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Hydrogel Based Transdermal Drug Delivery Systems

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Abstract
Administering medication by topical means is a highly practical and innovative method. The main challenge in administering medication through the skin is that most medications find it difficult to permeate through and penetrate its natural barrier. Traditional topical formulations have not shown to be successful in delivering drugs through the skin. Innovative medication delivery methods have a lot of promise for topical administration. Among these, hydrogels and other polymeric gels have been proposed as a solution to the issues with traditional distribution methods. Swellable polymeric polymers called hydrogels have been extensively studied as potential drug delivery system carriers. The unique properties of these biomaterials, such as their sensitivity to pH and temperature changes, swelling in aqueous media, or susceptibility to additional stimuli and compatibility with the body. This review reveals the practicality of hydrogel as a topical medication delivery method via the ophthalmic, rectal, vaginal, and cutaneous routes, anyplace in the body.

Keywords: Topical drug delivery, Hydrogels, Biocompatible.

1. Introduction

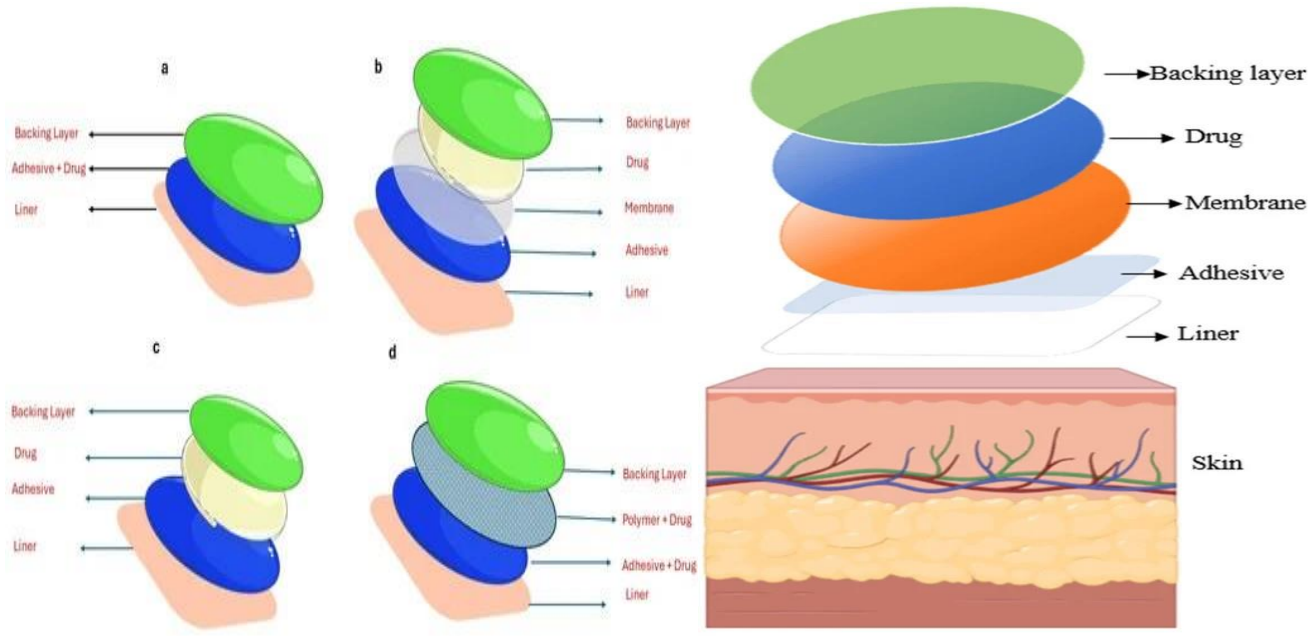
Compared to oral and injectable medication delivery, local application of medicinal substances offers several advantages, either directly onto the skin or into the systemic circulation after passing through the skin. (1) These possible benefits include avoiding hepatic first-pass metabolism, enhancing patient adherence, and being simple to apply topically.(2)

A wide range of research has been done in the field of drug delivery systems (DDSs) to provide better methods or processes for the therapeutic medication administration process [3]. The goal of DDS design is to regulate the rate, timing, and place of drug release inside the body in order to enhance the safety and effectiveness of current treatments [4]. Different therapies administer medications to the body by oral, parenteral, sublingual, and other methods. nasal, vaginal, topical, ophthalmic, transdermal, and rectal [5]. For the past few decades, transdermal DDSs have been researched as an improved traditional oral medication administration method. Transdermal drug delivery systems (TDDSs) release medications through the skin, providing as an alternative to transmucosal, subcutaneous, intravascular, and oral routes [2] Drugs must be transported to the designated target by an ideal DDS at a controlled speed over a predetermined amount of time. One of a TDDS's main advantages is its ability to provide regulated drug penetration through the skin, avoiding the liver's and GI tract's metabolic processes. Consequently, The quantity needed for medication administration is comparatively less than the pace connected with oral methods. TDDSs can maintain stable blood levels for a period of time between one and 7 days, encouraging improved patient compliance (3,4). This gives TDDSs a lot of leverage.in contrast to traditional techniques, which have drawbacks including low bioavailability, high first-pass metabolism, repeated dosage, variations in the drug's plasma concentration, etc. (5,6) TDDS-based drug administration may encompass local penetration enhancers, application formulations (such as gels), drug carriers (including liposomes, nanoparticles, and hydrogels), transdermal patches, and transdermal electrotransport, among others. The utilization of hydrogels as carriers has garnered significant attention in recent research. When compared to alternative carriers such as liposomes and nanoparticles, hydrogels exhibit a notable drug-loading capacity,(7) Recent research has focused on the use of hydrogels as carrier materials. Hydrogels outperform alternative carriers including liposomes and nanoparticles in terms of drug loading, regulated release, and little enzymatic breakdown (8). When the formulation comes into contact with the skin, it will create a semi-occlusive layer that covers the skin and concentrates the active component. formulation within a polymer matrix (9)They also have certain qualities that make them appropriate for transdermal medication delivery, namely the ability to retain water, biocompatibility, and control over swelling. The crosslinking process used to create hydrogels gives them a very porous structure. The permeability makes it easier to insert medications into the gel and releases them at a predetermined rate through dispersion. Hydrogels have the ability to slowly elute medicines for systemic medication administration. keeping the target and its surroundings high in drug concentration for a significant amount of time (10) Although transdermal drug delivery systems (TDDSs) have several benefits, the skin's low permeability limits how effective they may be. The administration of drugs transdermally is improved by the use of chemical and physical techniques. This study examines the advancements, difficulties, and prospects for hydrogel-based TDDSs. First, a thorough introduction to transdermal medication delivery is given, then by investigating the basic ideas behind hydrogels. Next, we explore how Skin diffusion facilitates medication absorption, and then an investigation of possible drug delivery using the use of hydrogels. Lastly, the conversation covers current issues and potential developments in transdermal medication delivery devices based on hydrogel. When topical preparations allow drugs to permeate into the underlying layers of skin or mucous membranes, they have localized effects at the application site. The main advantage of the topical delivery method is that it has the ability to specifically administer medication to a certain location (A targeted activity). It enables medication administration with rapid biological half-life and limited window of availability for treatment to the period of the activity (11) around 40% of freshly chemical substances have low solubility in the water and poses

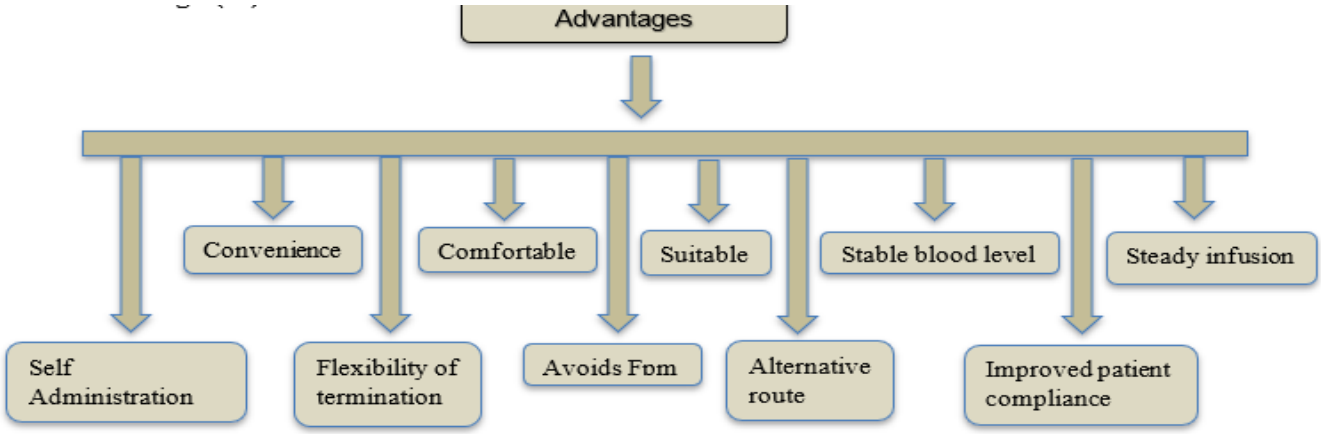
an important risk to recent drug delivery technologies. This helps in inadequate bioavailability, poor absorption, and insufficient dosage proportionality. But frequently, Oral delivery is inappropriate when the medication is in substantial deterioration inside the gastrointestinal system or is heavily metabolized by the first pass action in the liver. creation of subpar water Soluble compounds is a difficult undertaking because they frequently are not very soluble in most topical formulations. topical preparations like creams, which are able to dissolve substances at high concentrations are greasy and granular due to hydrophobic activities, which makes the formulation that patients find less palatable. An adequate concentration of a medicinal substance administered topically needs to be placed inside the car in order to

2. Outline of transdermal drug delivery systems

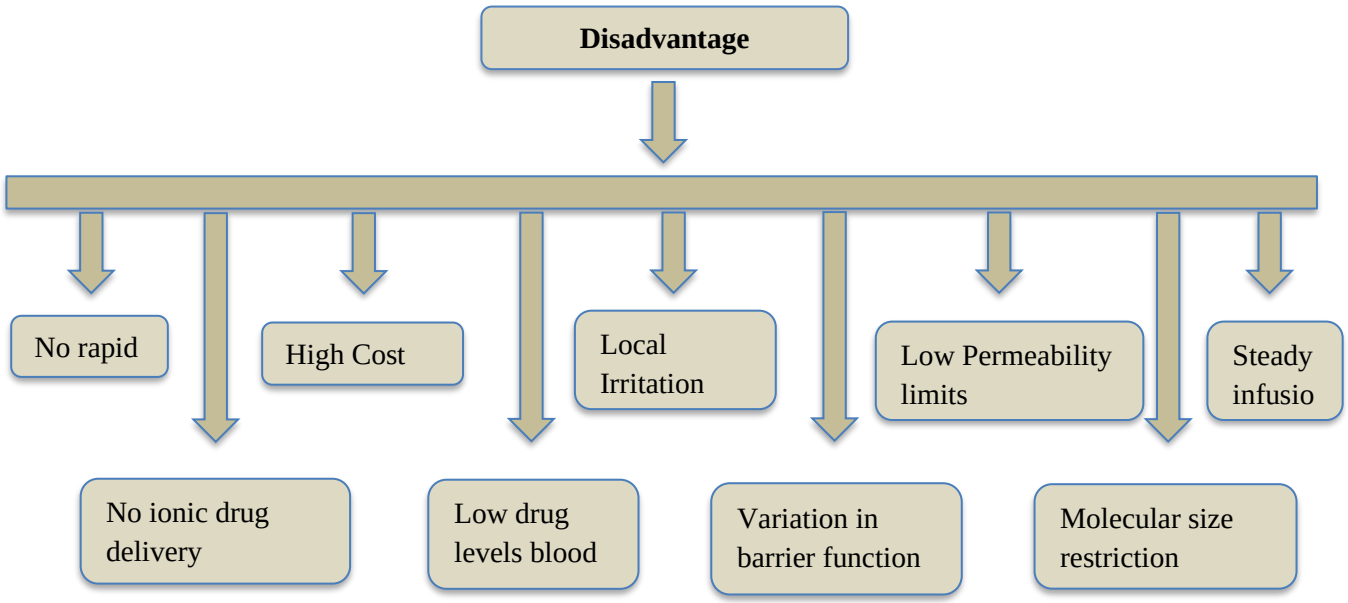
Transdermal drug delivery systems (TDDSs) are drug delivery devices that use the skin as a drug administration medium and have controlled release mechanisms. They are designed to carry out medication distribution at a preset, regulated rate by circulation throughout the body. The goal of TDDSs is to keep the medication input at a steady level for an rather than relying only on administration at will (12) Medicines seep into the skin and go into the bloodstream. The application of TDDSs, which has been around for a while, entails plant extracts or chemicals to the skin (13) The initial mechanism of systemic delivery was created. should use a 3-day scopolamine patch to cure motion sickness [13]. Other examples include the use of transdermal patches to deliver drugs such as fentanyl, nicotine, clonidine, and nitroglycerin to treat various medical circumstances (14). The use of TDDSs as a medication delivery system has benefits and drawbacks, just like other drug delivery systems. The primary advantages and disadvantage are shown in the below.



Advantages(15)



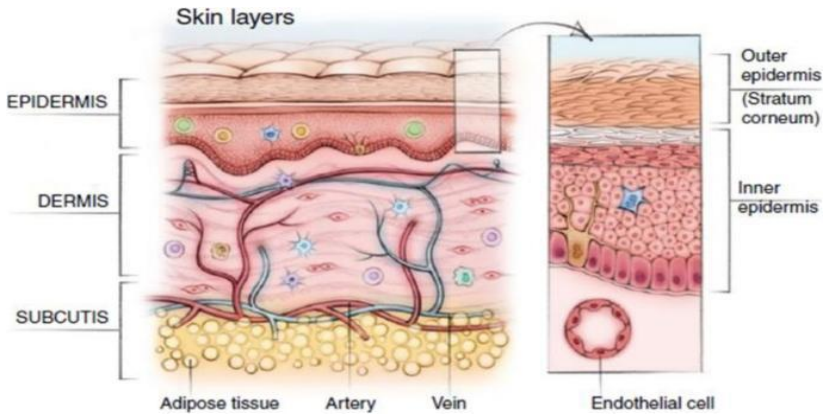
Disadvantage (15)



3. Transdermal Route & drug delivery systems:

The largest organ in the human body is the skin, which makes up roughly 16% of the overall weight. An adult male in good health has skin that is 1.5–2 m2 in length and weighs between 6 and 10 kg. 14 The cellular epidermis, underlying dermis, and subcutaneous layer are the three main cell layers that make up skin. The dermis layer is formed by the epidermis' rete ridges projecting downward (Fig. 1.1). In addition to giving the epidermis mechanical support, the dermal-epidermal interface serves as a partial barrier that prevents the exchange of big molecules and cells. The fatty layer of panniculus adiposus tissues, referred to as the subcutaneous layer, lies beneath the dermis. 15 There are two varieties of human skin: glabrous skin (also known as non-hairy skin).and the skin that bears hair. Thick epidermis and the presence of sensory organs in the dermis are characteristics of glabrous skin. It is devoid of sebaceous glands and hair follicles. The term "dermatoglyphics" refers to the distinctive individual structure of glabrous skin, which is primarily found on the palms and soles. It has a continuous grooved surface with alternating ridges and

sulci. On the other hand, the skin that bears hair has sebaceous glands and hair follicles, but no sensory organs. (16)



A) Skin Layers

a) Epidermis

It is the outermost layer of skin and is distinguished by the presence of tissues with stratified squamous epithelium, which are mainly made up of keratinocytes at varying stages of development. (17) The cells that make up the epidermis are called keratinocytes. Because the epidermis lacks blood vessels, it is dependent on the dermis to transport nutrients and eliminate waste via the basement membrane. (18)The epidermis is made up of four layers, although on the body part with the thickest skin, there are five layers.(18,19)

1. The lowest layer, known as the stratum basale (stratum germinativum), is connected to the dermis by hemi-desmosomes and is divided from it by the basement membrane (basal lamina). These are mitotically active stem cells that range in shape from cuboidal to columnar.
2. The layer of prickle cells, or stratum spinosum, are irregular, polyhedral cells with processes (sometimes called "spines") that extend that radiate outward and use desmosomes to make contact with nearby cells.
3. Stratum granulosum: a group of diamond-shaped cells that aggregate keratin filaments found in cornified cells and contain granules of keratohyalin.
4. Stratum lucidum: a thin, transparent layer that, if it exists, is primarily evident in people with thick skin and is made up of eleidin, a byproduct of keratohyalin transformation.
5. Stratum corneum: the outermost layer; often the thickest layer in callused skin; composed of keratin and horny scales, which were formerly living cells; dead cells called squamous (anucleate).

A variety of cells are also present in the epidermis, with keratinocytes accounting for the majority of these cells (about 95%). Merkel's cells, Langerhans' cells, and melanocytes are among the other cells. (20, 21)

Melanocytes:

1. derived from neural crest cells
2. produced melanin; primarily found in stratum basale and protective against UV radiation
3. melanocytes found between cells of stratum basale
4. produced by oxidation of tyrosine to 3,4-DOPA by tyrosinase and then there is the transformation of DOPA into melanin

Keratinocytes:

1. predominant cell type of epidermis;

2. originated in basal layer;
3. produced keratin;
4. formed epidermal water barrier;
5. produced melanin.

Melanin is "pigment donated" to nearby keratinocytes through keratinocyte phagocytosis of the tips of melanocyte processes iii. The Langerhans Cells

- Dendritic, antigen-presenting, and mostly visible in the stratum spinosum with certain staining
- Merkel cells are produced from bone marrow stem cells and are part of the mononuclear-phagocytic system. They express MHC I and MHC II molecules, uptake antigens in the skin, and transport them to lymph nodes.
- Stratum basale's altered epidermal cells; • Fine-touch sense, primarily in fingertips
- Have intermediate keratin filaments and are desmosome-bound to neighboring keratinocytes.

b) Dermis

it is located underneath the epidermis, the dermis is far thicker than the epidermal layer (1–5 mm thick). 19 The dermis is essential for maintaining and supporting the epidermis. Collagen fibers and a small amount of elastin make up the majority of the connective tissues found in the dermis. It is home to several specialized cells, including fibroblasts and mast cells, as well as anatomical components, including blood arteries, lymphatics, sweat glands, and nerves. (18)The two primary layers of connective tissues that make up the dermal layer are (19)

- The papillary layer is the thin layer of loose connective tissues that is visible on the outside.
- Reticular layer: made up of bundles of collagen fibers and dense connective tissue, it is a deeper, thicker, and less cellular layer. (Fibers of collagen I and III in 3:1 ratio) (22)

The viscous gel that surrounds these two layers lubricates the collagen and elastic fibers, enables waste products, nutrition, and hormones to move through the dermis, and gives the dermis bulk so it may function as a shock absorber. (23)

c) hypodermis

It is also referred to as the Panniculus layer or the subcutaneous layer of fat. It is the layer that lies beneath the dermis and serves as a link between the skin and the underlying fascia, or fibrous tissue, of the muscles and bones. In order to operate as an energy reserve, insulate the body to prevent heat loss, and act as a cushion to protect beneath structures from stress 22, the hypodermis is composed of loose, areolar connective tissues that are well-vascularized and adipose tissues. It is the primary location in the body for fat accumulation and is networked with blood vessels and neurons.

B) Function of skin

Protection: The main physical barrier separating the human body from the outside world is the skin. The skin shields the body from pathogens, pollutants, dehydration, UV radiation, and mechanical harm.

- Sensation: to touch, deep pressure, temperature, and pain.
- Mobility: enabling fluid bodily motion.
- Endocrine activity: Vitamin D synthesis, which is necessary for calcium absorption and healthy bone metabolism, is started by the skin.
- Exocrine activity: urea, ammonia, and water are released. In addition to secreting chemicals like perspiration, pheromones, and sebum, skin also secretes bioactive molecules like cytokines, which

have a significant impact on immunologic processes.

- Immunity: the defence system against infections.
- Temperature Regulation: The skin contributes to the body's water and homeostatic balance by absorbing and releasing heat.(24.25)

1) A) Hydrogels

Definition

Hydrogels are three-dimensional networks of hydrophilic polymers that can retain large amounts of water while maintaining their structure. They are characterized by their ability to swell and hold water without dissolving, making them useful in various applications such as drug delivery, wound care, and tissue engineering. (26,27)

B) Types of Hydrogels

1. Natural Hydrogels: Derived from natural sources, these include:

a. Alginate: Extracted from brown seaweed, used in drug delivery and tissue engineering.
b. Chitosan: Derived from chitin, effective for wound healing and drug delivery.
c. Gelatin: A protein-based hydrogel used in biomedical applications.

2. Synthetic Hydrogels:

Made from synthetic polymers, these can be tailored for specific applications:

a. Polyethylene glycol (PEG): Biocompatible and used in drug delivery systems.
b. Polyvinyl alcohol (PVA): Known for its mechanical strength and biocompatibility.
c. Polyacrylamide: Often used in laboratory settings for separation processes.

3. Smart Hydrogels:

These respond to external stimuli, such as:

a. pH-sensitive hydrogels: Swell or shrink in response to changes in pH.
b. Temperature-sensitive hydrogels: Change properties with temperature fluctuations.
c. Electrically responsive hydrogels: Alter their swelling behavior in response to electric fields.

4. Interpenetrating Network (IPN) Hydrogels:

Composed of two or more polymer networks that are interlaced without covalent bonding, enhancing mechanical properties and functionality.

5. Bioresponsive Hydrogels:

Designed to respond to biological signals, such as enzymes or specific ions, making them suitable for targeted drug delivery. (28,29,30)

C) properties of hydrogels:

1. **Water Absorption:** Hydrogels can absorb and retain water, leading to significant swelling. This property is crucial for applications in drug delivery and tissue engineering.
2. **Biocompatibility:** Many hydrogels are biocompatible, making them suitable for medical applications such as wound dressings and implants.
3. **Mechanical Properties:** The mechanical strength and elasticity of hydrogels can vary widely, depending on their composition and cross-linking density. They can be designed to mimic the mechanical properties of biological tissues.
4. **Porosity:** Hydrogels can be porous, which allows for the diffusion of nutrients and waste products, an important factor in tissue engineering.

5. **Thermo-Responsive Behavior:** Some hydrogels exhibit changes in properties in response to temperature, which can be exploited in controlled drug release systems**.**
6. **pH-Sensitivity:** Certain hydrogels can change their swelling behavior in response to pH changes, making them useful for targeted drug delivery in specific environments.
7. **Degradability:** Biodegradable hydrogels can be designed to break down in the body over time, which is beneficial for many biomedical applications.
8. **Self-Healing:** Some hydrogels have self-healing properties, allowing them to recover from damage and maintain functional

Synthesis of hydrogels

Synthesis of hydrogels involves several methods, typically categorized into physical and chemical crosslinking processes. Here are some common approaches:

1. Physical Crosslinking:

This involves non-covalent interactions, such as hydrogen bonding, ionic interactions, or hydrophobic effects. Examples include:

Freeze-thaw cycling:

Repeatedly freezing and thawing a polymer solution induces phase separation and physical gelation.

Self-assembly:

Certain amphiphilic block copolymers can spontaneously form hydrogels through micellization or other self-assembling processes.

2. Chemical Crosslinking:

This involves covalent bonds formed between polymer chains, often using crosslinking agents. Common methods include:

Radical polymerization:

Initiators are used to polymerize monomers (e.g., acrylates) into hydrogels, which can be further crosslinked using a crosslinker like N,N'-methylenebisacrylamide .

Click chemistry:

Reactions such as azide-alkyne cycloaddition (CuAAC) can create highly efficient crosslinked networks.

3. Hybrid Methods:

Combining physical and chemical methods can enhance the properties of hydrogels. For instance, using physical interactions for initial gel formation followed by chemical crosslinking to strengthen the structure. (34,35,36)

Chemical test of Hydrogels

Testing hydrogels involves several chemical assessments to evaluate their properties and behavior. Here are some common chemical tests and their references:

1. **Swelling Ratio:** This test measures how much a hydrogel expands when immersed in a solvent. The swelling ratio (SR) can be calculated using:

[SR = \frac{(W_s - W_d)} {W_d} \]

where \(W_s\) is the weight of the swollen hydrogel and \ (W d\) is the weight of the dried hydrogel. (37)

2. pH Sensitivity:

This involves measuring the hydrogel's response to different pH levels, which is crucial for drug delivery

applications. pH-sensitive hydrogels can swell or shrink depending on the pH of the surrounding medium. (38)

3. **Rheological Properties:** Dynamic mechanical analysis can determine the viscoelastic properties of hydrogels, which are essential for understanding their mechanical behavior. (39)
4. **Conductivity Test:** This assesses the ionic conductivity of hydrogels, which can indicate the presence of electrolytes. Higher conductivity often suggests better ion transport properties. (40)
5. **Fourier Transform Infrared Spectroscopy (FTIR):** This is used to identify functional groups in the hydrogel and confirm the chemical structure. (41)
6. **Thermogravimetric Analysis (TGA):** TGA helps determine the thermal stability of hydrogels by measuring weight changes as a function of temperature. (42)
7. **Mechanical Testing:** This includes tensile and compressive strength tests to evaluate the mechanical integrity of the hydrogel. (43)

Hydrogels based transdermal drug delivery systems

Hydrogels-based transdermal drug delivery systems (TDDS) have garnered substantial attention in recent years due to their unique properties that allow controlled and efficient drug delivery. This system provides a non-invasive and patient-friendly method of drug administration. Below is a detailed overview, including their importance, challenges, applications, and factors affecting hydrogel-based TDDS, with references to support each point.

1. Importance of Hydrogel-Based Transdermal Drug Delivery Systems

1.1. Controlled and Sustained Drug Release

Hydrogels are ideal for controlled drug delivery because they can absorb significant amounts of water while maintaining their structure. This hydration allows drugs to diffuse through the hydrogel matrix and be delivered at a sustained rate. This is particularly beneficial for drugs that require long-term release. (44)

1.2. Patient Comfort and Compliance

Transdermal delivery via hydrogels is non-invasive, avoiding the discomfort associated with injections or oral medications. The soft, flexible nature of hydrogels can easily conform to the skin, providing comfort and improved patient compliance.(45)

1.3. Avoidance of First-Pass Metabolism

Drugs delivered through the skin bypass the liver's first-pass metabolism, which can degrade a significant portion of orally administered drugs, making TDDS a more efficient route for certain medications. (46)

2. Challenges in Hydrogel-Based TDDS

2.1. Skin Barrier (Stratum Corneum)

The main challenge for TDDS is the skin’s outer layer, the stratum corneum, which acts as a strong barrier against the penetration of most drugs. Enhancing the permeability of hydrogels without causing skin irritation is a significant challenge. (47)

2.2. Limited Drug Molecules

Hydrogel-based TDDS is limited to delivering drugs that are lipophilic or have the right molecular size and properties to penetrate the skin. Hydrophilic or large molecule drugs, like proteins or peptides, face difficulties in permeating the skin.(48)

2.3. Hydrogel Stability

Maintaining the physical and chemical stability of hydrogels is crucial, especially for long-term storage

and use. Many hydrogels may dry out over time or undergo degradation under environmental conditions, which can affect drug release rates. (49)

3. Applications of Hydrogel-Based TDDS

3.1. Pain Management

Hydrogels are used to deliver analgesics transdermally, which can provide controlled pain relief for conditions like arthritis and postoperative pain. Examples include lidocaine and diclofenac gels. (50)

3.2. Hormone Replacement Therapy

Hormones like estradiol and testosterone can be delivered via hydrogels in transdermal patches, offering a convenient and steady release method for patients undergoing hormone therapy. (51)

3.3. Anti-inflammatory and Psoriasis Treatments

Drugs like corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) can be delivered using hydrogel TDDS for conditions like psoriasis, reducing inflammation and itching.(52)

3.4. Wound Healing

Hydrogels not only deliver antimicrobial agents for wound healing but also provide moisture to the wound environment, promoting faster recovery. (53)

4. Factors Affecting Hydrogel-Based TDDS

4.1. Drug Properties

The molecular weight, polarity, and lipophilicity of a drug affect its ability to be delivered through hydrogels. Smaller, more lipophilic drugs tend to permeate the skin more effectively than larger, hydrophilic molecules. (54)

4.2. Hydrogel Composition

The polymer type, crosslinking density, and water content of the hydrogel can significantly influence drug release rates and skin permeability. Hydrogels with higher water content may release drugs more quickly but may also be less structurally stable. (55)

4.3. Environmental Factors

External factors like temperature, humidity, and skin condition can affect the rate of drug release from hydrogel-based TDDS. For example, higher temperatures can increase the skin's permeability and the rate of drug diffusion. (56)

4.4. Penetration Enhancers

The inclusion of penetration enhancers such as ethanol, surfactants, or nanoparticles can significantly increase drug permeation through the skin, which is crucial for delivering hydrophilic drugs that would otherwise struggle to penetrate the skin barrier. (57)

Conclusion

Hydrogels-based transdermal drug delivery systems present a promising technology due to their ability to deliver drugs in a controlled, non-invasive manner. However, overcoming the skin barrier, ensuring drug stability, and optimizing hydrogel properties are challenges that must be addressed for wider clinical application. By carefully considering the drug's properties, hydrogel composition, and environmental factors, TDDS can be fine-tuned for a range of therapeutic applications.

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