Hydrogels as Controlled Drug Delivery Systems for Pigmentation Therapy in Stable Vitiligo - A Review

Ms. Prajakta C. Patil*, Ms. Prajakta B. Borhade*

Assistant Professor of SMBT Institute of Diploma Pharmacy, Affiliated to MSBTE,

Student of SMBT Institute of Diploma Pharmacy, Affiliated to MSBTE,

Maharashtra, India -422001

Corresponding Author,

Ms. Prajakta C. Patil,

Abstract

Vitiligo is a chronic disorder resulting in parts of skin that are depigmented due to the loss of functional melanocytes. Topical corticosteroids, calcineurin inhibitors, and phototherapy are examples from conventional therapies that have been demonstrated to have issues with patient noncompliance, systemic side effects, or limited efficacy. Hydrogels have been marketed as sustained release carriers for locally given pigmentation treatments in recent years, offering a fresh approach to treating stable vitiligo patches. A three-dimensional, hydrophilic network of polymers, hydrogels can contain a variety of bioactive substances and release them under specific circumstances at their intended site. Due to their high water content, biocompatibility, and ability to mimic the extracellular matrix, these systems have been extensively utilized for skin applications. This paper highlights the latest advancements in hydrogel-based drug delivery systems for vitiligo treatment in terms of guaranteeing the continuous release of pigmentation agents, such as melanocyte-stimulating factors, herbal extracts, and small molecules. A thorough explanation of the procedure is included. Hydrogel mediation has the potential to improve therapeutic efficacy, bioavailability, patient adherence, and less side effects. It can also demonstrate long-lasting and promising outcomes for vitiligo.

Keywords

Hydrogels, Vitiligo, Pigmentation agents, melanocytes, drug delivery

1. Introduction

Vitiligo is a chronic skin illness that results in the gradual death of pigment-producing skin cells, leaving white, unpigmented patches of skin. Patients experience psychological
Discomfort due to the disease's obvious skin changes, which frequently result in social prejudice.

Vitiligo affects between 0.5 and 2.0 percent of people worldwide, yet there are currently insufficient treatment options due to the disease's complex etiology, limited efficacy, and safety issues. Localized and sustained treatment options prove most effective for stable vitiligo which shows no new lesion growth or existing patch expansion over a 6-12 month duration. [1]

Topical corticosteroids, calcineurin inhibitors, phototherapy, and surgical grafting are the main therapeutic approaches. These therapeutic methods usually have limited skin absorption, require several administrations, have short drug retention periods, and have adverse consequences with prolonged use. The need for advanced therapeutic methods that improve drug delivery systems and skin retention capabilities remains critical [2] [3]

Hydrogel-Based Drug Delivery Systems in Vitiligo

The use of hydrogels as novel drug delivery systems (NDDS) brings various benefits when compared to traditional topical treatments. Hydrogels' three-dimensional polymeric networks are rich in water, which produces biocompatible and adjustable qualities appropriate for skin applications.

They offer:

- With regulated delivery methods, the medicinal substances undergo sustained release.
- Therapeutic chemicals are delivered straight to the afflicted parts of the vitiligo patch.
- The administration method prevents excessive absorption into the body while improving the retention of therapeutic substances on the skin.

The therapy results in fewer adverse effects while patients find it easier to adhere to the treatment plan.[4]

MC1R Peptide Agonist-Based Hydrogel

Targeting the Melanocortin 1 Receptor (MC1R), a critical pigmentation regulator, is one novel hydrogel strategy. A new MC1R peptide agonist that self-assembles into Nano fibrils and forms a durable hydrogel matrix under physiological conditions was discovered in a recent study.

Important MC1R Hydrogel Features:

- Stability: More stable than unbound peptides.
- Controlled Release: Makes it possible for the peptide to be released continuously.

- Rheological Properties: It is perfect for topical application since it quickly recovers after shear-thinning.
- Protease Resistance: Exhibits improved resistance to enzymatic breakdown, sustaining activity for prolonged periods of time.

A novel MC1R peptide agonist that self-assembles under physiological conditions to generate Nano fibrils and a stable hydrogel structure was recently discovered

Therapeutic Mechanism:

The MC1R agonist hydrogel promotes melanogenesis because it enhances the activity of critical melanin production enzymes:

Tyrosine

Tyrosine-Related Protein 1 (TYRP-1) Tyrosine-Related Protein 2 (TYRP-2)

The hydrogel demonstrated superior pigmentation induction compared to the free peptide agonist during mouse preclinical tests which indicates its potential as a topical drug for vitiligo treatment. [5]

Autologous Epidermal Cell Transplantation Using HA-Based Hydrogels

When autologous epidermal cells are transplanted, the use of cell therapy for stable vitiligo shows encouraging results. During the process, patients' skin cells are applied to areas of their bodies that have lost pigment.

Maintaining transplanted cells' viability and functionality once they enter the body is the primary challenge in this process. Researchers developed a novel technique for obtaining cells while attaching them to a three-dimensional biocompatible scaffold using crosslinked hyaluronic acid (HA).

Innovations in the Cell-Based Strategy:

New Extraction Method: This method yields very viable extracted epidermal cells at 37°C for two hours.

HA Hydrogel Scaffold: BDDE (1, 4-butanediol diglycidyl ether) crosslinking provides:

- Biocompatibility
- Encapsulation of cells
- Extended preservation of cells
- Increased effectiveness of treatment

This integrated strategy guarantees continuous cell delivery without compromising viability, opening the door to less invasive, efficient, and time-saving treatments for stable vitiligo.[7]

Ethosomes-Based Hydrogel for Methoxsalen Delivery

Methoxsalen, which functions as a photosensitizer in PUVA therapy for the treatment of vitiligo, can be effectively administered using ethosome-based hydrogels.

Ethanol is added to lipid vesicles to create ethosomes, which enhance medication penetration through the epidermal barrier. Before incorporating the ethosomes into hydrogels based on Carbopol® 934 for the investigation, researchers used central composite design (CCD) to optimize the ethosome formulation.

Physicochemical Description:

- Vesicle Size and Shape: The vesicles had a uniform Nano metric size distribution and looked spherical with many lamellae.
- Stable particle dispersion was shown by the zeta potential measurement.
- Excellent encapsulation capacity and decreased drug leakage are demonstrated by the system.
- The physical characteristics of the formulation are suitable for dermatological applications. [6]

Skin Interaction Studies:

Improved skin penetration, dermal layer retention, and extended drug delivery were shown by the skin interaction investigations, which comprised both in vitro and ex vivo testing. Rhodamine 123 fluorescence microscopy demonstrated the compound's deep skin penetration. When compared to traditional methoxsalen cream formulations, photo toxicity testing showed less erythema effects and reduced levels of skin irritation.

Methoxsalen's improved therapeutic index and reduced side effects are provided by this formulation, which is crucial for patient comfort and long-term treatment compliance.

One significant development in the treatment of stable vitiligo patients is the use of hydrogel-based medication and cell delivery devices. The three novel systems—MC1R peptide agonist hydrogels, HA-based scaffolds for cell therapy, and ethosome-based methoxsalen formulations—overcome the drawbacks of conventional therapies.

These approaches offer:

1. Enhanced skin penetration
2. Prolonged therapeutic effects
3. Improved safety profiles

This review aims to explore the potential of hydrogels as carriers for pigmentation agents in the treatment of stable vitiligo patches, focusing on prolonged release mechanisms, improved therapeutic outcomes, and future prospects for clinical application.[8]

2. Pathophysiology of Vitiligo

Vitiligo has a complicated etiology and is frequently referred to as a multifactorial polygenic condition. Both hereditary and non-genetic variables are frequently linked to it. Although a number of theories on its pathogenesis have been put forth, the precise etiology is still unknown. The widely accepted theory is that vitiligo skin with melanocyte loss lacks melanocytes due to their destruction. Melanocyte counts gradually decline as a result of the damage. Cytotoxic mechanisms, autoimmune mechanisms, intrinsic melanocyte abnormalities, neurological mechanisms, and oxidant-antioxidant mechanisms are among the theories regarding melanocyte loss.

According to the neural theory, melanocytes are typically destroyed and melanin production is reduced by a neurochemical mediator. Melanocytes are destroyed by intermediate or metabolic products of melanin production in oxidative and antioxidant pathways. In the intrinsic defect of melanocytes, there is an inherent abnormality that impedes their growth and differentiation.
Another hypothesis is autoimmune or cytotoxic, where there is an alteration in humoral and cellular immunity that causes the destruction or dysfunction of melanocytes. This theory supports the hypothesis that non segmental vitiligo is more commonly associated with autoimmune disorders than the segmental type of vitiligo.[9]

Oxidative stress

Oxidative stress is the primary cause of melanocyte loss in vitiligo. Because of their energy- intensive melanogenesis mechanism, melanocytes are inherently sensitive to environmental stressors including UV light and per oxidizing chemicals. Patients with vitiligo have higher levels of reactive oxygen species (ROS) in their skin, such as hydrogen peroxide and peroxynitrite, their systems produce lower levels of antioxidant enzymes like glutathione reductase and catalase.

Melanocytes in vitiligo patients' skin exhibit higher reactivity to reactive chemicals, develop aberrant shape, and become more vulnerable to oxidative stress. Catalase is one antioxidant that helps lessen these negative consequences. The immune system may initiate autoimmune responses because oxidative stress causes the release of HMGB1 molecules which stimulate immune activity that sends T-cells to the skin.[10]Because oxidative stress damages DNA and activates repair processes along with transcription factors like Nrf2, detoxification genes like HO-are activated. This process inhibits the WNT/β-catenin signaling pathway, despite its critical function in the production and restoration of melanocytes. This mechanism results in the downregulation of melanogenesis genes like MITF, MC1R, and TYRP1. When the WNT pathway is pharmacologically activated, melanocyte function can be restored.

The active form of Vitamin D3 (1, 25-dihydroxyvitamin D3) defends melanocytes through WNT pathway activation which demonstrates its essential function in maintaining melanocyte survival and functionality.[11]

Types of vitiligo

There are two main forms of vitiligo: segmental vitiligo and nonsegmental or generalized vitiligo.

The most prevalent type is generalized vitiligo. There are white spots on both sides of the body, and during a person's lifespan, the patches continue to appear all over the body. The color loss is seen to happen quickly and to occupy a large portion of the body.

One uncommon kind of vitiligo is segmental vitiligo. It is an autoimmune disorder that causes skin depigmentation, it is also known as localized or unilateral vitiligo, as the white patches only affect one area of the body. The SV moves quickly before stopping suddenly. [12]

Stability is the most important feature to take into account when selecting any transplanting technique to treat vitiligo. It has been demonstrated, nevertheless, that grafts at the recipient site can concurrently depigment and repigment at the donor site. It has also been demonstrated that following donor site depigmentation, the recipient area fully repigments, with pigment multiplying from each graft. Additionally, effective repigmentation after regrafting in earlier punch failure cases has been reported. Koebner's historical phenomenon (Kp-h) and test grafting were the only methods available to assess stability. Ironically, there seems to be no consensus among practitioners regarding the optimal duration required for stability despite forty years of expertise with vitiligo surgery.

Furthermore, it is still difficult to define stability precisely in vitiligo. Sometimes it can be misleading to rely too heavily on TG or KpH in vitiligo. These two only demonstrate the disease's seeming clinical stability, which may not be a reliable indicator of its molecular stability. Antimelanocyte cytotoxic reaction was demonstrated by CD8+ TCC obtained from perilesional biopsies of vitiligo patients. In addition to using electron microscopy and histoenzymological analysis of the nonlesional and perilesional skin of vitiligo patients, a thorough comprehension and definition of stability should be sought from a clinical perspective. It is likely that some growth agents that stimulate melanocytes both mitogenically and melanogenically should also be considered.[13]

Role of Melanocytes in Stable Vitiligo

White patches result from the absence or malfunction of melanocytes, the cells that produce pigment, in persistent vitiligo. According to research, melanocyte destruction is largely caused by an autoimmune reaction. An analysis of melanocytes' function in stable vitiligo.

1. Melanocyte destruction

In vitiligo, the immune system unintentionally targets and kills melanocytes, which are the cells that produce melanin in skin, hair and eyes. It leads to white patches over the skin. Even if the Melanocytes may be present in the area they are mostly dysfunctional.

2. Immune System Participation

Cytotoxic T-cells, which is an overactive immune system, it is a minor factor in melanocyte destruction. Through a variety of processes, such as apoptosis, these T-cells begin the destruction of melanocytes by targeting them as foreign cells.

Melanocyte Reservoir

They are stored in melanocytes, which are present in hair follicles. These melanocytes may be crucial for repigmentation in stable vitiligo if they can be activated.

3. Repigmentation Difficulties

While some people may have spontaneous repigmentation, it is usually transient and may not be permanent. Repigmentation may be challenging due to the autoimmune attack on melanocytes and the potential for keratinocyte dysfunction. Immune system targeting treatments and melanocyte stimulation are often needed to promote repigmentation. [14]

Limitations for Conventional Therapies

Vitiligo in children can cause psychological trauma for both patients and their parents, which can result in mental diseases like melancholy or anxiety, low self-esteem, and low quality of life scores. The primary objective of a dermatologist is to treat vitiligo and assist patients in managing their stigmatizing condition.

Thankfully, a wide range of medical and surgical procedures are now available.

Topical agents

Localized vitiligo, particularly on the face and torso, can be effectively treated with topical corticosteroids (TCS). They work by suppressing the immune system and reducing inflammation. For children, mid-potency steroids (such as betamethasone dipropionate 0.05% and clobetasol propionate 0.05%) are frequently recommended.

A 45–60% response rate is shown in childhood vitiligo, especially in its inflammatory forms. Patients should apply the treatment once or twice daily, either continuously or on alternate days.

Because these drugs have several systemic and local side effects (skin atrophy, striae, HPA axis suppression, Cushing's syndrome), prolonged usage of them for longer than two to four months should be avoided. Because it increases the risk of glaucoma and other issues, facial usage must be limited.

For small, resistant areas, strong corticosteroids like betamethasone valerate and extremely strong corticosteroids like clobetasol propionate are regarded as first-line treatments. Acral areas perform worse than sun-exposed parts. Low-potency steroids or topical calcineurin inhibitors (TCIs) are recommended for sensitive areas such as the face, neck, and genitalia.

If the treatment proves successful, it should be continued with daily use for three months before transitioning to an intermittent schedule for an additional three months. If there is no progress after three to four months, patients should discontinue the treatment. According to a meta-analysis, extremely potent TCS achieved 55% success in achieving ≥75% repigmentation, whereas potent TCS treatment produced 56% success.

Phototherapy

Ultraviolet radiation (UVR), which contains both UVB and UVA rays, is considered a first-line treatment because of its high tolerance and efficacy, especially for severe vitiligo. UVR has two effects: it boosts melanocyte activity and inhibits the immune system [16]. Narrow-band UVB, oral PUVA, topical cream PUVA, bath PUVA, and PUVA sol are among the several phototherapies that are currently available. Broad band UVB should no longer be used due to its reduced effectiveness and sunburn danger.

The proopiomelanocortin pathway in the hypothalamus' arcuate nucleus, the central hypothalamic-pituitary-adrenal axis, and immunosuppressive and opioid genic effects are just a few of the systemic effects of ultraviolet radiation, especially UVB (280–320 nm) as opposed to UVA (320–400 nm). These effects are produced by an upregulation of the local neuroendocrine axis. The mechanisms by which nb-UVB (wavelength of 311 nm) phototherapy treats vitiligo include melanocyte migration from perilesional skin, melanocyte differentiation, melanin production, and immunosuppression. Total body UVB is recommended for widespread vitiligo that covers more than 15% to 20% of the body's surface area and for vitiligo that advances rapidly.

Surgical grafting

The goal of vitiligo surgery is complete repigmentation that visually mimics the surrounding normal skin. Selecting the correct patients is crucial to achieving the best outcome because not all patients or vitiliginous skin locations are suitable for surgery. Prior to surgery, the following patient factors should be considered:

- The patient's age
- Expectations of patient
- Stability of disease
- The vitiligo patch's dimensions and placement
- The suggested surgical technique
- The suggested donor location

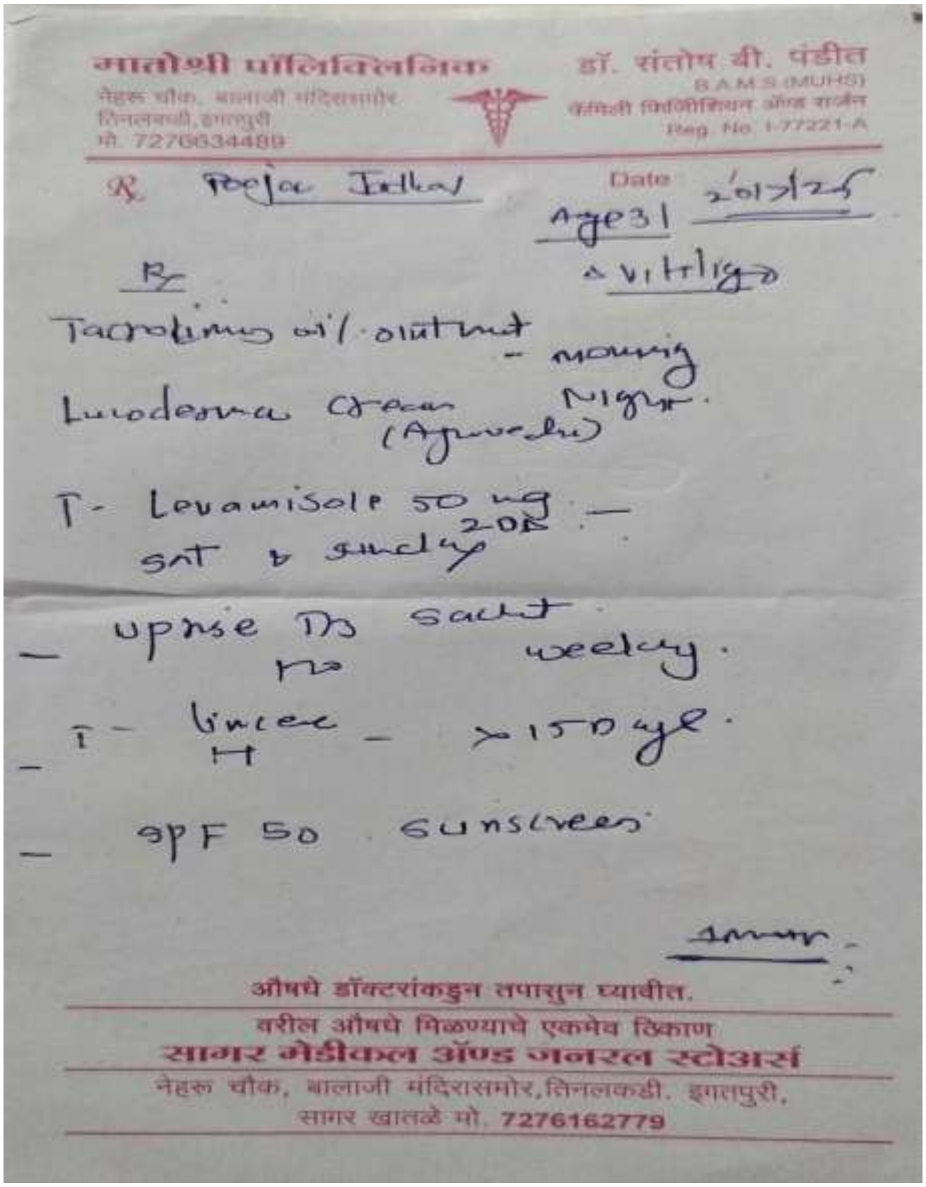
Typical surgical methods for repigmentation include:

Types of Vitiligo Surgery	
Grafting of melanocyte-rich tissue	**Grafting of melanocyte cell suspension**
• Punch grafting in miniature (MPG) • Grafting with suction blisters • Grafting with split thickness	• Suspension of autologous, uncultured epidermal cells • suspension of cultured melanocytes

Surgical grafting are used in stable vitiligo. Segmental vitiligo has better surgical outcomes. The results also varies depending upon the site of body. [15]

Medications that try to control pigmentation and stabilize growth are frequently used in traditional vitiligo treatments. Corticosteroids, calcineurin inhibitors, systemic supplements, antioxidants, and narrowband UV phototherapy are frequently used in the treatment.

The prescription that follows is a typical treatment that a doctor would administer to a patient who has vitiligo. It highlights the reliance on topical corticosteroids and immunomodulators to enhance pigmentation. Despite their widespread use, these drugs have some local adverse effects, such as skin thickening, burning, itching, etc., and there are hazards associated with long-term use. This brings in the for the use of novel therapies which includes advanced drug delivery systems such as hydrogels to achieve desired effects with fewer side effects, improved safety, bioavailability and patient adherence.



मातोश्री पॉलिक्लिनिक
नेहरू चौक, बालाजी मंदिरसमोर
तिनलकडी, इगतपुरी
मो. 7276634489

डॉ. संतोष बी. पंडीत
B.A.M.S (MUHS)
Reg. No. I-77221-A

Pooja Jadhav   Date 20/7/25
Age 31
Rx   ∆ vitiligo

Tacrolimus 0.1% ointment - morning
Leucoderma cream (Ayurvedic) Night.
T- Levamisole 50 mg 2 OD —
sat & sunday
— upmse D3 sachet weekly.
— T- Vincee H — x 15 D
— SPF 50 sunscreen

औषधे डॉक्टरांकडुन तपासुन घ्यावीत.
वरील औषधे मिळण्याचे एकमेव ठिकाण
सागर मेडीकल ॲण्ड जनरल स्टोअर्स
नेहरू चौक, बालाजी मंदिरासमोर, तिनलकडी, इगतपुरी,
सागर खातळे मो. 7276162779

Fig-1 Sample prescription illustrating conventional medication treatment for Vitiligo.

.

Comparison of Limitations of Conventional Vitiligo Treatments [16] [17] [18]

Treatment Modality	Limitations
Topical agents	• Restricted access to the skin's deeper layers • Requires long-term, persistent use for obvious benefits; frequently unsuccessful for widespread or stable vitiligo • Variable efficacy according on place (e.g., hands, feet) and skin type; • Risk of local adverse effects, such as skin atrophy (with corticosteroids)
Phototherapy	• Needs regular sessions (two to three times a week for several months). • Limited availability in areas with limited resources or in rural areas • Prolonged exposure increases the risk of photodamage, early aging, or carcinogenesis. • It can be expensive and time-consuming; it is less effective on acral areas (hands, feet, and joints).
Surgical grafting	• Not practical for large or numerous depigmented patches. • Only appropriate for stable vitiligo (non-progressive for 6–12 months); • Invasive procedure with risks like scarring, infection, and keloid formation. • Possibility of graft rejection or pigment mismatch. • Requires specialized equipment and trained personnel

3. What are hydrogels?

Hydrogels are three-dimensional networks of crosslinked polymers rich in hydrophilic groups that can absorb large amounts of water without dissolving and maintain their structure. They are classified as either natural (agar, chitosan, alginate) or synthetic (PVA, PEO, PAA) polymers according to their structure (amorphous, semi crystalline etc.) and polymer type (homopolymeric or copolymeric). Crosslinking, which can be covalent or physical (ionic, hydrogen bonding, or hydrophobic contacts), is crucial to their integrity and swelling behavior. Despite having a small electrochemical window (~1.2 V), ionically conductive hydrogels are attractive as solid-state electrolytes due to their safety, affordability, and environmental friendliness. [19]

Their fragility prevents them from being used in flexible and stretchable energy devices, but new developments such as double-network (DN) hydrogels, which combine covalent and ionic crosslinking, have created hydrogels with exceptional toughness and stretch ability (up to 20 times their length). To boost mechanical strength, these robust hydrogels employ hysteresis from ionic bond unzipping, fracture bridging, and reversible weak bonds. In 1960, PHEMA, the first modern hydrogel, was used for the first time in contact lenses due to its ability to retain moisture.

The hydrophilicity of functional groups (like -OH, -COOH, and $-NH_2$) and the strength of the crosslinking are the main factors that determine water absorption and structural stability, which qualifies hydrogels for use in energy and biomedical applications. [20]

4. How hydrogels work?

DNA's capacity to store genetic information has developed into a programmable tool that allows researchers to create precise nanostructures in two and three dimensions. Complementary DNA strands that swell when exposed to water-based solutions can be used by scientists to create crosslinked networks. The networks work as hydrogels based on DNA. The substance is appropriate for gene control applications because it interacts with nucleic acid molecules, such as siRNA and miRNA. These structures' geometry makes it possible for DNA-binding drugs to be loaded efficiently, making them useful platforms for targeted therapeutic delivery.

These hydrogels exhibit several desirable properties, including:

- High solubility
- Outstanding biocompatibility
- Structural adaptability
- Responsiveness to the environment

One major accomplishment in this field of study is the creation of DNA hydrogels based on quantum dots (QDs). Researchers may do simultaneous imaging and drug administration in both lab-based and living organism environments thanks to the development of fluorescent quantum dot-based DNA hydrogels. Zhang and his research team developed a zinc sulfide QD-doxorubicin-DNA hydrogel which delivered multiple functional enhancements: Adjustable optical characteristics and particle size Effective loading and release of drugs Better cellular uptake and tumor targeting In vitro, three times as effective as free doxorubicin Real-time bio imaging tools to track the development of tumors These intelligent hydrogels function to target specific cells when scientists add aptamers such as siRNA which enables exact gene expression management while decreasing non-targeted effects.[22]

5. Hydrogels in Dermatology

The skin barrier is rebuilt by hydrogels' tunable porosity, stiffness/viscoelasticity, degradability, excellent adhesiveness, controlled drug administration ability and moisturizing capacity.
Additionally, hydrogels can be employed as drug delivery platforms, namely as Nano carriers, to deliver therapeutic medications either intracellularly or extracellularly to inflammatory regions. Because of these qualities, hydrogels are a very effective choice for the localized treatment of conditions including atopic dermatitis and psoriasis.

Hydrogels stand apart from all other dermatological and cosmetic formulations due to a number of unique characteristics. When subjected to different chemical and physical stimuli, these biomaterials exhibit remarkable swelling potential, which enables them tissue-like flexibility to switch between their gel and sol forms. Hydrogel structures release therapeutic chemicals in response to temperature changes, local pH variations, physical stimulation, and the presence of enzymes. Various methods exist for modifying hydrogel pore size along with surface characteristics because these adjustments help achieve desired drug release kinetics and mechanical properties for different applications.[23]

Hydrophilic polymer chains with covalently bonded monomer unit's crosslink to form hydrogels. Gene-loaded nanoparticles are evenly distributed throughout the hydrosol, the pre-crosslinked precursor solution, during the synthesis process. The hydrosol becomes a stable three-dimensional hydrogel network with embedded genes when covalent connections are formed between polymer chains during further polymerization. By balancing osmotic swelling forces against elastic rebound, the technique creates interconnected micropores with 10–500 nm widths through controlled interchain spacing to achieve native extracellular matrix (ECM) biomechanical properties.

Crosslinking polymer chains produces hydrogels. Hydrogels come in a wide variety of forms, including natural, synthetic, and semi-synthetic polymers. Hydrogels can be classified as natural, synthetic, or semi-polymer

hydrogels based on the polymer's source. Cellulose, chitosan, collagen, alginate, agarose, hyaluronic acid, gelatin, fibrin, and other materials are examples of naturally occurring hydrogels. They are naturally biocompatible, bioactive, and biodegradable despite having comparatively low mechanical strength and stability. Although some of its elements may occasionally cause sensitivities, most people can safely utilize natural hydrogels. Therefore, using natural hydrogels to treat sensitive people may pose immunological hazards.
Synthetic polymers are used to create synthetic hydrogels.[24]

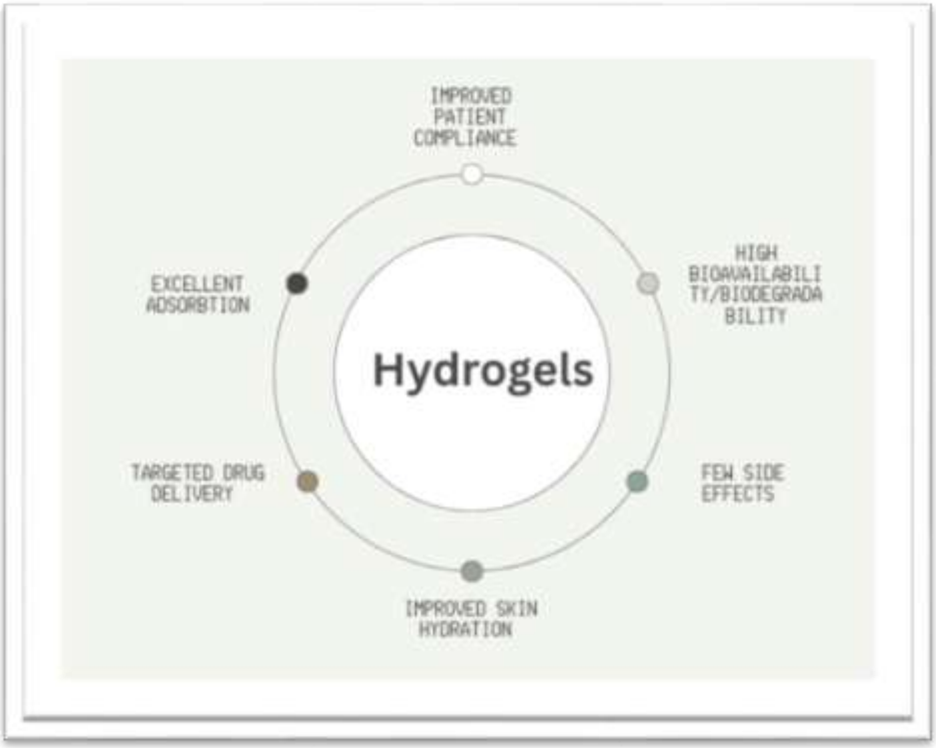
Polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyethylene oxide (PEO), poly-2-hydroxyethyl methacrylate (PHEMA), poly-N-isopropyl acrylamide (PNIPAM), polyacrylic acid (PAA), and polyacrylamide (PAAM) are a few examples of synthetic polymers made by polymerizing a monomer. They are mechanically strong and stable, despite the fact that some of them—like PAAM—are biocompatible. Natural polymers that have undergone chemical modification or a blend of natural and synthetic polymers used to make semi-hydrogels are examples of semi-synthetic polymers. Methacryloyl-modified gelatin (GelMA) and acrylate-modified hyaluronic acid (AcHyA) are examples of natural polymers that have undergone chemical modification. It could also be a blend of synthetic and natural
Polymers, like gelatin and albumin or PEG-conjugated fibrinogen. Natural hydrogels include bioactivity qualities, but they also offer multitunable capabilities through a variety of chemical factors.[26]

By changing the gel matrix's cross-linking density using a range of physical and chemical cross-linking methods, the drug delivery application of porous hydrogels can be enhanced and altered.

When actives are trapped inside the gel matrix because of its porosity, the rate of release is determined by the diffusion coefficient across the three-dimensional polymer network. By altering the permeability in response to external stimuli, surface-specific modification or grafting on polymer structures can alter the drug flux and, consequently, release kinetics. The hydrogel's high water content contributes to its biocompatibility, and its mechanical and physicochemical properties—which are comparable to those of the natural extracellular matrix—make it perfect for wound dressings. Additionally, hydrogels can be tailored to the type of surface.[25]

By regulating the interactions between the hydrogel and entrapped molecules, various gelators at varying concentrations or timeframes can be employed to maximize the release rate and/or give the injectable hydrogels mechanical strength. The exact placement and application of a drug-loaded hydrogel in high-stress locations, such cartilage tissue, typically dictates the tensile strength required from the hydrogel. By adding hydrophobic binding sites to polymer networks using straightforward techniques such solid molecular dispersion, it should be able to boost the loading of poorly soluble medications while preventing drug recrystallization in aquatic conditions. Cartilage as well as other vesicular sites. It may be possible to increase the loading of poorly soluble drugs while preventing drug recrystallization in aquatic environments by incorporating hydrophobic binding sites into polymer networks using simple methods like solid molecular dispersion. [27]

6. Advantages of Hydrogels



7. Hydrogel Strategies for Vitiligo

Narrow-band phototherapy, cell transplantation, epidermal transplantation, and drug therapy, such as Janus Kinase Inhibitors, are now used by medical professionals to treat vitiligo. The duration of the treatment cycle increases while the effects of medicine and narrow-band phototherapy therapy are not statistically significant. Excessive scarring and significant skin injury from vitiligo epidermal transplantation lead to poor scar development. Due of its potential for successfully treating stable vitiligo, cell transplantation has drawn interest from researchers and medical professionals. Healing results from cell suspension injections deteriorated because implanted cells were lost before they could reach their intended location. The degree to which the transplanted cells endure and stay in the vitiligo areas determines the outcome of healing.
Biomaterial-based cell delivery systems are used in medical procedures to address issues that arise during cell transplantation therapy.

Recently, cell transplantation therapy has made use of a variety of biomaterials, such as collagen, chitosan, and hyaluronic acid hydrogel, because of their good biocompatibility and degradability, which maintain cell form and partly promote cell movement. The most common use of collagen patches is as a vehicle for suspensions of epidermal cells. To prevent the loss of epidermal cells, they frequently apply the cell suspension to the area of the post-dermabrasion lesion. Next, a collagen patch is put on. [28]

Fan et al. use multicellular melanocyte spheroids to form a chitosan membrane; a similar process is used for skin transplantation. The results demonstrated that the insertion of a chitosan-based melanocyte spheroid patch in that epidermal ablation model where PUVA-induced sunburn reacts can facilitate the melanocyte transplanting procedure. Ghorbani et al. covered the vitiligo area with a hyaluronic acid gel and autologous, non-cultured trypsinized melanocyte solution.
The results showed that autologous non-cultured plus trypsinized melanocyte grafting effectively and safely treats resistant vitiligo. Actually, the majority of research on the application of melanocytes and biomaterials in vitiligo

treatment includes applying or covering paste. Cell infiltration is the subject of additional research. Nevertheless, there exist several disadvantages, such as oxygen and nutrient shortage-brought-on poor cell survival. The dressing needs changing frequently, etc. So a novel plan treating vitiligo has to be made.

The hyaluronic acid solution's rapid biodegradation and shattered chemical One of the primary constituents of the skin's extracellular matrix, or ECM, is hyaluronic acid. The fermentation of bacteria produces hyaluronic acid, which is more biosafe than biomaterials derived from animal tissue. Hyaluronic acid-derived biomaterials are currently widely used in the treatment of skin conditions. For example, Wang et al. created a novel hydrogel platform using olive leaf-derived exosome-like Nano vesicles filled with hyaluronic acid and tannic acid. RNA sequencing and cluster analysis of predicted miR-168a-5p targets revealed that this composite hydrogel drastically downregulated the NF-κB signaling network, which controls Inflammatory responses, and efficiently decreased UV-induced skin damage, promoting cutaneous regeneration and repair. However, this prevented it from offering sufficient long-term assistance for cell retention. Thus, cross-linked HA aids in resolving these issues. To create a stable three-dimensional structure, HA was often crosslinked with BDDE (butylene glycol glycidyl ether), DVS (divinyl sulfone), ADH (diacetyl hydrazide), EDC (carbodiimide), GMA (glycidyl methacrylate), and PEG.[29]

However, BDDE and DVS are the most significant and advanced methods. However, BDDE is the most important, advanced, and widely promoted approach. It is explained by the crosslinking properties of the epoxy groups at opposing ends of the molecule. These epoxy groups preferentially create ether bond connections with the hyaluronic acid backbone's most accessible primary alcohols when exposed to alkaline circumstances.

Thus, hyaluronic acid (HA) crosslinked with BDDE was employed in this investigation to transport cells. The three-dimensional structure of crosslinked HA may help transplanted cells degrade more slowly and stay in place longer. In situ injection therapy ensures effective cell survival by allowing the body to provide nutrients and a three-dimensional microenvironment. Additionally, biomaterials can enhance cell preservation and reduce cell loss. An HA-based cellular delivery system for the management of chronic vitiligo was developed as a result of this logic. To guarantee a significant output of very viable cells (approximately 85% viability) in a considerably shorter processing time, the extraction method for epidermal cells needs to be enhanced. A suspension of HA-epidermal cells was then prepared for in vivo cell administration. Improved cell survival without sacrificing cell viability was found in animal tests. Finally, this method is highly successful and appears to be a fantastic therapy choice for stable vitiligo in hospital settings because HA is produced from an approved medical device.[30]

8. Conclusion

Patients' quality of life is greatly impacted by the obvious, progressive character of vitiligo, a chronic pigmentary disorder. Because the lesions stay the same for a long time, stable vitiligo offers a special therapeutic window for focused treatment regimens. However, traditional topical and systemic treatments frequently result in temporary benefits because of their low skin retention, quick clearance, and requirement for frequent reapplication. In this regard, hydrogels have drawn a lot of interest as a cutting-edge and efficient drug delivery method. Their ability to store vast amounts of water, which mimics the physiological environment of the skin, and their three-dimensional hydrophilic polymeric networks allow for the regulated and prolonged release of medicinal medicines. Additionally, hydrogels have improved skin penetration and moisturizing qualities, as well as patient-friendly qualities like comfort, clarity, and convenience of administration. Their capacity to combine numerous medications, such as antioxidants or anti-inflammatory compounds, offers prospects for multifactorial therapy of vitiligo in a single preparation. Despite these benefits, a number of issues still need to be resolved, including getting the best drug stability in hydrogels, getting sufficient penetration into skin layers that contain melanocytes, and confirming effectiveness in carefully planned clinical trials. Technological developments in nanotechnology, bio-responsive systems, and smart hydrogels can expand their use and improve their functionality. In summary, hydrogel-based medication delivery devices offer a practical, patient-friendly method of treating persistent vitiligo lesions. These systems hold promise for more efficient and long-lasting repigmentation treatments for the treatment of vitiligo and have the potential to become a standard treatment with additional study, formulation improvement, and clinical verification..

References

1. Vitiligo: StatPearls Naila.Ahmed Jan, Sadia Masood https://www.ncbi.nlm.nih.gov/books/NBK559149/

2. Vitiligo: An Updated Narrative Review
Alexander K C Leung , Joseph M Lam, Kin Fon Leong, Kam Lun Hon https://pubmed.ncbi.nlm.nih.gov/33302860/

3. The enigma and challenges of vitiligo pathophysiology and treatment
Zalfa A. Abdel-Malek, Christian Jordan, Tina Ho, Parth Rajendrakumar Upadhyay, Alan Fleischer, Iltefat Hamzavi https://onlinelibrary.wiley.com/doi/10.1111/pcmr.12878

4. Recent trends in the treatment of vitiligo using novel drug delivery system Nandita Sahu Parag Jain Deepika Sahu Kulvinder Kaur Kushagra Nagori Ajazuddin https://www.sciencedirect.com/science/article/abs/pii/S0378517324013401

5. MC1R Peptide Agonist Self-Assembles into a Hydrogel That Promotes Skin Pigmentation for Treating Vitiligo Ci ZhuTingting LiZhuole WangZenghui LiJiaying WeiHong HanDan YuanMinying CaiJunfeng Shi https://pubs.acs.org/doi/10.1021/acsnano.3c01960

6. Nanosized ethosomes-based hydrogel formulations of methoxsalen for enhanced topical delivery against vitiligo: formulation optimization, in vitro evaluation and preclinical assessment Bhawna Jain Garg, Neeraj K Garg, Sarwar Beg, Bhupinder Singh, Om Prakash Katare
https://pubmed.ncbi.nlm.nih.gov/26267289/

7. Emerging Therapeutic Innovations for Vitiligo Treatment Weiran Li, Penghao Dong, Guiyuan Zhang, Junjie Hu, Sen Yang https://pmc.ncbi.nlm.nih.gov/articles/PMC11940846/Concise review of recent studies in vitiligo Mohamed Allam, Hassan Riad https://pmc.ncbi.nlm.nih.gov/articles/PMC4080492/

8. Update on the pathogenesis of vitiligo
Helena Zenedin Marchioro a, Caio César Silva de Castro b, Vinicius Medeiros Fava c, Paula Hitomi Sakiyama d, Gerson Dellatorre a, Hélio Amante Miot e, https://pmc.ncbi.nlm.nih.gov/articles/PMC9263675/

9. The Role of Oxidative Stress in Vitiligo: An Update on Its Pathogenesis and Therapeutic Implications
Wei-Ling Chang 1,Chi-Hsiang Ko https://pmc.ncbi.nlm.nih.gov/articles/PMC10047323/

10. Białczyk, A., Wełniak, A., Kamińska, B. et al. Oxidative Stress and Potential Antioxidant Therapies in

Vitiligo: A Narrative Review. Mol Diagn Ther 27, 723–739 (2023). https://doi.org/10.1007/s40291-023-00672-z

11. Vitiligo Overview: Types, Causes, Symptoms and Treatment https://www.pfizer.com/disease-and-conditions/vitiligo
12. The Concept of Stability of Vitiligo: A Reappraisal Koushik Lahiri , Subrata Malakar https://pmc.ncbi.nlm.nih.gov/articles/PMC3352651/

13. Mechanisms of melanocyte death in vitiligo Jianru Chen , Shuli Li , Chunying Li https://pmc.ncbi.nlm.nih.gov/articles/PMC7983894/

14. Felsten LM, Alikhan A, Petronic-Rosic V; Vitiligo: A comprehensive overview. Part II: Treatment options and approach to treatment. J Am Acad Dermatol 2011; 65 (3):493–514. PubMed https://www.sciencedirect.com/science/article/abs/pii/S0190962211000399

15. Updates and new medical treatments for vitiligo (Review)
David Emmanuel Kubelis-López , Natalia Aranza Zapata-Salazar , Salvador Luis Said-Fernández , Celia Nohemí Sánchez-Domínguez , Mauricio Andrés Salinas-Santander , Herminia Guadalupe Martínez-Rodríguez , Osvaldo Tomás Vázquez-Martínez , Uwe Wollina, Torello Lotti ,Jorge Ocampo-Candiani https://pmc.ncbi.nlm.nih.gov/articles/PMC8170669/#:~:text=The%20side%20effects%20of%20TCS,and%20methylprednisolone%20aceponate%20(26).
16. Recent trends in the treatment of vitiligo using novel drug delivery system Nandita Sahu Parag Jain Deepika Sahu Kulvinder Kaur Kushagra Nagori Ajazuddin https://www.sciencedirect.com/science/article/abs/pii/S0378517324013401#:~:text=ri ghts%20and%20content-,Abstract,promising%20alternatives%20for%20better%20therapy.

17. Various Treatments for Vitiligo: Problems Associated and Solutions Dhvani M. Lakhani, Ashwini S. Deshpande https://japsonline.com/admin/php/uploads/1378_pdf.pdf
18. Hydrogels: a promising therapeutic platform for inflammatory skin diseases treatment Huali Cao ORCID logoab, Ming Wang ORCID logoa, Jianwei Ding ORCID logoa and Yiliang Lin https://pubs.rsc.org/en/content/articlehtml/2024/tb/d4tb00887a#:~:text=By%20creating%20a%20moist%20environment%2C%20hydrogels%20promote,the%20release%20of%20alarmins%20and%20subsequent%20inflammation.

19. Hydrogels: Properties and Applications in Biomedicine
20. Tzu-Chuan Ho, Chin-Chuan Chang, Hung-Pin Chan , Tze-Wen Chung , Chih-Wen Shu, Kuo-Pin Chuang , Tsai-Hui Duh, Ming-Hui Yang,Yu-Chang Tyan https://pmc.ncbi.nlm.nih.gov/articles/PMC9104731/#:~:text=Hydrogels%20are%20crosslinked%20polymer%20chains,they%20closely%20resemble%20living%20tissues.

21. Fundamental Concepts of Hydrogels: Synthesis, Properties, and Their Applications Shahid Bashir ,Maryam Hina , Javed Iqbal , A H Rajpar,M A Mujtaba, N A Alghamdi, S Wageh, K Ramesh, S Ramesh https://pmc.ncbi.nlm.nih.gov/articles/PMC7697203/

22. Hydrogel-Based Active Substance Release Systems for Cosmetology and Dermatology Application: A Review Martyna Zagórska-Dziok,Marcin Sobczak https://pmc.ncbi.nlm.nih.gov/articles/PMC7284449/

23. Cutting-edge developments in the application of hydrogels for treating skin photoaging Lili Cao Xiaoying QianXiaoying Qian Jie MinJie Min Zhongfeng ZhangZhongfeng Zhang Meiping YuMeiping Yu Dan YuanDan Yuan https://www.frontiersin.org/journals/materials/articles/10.3389/fmats.2024.1443514/f ull

24. Hydrogels for localized drug delivery: a special emphasis on dermatologic applications Shammy Jindal, Rajendra Awasthi, Kamya Goyal, Giriraj T Kulkarni https://onlinelibrary.wiley.com/doi/abs/10.1111/dth.15830

25. Polymeric nanoparticles-based topical delivery systems for the treatment of dermatological diseases Zheng Zhang , Pei-Chin Tsai , Tannaz Ramezanli, Bozena B Michniak-Kohn https://pmc.ncbi.nlm.nih.gov/articles/PMC3631287/

26. Injectable hyaluronan-based thermoresponsive hydrogels for dermatological applications Si Gou, Alexandre Porcello, Eric Allémann, Denis Salomon, Patrick Micheels, Olivier Jordan, Yogeshvar N Kalia. https://www.mdpi.com/1999-4923/15/6/1708

27. Injectable crosslinked HA hydrogel: a promising carrier for cell transplantation to treat stable vitiligo Qianren Zhen Jie Chen Yixun HuangWeikai Chen Dandan Cheng Qianqian JiaMeiqin Zhu Youguo Liao Qiulin He,Shunli Wu, https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2025.1583271/fu ll

28. Vitiligo – New Treatment Approach Veronika A Konstantinova , Olga Yu Olisova , Victor V Gladko , Ekaterina P Burova https://pmc.ncbi.nlm.nih.gov/articles/PMC6927254/

29. Understanding of Pathomechanisms and Clinical Practice for Vitiligo Atsushi Tanemura https://pubmed.ncbi.nlm.nih.gov/37830414/