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POLYMERS AND PATCH TECHNOLOGIES IN TRANSDERMAL DRUG DELIVERY: A COMPREHENSIVE REVIEW

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Abstract

Transdermal drug delivery systems (TDDS) are advanced therapeutic platforms designed to deliver drugs across the skin into systemic circulation. They offer several advantages over traditional routes, such as oral or injectable administration, including avoidance of first-pass metabolism, sustained and controlled drug release, reduced dosing frequency, and enhanced patient compliance. The effectiveness of TDDS is largely dependent on its key components like, the choice of ***polymers, pressure-sensitive adhesives (PSA), penetration enhancers, membranes, backing layers, and release liners***. Each component contributes uniquely to the overall performance, with polymers playing a particularly crucial role. The incorporation of PSAs ensures intimate skin contact, while penetration enhancers temporarily reduce the stratum corneum barrier to increase drug permeation. ***Polymers form the matrix or reservoir that governs drug entrapment, release, and stability***. Their physicochemical properties - such as molecular weight, hydrophilicity or hydrophobicity, and compatibility with the drug and other excipients - significantly influence drug diffusion rates and therapeutic outcomes. ***A balanced hydrophilic-lipophilic polymer blend is essential to modulate drug release, ensuring neither a burst release nor overly slow diffusion***. Among the various types of transdermal patches, matrix-type drug-in-adhesive patches are generally preferred due to their simple design, ease of manufacturing, uniform drug distribution, and reliable adhesion to the skin. These patches integrate the drug within a polymer-adhesive matrix, eliminating the need for a separate reservoir or membrane. Other types, such as reservoirs, micro-reservoirs, and vapor patches, are also used based on specific therapeutic goals but involve more complex fabrication. Recent advancements in patch design and permeation technologies continue to enhance the efficiency and applicability of transdermal drug delivery systems (TDDS) across a wide range of therapeutic areas. ***This review highlights the essential components and design considerations critical to optimizing TDDS performance. TDDS continues to evolve, expanding its application across diverse medical conditions.***

Keywords: Transdermal, Micro-reservoirs, Vapor-patch, Permeation-enhancer, Transdermal-Polymer

INTRODUCTION

It has been determined that drug delivery systems (DDS) are useful tools for enhancing the pharmacological and therapeutic qualities of medications. These systems assist medications get past obstacles like poor solubility brought on by hydrophobicity and reach the intended tissues without degrading too quickly. They also help pharmaceuticals be handled and administered more effectively [1][2]. ***Drug delivery via a patch is a more patient-friendly method that provides the potential for regulated release over time when oral administration of medications is not practical because to inadequate drug absorption or enzymatic breakdown in the liver or gastrointestinal tract*** [3][1]. A patch-like device may be applied and absorbed onto the skin's surface thanks to its wide and easily accessible surface area, making this a non-invasive process that will support ongoing intervention [1][4]. Drug application on the skin may serve two purposes according to the nature of the skin: transdermal medication administration or local treatment (dermal) [5][6]. Drug absorption through each layer of the skin, drug access to the microcirculation, and subsequent systemic distribution are all implied by the transdermal delivery concept, whereas, dermal delivery describes the bulk transport of medications applied to the skin to different skin strata [5][7]. Drugs can therefore be applied to the skin for a variety of reasons: a) to protect the body or combat living things on the skin's surface *(e.g., sunscreens, repellents, or antifungal/antibacterial products)*[8]; b) to treat various skin appendage disorders *(e.g., infections or antiperspirants)*[9]; c) to treat various affections of the stratum corneum and viable epidermis *(e.g., emollients, exfoliants, anti-inflammatory, antihistaminic drugs, etc.)*; d) to alter the function of the skin barrier to enhance the absorption of other medications; and e) transdermal drug delivery system [5]. All topically applied medication formulations meant to release the active ingredient into the general circulation are collectively referred to as transdermal delivery systems. Drugs can be continuously and precisely delivered via the skin to the systemic circulation with transdermal therapy devices. ***Additionally, it avoids a number of adverse effects, such as uncomfortable drug administration and first-pass metabolism of the medication that happens with conventional drug delivery methods. As a result, transdermal medication administration has obtained a lot of attention currently*** [10][11]. The regulated drug release and painless medication are the primary benefits of this approach. The drug is mostly applied to the skin using a transdermal patch, which adheres to the skin. The components of a transdermal patch that are crucial to the delivery of drug through skin include the drug release ***membranes, adherents, liners, and drug reservoirs***.

The medicine can be delivered from the transdermal patch using a variety of patch types and application techniques [10]. Drug patches can be classified as reservoir, matrix, or drug-in-adhesive types. Within an organic polymer matrix, which can be either lipophilic or hydrophilic, the medication is uniformly distributed in matrix patches [12]. Polymers are essential for regulating the transdermal patch's medication delivery. Because patches include a larger percentage of hydrophilic polymer, the medication releases more quickly *(burst effect)*, making it more difficult to regulate the drug's release rate over an extended period of time. On the other hand, a less-than-ideal therapeutic impact results from the limited drug release of patch caused by the use of a more hydrophobic polymer. For medication release from patches to be modulated effectively, ***a polymer or polymer blend must have a balance between hydrophilicity and hydrophobicity*** [12][13]The nitro-glycerine patch was one of the earliest transdermal patches created in 1985. A rate-regulating ethylene vinyl acetate membrane is used in the patch, which was created by Gale and Berggren. Numerous medications, such as scopolamine *(hyoscine)*, nicotine, fentanyl, clonidine, estradiol, and estradiol with norethisterone acetate, are currently offered as transdermal patches [14]. Depending on the therapeutic categories of drugs, the application site or location may change. ***For instance, you can apply estradiol to the buttocks or abdomen and nitro-glycerine to the chest***. Additionally, the length of time a medication, i.e., the release of drugs from the patch or adhesive varies according to its use first (up to nine hours) and last (up to nine days) [14][15].

ADVANTAGES OVER OTHER DOSAGE FORM

An attractive substitute for traditional medication delivery methods including parenteral and oral routes is transdermal drug administration. For the following five reasons, it offers several benefits over alternative administration method:

1. It is a non – invasive medication administration method that keeps the drug's plasma level constant and boosts its effectiveness [16][17].
2. It keeps the medication at its therapeutic level for extended periods of time by keeping the level in the systemic circulation within the therapeutic window—that is, above the minimum effective concentration but below the level at which side effects start to show [18][19].
3. By offering constant blood concentration, the transdermal medication delivery system prevents plasma level peaks and troughs as compared to oral and intravenous routes of administration [16].
4. It also enhances patient compliance and acceptance of pharmacological therapy by preventing drug breakdown in the gastrointestinal system and removing the first-pass impact [18][19].
5. The patient can quickly remove the patch if any negative effects manifest [18][19].

Because of the advancement of technology in recent years, TDD systems have shown even more benefits. The mentioned features include the ability to have regulated input kinetics, which is especially important for pharmaceuticals with limited therapeutic indices, and prolonged release, which is beneficial for medications with short biological half-lives that need to be administered often orally [20][21].

ANATOMICAL AND PHYSIOLOGICAL INTERVENTION OF SKIN UPON DRUG ABSORPTION

One adult's skin surface area is approximately 2 m^2 or 15% of the total weight of the body and receives about one-third of the blood circulation through the body, is the biggest organ in the human body [22][23][24]. The skin layer serves as the body's natural defence against dangerous substances that are physical, biological, or chemical *(such as asbestos, staphylococcal enterotoxin, or mercury)* [22][25][26]. Along with performing vital tasks like temperature regulation, water and fat storage, protection, and the preservation of electrolytes and water, skin serves as the body's life-sustaining interface with the outside world. It also has a significant impact on the endocrine layer *(Hypodermis)* and dermis make up the skin. As contrast to the dermis and hypodermis, which originate from the mesoderm, the epidermis is ectodermal [22][27]. Additional remarkable anatomical characteristics include appendages such as sweat glands *(eccrine and apocrine glands)* and hair follicles and related sebaceous glands *(pilosebaceous units)* [18][28]. Drug delivery on the skin can have two goals due to the structure of the skin i.e., ***transdermal delivery (Systemic Effect) & local therapy (Local Effect) (dermal)***[6]. The term **"dermal delivery"** describes the process of applying drugs to the skin in large quantities to different layers of the skin, whereas, the concept of transdermal delivery suggests that drugs will be absorbed through the skin's layers, enter the microcirculation, and then travel throughout the body [7][5]. The Epidermis, Dermis, and Subcutaneous layer (sometimes known as the Hypodermis) are the three primary layers that make up skin [18].

THE EPIDERMIS

The entire outer surface of the body is covered by the epidermis, a continuously self-renewing, stratified squamous epithelium that is primarily made up of two types of cells: the living or viable cells of the malpighias layer (viable epidermis) and the dead cells of the stratum corneum, also known as the horny layer [27]. Keratinocytes are the primary cell type of the epidermis, which is a layered, terminally differentiated squamous epithelium. Langerhans cells (LCs), a subtype of dendritic cells, are also found in the epidermis [29][22].

Four separate layers make up the additional classification of Viable Epidermis [30][31].

- Stratum lucidum

- Stratum granulosum
- Stratum spinosum
- Stratum basal

STRATUM CORNEUM [22]

- The top layer of skin, or Stratum Corneum, is also known as the horny layer. The rate limiting barrier is what prevents chemical compounds from moving both inward and outside.
- The horny layer's contents, which consist of 75–80% proteins, 5–15% lipids, and 5–10% ondansetron material on a dry weight basis, are crucial to the barrier nature of the layer [30]. The stratum corneum is around 10 mm thick when dry, but it enlarges significantly when completely moistened. Although flexible, it is largely impermeable. Modelling the architecture of the horny layer as a wall-like structure made of protein bricks and lipid mortar is possible [32].
- It is made up of corneocytes, horny skin cells, which are linked by desmosomes, which are protein-rich extensions of the cell membrane. The lipid matrix in which the corneocytes are embedded has a big impact on how permeable the skin is to substances [30].
- Presumably, the primary obstacle to drug transportation is the SC. The unique composition of the SC, which includes corneocytes and intercellular lipids, offers the structural "brick and mortar" that is connected to the human skin's barrier performance. A number of lipid bilayers made up of cholesterol, ceramides, cholesterol esters, and fatty acids make up the "mortar," whereas the corneocytes are referred to as the "bricks" [33][22].

VIABLE EPIDERMIS

Directly under the stratum corneum lies the viable epidermis (VE), which is 50–100 μm thick and devoid of blood vessels. About 15% to 20% of the keratinocytes that make up the viable epidermis are lipids, 40% are water, and 40% are protein [34][22].

- With a thickness ranging from **0.06 mm** on the eyelids to **0.8 mm** on the palms, it lies beneath the stratum corneum.
- The stratum basal, stratum lucidum, stratum granulosum, and stratum spinosum are some of the layers that make up the interior [35].
- The basal layer's continual cell division, or mitosis, replaces the epidermis and makes up for the loss of dead, horny skin cells by causing a proliferation of new, healthy cells.
- As the basal layer's cells proliferate outward, they undergo keratinization to form the stratum corneum's top layer by changing morphologically and histochemical [30].

DERMIS

The layer just underneath the epidermis is called the dermis, and it is innervated and vascularized. It is a network of proteins with noteworthy elastic qualities, primarily collagen and elastin. The cells in this layer include leukocytes, macrophages, and fibroblasts [36]. This layer's irrigation eliminates metabolites and supplies nutrients to the dermal and epidermal cells. Since any chemical that enters the dermis microcirculation has the potential to be absorbed, this procedure enables the systemic absorption of medications when they are administered [5][22][37][38]. The skin's dermis, which is 3 to 5 mm thick and made up of a matrix of connective tissues that includes blood arteries, lymph vessels, and nerves, is the layer that lies just below the epidermis. A vital role in controlling body temperature is played by the cutaneous blood supply. Along with cleansing the skin of impurities and waste materials, it also gives the skin nutrition and oxygen [39]. For many molecules that penetrate the skin barrier, capillaries, which are located 0.2 mm or less from the skin's surface, provide sink conditions. As a result, the blood supply maintains a very low dermal concentration of permeation, and the ensuing concentration differential across the epidermis serves as the primary driving factor for transdermal permeation [40]. The dermal barrier may be important when delivering highly

lipophilic compounds because this layer is sometimes thought of as essentially gelled water in terms of transdermal drug administration and thus presents a minor barrier to the transport of most polar medicines [40].

HYPODERMIS

The dermis and epidermis are supported by the hypodermis, or subcutaneous fat tissue. It functions as a place to store fat. This layer offers mechanical protection, nutrient support, and assistance with temperature regulation. Principal blood arteries, nerves, and possibly pressure-sensing organs are carried there to the skin. To be effective for transdermal medicine delivery, a substance must cross all three layers and enter the bloodstream [41]. The skin contains adnexa, also known as epidermal appendages, which are structures produced from ectodermal tissue in addition to the epidermis. Nails, eccrine ducts, apocrine glands, and pilosebaceous units are among them [27]. The most important structures in TDD are the sweat ducts, hair follicles, and lymphatic and blood arteries. Sweat glands are in charge of excreting bodily wastes and acids as well as controlling body temperature. Sweat is expelled from each 60–80 μm diameter orifice at a rate of 2–20 μL/min. Hair follicles connected to the sebaceous glands make up the pilosebaceous units. The sebaceous glands' produced sebum can be released through the hair follicles [18]. Depending on the location of the body, sebum is expelled from orifices ranging in diameter from 10 to 210 μm. Both big and tiny hydrophilic molecules have the chance to penetrate the skin thanks to these appendageal structures [18].

MATERIALS ASSOCIATED WITH TRANSDERMAL FORMULATION

POLYMER MATRIX \ DRUG RESERVOIR

Polymers are the fundamental component of TDDS, regulating the drug's release from the apparatus through the polymer matrix and drug reservoir. Dispersion of the medicine in a liquid or solid-state synthetic polymer base can be used to produce a polymer matrix. When it comes to the medication and other elements of the system, including PSAs and penetration enhancers, the polymers utilized in TDDS should be both chemically and biologically compatible. They should also be safe and offer a medicine in an efficient and consistent manner for the duration of the product's intended shelf life [42]. When choosing the polymer to be utilized in the transdermal system, the following standards ought to be given priority [6][43]:

I. To ensure that a particular medicine diffuses and is released through a polymer, its molecular weight, glass transition temperature, and chemical functionality must be ideal.
II. Stability, lack of drug reactivity, ease of fabrication into the intended product, and affordability are all important requirements for the polymer.
III. There must be no toxicity or antagonistic effects on the host from the polymer or its breakdown products.
IV. When a polymer contains a lot of active components, the polymer's mechanical qualities shouldn't diminish too much.

Table 1: Classification of different kind of polymer [44][15]

Natural Polymer	***Synthetic Elastomers***	***Synthetic Polymer***
Cellulose derivatives	Polybutadiene	Polyvinyl alcohol
Gelatine	Polysiloxane	Polyethylene
Natural rubber	Silicon rubber	Polyacrylate
Starch	Butyl rubber	Polyamide
Waxes	Acrylonitrile	Polyurea
Proteins	Neoprene	Polyvinylpyrrolidone
Gums and their derivatives	Hydrin rubber	Polymethylmethacrylate

MEMBRANE

When constructing a patch, a membrane can be employed as a single layer or sealed to the backing to create a pocket that encloses the drug-containing matrix. How readily the medication and/or excipients are available to the skin is determined by the membrane's diffusion characteristics. Several materials are utilized as rate-controlling membranes, such as silicone rubber, polyurethane, and ethylene vinyl acetate [15][44].

DRUG

Careful selection of the medicine is necessary for the effective development of a TDDS [33][45][46].

Table 2: Properties of drug moiety to prepare an effective TDDS

Physiological properties	***Biological properties***
Lower molecular weight less than 1000daltons	Should be potent with a daily dose of few mg/days.
Should have low melting point.	Half-life should be short.
Partition co – efficient.	Must no induce allergic reaction.
Solubility.	Which degrades in the GI tract.
Biotransformation	Inactivated by hepatic first – pass effect.

PENETRATION ENHANCER

Primary barrier function of skin is provided by the stratum corneum. Drugs can enter the systemic circulation via penetrating deeper layers of the skin with the help of penetration (or permeation) enhancers, which are chemical substances that effectively and reversibly decrease the stratum corneum barrier qualities. To find more effective and inert permeation enhancers to use in transdermal patches, a wide range of chemical substances have been investigated [15][17]. The use of penetration enhancers, also known as sorption promoters or accelerators, to improve the permeability of the SC to achieve greater therapeutic levels of the drug candidate, is a well-established method for enhancing TDD [42][47]. By altering the barrier functions of the SC by interaction with its structural elements, penetration enhancers improve permeability. Polar, nonpolar, and polar/nonpolar channels are proposed as the three routes by which drugs may permeate skin. By modifying one of these routes, the enhancers work. By inducing changes in protein structure or solvent swelling, the polar route can be modified [42][48]. The crystalline channel must be made more fluid (which significantly enhances diffusion) and the lipid structure must become less rigid in order to change the nonpolar pathway. The processes listed below are only a few ways in which the penetration enhancers may manifest their effects [47][49].

- Through the disintegration of lipids in the stratum corneum.
- By means of intercellular protein interactions.
- Via better solvent delivery, co-enhancer, or medication partitioning into the stratum corneum.
- Diffusion of the medication from its vehicle to the skin's surface.
- Medication dissolution in its vehicle [50].

Therefore, an efficient permeation booster:
(a) May raise the drug's diffusion coefficient in the stratum corneum (i.e., disturb the stratum corneum's barrier nature);
(b) Act to increase the drug's effective concentration in the vehicle (by, for example, acting as an anti-solvent);
(c) Develop partitioning within the formulation and the stratum corneum (perhaps by modifying the skin membrane's solvent nature to improve partitioning into the tissue);
(d) Less likely, by reducing the thickness of the skin (perhaps by giving a permeation 'shortcut' rather than a difficult pathway for a permeant) [47][51].

As penetration enhancers working beneath the skin, some of the more desired characteristics are as follows [52][53]:

- They need to be free of toxins, allergens, and irritants.
- The ideal outcome would be for them to act quickly and for the effect's duration and activity to be repeatable.
- Their pharmacological activity, or their ability to bind to receptor sites, should be absent from the body.
- Permeation enhancers ought to function unidirectionally, permitting therapeutic drugs to enter the body while halting the extrusion of native material.
- The skin's barrier characteristics ought to fully and quickly restore after removal.
- The penetration enhancers must be suitable for incorporation into a range of topical formulations, meaning they should be harmonious with the medicine and excipient [42].

PRESSURE SENSITIVE ADHESIVES (PSA)

A transdermal device's ability to adhere is dependent on the transdermal patch preparation. Effective medication administration requires the patch to make total, close contact with the skin's surface. The attraction forces between the molecules that PSAs create and the skin are responsible for this interaction [15][54]. When applied under low pressure, PSAs, which are viscoelastic chemical materials, stick to the skin [55]. To achieve the desired level of contact, PSAs must flex under force. With only a little finger pressure, PSAs may be removed off a smooth surface without leaving any trace behind. They also exert a significant gripping force and are aggressively and permanently sticky. Acrylic, silicone, and polyisobutylene-based adhesives are the most common types used in transdermal patches [15][56]. Pressure-activated adhesive substance flows like liquid, causing the skin's surface to become moist and facilitating adhesion. The process of bond breaking involves the storage of elastic energy, which leads to adhesion. The balance between elastic energy and viscous flow therefore defines the material's practicability, and viscoelastic materials exhibit pressure-sensitive adhesion [15][44]. In transdermal patch designs, silicone-based adhesives, acrylics, thermoplastic elastomers, and natural rubber are typically utilized. A good adhesive should consider the drug's composition, the design of the patch, and how well it works with the skin and other patch components. Due to their ease of use, environmental friendliness, and lack of solvent, pressure-sensitive adhesives are becoming more and more important [57][44][15].

Table 3: Characteristics of different kind of Penetration enhancers[17] [53] [49] [58] [51]

Sl. No.	*Types of penetration enhancers*	*Mechanism of action*	*Techniques of penetration enhancers OR Example*
1	Physical enhancers [50] [39] [51]	Rate control over the release and transdermal permeation of drugs	1.Iontophoresis 2.Sonophoresis 3.Phonophoresis 4.Magnetoporation 5.Electroporation 6.Thermophoresis 7.Radiofrequency 8.Needleless injection.
2	Chemical enhancers	Interrupt structure of Stratum corneum lipid	• **Surface-active-agents** [53] Sodium-lauryl-sulphate (SLS), [59] Benzalkonium chloride. • **Cyclodextrins** [58] • **Amine and Amides** [49] • **Azones** [53] • **Pyrrolidones** [49] • **Sulphoxides** [49] Diethylsulphoxides(DMSO) [60] Dimethylformamide (DMF) Diethyl acetamide (DMAC)

			Fatty acids [53] Lauric acid, Myristic acid, Capric acid.
3	Natural Penetration Enhancers	Partition coefficient. Diffusion coefficient. Lipid Extraction. Drug solubility Molecular orientation of terpenes molecule with lipid bilayer.	• **Terpenes-**Menthol, Linalool, Limonene, Carvacrol.[53] [58] [61] • **Essential oil-**Basil oil, Neem oil, Eucalyptus, Chenopodium [58]
4	Drug Vehicle Based [39]	Oppositely charged species to a charged drug, formation of an ion pair in which charges are neutralized so drug permeate through the stratum corneum	Ion pairs and complex Coacervates Chemical potential adjustment

BACKING MEMBRANE

The most comfortable backing will be the one that exhibits the lowest modulus or high flexibility, good oxygen transmission, and a high moisture vapor transmission rate. Examples of backing materials include vinyl, polyethylene, polyester films, aluminium, and polyolefin films. Backings are chosen for appearance, flexibility, and the need for occlusion; therefore, while designing a backing layer, the most important consideration is the chemical resistance of the material. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug, or penetration enhancer through the layer [33][56].

RELEASE LINER

Before the patch is applied to the skin, the protective liner covering it is taken off and thrown away if it is being stored. It is important for the liner to be chemically inert since it will come into close contact with the TDDS. Release liners are usually comprised of two layers: an occlusive base layer (such as paper fabric) or nonocclusive base layer (such as polyethylene, polyvinyl chloride) with a silicon or Teflon release coating layer sandwiched in between. Metalized laminates and polyester foil are other materials utilized in TDDS release liner manufacturing [33][42][56].

OTHER EXCIPIENTS

PLASTICIZERS

Additionally, plasticizers have been used into several formulations with weight percentages ranging from 5 to 20% (w/w, dry basis). It is also in charge of the film's brittleness, ductility, adhesiveness to other surfaces or membranes, and increase in strength. Examples of these include sorbitol or glycerol at 15% w/w, dry basis; phthalate esters; phosphate esters; fatty acid esters; and glycol derivatives like PEG 200 and PEG 400. Both the mechanical characteristics and the permeability of medications are significantly impacted by the choice of plasticizer and its concentration [33][62][63].

SOLVENTS

To produce the drug reservoir, a variety of solvents are utilized, including dichloromethane, acetone, methanol, chloroform, and isopropanol [42].

DIFFERENT METHODS TO PREPARE VARIOUS TYPES OF TRANSDERMAL PATCH

1. ASYMMETRIC TPX MEMBRANE METHOD [11][44]

This method utilizes asymmetric membranes made from TPX (a polymethylpentene polymer) for evaluating drug diffusion in TDDS. These membranes consist of a dense skin layer and a porous sublayer, mimicking the barrier properties of human skin. They are typically prepared using a dry/wet inversion technique, where polymer solutions are cast and immersed in a non-solvent bath, leading to phase separation. The asymmetric structure allows for controlled drug diffusion and is used to assess permeation characteristics of formulations under laboratory conditions. These membranes

provide reproducible, synthetic alternatives to biological membranes and are particularly useful in screening formulations before in vivo testing.

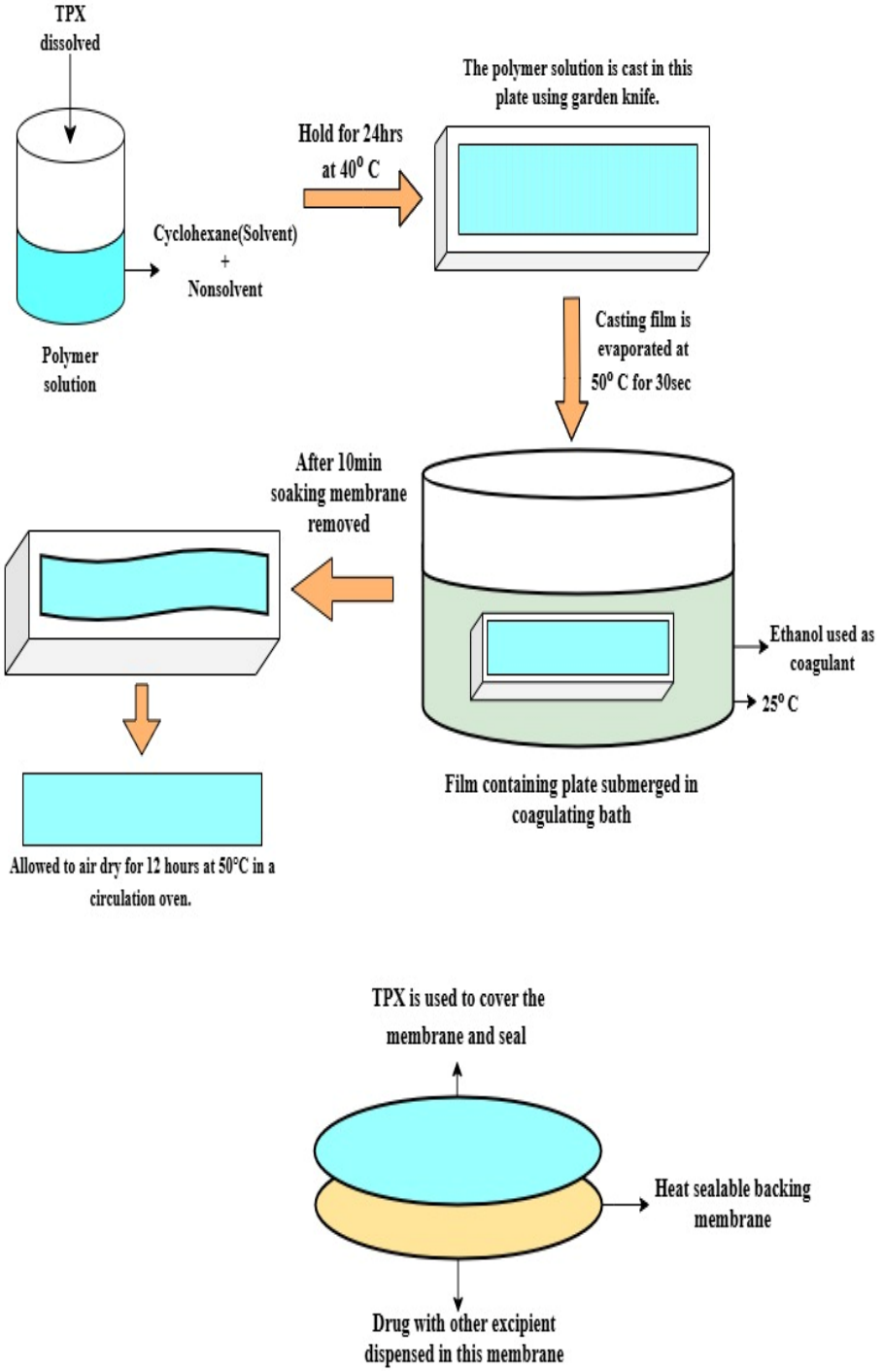

Figure 1: Asymmetric TPX membrane method

2. CIRCULAR TEFLON MOULD METHOD [11][64]

In this method, drug-loaded polymeric films for transdermal patches are prepared using circular Teflon moulds. The polymer solution (containing drug, plasticizer, and other excipients) is poured into a Teflon mould of fixed diameter and allowed to dry, forming uniform circular films. Teflon is chosen for its non-stick properties and chemical resistance, ensuring easy film removal without damage. This technique enables consistent patch thickness and drug distribution, critical for reproducible drug release. The method is simple, cost-effective, and widely used in the lab-scale fabrication of matrix-type transdermal systems for preliminary evaluation and characterization.

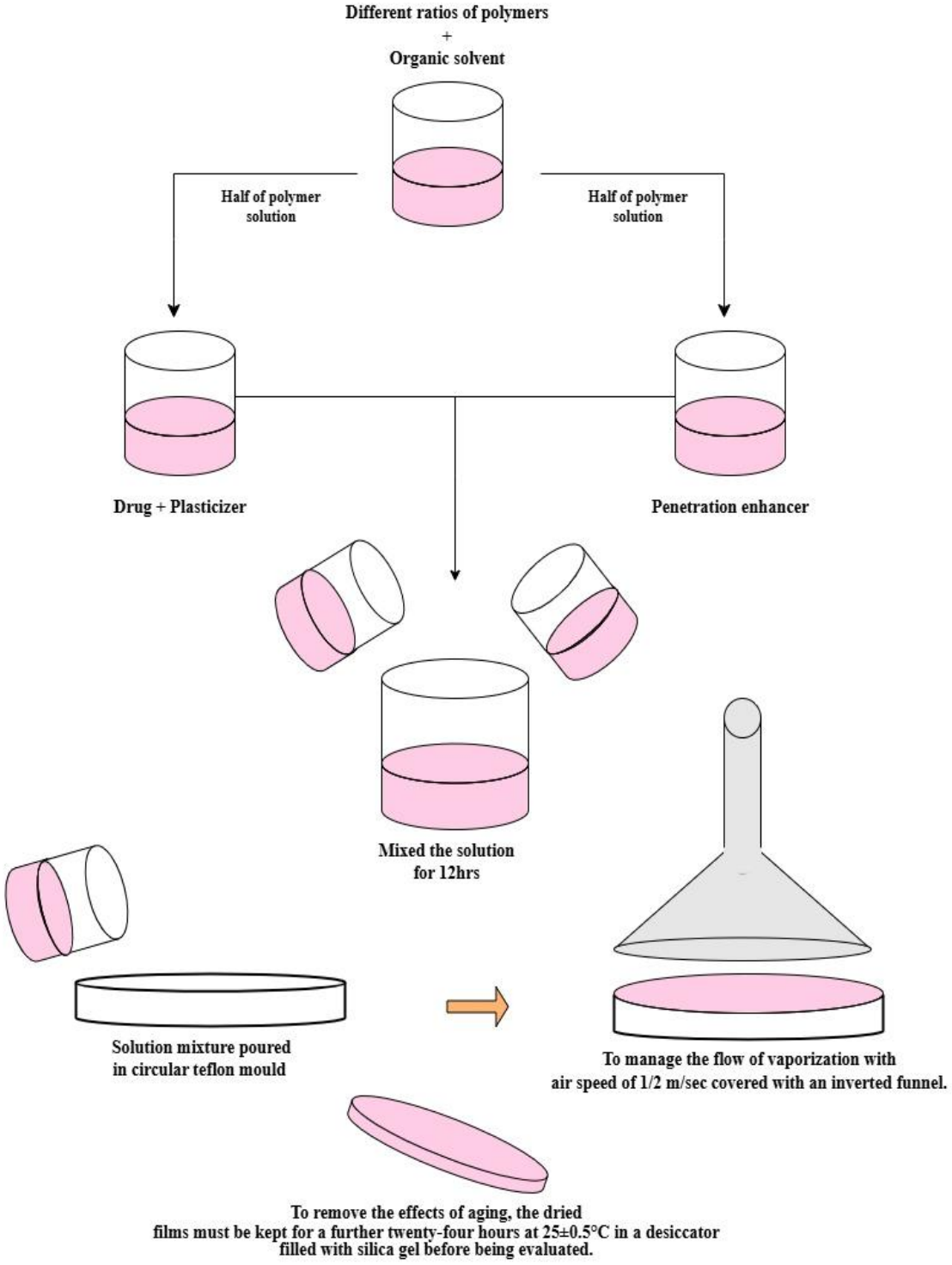

Figure 2: Teflon mould method

3. MERCURY SUBSTRATE METHOD [11]

The mercury substrate method is a traditional technique for casting drug-loaded films for TDDS. In this method, a polymeric solution containing the drug is poured over a mercury surface, where it spreads uniformly and is allowed to dry, forming a thin film. Mercury provides a flat, smooth, and non-adhesive surface, ensuring uniform film formation and easy removal. While effective for creating consistent films, the use of mercury raises significant safety and environmental concerns. Hence, although this method provides a benchmark for film uniformity, it is largely replaced by safer alternatives in modern research.

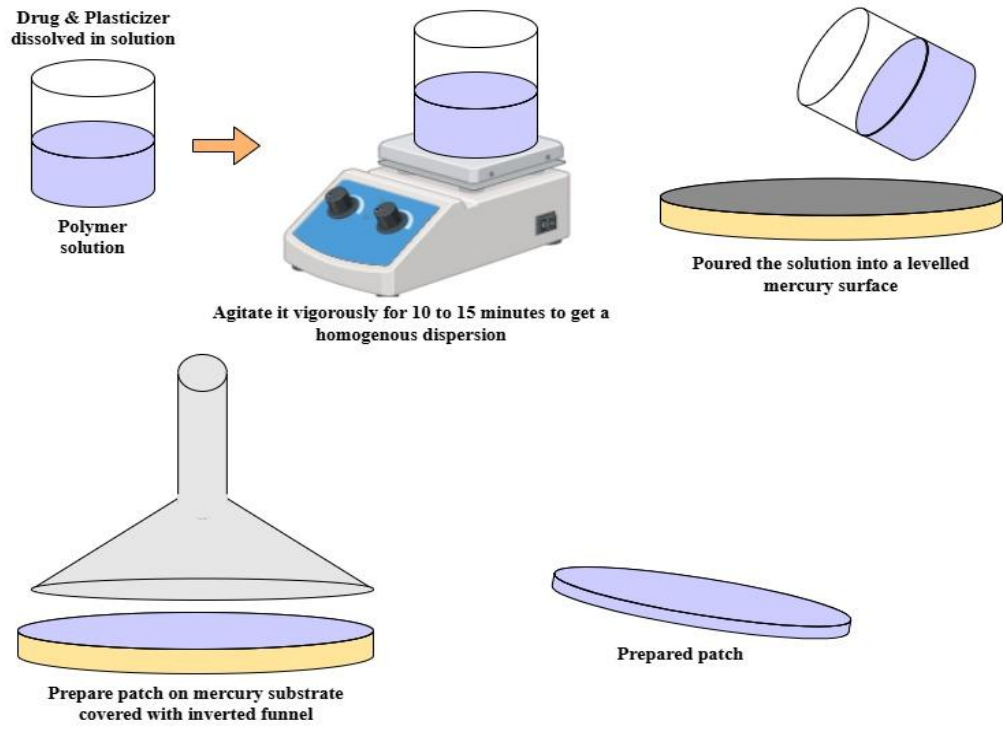

Figure 3: Patch preparation by mercury substrate method

4. USE OF "IPM" MEMBRANE'S METHOD [11] [64]

Isopropyl myristate (IPM) membranes are synthetic lipid-based membranes used in in vitro permeation studies for TDDS. These membranes mimic the lipophilic nature of the stratum corneum and are particularly useful in evaluating drug diffusion behaviour across skin-like barriers. Formulations are placed on the IPM membrane, which is mounted on Franz diffusion cells, and the amount of drug permeating through the membrane is measured over time. This method is valuable for comparing different formulation strategies and penetration enhancers. IPM membranes offer reproducibility, ethical advantages, and help screen formulations before animal or clinical studies.

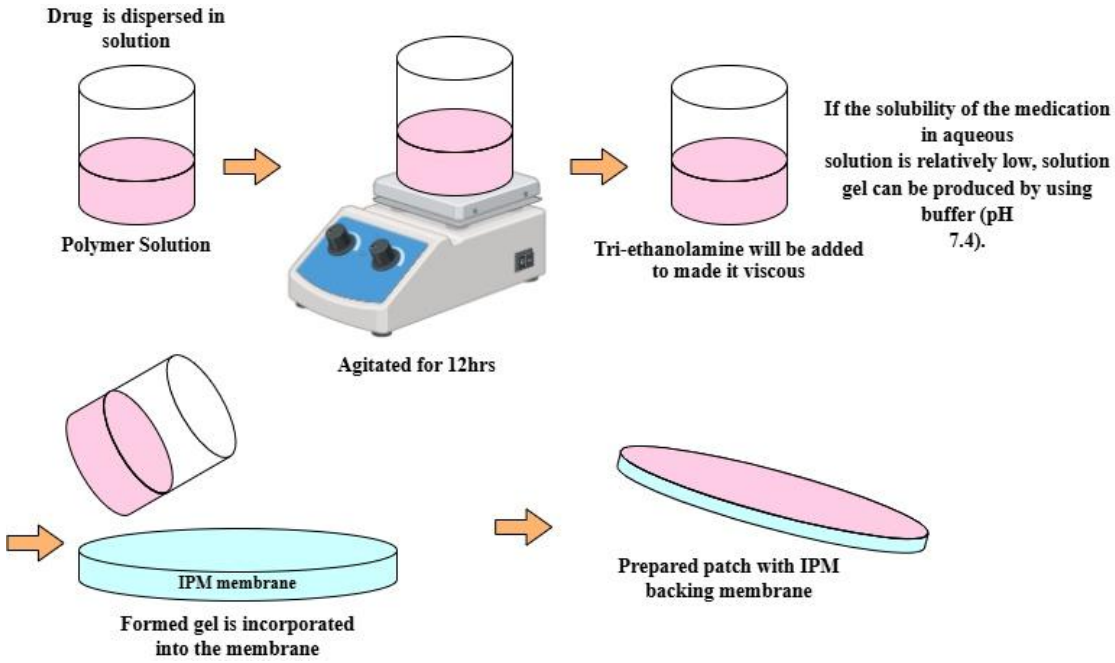

Figure 4: "IPM" membrane method

5. USE OF "EVAC MEMBRANES" METHOD [11] [65]

Ethylene vinyl acetate copolymer (EVAC) membranes are synthetic membranes employed in transdermal drug release and permeation studies. These membranes are semi-permeable and provide a consistent barrier for evaluating diffusion characteristics of TDDS formulations. In this method, the drug-containing patch is applied over the EVAC membrane, typically using a diffusion cell setup like Franz cells, to measure the rate and extent of drug permeation. The EVAC membrane serves as a stable, non-biological alternative to animal skin, offering high reproducibility and minimizing ethical concerns. It is particularly useful in early-stage formulation screening and for comparing the effect of formulation variables.

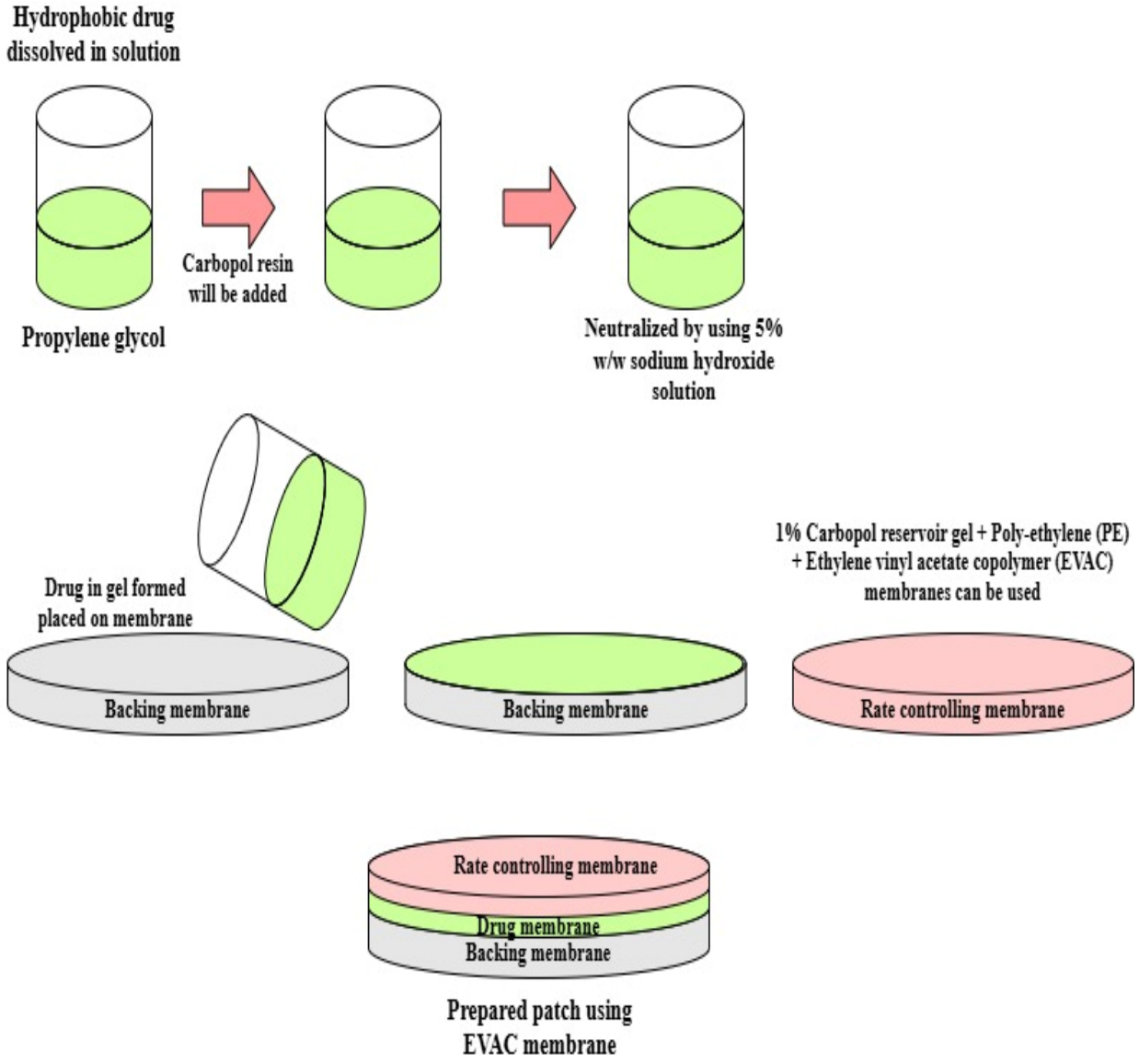

Figure 5: "EVAC" membrane method

6. ALUMINIUM BACKED ADHESIVE FILM METHOD [11] [66]

This method involves the preparation of drug-loaded films with an aluminium foil backing layer. The backing provides structural support, prevents drug loss through the non-application side, and shields the drug from light, moisture, and environmental factors. The adhesive layer, containing drug and polymer, is cast directly onto the aluminium foil, forming a matrix-type TDDS. This design ensures unidirectional drug release toward the skin and enhances formulation stability. Aluminium-backed films are widely used in commercial transdermal patches due to their durability, flexibility, and protective properties.

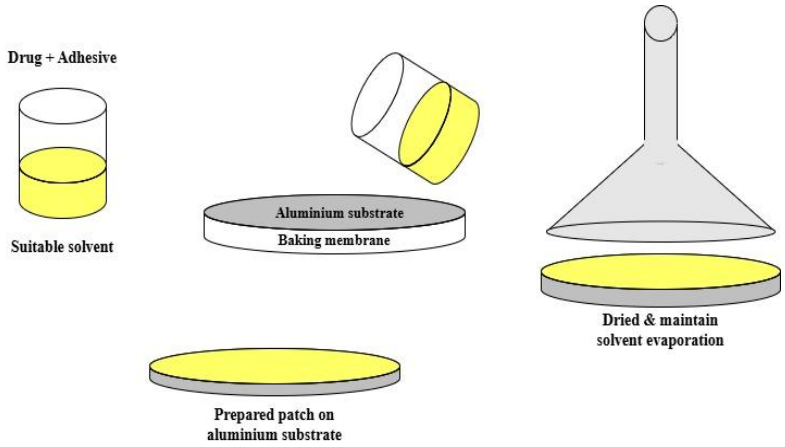

Figure 6: Adhesive film method

7. PREPARATION OF TDDS BY USING PROLIPOSOMES [67][68]

Proliposomes are dry, free-flowing granular formulations that form liposomes upon hydration. In TDDS, proliposomes are used to improve the permeability and stability of lipophilic and hydrophilic drugs. They are prepared by mixing the drug with phospholipids and cholesterol in a suitable solvent, which is then absorbed onto a carrier like maltodextrin. The resulting powder can be incorporated into a gel or film base to form a transdermal patch. Upon skin contact and hydration, proliposomes convert into liposomes, enhancing drug penetration through the stratum corneum via lipid interaction. This method offers controlled release and improved bioavailability.

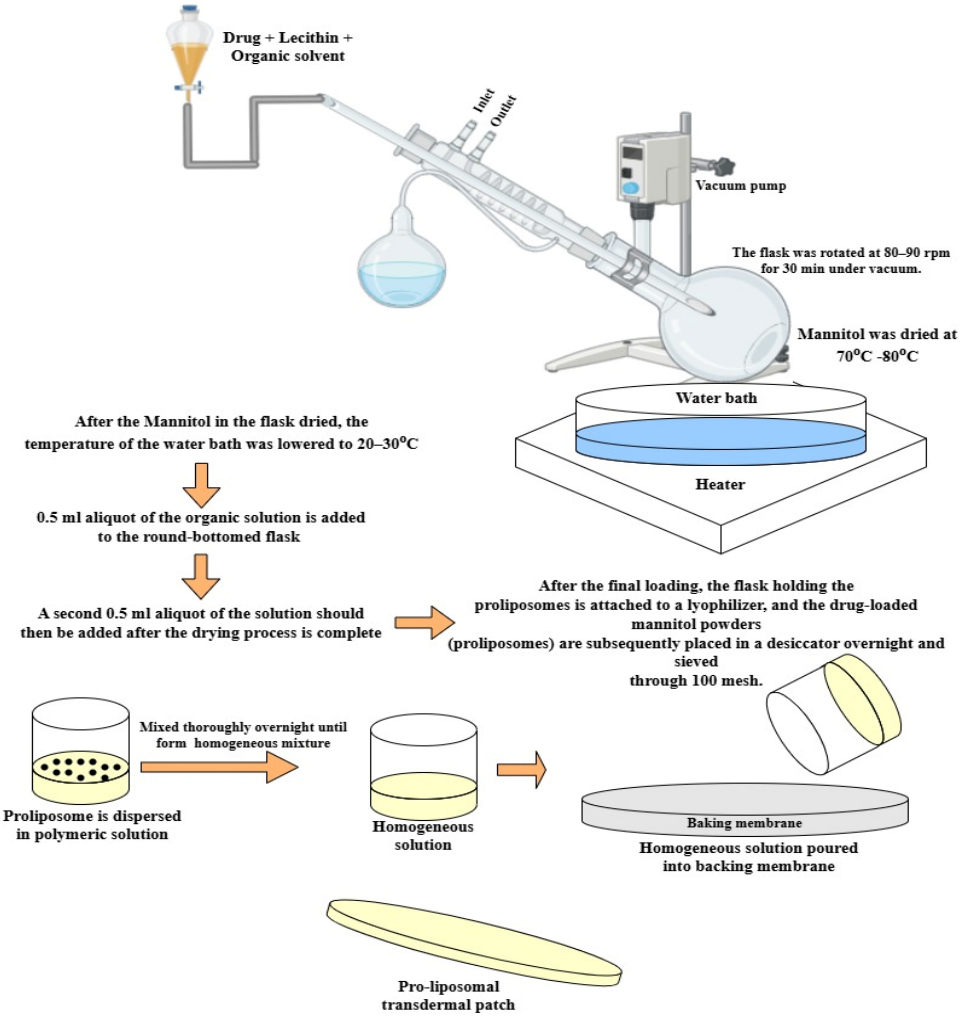

Figure 7: Using proliposomes method

8. USE OF FREE FILM METHOD [11][63]

The free film method is a straightforward approach to fabricate drug-loaded films without a substrate or backing layer. A polymer-drug solution is poured into a flat, inert surface like glass or Teflon and allowed to dry, forming a flexible film. These films are "free-standing" and can be evaluated for mechanical properties, drug content, thickness, and in vitro release. This method is commonly used in early research stages to screen polymer combinations, plasticizers, and drug loading. While not always suitable for final product development, it enables rapid prototyping of TDDS formulations for further optimization.

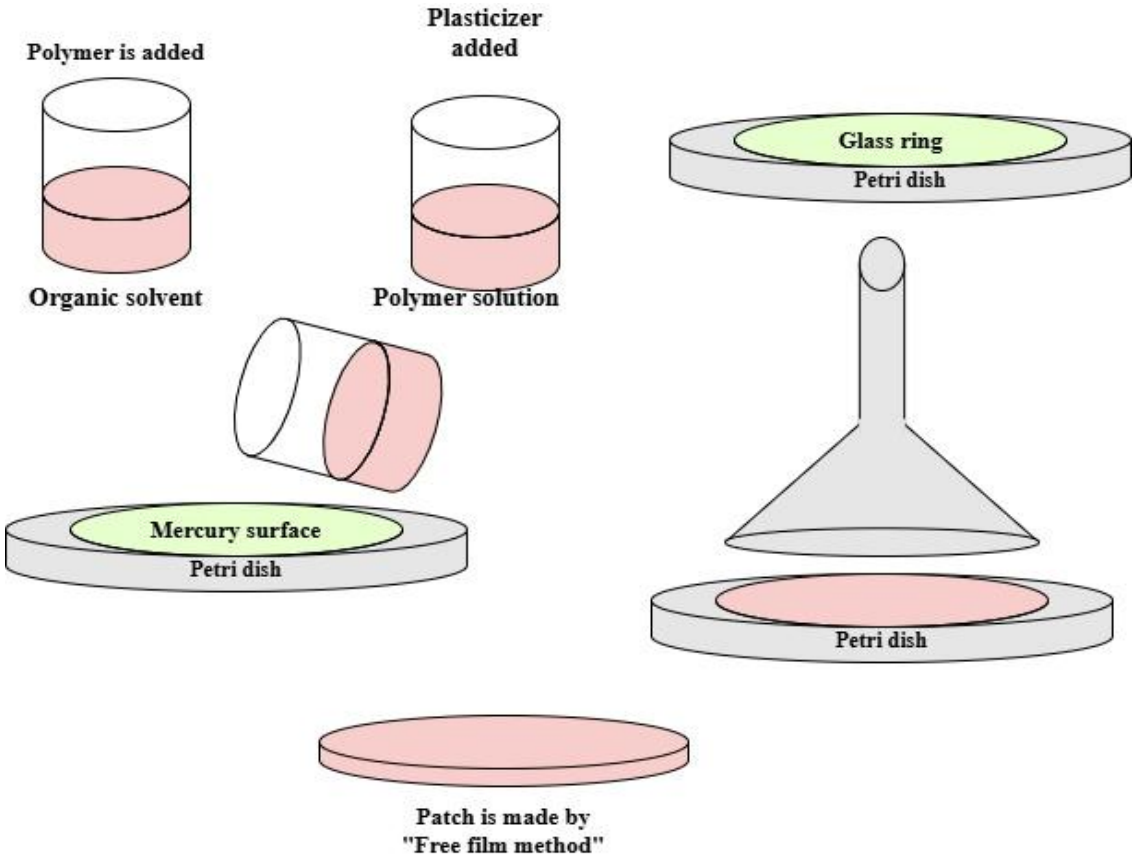

Figure 8: Using free film method

STRATEGIES FOR DESIGNING OF TRANSDERMAL MEDICATION SYSTEMS FOR ADMINISTRATION

Single-layer drug in adhesive patch

To spread the medication and to hold medication dispersion, a reservoir-a single polymer layer with sticky properties is used. An impermeable backing laminate is put on top of this single layer. The backing laminate layer, which supports the drug reservoir, releases the medication that is within and sticks to the polymer layer. ***Daytarana*** is an example of a transdermal patch that has a single layer of medication embedded in adhesive and includes methylphenidate [15][33][17].

Multi-layer drug in adhesive patch

A drug reservoir layer and an adhesive layer with time-released drug delivery are the two layers that make up multilayer transdermal patches. Multiple layers of protection consist of a permanent backing laminate and a temporary protective layer. Drug administration can be extended for up to seven days using multilayer patches [15][33]. The sticky layer and drug reservoir layer work together to manage the release of the medicine over time. Drug release from the reservoir can be controlled in one layer, whereas drug release from the reservoir can occur immediately in another [15][17]. Hormone therapy,

smoking cessation therapies, and pain relief are all administered via multi-layer patches, which have a seven-day duration [15].

Vapour transdermal patch

Vapours may be released from these patches thanks to their single adhesive polymer layer that has a vapor release capability. For diverse uses, there are several types of vapor dermal patches available. One product that helps people stop smoking is ***Nicoderm CQ®***, a transdermal nicotine patch with essential oils included. Releasing these oils helps people stop smoking; it was first introduced to the European market in 2007. ***Altacura vapor patches*** are another kind that are meant to relieve congestion. They are made with essential oils. On the market, there are also vapor patches that are intended to function as sedatives or antidepressants [17][15][69].

Membrane moderate transdermal reservoir patch

The drug reservoir is fully immersed in a compartment that has been moulded between a rate-controlling polymeric membrane and a drug-impermeable backing laminate in this system [70]. By simply diffusing through the pores, the drug molecules are allowed to pass through the rate-controlling membrane. Drug solids are distributed uniformly in reservoir compartments either by dissolving in a releasable solvent (such as alkyl alcohol) to form a gel-like in solution, or by suspending the solid polymeric matrix (such as polyisobutylene) in an un-leachable viscous liquid medium (such as silicon fluid). A microporous or non-porous polymeric membrane, such as an ethylene-vinyl acetate copolymer, with particular drug permeability can serve as the rate-controlling membrane. To allow the TDD system to have close contact with the skin surface, a small coating of drug-compatible adhesive polymer, such as silicone adhesives, can be placed to the polymeric membrane's exterior. The permeability coefficient, thickness, and polymer composition of the rate-controlling membrane and adhesive may all be adjusted to customize the release rate from this kind of TDS [33]. ***TransdermScop (Scopolinome)***, which provides three days of motion sickness protection, and TransdermNitro (Nitroglycerine), which provides angina pectoris medicine once a day, are two examples of this technology [33][71].

Micro-reservoir transdermal patches

Matrix dispersion and medication reservoir are combined in transdermal micro-reservoir patches. A lipophilic polymer is used to uniformly disperse the drug suspension after it has been suspended in an aqueous solution of a hydrophilic polymer, forming the reservoir. There are many tiny, non-leachable spheres formed as a result of this dispersion process, which uses high shear mechanical stress. The drug level in the plasma is consistently maintained by the zero-order kinetic rate of drug release from these patches. Polymeric agents that crosslink is commonly added to medication dispersions in order to preserve thermodynamic stability [17][72].

Matrix system: Drug-in-adhesive

The drug reservoir is made to distribute the medication on an adhesive polymer through single or multilayer transdermal patches. The sticky polymeric components are melted or cast in a solvent to create the drug-polymer matrix, which is coated on an impermeable backing layer. There are several commercial products of this kind of transdermal patch on the market. ***Climara®***, for instance, has 100 micrograms of estradiol for a single application day, and NicoDerm® CQ has nicotine to support quitting smoking for ten weeks [15][72].

Matrix systems: Matrix-dispersion

An impermeable laminate backing plate is placed atop the drug-polymer matrix to ensure homogeneous drug dispersion in a transdermal patch when the reservoir is a hydrophilic or lipophilic polymer matrix. Commercially available matrix dispersion patch products allow a continuous medication flow through undamaged skin, such as ***Nitro-Dur®***, which comprises ***Minitran and Nitroglycerin*** [15][33].

EVALUATION PROCESS OF TRANSDERMAL PATCH

Interaction study

Practically every pharmaceutical dose form includes excipients as a necessary ingredient. The drug's compatibility with the excipients determines a formulation's stability among other things. Finding any potential physical or chemical interaction between the medicine and the excipients is essential because it might impact the medication's stability and bioavailability. A stable product depends on the drug and the excipients working well together. Compatibility studies are crucial in the creation of novel formulations if the excipients have never been utilized in formulations with the active ingredient. By contrasting their physicochemical characteristics, such as assay, melting endotherms, distinctive wave numbers, etc., interaction studies are frequently conducted in thermal analysis, Fourier Transform Infrared spectroscopy, UV, and chromatographic procedures [42][17][73].

Thickness

A digital micrometre is used to measure the thickness of the drug-loaded patch at various spots, and the thickness of the created patch is ensured by calculating the average thickness and standard deviation. Transdermal film thickness can be measured at various places along the film using a micrometre, screw gauge, or moving microscope dial gauge. Every site at which thickness is measured will show a consistently thick patch [17][62][74].

Weight uniformity

Weighing is done when the patches are dried at 60°C. Cut 1 cm^2 pieces from three patches and weigh each one separately to determine weight homogeneity. It is ensured that there is no considerable deviation between the individual weights and the average weight by computing the weight variation. The patch's weight is determined by taking the three components' average weight [17][75][76].

Folding endurance

A strip of film or patch is repeatedly folded in one spot until it breaks or has been folded up to 300 times, which is how folding endurance is measured. The patch's folding durability is shown by the number of folds it can withstand without breaking. This statistic reveals the patch's degree of flexibility [42][77][78].

Percentage moisture content

Following a preliminary weight, the individual patches are kept in desiccators with fused calcium chloride for a whole day at a predetermined temperature. After this time, the patches are weighed again, and using the weight difference between the pre- and post-desiccation weights, the % moisture content is determined. This technique aids in ascertaining the patches' moisture content [17][42][79].

Moisture content percentage = [Initial weight – Final weight / Final weight] × 100

Percentage moisture uptake

The weighted films are initially subjected to 84% relative humidity for 24 hours in another desiccator that uses potassium chloride to achieve this goal. Until the films achieve a stable weight, they are frequently reweighed. By determining how the films absorb and hold moisture under particular humidity settings, this technique offers important insights about the stability and functionality of the films [17][80].

Moisture uptake percentage = [Final weight – Initial weight / initial weight] × 100

Investigations on water vapor transfer (WVT) / Permeability assessment of water vapor (WVP)

One gram of calcium chloride should be weighed and then added to appropriately sized, previously dried vials to determine WVT. Using a silicon adhesive grease-type glue, the polymer sheets are adhered to the brim and left for five minutes to solidify. After precisely measuring the vials, they are

put in a humidity chamber with a 68% relative humidity. A weight rise was regarded as a quantitative indicator of the amount of moisture transferred via the patch. The vials are weighed once more after the conclusion of the first, second, and third days, up to seven days in a row [81][82][69].

$$WVT = W/ST.$$

T is exposure duration; S is film exposure area (cm^2); and W is weight gain in a 24-hour period.

Drug content

The film, which has a predetermined weight and area, is dissolved in a suitable solvent—such as phosphate buffer(pH7.4) or methanol before being filtered. Using UV or HPLC (High-Performance Liquid Chromatography) techniques and a standard curve, the drug concentration is ascertained following the creation of appropriate dilutions. The drug concentration in the film sample is quantified with the aid of this analytical procedure [17][83].

Polariscope investigation

The purpose of this test is to use a polariscope to look at the drug crystals that were removed from the patch. To determine if the drug is present in the patch in an amorphous or crystalline form, a portion of the piece's surface must be maintained on the object slide and examined for drug crystals [42].

Test for shear adhesion

The cohesive strength of an adhesive polymer is to be measured using this test. It can be affected by the polymer's composition, molecular weight, degree of crosslinking, and kind and quantity of tackifier used. Applying an adhesive-coated tape to a stainless-steel plate causes it to pull in a direction parallel to the plate when a specific weight is suspended from it. By timing how long it takes to remove the tape from the plate, shear adhesion strength may be calculated. The shear strength increases with the length of time required for removal [42][69][84].

Test for Peel Adhesion

For the purposes of this test, peel adhesion is the force needed to remove an adhesive covering from a test substrate. The parameters that affected the peel adhesion characteristics were the kind and quantity of additives, as well as the molecular weight of the sticky polymer. The application of a single tape to a preferred backing membrane or stainless-steel plate is followed by a 180º angle pull of the tape from the substrate, and the force needed to remove the tape is measured [42][84][85].

Thumb tack test

The force required to pull an item, such as a thumb, off an adhesive surface indicates the tackiness of the material. The purpose of the test is to determine the adhesive's tack properties through qualitative means. To detect the relative tack characteristic, just push the thumb down on the adhesive [84].

Test for flatness

The centre of transdermal patch and both its left and right sides are sliced using strips in order to test for flatness. Following the measurement of each strip's length, the following formula is used to determine the length variation as a percentage constriction:

Proportion of Constriction = (Initial Length - Final Length) / Initial Length x 100

100% flatness is indicated by a percentage of constriction of 0%, indicating that the patch will not contract with time and will continue to have a smooth surface [17][86].

Rolling ball tack test

The softness of a polymer related to speech is measured by this test. In order for the 7/16-inch-diameter stainless steel ball to roll down an inclined track and come into touch with an exposed, horizontal, and upward facing adhesive surface, it must be released. Tack, which is measured in

inches, is determined by how far the ball moves along the adhesive. The adhesive's capacity to stick to a surface right away after contact is measured by its tackiness [17][69].

Quick stick (peel-tack) test

At a pace of 12 inches per minute, the tape is dragged away from the substrate in this test at a 90º angle. Tack value, which is given in ounces or grams per inch width, is the peel force needed to break the binding between the adhesive and the substrate. It is measured and documented [56][87].

Probe tack test

The adhesive is tested by coming into contact with the tip of a clean probes that has a predetermined surface roughness. Furthermore, the act of removing the probe later on mechanically destroys the connection that has formed between the adhesive and the probe. Packed with grams, tack is the force needed to extract the probe from the glue at a certain pace. [42][84][87].

Tensile strength test

Corked linear iron plates are positioned between polymeric sheets to measure their tensile strength. The films are held in place at one end by an iron screen, and at the other end by a freely moveable thread that is attached to a pulley. With the dangling end of the thread connected, the pan is progressively filled with weights. The elongation of the film is measured with a pointer on the thread. Noted is the weight that would just barely shatter the film [88][89].

The patch's tensile strength may be calculated as follows:

$$\textbf{Tensile strength} = \textbf{break force} / \textbf{a} \times \textbf{b}\ (1 + \Delta L/L)$$

where ΔL is the patch's elongation at the breakage point, a, b, and L are the patch's width, thickness, length, and break force are the weight (kg) necessary for the patch to break [11][15]. A texture analyser was used in a different investigation to measure the film's tensile strength. When the films broke, measurements of force and elongation were made [15].

Test for Swellability

Applying the sample to a pre-weighed cover slip in a Petri dish with 50 mL of pH 7.4 phosphate buffer is how one finds out if a transdermal patch is swellable. Time t (typically around 30 minutes) is when sample absorption occurs. Time t is then used to take the cover slip from the Petri dish, wash it, and weigh it. The mass that the patch absorbs from the water is equal to the change in mass [15][90].

The following equation gives the percentage Swelling (S).

$$\boldsymbol{S}\ \% = \frac{\boldsymbol{W_t - W_0}}{\boldsymbol{W_0}} \times \mathbf{100}$$

where $\boldsymbol{S}$ = % swelling, W_0 = original mass of the patch at time zero, W_t = patch mass at time *t* after swelling.

***In-vitro* drug release study**

A variety of techniques can be employed to assess drug release from a transdermal formulation with an appropriate, non-rate-limiting membrane. These techniques include:

i) The paddle over disc *(USP apparatus 5/PhEur 2.9.4.1)*, which is comparable to the USP paddle dissolution apparatus but with the temperature adjusted to skin temperature (32 ± 5 °C) and a disc or cell containing the formulation submerged at the bottom of the vessel [91];

ii) The United States Pharmacopeia *(United States Pharmacopeial Convention, Inc.)* (USP) basket *(USP apparatus 6 / PhEur 2.9.4.3)* modified cylinder method, which is comparable to the USP basket type dissolution apparatus method, with the exception that a hollow cylinder is immersed in a medium and kept at a temperature of 32 ± 5 °C [15];

iii) The method of the reciprocating disc *(USP apparatus 7)* involves placing the formulation into holders and oscillating it in small volumes of buffer medium;
iv) The paddle over extraction cell method *(PhEur 2.9.4.2)* may also be utilized [15].
In addition, diffusion cells are commonly used to assess drug release from transdermal formulations. These include the Franz-diffusion cell and its variant, the Keshary-Chien cell. Using magnetic beads, the solution in the receiver compartment is continuously stirred throughout the experiment. The transdermal system is positioned between the donor and receptor compartments of the diffusion cell, facing the receptor compartment where the receptor fluid *(such as drug solution)* is placed. The temperature and agitation speed are maintained constant throughout the assembly, and the receptor fluid is removed for analysis and replaced with an equal volume of fresh receptor fluid at predetermined intervals. The drug concentration is determined by an appropriate analytical method [91][92].

A UV spectrophotometer or HPLC can be used to evaluate samples (5-mL aliquots) that are taken out at suitable intervals for up to 24 hours. It is possible to compute the mean value by carrying out the experiment in triplicate [92]. The ***higuchi, first order, zero order, peppas, and korse-meyer*** mathematical models can all be used to explain the kinetics of drug release from a transdermal patch. The model that best matches the data is then utilized to identify the mechanism of kinetic drug release once data have been gathered and included into these models [11][15].

Studies on *In-vitro* permeability
Following release from the polymeric films, the drug reaches the skin's surface and is subsequently transported to the dermal microcirculation by permeating through epidermal cells and/or between epidermal cells through skin appendages. Permeation studies are typically conducted by inserting a synthetic membrane or rat skin with apply of transdermal patch between the donor and receptor compartment in a vertical diffusion cell, such as a Franz diffusion cell or Keshary-Chien diffusion cell [93]. The transdermal system is placed on the hydrophilic portion of the membrane and then mounted in the diffusion cell with the lipophilic front in contact with receptor fluid. Continuous, steady stirring is applied to the buffer medium inside the inner compartment. Typically, samples containing around 500 µL are collected at predetermined times. A volume of buffer equivalent to the sample is put back in after it is taken [94]. The recipient compartment is then maintained at an appropriate temperature (usually 32±5°C for skin) along with is continuously stirred at a constant rate. An appropriate analytical procedure is used to estimate the samples once they have been diluted adequately. For every time period, the quantity of medicine infused per square centimetre is computed. There are several factors that can impact the in-vitro drug properties, such as system design, patch size, skin thickness, surface area, and temperature. As a result, the permeation studies include sample analysis and flux calculation (i.e., medication permeated per unit area per unit time), skin preparation, placement of the skin on permeation cell, developing of experimental variables like the temperature, vigorous stirring, sink conditions, and sample withdrawal at various hours [95].
Permeability coefficients were established by dividing the flux by the initial drug load (mg/cm2). Flux may be calculated directly as the slope of the curve between the steady state values of the quantity of drug penetrated (mg/cm2) versus time in hours [11][15][74][78].

Study on skin irritation
The (Primary Irritation Index) PII test can be used to visually assess the erythema and edema associated with various transdermal patches to determine their propensity for causing skin irritation. Alternatively, a light microscope can be used to look for any histological abnormalities [15]. Testing transdermal patches for skin irritation can be done on albino rats with an average weight of up to 230 g. patches placed over 8.1 cm2 of the rat's back 24 hours before the experiment after it has been washed with rectified spirit and shaved. After the patch has been in place for 24 hours, it is taken off and a disinfection swab is used to clean the region. Visual examination of the application sites is done to look for any changes in erythema and edema of the skin. Changes in erythema and edema can be

scored on the Draize scale from 0 to 4 [96]. The intensity of the skin responses determines how this is assessed. The following formula is used to compute:

Intensity of Skin Response (PII) = {Total erythema grade over several days + Total edema grade over several days}/Number of animals.

The PII values were used to classify the degree of irritation as minimal (PII = 0-0.4), minor (PII = 0.5–1.9), moderate (PII = 2-4.9), or severe (PII = 5–8) [97][98].

Study on Stability

As directed by the International Council for Harmonization (ICH), stability testing is carried out. During six months, the transdermal patches that have been manufactured are kept at a temperature between 40°C±0.5°C and with a relative humidity between 75°C±5%. After being stored for six months, the samples are removed and their drug content is measured at intervals of 0, 30, 60, 90, and 180days. As such, Testing guarantees that the transdermal patches will remain stable and of high quality for a long amount of time when stored in the recommended manner [99][17][100].

CONCLUSION

Transdermal Drug Delivery Systems (TDDS) have revolutionized the field of pharmaceutical sciences by offering a non-invasive, sustained, and patient-friendly alternative to conventional drug administration routes such as oral or parenteral. Through the utilization of the skin as a portal for systemic drug absorption, TDDS effectively bypasses the hepatic first-pass metabolism and gastrointestinal degradation, which are common limitations associated with traditional dosage forms. This not only enhances the bioavailability of the drug but also allows for steady-state plasma concentrations, minimizing fluctuations that could lead to sub-therapeutic effects or adverse reactions. The success of TDDS relies heavily on the strategic selection and optimization of its key components. Among these, polymers play a vital role by forming the matrix or reservoir that controls drug entrapment and release kinetics. A proper balance between hydrophilic and hydrophobic characteristics of the polymer matrix is crucial to ensure controlled drug diffusion while avoiding burst release or overly delayed delivery. Similarly, penetration enhancers are employed to transiently disrupt the skin barrier, particularly the stratum corneum, thereby facilitating the efficient passage of the drug into deeper layers of the skin and systemic circulation. Pressure-sensitive adhesives ensure adequate contact with the skin, and backing membranes, release liners, and plasticizers contribute to the physical integrity and functionality of the patch. Different types of transdermal patches, including reservoir, matrix, micro-reservoir, vapor, and drug-in-adhesive types, offer diverse release profiles suited to a variety of therapeutic needs. Among these, matrix-type and drug-in-adhesive patches are particularly favoured due to their ease of fabrication, cost-effectiveness, and reliable performance. In recent years, advancements in material science, polymer engineering, and permeation enhancement technologies have significantly broadened the scope of TDDS. Innovative fabrication methods and improved evaluation techniques have contributed to the development of more efficient and safer transdermal formulations. Furthermore, the incorporation of nanotechnology, microneedle arrays, and smart delivery systems promises even greater precision and control over drug administration. In conclusion, TDDS stands as a promising and continually evolving platform with immense potential for delivering a wide range of drugs, including small molecules and biologics. With ongoing research and interdisciplinary collaboration, TDDS will likely continue to transform the landscape of drug delivery by offering personalized, controlled, and convenient therapeutic options for patients across various medical conditions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this work. All authors have contributed to the manuscript impartially, without any financial, personal, or professional relationships that could influence or appear to influence the content or outcomes of the study.

STATEMENT

The authors acknowledge the use of an AI-based tool to assist in contextualizing and refining the content of this review article. The tool was utilized to enhance clarity, ensure coherence, and support literature organization, while all critical analysis, interpretation, and final writing were conducted by the authors themselves.

AUTHOR CONTRIBUTIONS

Author 1: Conceptualization of the review topic, overall supervision, and critical revision of the manuscript. **Author 2:** Literature search, data collection, and drafting of sections related to formulation components and membrane methods. **Author 3:** Contributed to the analysis and summarization of evaluation techniques and polymer selection. **Author 4:** Assisted in manuscript structure design and writing of advancements and applications in TDDS. **Author 5:** Compiled graphical content, tables, and ensured proper formatting and citation of references. **Author 6:** Reviewed and edited the final draft for consistency, clarity, and scientific accuracy. **Author 7:** Supported in proofreading, language refinement, and integration of AI-assisted content enhancement. All authors have read and approved the final version of the manuscript.

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