved by administration of a therapeutic transgene, using adenoviral-type 5(dE1/E3) (Cytomegalovirus promoter) as a vector, before cisplatin administration. Collectively, these point to the medicinal potential of multi-drug remedies. Regardless of this, the efficiency of multi-drug therapies may be fraught with if the co-delivered drugs are not well suited with each other. This is one of the foremost tasks to be addressed for multi-drug administration.

9 Conclusion

The significant headway in hydrogel study is shown to divulge a fast expansion of hydrogel-based systems during the last a few decades, from a simple crosslinking of macromolecular networks by chemical or physical process to further cutting-edge formulation systems for biomedical application. With particular focus on in vivo framework, this chapter has offered a concise picture of current progress in design and development of hydrogel nanoparticles for skin disease and has comprehensive approaches for change in the properties of the nanoparticles for drug delivery. With the improved knowledge in hydrogel chemistry, the practical application of hydrogel formulations has an extraordinary chance to be studied further. Transformation of hydrogel research into in vivo and therapeutic drug delivery applications is, consequently, expected to continue to advance at an astonishing rate. Taking this into consideration, what we anticipate in the hydrogel platform is the wide spread uses of technologies built on hydrogel-based formulations in the clinical setting for several therapeutic applications.

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