Review on Polymers Used in Transdermal Drug Delivery System

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ABSTRACT

Transdermal drug delivery systems (TDDS) are a promising alternative to conventional oral and intravenous drug administration, offering high bioavailability, absence of first-pass hepatic metabolism, steady drug plasma concentrations, and non-invasive therapy. These systems are particularly beneficial for patients who cannot swallow or remember to take their medications. However, the transdermal route faces challenges such as enzymatic degradation in the gastrointestinal tract and first-pass metabolism in the liver, which can decrease drug bioavailability. Transdermal drug delivery is the administration of therapeutic agents through intact skin for systemic effect. Transdermal delivery increasingly offers a promising alternative route for drug administration. The main obstacle to permeating drug molecules is the outermost layer of the skin, the stratum corneum. To address these issues, researchers are exploring ways to enhance TDDS by overcoming the stratum corneum layer, which is the main obstacle to permeating drug molecules. TDDS is primarily composed of polymers that regulate the drug's release from the apparatus. By dispersing the medication in a liquid or solid-state polymer base, the polymer matrix can be created. The polymers employed in TDDS should deliver consistent and repeatable drug release, as well as good stability and compatibility with the drug and other system components. Selecting the appropriate polymers is crucial for optimizing the formulation's properties and ensuring secure and effective drug delivery across the epidermal barrier.

Keywords: *Transdermal, Polymer, Microneedle, Biocompatibility.*

INTRODUCTION

Transdermal drug delivery systems represent a beneficial innovation for drug delivery, particularly in patients who cannot swallow or remember to take their medications. Clinicians and other allied health professionals should understand the appropriate administration techniques for transdermal systems to ensure optimal patient outcomes and to ensure the safety of all who encounter patients who use TDDS[1] . Transdermal drug delivery is the administration of therapeutic agents through intact skin for systemic effect. Transdermal delivery increasingly offers a promising alternative route for drug administration. The conventional and widespread use, oral and intravenous routes of drug administration face several limitations. In particular, orally administered drugs undergo enzymatic degradation in the gastrointestinal tract and first-pass metabolism in the liver, which tend to decrease their bioavailability. Intravenous infusions of medications are invasive, painful and stressful for patients and carry the risk of infections, tissue damage and other adverse reactions. Despite their conventional and widespread use, oral and intravenous routes of drug administration face several limitations. In order to account for these disadvantages, alternative routes of drug delivery, such as transdermal drug delivery system have been considered[2] . In recent years, there has been increased interest in transdermal drug delivery (TDD) as a non-invasive delivery approach that is generally regarded as being easy to administer to more vulnerable age groups, such as paediatric and geriatric patients, while avoiding certain bioavailability concerns that arise from oral drug delivery due to poor absorbability and metabolism concerns. TDD is safe and well-torelated drug delivery approach with potential to combine dosing accuracy & ease of administration associated with oral dosage forms with the metabolism free delivery of therapeutic agents to plasma associated with parentral drug delivery. The transdermal route has numerous advantages over the more traditional drug delivery routes. These include high bioavailability, absence of first pass hepatic metabolism, steady drug plasma concentrations, and the fact that therapy is non-invasive. The main obstacle to permeating drug molecules is the outermost layer of the skin, the stratum corneum. Consequently, research into enhancing transdermal drug delivery (TDD) by overcoming this layer is an area of prime interest. [3]

ADVANTAGE[4]

1. They can prevent problems with gastrointestinal drug absorption brought on by changes in the pH of the gastrointestinal tract, enzymatic activity, and interactions between pharmaceuticals taken orally and food and beverages.
2. In cases where oral drug administration is not appropriate, such as in cases of vomiting or diarrhea, they can serve as a substitute.
3. They avoid the first-pass effect, which is the initial passage of the pharmacological ingredient "s" through the portal and systemic circulation after it is absorbed through the gastrointestinal tract, perhaps preventing it from being deactivated by the liver and digestive enzymes.
4. They avoid the complications of parenteral therapy because they are non-invasive.
5. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
6. The activity of drugs having “s” short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
7. Drug therapy may be terminated rapidly by removal of its application from the surface of the skin.
8. They are easily and rapidly identified in emergencies (for example, unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.

LIMITATION [5]

1. Only small lipophilic drugs can be delivered currently through the skin.
2. Drug molecule must be potent because patch size limits the amount that can be delivered.
3. Not suitable for high drug doses
4. Adhesion may vary with patch type and environmental conditions.
5. Adhesion may vary with patch type and environmental conditions
6. Skin irritation and hypersensitivity reactions may occur
7. The barrier functions of the skin change from one site to another on the same person, from person to person and with age.

1. Skin as a barrier:

Skin, an external organ with the largest epithelial surface, is vulnerable to various environmental factors such as microorganisms and hazardous chemicals. The average adult human's skin, the largest epithelial surface in the human body, covers an area of 2 m^2. The skin, divided into epidermis, dermis, and hypodermis, serves as a protective barrier against external agents and water loss.[6]

1 Epidermis:

The epidermis consists of non-viable and viable epidermis, with the stratum corneum being the nonviable and the viable epidermis below. Blood capillaries and nerve fibers reach the epidermis through the dermis and subcutaneous fat layer.

i. **Stratum corneum (horny layer)**
ii. **Stratum lucidum (clear layer)**
iii. **Stratum granulosum (granular cell layer)**
iv. **Stratum spinosum (prickle cell layer)**
v. **Stratum basale (basal cell layer)**

2 Dermis:

Drug molecules pass through the stratum corneum, deeper epidermal tissues, and enter the dermis, a fibrous, 1-2mm thick tissue with a rich supply of blood vessels, where they are absorbed into the general circulation.

1.3 Hypodermis:

The subcutis, or hypodermis in histology, is the third layer below the dermis, consisting of an elastic layer with a large amount of fat cells that act as shock absorbers for blood vessels and nerve endings, with an average thickness of 4-9 mm.[7]

2. Types of Transdermal Drug Delivery system:

2.1 Single layer drug in adhesive: The adhesive layer in this type contains the drug, forming a protective barrier and releasing it to the skin, surrounded by a temporary liner and a backing layer.[8]

2.2 Multi -layer drug in adhesive: This type is also similar to the single layer but it contains an immediate drug-releaselayer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

2.3 Vapour patch: The patch with an adhesive layer not only binds surfaces together but also releases vapor. Vapour patches are a new market product that release essential oils for decongestion and improve sleep quality. They are also available to reduce cigarette smoking conditions and reduce smoking conditions.

2.4 Reservoir system: The system involves a drug reservoir embedded between an impervious backing layer and a rate controlling membrane, which releases the drug only through the membrane, which can be micro or non-porous. The drug can be in various forms, such as solution, suspension, gel, or solid polymer matrix.[9]

2.5 Matrix system:

i. **Drug-in-adhesive system:** A drug-in-adhesive patch is created by mixing a drug with an adhesive polymer, creating a reservoir, and spreading it on an impervious backing layer using solvent casting or melting. The top is protected by unmediated polymer layers, and can be categorized into single-layer and multi-layer versions.[10]

ii. **Matrix-dispersion system:** The drug is dispersed in a hydrophilic or lipophilic polymer matrix and transformed into a medicated disc. This disc is fixed to an occlusive base plate in a compartment with a drug impermeable backing layer. The adhesive is spread along the circumference instead of on the reservoir's face, creating a strip of adhesive rim.[11]

2.6 Micro reservoir system: The micro reservoir system is a combination of a reservoir and matrix-dispersion system, consisting of microscopic spheres of drug reservoirs that release drugs at a zero order rate to maintain constant drug levels.[12] Cross-linking agents stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer.[13]

3. Basic Components of TDDS:

3.1. Backing Films: Backing films are crucial in transdermal patches and systems, protecting the active layer, system stability, and affecting skin permeation and tolerance. Common release liners include polypropylene, polyesters, PVC, and nylon, depending on occlusion or breathability.[14]

3.2. Release Liners: Release liners, which are used to protect the system in the package, are coated with an anti-adherent material. They are crucial for the stability, safety, and affectivity of the patch. Common films used for release liners include paper-based, plastic film-based, and composite films, with silicones and fluoro-polymers being the major coating classes.[14]

3.3. Pressure Sensitive Adhesives: Pressure-sensitive adhesives (PSAs) are crucial in TDDS, serving as a matrix for transferring active ingredients and ensuring patch adhesion to the skin. There are three categories: rubber-based, acrylic solutions, emulsion polymers, and silicon PSAs.[15]

3.4. Penetration Enhancers: Chemical substances belonging to the same family increase the permeation rate of the active ingredient through the skin by several times.[16]

3.5. Micro porous or Semi-Permeable Membranes: The membranes with pores are a unique kind of membrane that are utilized in some matrix-type patches and liquid transdermal patches. They control the flow of semisolid chemical and serve as rate-limiting membranes for systems.[17]

There are two types of porous membranes as shown below.

A. Ethylene Vinyl Acetate Membrane.

B. Micro porous Polyethylene Membrane[18]

4. Polymers in Transdermal Drug Delivery system:

The transdermal drug delivery method is built on polymers. Controlled medication release from patches and mechanical properties are made possible in large part by polymers. Transdermal drug delivery devices with significant flexibility have been made possible by developments in polymeric technology.[19] Choosing the right polymers is essential to maximizing the qualities of the formulation and guaranteeing safe and efficient medication penetration through the skin barrier. When it comes to the drug and other components, including PSAs and penetration enhancers, the polymers utilized in TDDS should be both chemically and biocompatible with each other. They should also be safe and offer reliable and efficient drug delivery for the duration of the product's stated shelf life. In the creation of a transdermal drug delivery system, the appropriate polymer or mix of polymers is selected depending on the particular medication, the intended release profile, and additional formulation variables.

The transdermal patch's ability to regulate medication release is greatly influenced by polymers. The increased percentage of hydrophilic polymer in patches allows for faster release of the medicine (burst effect), which makes it more difficult to regulate the

drug's release rate over an extended period of time. On the other hand, using a more hydrophobic polymer results in less drug release from the patch, which has a less than ideal therapeutic outcome. Effective regulation of medication release from patches requires a polymer or polymer mix to have an equilibrium between hydrophilicity and hydrophobicity. TDDS is primarily composed of polymers that regulate the drug's release from the apparatus. By dispersing the medication in a liquid or solid-state polymer base, the polymer matrix can be created. The polymers employed in TDDS should deliver consistent and repeatable drug release, as well as good stability and compatibility with the drug and other system components. Businesses in the transdermal delivery space focus on a small number of specific polymeric technologies. For instance, Searle Pharmacia focuses on silicon rubber, while Alza Corporation primarily focuses on microporous polypropylene or ethylene vinyl acetate (EVA) copolymers.[20]

5. Classification of polymers :

5.1 Natural polymers: eg. Xanthan gum, Sodium aliginate, Chitosan,etc
5.2 Semi Synthetic :eg. Hydroxypropyl methylcellulose, Ethyl cellulose (EC), Carboxymethylcellulose,etc.
5.3 Synthetic: eg. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, etc.

6. Ideal characteristics of polymers used in TDDS:

- **Permeability:** It should be possible for the polymer to help the medication pass past the epidermal barrier. This entails facilitating controlled release in addition to improving drug solubility in the polymer matrix.[21]
- **Biocompatibility:** When polymers come into touch with the skin, they should be biocompatible to prevent undesirable responses or skin irritation. Biocompatible polymers lessen the possibility of irritation or skin sensitivity.[22]
- **Stability:** Under storage, polymers need to stay stable and not degrade in a way that would impair the medication's effectiveness or result in undesirable side effects.[23]
- **Flexibility:** In order to provide patient comfort and encourage constant contact between the TDDS and the skin, the polymer should be flexible enough to adhere to the contours of the skin.
- **Compatibility with Drugs:** For the purpose of accommodating various therapeutic treatments, polymers need to be compatible with a broad spectrum of medications. Compatibility guarantees the drug's stability within the polymer matrix and preserves its therapeutic efficacy.[24]
- **Non-toxicity:** Both in its initial state and as its breakdown products, the polymer need to be non-toxic. This feature is essential to safeguard the patient's safety and the TDDS's overall security.
- **Cost-Effectiveness:** In order to produce TDDS on a wide scale and maintain the drug delivery system's economic viability, the polymer should be reasonably priced.[25]

7. Roles of polymers in TDDS:

Polymers are essential to TDDS. They serve as matrix formers, pressure-sensitive adhesives, backing laminates, release liners, and rate-controlling membranes.[26] Therefore, choosing the right polymer is crucial for formulation.

The following table provides details on the functions of the polymers in TDDS along with a few examples:

Roles	Examples	Ref. no.
Matrix formers	PEGs, Eudragit E-100 ,etc.	**27-28**
Rate- controlling membranes	EVA, Silicone Rubber, Polyurethane.	**29**
Pressure-sensitive adhesives (PSAs)	Polyisobutylene, Polyacrylates, Silicones	**30**
Backing layers	CoTran 9707, CoTran 9722	**31**
Release liners	ScotchPak 9744, ScotchPak 1022	**32**

Table no. 1. Roles of polymers in TDDS.

8. Criteria for selection of polymers for TDDS:

Drug Compatibility: For the purpose of accommodating various therapeutic treatments, polymers ought to be compatible with a broad spectrum of medications. Compatibility guarantees the drug's stability within the polymer matrix and preserves its therapeutic efficacy.

Controlled Release Properties: For the intended amount of time, the polymer matrix should enable the medicine to release under controlled and sustained conditions. This is essential to preventing drug concentration peaks and troughs and reaching therapeutic levels of the medication in the bloodstream.

Skin Permeation Enhancement: It should be possible for the polymer to increase the drug's permeability through the skin. In order to promote transdermal absorption, this entails taking into account the molecular weight, structure, and interaction of the polymer with the medication.

Biocompatibility: For the purpose of preventing skin irritation, sensitization, or other negative reactions, the chosen polymer needs to be biocompatible with skin. The TDDS may be applied to the skin safely and painlessly for prolonged periods of time thanks to its biocompatibility.

Mechanical Properties: For the TDDS to be used as intended, the polymer must have enough mechanical strength to resist handling, application, and wear.

Solubility of Drugs: In order to guarantee that the medicine may be evenly dispersed throughout the polymer matrix, the polymer should be compatible with a broad variety of medications. To achieve controlled drug release, this is crucial.

Manufacturing Compatibility: The chosen polymer ought to be compatible with the TDDS manufacturing techniques, including solvent casting, hot-melt extrusion, and pressure-sensitive adhesive formulation. Cost-effectiveness and scalability of production are enhanced by ease of manufacturing.[33]

9. Types of polymers used in TDDS:

Types	Characteristics	Uses	Ref.no.
1.Silicone Elastomer.	Biocompactabile, durable & flexibile	Drug reservoir & matrix system	34
2.Acrylic polymers	Good adhesive propety	Pressure-sensitive adhesives	34
3.Polyurathanes	Maintain patch integrity	Backing layer	34
4.Natural Polymer	Reduce skin irritation	Permeation enhancer	35
5.Polyethylene oxide	Enhance drug solubility	Control drug release	36
6.Organogels	Incorporate W.S & L.S drugs	Matrix formers & permeation enhancer	37
7.Fluoro polymers	Inert & penetration enhancer	Release Liner	38

Table no. 2: Types of polymers used in TDDS

10. Recent Developments:

a. **Microneedles:** Drugs are administered to the circulatory system via a needle in the innovative microneedle drug delivery system. Research is now being conducted in this area, which is one of the most widely used techniques for transdermal medication delivery.[39] Drugs are diffused across the epidermal layer by means of a mechanism whereby tiny needles puncture

the skin's surface layer. These short, thin microneedles carry medications directly to the blood capillary area for active absorption, reducing the risk of pain.[40]

Different types of microneedles for percutaneous penetration are given below.

Category	Polymer used	Ref.no.
1. Solid Microneedles	Silicon, titanium, stainless steel, and other polymer materials insoluble in water.	41
2. Coated microneedles	Metal or polymer materials	41
3. Hollow microneedles	Polymer materials that are insoluble in water, including silicon, glass, stainless steel, etc.	41
4. Soluble microneedles	Polymer materials with degradability and biocompatibility (e.g., maltose, carboxymethyl cellulose, etc.)[40]	42
5. Hydrogel microneedles	Expandable hyperlinked polymer.[41]	43

11.2 Responsive polymers: The field of "smart" polymers has seen numerous advancements over the past few decades. These advancements are based on polymeric vehicles that exhibit enhanced stability, enabling them to withstand harsh chemical and physical conditions and possess flexible structural parameters. Additionally, these vehicles can deliver drugs in their native structures and release them in response to specific stimuli, such as changes in pH, temperature, electro-conductivity, etc. Treatments for a number of illnesses, including cancer, heart disease, infections, and others, have demonstrated encouraging outcomes with these stimuli-responsive polymers.[44]

These polymers can be categorized using different stimuli, such the following, to study them:

a. **Internal stimuli:** temperature, enzymatic activity, pH, redox reaction, etc.[45]
b. **External stimuli:** applying magnetic fields, electric fields, ultrasound, mechanical pressure, etc.[46]

A. Internal Stimuli-Responsive polymers :

1. **pH-Responsive polymers:** For pH-responsive polymers, the varying pH levels in various bodily parts can offer an appropriate physiological stimulus. For instance, the pH range of the stomach is 1.5–3.5, the intestine's pH ranges from 5.5–6.8, the colon's pH ranges from 6.4–7, and the blood pH ranges up to 7.4. Polyelectrolytes having ionizable groups in their side, end, or backbone groups are known as pH-sensitive polymers.[47] These pH-sensitive polymers undergo conformational changes as a result of ionization brought on by variations in the pH of an aqueous solution. In reaction to pH variations in their surroundings, these "smart" polymers have the ability to either give or receive H+ ions. Through electrostatic repulsion of the produced charges, the protonation or deprotonation of these ionizable groups can cause changes in the structure of the polymer chain, causing the chains to extend from a compressed condition.[48]
2. **Temperature-Responsive polymers:** For several biomedical applications, including temperature-sensitive gels, liposomes, micelles, colloidal particles, mRNA recovery, and gene transfer, temperature-sensitive polymers are employed to create this responsive DDS.[49] Even at slight temperature changes, the encapsulated active ingredient can be released by these thermosensitive polymers. Poly(ethyleneoxide) (PEO), Poly(propylene oxide) (PPO) (pluronic copolymers), core shell thermoresponsive NPs, polymeric nanotubes, polymeric micelles, layer by layer (LBL) assembled nanocapsules, microbeads (MBs), and elastin like polypeptides (ELPs) are just a few examples of the thermosensitive compounds that are used to create thermoresponsive hydrogels in DDS applications.[50]
3. **Enzyme-Responsive polymers:** In order to include the therapeutic substance and release it in a targeted manner when the body's enzyme is present, enzyme-responsive polymers are utilized. The hydrolases, which include lipases, glycosidases, and proteases, are the most frequently utilized enzymes for drug delivery systems because of their straightforward design, which calls for the attachment of bioactive moieties to the carrier through an enzyme cleavable unit.[51]

B. External Stimuli-Responsive polymers:

1. **Magnetic-Responsive polymer:** The magnetic responsive drug delivery systems are the most well-researched cancer medication delivery devices that respond to external stimuli. The realization of such intelligent medication delivery systems is contingent upon the nanocarrier's robust magnetic properties and its ability to be utilized by an external magnetic field. The therapeutic substance is attached to or encapsulated in magnetic nano/microparticles, which is the mechanism of the magnetic drug delivery system. In order to deliver the magnetic responsive DDS to the intended tissue, it is first attached, then injected into the circulation as a biocompatible ferrofluid and exposed to a magnetic field. Iron, cobalt, nickel, metallic oxides, mesoporous silica, calcium silicates, liposomes, and polymers are the most often used bases for magnetic sensitive nanocarriers.[52]

2. **Photo-Responsive and Photothermal-Responsive polymers:** When it comes to the controlled release of medications utilizing light sources including ultraviolet (UV), visible, and near infrared (NIR) light, photoresponsive drug delivery systems have shown to be an appealing alternative. The most widely used light-responsive compounds are irreversible (like nitrobenzy, pyrenylmethyl, and coumarin) and reversible (like azobenzene, spiropyran, dithienylethene, and diazonaphthoquinone).[53]

11.3 Biodegradable & biocompatible polymers:

For TDDS, biodegradable and biocompatible polymers are recommended to guarantee environmental friendliness, safety, and effectiveness. Here are some examples:

1. **Polyethylene glycol (PEG)**[54]
2. **Chitosan**[55]
3. **Poly(lactic-co-glycolic acid) (PLGA)** [56]

11.4 Improved adhesive polymers: Transdermal drug delivery systems (TDDS) are more reliable and effective when they are made with improved adhesive polymers. Adhesive polymers facilitate the patch's skin adhesion, guaranteeing steady and regulated medication delivery. The following are a few instances of enhanced sticky polymers utilized in TDDS:

1. **Silicone-based Adhesives**
2. **Polyvinylpyrrolidone (PVP)**
3. **Hydrogels**[57]

11. Conclusion:

To sum up, this overview of polymers utilized in Transdermal Drug Delivery Systems (TDDS) highlights how important polymers are to improving the viability and efficacy of this drug delivery technique. The wide range of polymers—natural, synthetic, and hybrid varieties—offers a variety of solutions to deal with particular TDDS-related problems. For the intended drug release profile, skin penetration, and overall therapeutic efficacy, the right polymer must be chosen. The biocompatibility and biodegradability of natural polymers, including chitosan and cellulose derivatives, add to the sustainability of TDDS. However, synthetic polymers such as polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) provide accurate control over the kinetics of drug release.

Moreover, the utilization of hybrid polymers is a growing trend that integrates the benefits of natural and synthetic materials, offering an adaptable framework for TDDS enhancement. Researchers may fine-tune characteristics like adhesion, flexibility, and permeability by customizing polymer blends, enabling TDDS to be tailored to individual medication and patient needs. The research and commercialization of polymer-based TDDS continue to face obstacles including stability, scalability, and regulatory concerns, despite the achievements noted in the study. To advance the discipline, future study endeavors ought to concentrate on tackling these obstacles and investigating inventive polymer technologies.

Polymers are essentially essential to the design and optimization of targeted drug delivery systems (TDDS), providing a potential path for bettering drug delivery systems, raising patient compliance, and advancing pharmaceutical research. We expect more discoveries as science works to better understand the complex relationships between polymers and drugs, which will ultimately lead to the development of effective and patient-friendly transdermal drug delivery systems.

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