Available online on 15.12.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

Open Access

Review Article

Comprehensive Review of Transdermal Drug Delivery Systems: Mechanisms, Materials, and Modern Innovations

Patil Vaishnavi D*, Dr. Gosavi Sheetal B

Pravara Rural Education Society's College of Pharmacy (For Women's), Chincholi , Nashik , Maharashtra , 422102

A B S T R A C T

Transdermal Drug Delivery Systems (TDDS) provide an innovative and non-invasive route for controlled and sustained drug administration through the skin. This review highlights the historical development, formulation components, classification, evaluation parameters, and regulatory perspectives of TDDS. Advantages such as bypassing first-pass metabolism, maintaining consistent plasma levels, and improving patient compliance are emphasized, along with challenges like limited permeability and skin irritation. Furthermore, emerging technologies including nanocarriers, molecularly imprinted polymers, microneedles, and 3D-printed systems are discussed for their potential to enhance drug permeation and therapeutic efficacy. Overall, TDDS continue to evolve as efficient, patient-oriented alternatives to conventional dosage forms.

Keywords: Transdermal drug delivery, Controlled release, Nanocarriers, Microneedles, Molecular imprinting, 3D printing, Patient compliance

A R T I C L E I N F O: Received 17 Sept. 2025 ; Review Complete 16 Oct. 2025; Accepted 19 nov. 2025 ; Available online 15 Dec. 2025

Cite this article as:

Patil V D*, Gosavi S B, Comprehensive Review of Transdermal Drug Delivery Systems: Mechanisms, Materials, Modern Innovations, Asian Journal of Pharmaceutical Research and Development. 2025; 13(6):154-167, DOI: http://dx.doi.org/10.22270/ajprd.v13i6.1668

*Address for Correspondence:

Patil Vaishnavi D, Pravara Rural Education Society's College Of Pharmacy (For Women), Chincholi, Nashik, 422102 (Maharashtra), India.

INTRODUCTION:

With an area of 1.5 to 2.0 m2 in grown-ups, the skin is the biggest organ in the mortal body by mass. Since the foremost given medical records of man, medicines have been applied to the skin to cure superficial conditions, to administer curatives transdermally to manage systemic conditions, and as cosmetics. In ancient Egypt and sumptuous drug (c. 3000 BC), for illustration, the use of dressings, ointments, potions, and indeed patches made of factory, beast, or mineral excerpts was formerly common (Magner, 2005; Geller, 2010). still, it was not until the ultimate part of the 20th century that transdermal delivery systems came extensively used, thanks to advancements in delivery technology that made it possible to administer specifics through the skin precisely and constantly for systemic goods.

With a special emphasis on the development and contemporary operation of transdermal patches, this review aims to give a comprehensive overview of the rich history of topical and transdermal distribution that has developed over thousands of times. P.O. or parenteral administration can be used to read or compare drug blood position – time biographies, which are frequently used to establish the technology's implicit efficacity and adequacy for systemic remedy. The volume of drug delivered into the body from the operation point and the delivery system determines these blood medicine attention. Deep within or beneath the skin, transdermal administration is also employed to produce clinical goods similar original anesthesia and anti-inflammatory action. On the other hand, topical administration uses a veritably original action to address superficial but sometimes extremely serious — skin issues. (1)

Drugs given in traditional dose forms typically cause a wide range of variations in plasma drug concentrations, which can result in unfavorable toxicity or ineffectiveness. These elements, along with additional elements like recurrent dosage and irregular absorption, gave rise to the idea of the controlled drug delivery system of treatment. A controlled drug delivery system is a dosage form that delivers one or more medications systemically or to a

designated target organ continuously in a predefined pattern for a predetermined amount of time. Ensuring drug safety, increasing treatment efficacy, and improving patient compliance are the main goals of controlled drug delivery. Less frequent dosing and improved control of plasma drug levels are the means by which this is accomplished. When applied to intact skin, transdermal treatment devices are self-contained, discrete dosage forms that distribute the drug or drugs to the systemic circulation at a regulated pace through the skin. (2-4)

The medication Scopolamine was used to cure motion sickness in the first Transdermal Drug Delivery (TDD) system, Transderm-Scop, which was created in 1980. A membrane-moderated system is the transdermal device. This system uses a microporous polypropylene film as its membrane. The medicine is dissolved in a mixture of mineral oil and polyisobutylene to form the drug reservoir. The duration of this study release is three days. (2,5)

HISTORY:

Early Topical Products (Pre-1960s to 1990s)

These were the first attempts at delivering medicines through the skin. They substantially reckoned on simple operation styles.

A. 30 Chloral/ ethanol (Pre-AD)

- Medicines were applied as a result or ointment directly on the skin.
- Illustration Bedaubing or rubbing onto the skin.
- Limitation Poor control over immersion, inconsistent dosing.

B. Cold delicate/ ranch w o conflation

- Early conflation- grounded creams, which spread medicines over the skin face.
- Better than direct rubbing, but immersion remained variable.

C. Mustard Cataplasm (1960s)

- A simple treated cataplasm applied on the skin.
- Handed localized treatment but unbridled dosing and possible skin vexation.

D. Active Patch(1990s)

- Early tenacious patches that sluggishly release medicines.
- Advanced convenience and controlled delivery.

E. Minimally invasive patch with release liner

- Incorporated a defensive liner to control medicine release onto the skin.
- Reduced direct skin vexation and bettered dosing thickness.

Controlled Dosing & Invasive Patches (1980s – 1990s)

These systems introduced more sophisticated technology to deliver medicines steadily, frequently incorporating force or matrix systems for controlled release.

A. Reservoir Patch(1990s)

- Medicine is stored in a liquid or gel force.
- Released at a controlled rate through a semi-permeable membrane.

B. Matrix Patch(1980s)

medicine bedded within a polymeric matrix.

Provides sustained release as the medicine diffuses through the matrix into the skin.

C. Matrix Patch 2(1980s)

- An bettered interpretation of the matrix patch with better control over medicine release and adhesion.

D. Drug- Adheind Patch (1980s)

- Combines tenacious and medicine- containing layers.
- Ensures steady medicine delivery with minimum destruction (1)

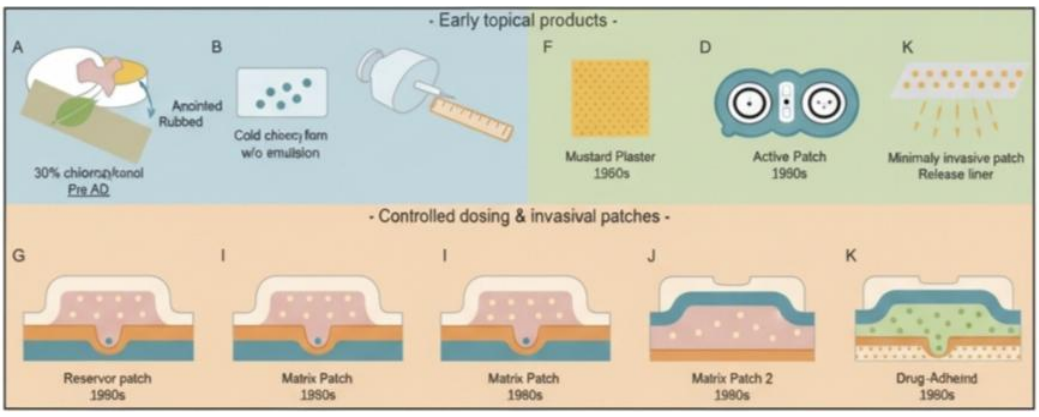


Figure 1: Evolution of topical and transdermal drug delivery (1)

Advantages:

- This procedure is easy to use and just needs to be applied once a week. A straightforward dosage schedule like this can help patients stick to their medication routine.
- Patients who are unable to take oral dosage forms may benefit from transdermal medication delivery as an alternate method of administration.
- It is quite beneficial for people who are unconscious or experiencing nausea.
- Since transdermal distribution avoids direct effects on the stomach and intestine, medications that induce gastrointestinal distress may be suitable candidates for this delivery route.
- A Medications that are broken down by the gastrointestinal system's acids and enzymes could also make good targets.
- Transdermal injection circumvents first pass metabolism, another restriction on oral medication delivery.
- Transdermal drug administration is a great option for medications that need comparatively constant plasma levels. (6,7)
- The medications increase bioavailability by avoiding pre-systemic and hepatic metabolism.
- IV therapy's risks and drawbacks are avoided.
- decreased dosage frequency and a consistent, long-lasting, and sustained duration of effect
- simple way to stop taking medication
- Because there are fewer dose intervals, patients are more compliant.
- improved therapeutic effectiveness by avoiding the systemic drug level peaks and troughs that come with traditional distribution.
- Self-management is feasible. (2,8,9)

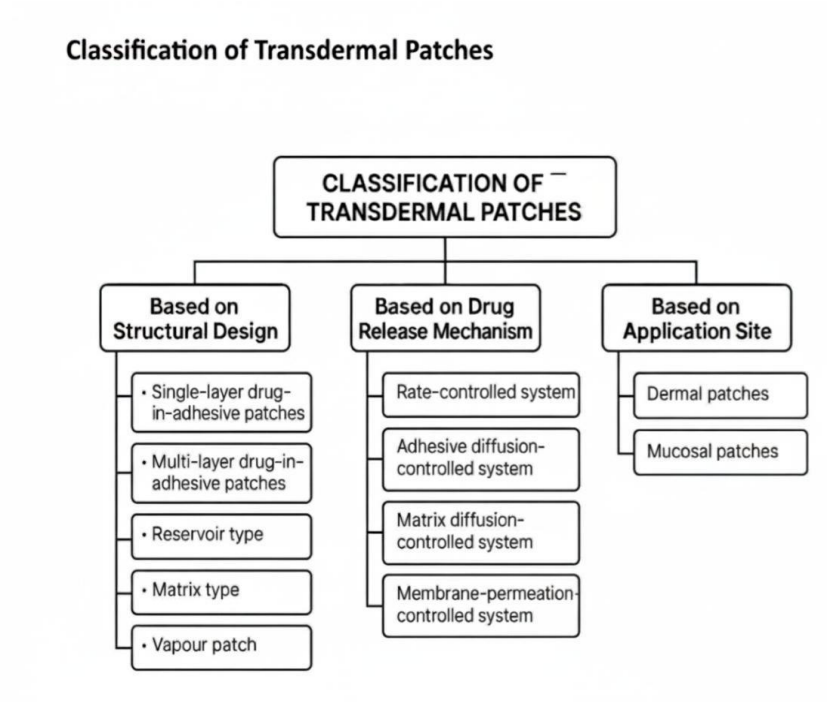
Disadvantages:

- The potential for local discomfort when the product is applied
- The medication, the adhesive, or additional excipients in the patch formulation may result in erythema, irritation, and local edema.
- Could result in allergic responses.
- It is imperative that the molecular weight be less than 500 Da.
- A log P (octanol/water) of 1 to 3 indicates adequate aqueous and lipid solubility, which is necessary for the permeate to cross the SC and underlying aqueous layers (6).

Table: Summary of various psychotropic drugs used as transdermal systems (10)

Medication (Transdermal System)	Category/Class	FDA Approved	Licensed for Target Illness	EMEA Approved for Clinical Use	MHRA Approved for Clinical Use
Rotigotine	Dopamine agonist	Approved	Parkinson's disease	Approved	No
Methylphenidate	CNS stimulant	Approved	ADHD	No, European patent approved	No
Dexamphetamine	CNS stimulant	Preclinical phase	ADHD	No	No
Selegiline	MAOI	Approved	Depression	No, pharmaceutical company looking for EU partner	No
Fluoxetine	SSRI	Preclinical phase	Depression	No	No
Nicotine	—	Approved	Smoking	Approved	Approved
Buprenorphine	Semisynthetic opioid	Approved	Opioid detoxification	Approved	Approved
Haloperidol	Antipsychotic	Preclinical phase	Psychosis	No	No

5. Classification of Transdermal Patches:



1. Based on Structural Design:

a) Single-layer drug-in-adhesive patches:

b) Drug is incorporated directly in the adhesive layer.

c) Example: Nicotine patch.

d) Multi-layer drug-in-adhesive patches:

e) Multiple adhesive layers, may contain drug in one or both.

f) Example: Clonidine patch.

g) Reservoir type:

h) Drug contained in a separate reservoir, controlled release via rate-controlling membrane.

i) Example: Nitroglycerin patch.

j) Matrix type:

k) Drug dispersed in a polymer matrix, diffusion-based release.

l) Example: Fentanyl patch.

m) Vapour patch:

n) Contains volatile active ingredients for inhalation through skin contact.

o) Example: Menthol patches for congestion.

2. Based on Drug Release Mechanism:

a) Rate-controlled system – Release rate is fixed by design.

b) Adhesive diffusion-controlled system – Drug release via adhesive layer.

c) Matrix diffusion-controlled system – Drug diffuses through polymer matrix.

d) Membrane-permeation-controlled system – Membrane regulates release.

3. Based on Application Site:

a) Dermal patches – Applied to skin for systemic or local effect.

b) Mucosal patches – Applied to buccal, sublingual, vaginal, or rectal mucosa. (11-13)

4. Based on drug consideration:

Category	Description	Example
Small, lipophilic drugs	Easily cross skin barrier due to high lipid solubility and low molecular weight.	Nicotine, Fentanyl
Hydrophilic drugs	Require penetration enhancers or iontophoresis for delivery.	Lidocaine, Estradiol
Peptides / Proteins	Large molecules; require microneedle patches or special enhancers.	Insulin (experimental), Desmopressin
Volatile agents	Released from patch as vapour, inhaled through nasal passages.	Eucalyptus oil patches

5. **Based on Disease treated:**

Therapeutic Area	Example of drugs	Example of patches
Pain management	Fentanyl, lidocaine	Duragesic®, Lidoderm®
Smoking cessation	Nicotine	Nicoderm CQ®
Hormone replacement therapy	Estradiol, Testosterone	Climara®, Androderm®
Cardiovascular disorders	Nitroglycerin, Clonidine	Nitro-Dur®, Catapres-TTS®
Neurological disorders	Rivastigmine, Selegiline	Exelon®, Emsam®
Motion sickness	Scopolamine Transderm	Transderm Scop®
Allergic rhinitis / congestion	Menthol,Camphor vapour patches	VapourPatch®

6. Components of Transdermal Patches:

1. Polymer Matrix

The polymer is responsible for controlling the release of the medicine from the patch.

The following criteria must be met for a polymer to be suitable for use in transdermal patches.

a) The molecular weight and chemical properties of the polymer should be compatible with the specific medicine, allowing it to diffuse properly and be released through the polymer.

b) The polymer should be chemically stable.

c) The polymer should be non-toxic.

d) The polymer should be easily manufactured.

e) The polymer should be cost-effective.

f) The polymer and its degradation products must be non-toxic or non-antagonistic to the body.

g) The polymer should be capable of incorporating a large quantity of the active ingredient.

Types of Polymers

- Natural Polymers: Cellulose derivatives, gelatin, waxes, proteins, gum, shellac, natural rubber, and resins.
- Synthetic Elastomers: Hydrogenated rubber, silicone rubber, nitrile, acrylonitrile, and neoprene.
- Synthetic Polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamide, polyurea, and the epoxy resin.

2. Medicine

The medicine comes into direct contact with the release liner.

Physiochemical Properties

- The medicine should have a molecular weight less than 1000 Daltons.
- The medicine should have an affinity for both lipophilic and hydrophilic phases.
- The medicine should have a low melting point.

Biological Properties

- The medicine should be potent with a daily dose of several milligrams.
- The half-life (t½) of the medicine should be short.
- The medicine should not cause an adverse immune response.
- Tolerance to the medicine should not develop under the near-zero-order release profile of transdermal patches.

3. Saturation Enhancer

The rate of medicine flow across the skin can be expressed as:

$J = D (dc/dx)$

Where:

J = the flux

D = diffusion coefficient

C = concentration of the diffusing substance

X = spatial coordinate

Detergents: These substances increase penetration by swelling the polar pathways.

Examples: Water-alcohol mixtures like methanol and ethanol, dimethyl acetamide, propylene glycol, and glycerol.

Surfactants: The ability of a surfactant to enhance penetration depends on the polar head group and the length of the hydrocarbon chain.

a) Anionic Surfactants: Sodium lauryl sulphate, diacetyl sulphosuccinate

b) Nonionic Surfactants: Pluronic F127, Pluronic F68

c) Bile Salts: Sodium taurocholate, Sodium Deoxycholate

Miscellaneous Chemicals: These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; and anticholinergic agents.

Some potential saturation enhancers have been recently described, but data on their effectiveness is limited.

These include eucalyptol, di-o-methyl-β-cyclodextrin, and soybean casein.

Enhancers of Saturation: Examples include urea and calcium thioglycolate.

4. Other Excipients

Adhesives: Pressure-sensitive adhesives can be applied to the front or back of the patch.

- The adhesive should not be irritating.
- It should be easily removable.
- It should not leave a residue on the skin.
- It should have good adhesion to the skin.
- It should be chemically and physically compatible with the medicine.
- It should not interfere with the release of the medicine.

5. **Liner:** Covers the patch during storage. The liner is removed before use.
6. **Backing**: Covers the patch from external forces. (14–21)

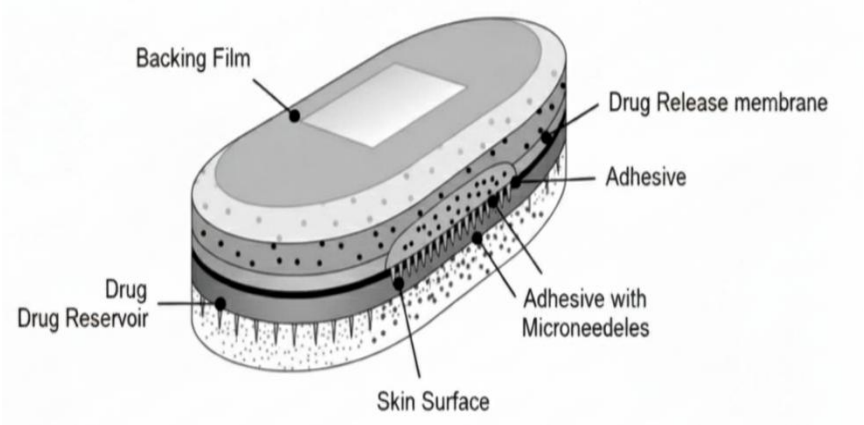


Figure 2: Different Parts of transdermal Patch [14]

Table : Components of a Transdermal Drug Delivery System and Their Functions

Component	Function	Example	Refrence
Drug	Produces the desired therapeutic effect	Nicotine, Fentanyl, Revastigmine	(11)
Polymer matrix/reservoir	Holds and controls release of the drug	Ethyl cellulose, Hydroxypropyl methylcellulose (HPMC), Polyisobutylene	(22,23)
Permeation enhancer	Increases skin permeability to	Oleic acid, Propylene glycol,	(24)
	enhance drug absorption	Dimethyl sulfoxide (DMSO)	
Backing layer	Provides structural support and protects patch from external environment	Polyester film, Polyethylene, Polyvinylidene chloride	(22,25)
Adhesive layer	Helps the patch stick to the skin for the required duration	Polyacrylate adhesive, Silicone adhesive	(22,26)
Release liner	Protects the adhesive and drug layer before application; removed before use	Siliconized paper, Polyethylenecoated paper	(22,23)
Plasticizer	Improves flexibility and spreadability of the film	Dibutyl phthalate, Triethyl citrate	(27)
Stabilizers/antioxidants	Prevent degradation of drug and patch components	Butylated hydroxytoluene (BHT), Butylated hydroxyanisole (BHA)	(26)

Table: Examples of Approved Transdermal Drug Delivery Systems (1,2)

Disease/Condition	Drug	Brand Name(s)	Patch Type	Duration of Release
Chronic Pain	Fentanyl	Duragesic®	Reservoir	72 hours
Angina Pectoris	Nitroglycerin	Nitro-Dur®, Minitran®	Matrix	24 hours
Hypertension	Clonidine	Catapres-TTS®	Reservoir	7 days
Smoking Cessation	Nicotine	NicoDerm CQ®, Habitrol®	Matrix	16-24 hours
Motion Sickness	Scopolamine	Transderm Scop®	Reservoir	72 hours
Hormone Replacement Therapy	Estradiol	Climara®, Estraderm®	Matrix	3-7 days
Contraception	Norelgestromin + Ethinyl Estradiol	Ortho Evra®, Xulane®	Matrix	7 days
Parkinson's Diaease	Rotigotine	Neupro®	Matrix	24 hours
Alzheimer's Disease	Rivastigmine	Exelon®	Matrix	24 hours
ADHD(Attention Decifit Disorder)	Methylphenidate	Daytrana®	Matrix	9 hours

Evaluation Parameters

1. **Content uniformity test**

Ten patches are chosen, and each patch's content is established. Transdermal patches pass the content uniformity test if the content of nine out of ten patches is between 85 and 115 of the prescribed value, and one patch has at least 75 to 125 of the stated value. still, 20 further patches are examined for medicine content if three of them contain content between 75 and 125. The transdermal patches pass tests if the range of these 20 patches is between 85 and 115. (28,29)

2. **Chance humidity content**

Each produced film must be counted independently and stored for 24 hours at room temperature in a desiccator filled with fused calcium chloride. The flicks must be revisited after 24 hours in order to ca7lculate the chance humidity content using the formula below. (28,30)

$$\text{Humidity content} = \frac{original\ weight - final\ weight}{final\ weight} x100$$

3. **Consistence of the patch**

Using a digital micrometer, the consistence of the medicine- loaded patch is measured at several spots, and the set patch's consistence is assured by calculating the average consistence and standard divagation. Transdermal film consistence is measured at several locales on the film using a micrometer, screw hand, or traveling microscope telephone hand. (29,30)

4. **Weight uniformity**

Before testing, the created patches are dried for four hours at 60 °C. A destined patch area must be sliced into several sections and counted using a digital balance. The individual weights must be used to get the average weight and standard divagation values. (30)

5. **Folding abidance**

It's necessary to cut a set length of strip constantly and fold it constantly at the same position until it breaks. The number of times the film can be folded in the same position without breaking is what gives it the folding abidance standing. (31)

6. **Humidity Uptake**

flicks that have been counted are stored for 24 hours at room temperature in desiccators. After that, they're removed and placed in desiccators with a impregnated potassium chloride result at 84 relative moisture until their weight remains constant. The formula for calculating chance humidity uptake is as follows (29,30)

$$\text{humidity uptake} = \frac{Final\ weight - Original\ weight}{original\ weight} x100$$

7. **Medicine content**

A certain volume of a suitable detergent must dissolve a defined patch area. After that, the result must be filtered through a sludge medium, and the medicine content must be examined using the applicable technology (either the HPLC or UV system). The normal of three distinct samples is represented by each value (29,31)

8. **Shear Adhesion test**

The purpose of this test is to determine an tenacious polymer's cohesive strength. The molecular weight, the degree of cross-linking, the type and content of the polymer, and the volume of tackifier supplied can all have an impact. A pristine sword plate is covered with tenacious- coated tape recording, and to make the tap recording pull resemblant to the plate, a destined weight is suspended from it. The time it takes to remove the tape recording from the plate is used to calculate the shear adhesion strength. The shear strength increases as junking time increases. (32)

9. **Peel Adhesion test**

Peel adhesion is the term used in this test to describe the force demanded to remove an tenacious covering from a test substrate. The variables that told the peel adhesion rates were the tenacious polymer's molecular weight and the kind and volume of complements. After applying a single piece of tape recording to a pristine sword plate or any favored backing membrane, the tape

recording is pulled 180 degrees from the substrate, and the force demanded to remove it's measured (32)

Water vapor transmission studies (WVT)

Weigh one gram of calcium chloride and put it in preliminarily dried, empty vials with the same periphery to determine WVT. Using an tenacious similar as silicon tenacious grease, the polymer flicks are applied to the brim and left to set for five twinkles. The vials are also precisely counted and put in a moisture chamber that's kept at 68 relative moisture. The vials are measured formerly more at the conclusion of the first, alternate, and third days for a aggregate of seven days in a row. A rise in weight was seen as a quantitative index of the quantum of humidity that was transferred via the patch.

In the other procedure that was published, vials containing 200 mL of impregnated sodium platitude and impregnated potassium chloride result were placed in desiccators. The desiccators were sealed tightly, and a hygrometer was used to measure the moisture within. After that, the process was repeated with the counted vials in desiccators.

$$WVT = \frac{W}{ST}$$

where W is the weight gain over a 24- hour period, S is the exposed film area (cm2), and T is the exposure duration (33)

10. Rolling ball method test

This test evaluates a polymer's talk- related wimpiness. In this test, a 7/ 16- inch- periphery pristine sword ball is dropped onto an grade track, rolling over and touching vertical, overhead- facing glue. method, which is measured in elevation, is determined by how far the ball moves along the glue. (34)

11. Quick Stick (peel- method) test

In this test, the tape recording is dragged 12 elevation per nanosecond down from the substrate at 90 degrees Celsius. The method value, which is measured and proved as the peel force necessary to break the tenacious- substrate bond, is given in ounces or grams per inch range. (34)

12. Inquiry Method Test

The purpose of this test is to determine whether a bond forms between the tenacious and a clean inquiry tip with a specified face roughness. It's mechanically broken when the inquiry is latterly removed. method, which is measured in grams, is the force demanded to remove the inquiry from the glue at a set rate (34)

13. In vitro medicine release studies

The medicine release from the manufactured patches is estimated using the paddle over slice system (USP outfit V). Dry flicks of a given consistence must be cut into precise shapes, counted, and stuck to a glass plate. After that, the outfit is equalized to 32 ± 0.5 °C and the glass plate is submerged in 500 mL of the phosphate buffer or dissolving media (pH 7.4).

After that, the paddle is deposited 2.5 cm down from the glass plate and driven at 50 rpm. 5- mL aliquots of samples can be taken out at suitable intervals for over to 24 hours and subordinated to HPLC or UV spectrophotometer analysis. Three duplicates of the trial are needed, and the mean value can be reckoned. (35)

14. In vitro skin saturation studies

At regular intervals, a specific volume of the sample must be taken out of the receptor cube and replaced with an original volume of new medium. After passing through a filtering media, samples can be examined using HPLC or spectrophotometry. The pitch of the wind connecting the steady- state values of the quantum of drug entered (mg cm- 2) vs. can be used to directly calculate flux. Permeability portions and time in hours were calculated by dividing the flux by the original medicine cargo (mg cm- 2)

15. Skin vexation study

Healthy rabbits (average weight 1.2 to 1.5 kg) can be used for skin vexation and sensitization tests. The rabbit's rearward face (50 cm2) should be gutted. Hair should be shaved from the clean rearward area, and the face should be gutted with remedied spirit and representative phrasings applied to the skin. After 24 hours, the patch must be taken off, and the skin must be examined and distributed into 5 grades according to the extent of the skin injury. (32)

16. Stability studies

In agreement with ICH recommendations, stability tests must be carried out by keeping the TDDS samples for six months at 40 ± 0.5 °C and 75 ± 5 relative moisture. Samples are taken out at 0, 30, 60, 90, and 180 days, and their medicine content is meetly anatomized. (35)

17. Polariscope Examination

The purpose of this test is to use a Polariscope to study the medicine chargers from the patch. To determine whether the medicine is present in the patch in crystalline or unformed form, a specified face area of the piece must be maintained on the object slide and examined for medicine chargers. (38)

18. Tensile Strength

A universal strength testing machine was used to determine the film's tensile strength. The machine had a perceptivity of 1 g. There were two cargo cell grips on it. The upper bone is malleable, while the lower one is fixed. Between these cell grips, a test film of 4 × 1 cm2 is placed, and force is applied gradationally until the film breaks (39). The dial reading in kilograms is used to determine the film's tensile strength. The following is an expression for tensile strength. Tensile

cargo at break divided by cross section area equals tensile strength.

19. Medicine excipients commerce studies

To produce a stable product, the drug and excipients must work well together, and any implicit physical or chemical relations must be set up. By comparing their physiochemical characteristics, similar as assay, melting endotherms, distinctive surge figures, immersion maxes, etc., commerce examinations are constantly conducted exercising thermal analysis, FT-IR studies, UV, and chromatographic ways. (40)

20. Flatness Test

Three longitudinal strips are to be cut from each film at different portion like one from the center, other bone from the left side and another bone from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent condensation, with 0 condensation original to 100 flatness. (41)

21. Swellability

After being counted, the 3.14 cm ² patches were placed in a petri dish with 10 ml of double- distilled water and left to soak. At destined intervals, the patch's weight increased until a constant weight was noted. (42)

The formula $S = \frac{Wt-W0}{W0} x100$ was used to determine the degree of swelling (S).

where Wo is the weight of the patch at time zero, Wt is the weight of the patch at time t, and S is the chance of swelling.

22. Chance extension Break Test

The length incontinently antedating the break point should be noted in order to calculate the chance extension break. This may be done using the formula that's described below. (43)

Chance of extension = $\frac{L1-L2}{L2} x100$

where L1 is each strip's last length and L2 is each strip's first length.

Regulatory and Commercial Aspects of Transdermal Patches

1. Regulatory Framework:

Since transdermal patches are governed as drug – device combination goods, they must cleave to both device and medicine laws for performance and safety as well as safety, efficacity, and quality (Ita , 2018). Regulatory authorities have different conditions.

United States- Food and Drug Administration (FDA)

Bracket Transdermal patches are classified as medicine – device combination products under U.S. law 21 CFR Part 3.

These are regulated primarily by the Center for medicine Evaluation and exploration (CDER).

Regulatory Pathways includes:

- New Drug Application (NDA) — For new active pharmaceutical constituents (APIs) or new delivery systems.
- shortened New Drug Application (ANDA) — For general patches with established APIs; requires demonstration of bioequivalence and adhesion performance.
- Crucial FDA Guidance Documents:
- Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs (2016).
- Transdermal and Topical Delivery Systems – Product Quality Tests (FDA, 2020).

Testing Conditions:

- In vitro release testing (IVRT), in vitro saturation testing (IVPT).
- Adhesion and wear studies (per FDA Guidance, 2016).
- Skin vexation/ sensitization studies.
- Residual medicine content analysis after wear and tear.

European Union- European Medicine Agency (EMA)

- The European Medicines Agency (EMA) regulates patches under the Medicinal Products Directive 2001 83/ EC.
- The EMA requires evidence of quality, safety, and efficacity, including specific data on medicine release, tenacious stability, and skin commerce.
- Bioequivalence in generics can be demonstrated through systemic pharmacokinetic studies or relative adhesion/ saturation evaluations (EMA, 2023).

India (CDSCO/ IPC)

- The Central medicines Standard Control Organization (CDSCO) and Indian Pharmacopoeia Commission (IPC) oversee nonsupervisory compliance.
- norms are defined in the medicines and Cosmetics Act, 1940, and the Indian Pharmacopoeia (IP, 2022) includes studies and test conditions for TDDS.
- Evaluation includes
- Medicine release kinetics

- Tenacious strength
- Stability testing
- Skin vexation implicit

2. Marketable Considerations

Request Overview

The global transdermal medicine delivery request was valued at over USD 7 billion in 2024, and is projected to grow at a CAGR of 4 – 5 due to the demand fornon-invasive, controlled release curatives (Markets and Markets, 2024).

Crucial remedial areas include

- Pain operation Fentanyl, Lidocaine
- Hormone remedy Estradiol, Testosterone
- Neurological diseases Rivastigmine, Methylphenidate
- Smoking conclusion Nicotine

. Crucial marketable Advantages

- Advanced case compliance due tonon-invasive and effortless delivery.
- Bypass of first- pass metabolism, allowing for lower dosing.
- Controlled medicine release, reducing dosing frequence and side goods.
- Reduced gastrointestinal adverse goods, especially for NSAIDs and hormones.

Challenges or limitations in commercialization:

- Limited to drugs with suitable physicochemical properties: low molecular weight (<500 Da), moderate lipophilicity, and potency.
- High manufacturing costs due to the complexity of layering drug, adhesive, and backing materials.
- Potential for skin irritation or allergic reactions due to adhesives and enhancers.
- Regulatory burden: Extensive testing required for adhesion, uniformity, safety, and skin compatibility.

Competitive Landscape

Major players include Novartis (Exelon®), Johnson & Johnson (Duragesic®), Teva

Pharmaceuticals (Lidoderm®), Hisamitsu (Salonpas®), and GlaxoSmithKline (Nicoderm®).

Competition is increasing with generic transdermal patches entering markets, especially in pain and hormone therapy.

Intellectual Property (IP) and Life-Cycle Management

Patent Strategies often focus on:

Adhesive formulation, permeation enhancers, backing material innovations, and drug– polymer interactions, controlled release membranes.

Product line extensions: Different sizes, release rates, or combination patches (e.g., multidrug delivery). (44-48)

9. Challenges for Transdermal Patches:

Physicochemical Limitations of Drugs

- Only drugs with low molecular weight (<500 Da), moderate lipophilicity (log P ~1–4), and low dose requirements are suitable for passive transdermal delivery.
- Hydrophilic macromolecules (e.g., peptides, proteins) face poor permeation due to the stratum corneum barrier (Prausnitz & Langer, 2008).

Skin Barrier and Variability

- Inter-individual differences in skin thickness, hydration, and metabolism influence drug absorption.
- Diseased or damaged skin may alter permeation unpredictably (Ita, 2018).

Adhesion and Wear Issues

- Long-wear patches may lose adhesion due to sweat, skin oils, or movement.
- Poor adhesion can cause dose variability and regulatory non-compliance.

Skin Irritation and Sensitization

- Prolonged use can cause erythema, itching, or allergic reactions from adhesives, enhancers, or drugs (Alexander et al., 2012).

Manufacturing and Quality Control

- Ensuring uniform drug content, consistent release, and adhesive performance is technically demanding.
- Stability issues may arise, especially for moisture-sensitive or volatile drugs.

Regulatory and Cost Barriers

- Combination-product classification requires meeting both drug and device regulations.
- Development and clinical testing costs are high compared to oral generics. (11,49)

10. NOVEL FORMULATION APPROACHES:

1. Film-Forming Formulations

After being applied to the skin, these liquid or semi-solid solutions dry to form a flexible drug-reservoir film. They combine high skin

substantivity, continuous release, and ease of application. Commonly used are organic solvents like ethanol and polymers including polyamides, PVP, and chitosan. Compared to traditional forms, inclusions such as mesoporous carriers or SMEDDS can increase penetration via amorphous dispersion by a factor of 10 or more. Applications include hydrogels based on nanocellulose that administer corticosteroids for atopic dermatitis, tazarotene, acyclovir, and chlorhexidine. (50)

2. Stimuli-Responsive / Smart Patch Systems

Even big or hydrophilic medications can be delivered by electricity-driven systems like iontophoresis and electroporation, which produce temporary skin pores. These methods are successful, but they need equipment and may have compliance issues. Ultrasound-triggered hydrogels: Smart hydrogels with drug cargo can swell or release when exposed to ultrasound waves, allowing for controlled dosage.

Add magnetic nanoparticles, responsive nanogels, or mesoporous silica to create magnetically-activated nanocomposite membranes or fibers. Alternating magnetic fields are used to remotely initiate on-off release with temperature control for accurate dosage (latest research showed that curcumin and ketorolac released effectively in pain/wound healing contexts).

Stretch-triggered patches: When the skin stretches or a joint moves, mechanically responsive elastomers release medication. There is potential for wearables that use motion, however the majority of research is currently in vitro. (22)

3. Nanocarrier-Enhanced Patch Technologies

Invasomes are terpene-ethanol-phospholipid vesicles that improve penetration and deform through constricted intercellular gaps by fluidizing the carrier and stratum corneum lipids. Although some have stability or irritation problems, other nanocarriers such as nanoemulsions, SLNs, NLCs, liposomes, ethosomes, transfersomes, dendrimers, and plant-derived exosome-like vesicles each have unique benefits, such as high loading, flexibility, skin compatibility, or improved penetration. (51)

4. Advanced Polymeric Systems & Molecular Imprinting:

Molecularly imprinted polymers, or MIPs, imprint drug-specific binding sites in polymer matrices to produce excellent selectivity and controlled release. beneficial for extended-release and long-acting patches.

Customized layer structures or reservoir/matrix geometries for specialized release profiles are made possible by 3D-printed polymer matrices. (52)

5. Microneedles & 3D-Printed Structures

The tips of dissolving microneedles: which are made of water-soluble polymers like silk fibroin, dissolve in the skin to release drug payloads without the need for removal.

Microneedles that generate hydrogel are made of hydrophilic polymers that expand in vivo, releasing medication as the interstitial fluid is absorbed.

Contemporary methods employ 3D printing to accurately create microneedles with intricate geometry for scalable or patient-specific clinical applications. (53)

6. Approaches in the development of transdermal therapeutic system

To enable rate control over drug release and transdermal penetration, a number of technologies have been developed with success.

These technologies include the following:

1. Adhesive dispersion type system

The drug reservoir, which is made by directly dispersing the drug in an adhesive polymer and then applying the medicated adhesive by solvent casting or hot melting onto a flat sheet of drug-impermeable backing to create a thin drug reservoir layer, is part of the system . In order to create an adhesive diffusion-controlled drug delivery system with a detachable release liner that, in an ideal scenario, is removed and the patch is applied to the skin for the necessary amount of time, a layer of non-medicated, rate-controlling adhesive polymer of constant thickness is applied on top (54).

. The adhesive substance must be compatible with the medication and stick to the skin for a long time without adhering to the release liner. The development and marketing of transdermal therapeutic systems, such as Valsartan (55), an angiotensin II type 1 selective blocker, and once-daily medications for angina pectoris, serve as examples of this sort of system.

2. Membrane permeation-controlled system

The drug reservoir is completely embedded in a compartment that is molded between a rate-controlling polymeric membrane and a drug-impermeable backing laminate in this system. (56,57) By simply diffusing through the pores, the drug molecules are allowed to pass through the rate-controlling membrane. The drug solids in the reservoir compartments are either dissolved in a releasable solvent (like alkyl alcohol) to create a gel-like solution, or they are uniformly distributed in a solid polymeric matrix (like polyisobutylene) suspended in an

unleachable viscous liquid medium (like silicon fluid). A microporous or nonporous polymeric membrane, such as an ethylene–vinyl acetate copolymer, with a particular drug permeability can be used as the rate-controlling membrane.

To provide close contact between the TDD system and the skin surface, a thin coating of drug-compatible adhesive polymer, such as silicone adhesives, can be placed to the polymeric membrane's exterior. By altering the polymer composition, permeability coefficient, and thickness of the rate-controlling membrane and adhesive, the release rate from this kind of TDS may be customized. TransdermScop (Scopolamine), which prevents motion sickness for three days, and TransdermNitro (Nitroglycerine), which treats angina pectoris once daily, are two examples of this technique. (58)

3. Matrix diffusion controlled system

This method, involves dispersing drug particles in a hydrophilic or lipophilic polymer matrix to create uniform drug reservoirs. A medicated disc with a specified surface area and regulated thickness is then formed from the resulting medicated polymer. Drug particles can be dispersed in a polymer matrix by either homogeneously blending drug solids with a rubbery polymer at a high temperature and/or under vacuum, or by mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer and then cross-linking the polymer chains (59). In a compartment made of a drug-impermeable backing, the polymer disc containing the drug reservoir is attached onto an occlusive base plate.

After that, the adhesive polymer is applied to the medicated disc to create a rim strip. The transdermal therapeutic system that releases nitroglycerin is the best example of this matrix kind of transdermal drug delivery system. Because the polymer cannot rupture, the transdermal system of the matrix dispersion type has the benefit of not requiring dose dumping (60)

4. Microreservoir type controlled system

This drug delivery method is a cross between a matrix-dispersion and reservoir type. In order to create thousands of inaccessible, microscopic drug reservoir spheres, the drug is first suspended in an aqueous solution of liquid polymer. The drug suspension is then uniformly distributed throughout a lipophilic polymer, such as silicone elastomers, using a high energy dispersion technique and shear mechanical force. The creation of the Nitro disc made use of this technology. Depending on the relative solubility of the drug in the liquid compartment and the polymer matrix, the release of a drug from a microreservoir-type device may follow either a partition-control or a matrix diffusion control (60,61).

Conclusion with Future Prospects

Transdermal Drug Delivery Systems (TDDS) have emerged as an efficient, non-invasive, and patient-compliant approach for the controlled and sustained delivery of therapeutic agents through the skin. These systems offer several advantages such as avoidance of hepatic first-pass metabolism, improved bioavailability, reduced dosing frequency, and enhanced patient adherence. Despite these benefits, challenges such as limited drug permeability, formulation stability, and potential skin irritation continue to restrict their broader application.

The future of TDDS lies in the integration of advanced materials and innovative technologies. Developments in nanocarrier-based formulations, microneedle-assisted delivery, molecularly imprinted polymers, and 3D-printed systems hold great promise for overcoming existing barriers. Furthermore, the incorporation of smart, responsive, and personalized drug delivery mechanisms may revolutionize transdermal therapy by providing precise, patient-specific treatments. With continuous interdisciplinary research and technological progress, TDDS are poised to play a pivotal role in the evolution of next-generation pharmaceutical care.

REFERENCE:

1. Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: history, development and pharmacology. Br J Pharmacol. 2015;172(9):2179–2209.
2. Prabhakar D, Sreekanth J, Jayaveera KN. Transdermal drug delivery patches: a review. J Drug Deliv Ther. 2013;3(4):231–221.
3. Panner Selvam R, Singh AK, Sivakumar T. Transdermal drug delivery systems for antihypertensive drugs – a review. Int J Pharm Biomed Res. 2010;1(1):1–8.
4. Kakkar AP, Gupta A. Gelatin based transdermal therapeutic system. Indian Drugs. 1991;29(7):308–315.
5. Chowdary KPR, Naidu RAS. Transdermal drug delivery: a review of current status. Indian Drugs. 1995;32(9):414–422.
6. Dhiman S, Singh TG, Rehni AK. Transdermal patches: a recent approach to new drug delivery system. Int J Pharm Pharm Sci. 2011;3(5):26–34.
7. Heather AE. Transdermal drug delivery: penetration enhancement techniques. Curr Drug Deliv. 2005;2:23–33.
8. Patel D, Patel N. Transdermal drug delivery system – review. Int J Biopharm Toxicol Res. 2011;1(1):61–80.
9. Alam MI, Alam N. Type, preparation and evaluation of transdermal patch: a review. Res Gate. 2013;2(4):2199–2233.
10. Isaac M, Holvey C. Transdermal patches: the emerging mode of drug delivery system in psychiatry. Ther Adv Psychopharmacol. 2012;2(6):255–263.
11. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261–1268.
12. Kumar S, et al. A review on transdermal drug delivery system. Int J Pharm Sci Res. 2010;1(1):18–23.

13. Guy RH. Current status and future prospects of transdermal drug delivery. Pharm Res. 1996;13(12):1765–1769.

14. Mali AD. An updated review on transdermal drug delivery systems. Skin. 2015;8(9):244–254.

15. Rajesh N, Siddaramaiah, Gowda DV, Somashekar CN. Formulation and evaluation of biopolymer based transdermal drug delivery. Int J Pharm Pharm Sci. 2010;2(2):142–147.

16. Hanumanaik M, Patil U, Kumar G, Patel SK, Singh I, Jadatkar K. Design, evaluation and recent trends in transdermal drug delivery system: a review. Int J Pharm Sci Res. 2012;3(8):2393–2406.

17. Chandrashekhar NS, Shobha Rani RH. Physicochemical and pharmacokinetic parameters in drug selection and loading of transdermal drug delivery. Indian J Pharm Sci. 2008;70(1):94–96.

18. Scheindlin S. Transdermal drug delivery: past, present, future. Mol Interv. 2004;4(6):308–312.

19. Aungst BJ. Structure/effect studies of fatty acid isomers as skin penetration enhancers and skin irritants. Pharm Res. 1989;6:244–247.

20. Ongpipattanakul B, Burnette RR, Potts RO, Francoeur ML. Evidence that oleic acid exists in a separate phase within stratum corneum lipids. Pharm Res. 1991;8:350–354.

21. Sinha VR, Kaur PM. Permeation enhancers for transdermal drug delivery. Drug Dev Ind Pharm. 2000;26:1131–1140.

22. Bird D, Ravindra NM. Transdermal drug delivery and patches—an overview. Med Devices Sens. 2020;3(6):e10069.

23. Yadav D, Saroha K, Singh G, Aggarwal A. Transdermal patches: a review. Int J Pharm Sci Rev Res. 2011;10(1):47–56.

24. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2012;64:128–137.

25. Chandrashekar NS, Shobha Rani RH. Physicochemical and pharmacokinetic parameters in transdermal drug delivery. Indian J Pharm Sci. 2008;70(1):94–102.

26. Aqil M, Ali A, Sultana Y, Ahmad FJ. Transdermal drug delivery systems: a review. Curr Drug Deliv. 2004;1(2):165–173.

27. Mishra AK, Mishra R, Panda P. Transdermal drug delivery systems: a review. Int J Pharm Sci Rev Res. 2011;8(2):1–7.

28. Aggarwal G, Dhawan S. Development, fabrication and evaluation of transdermal drug delivery system – a review. Pharmainfo.net. 2009;7(5).

29. Keleb E, Sharma RK, Mosa EB, Aljahwi AAZ. Transdermal drug delivery system – design and evaluation. Int J Adv Pharm Sci. 2010;1:201–211.

30. Rhaghuram RK, Muttalik S, Reddy S. Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. AAPS PharmSciTech. 2003;4(4):480–488.

31. Shaila L, Pandey S, Udupa N. Design and evaluation of matrix type membrane controlled transdermal drug delivery system of nicotine suitable for use in smoking cessation. Indian J Pharm Sci. 2006;68:179–184.

32. Aarti N, Louk ARMP, Russsel OP, Richard HG. Mechanism of oleic acid induced skin permeation enhancement in vivo in humans. J Control Release. 1995;37:299–306.

33. Baichwal MR. Polymer films as drug delivery systems. In: Advances in drug delivery systems. Bombay: MSR Foundation; 1985. p.136–147.

34. Vyas SP, Khar RK. Targeted and controlled drug delivery: novel carrier system. 1st ed. New Delhi: CBS Publishers and Distributors; 2002. p.411–447.

35. Singh J, Tripathi KT, Sakia TR. Effect of penetration enhancers on the in vitro transport of ephedrine through rat skin and human epidermis from matrix based transdermal formulations. Drug Dev Ind Pharm. 1993;19:1623–1628.

36. Ghosh B, Preethi GB, Mishra R, Parcha V. Transdermal delivery of ibuprofen and its prodrugs by passive diffusion and iontophoresis. Int J Pharm Pharm Sci. 2010;2(1):79–85.

37. Sharma T, Rawal G. Transdermal therapeutic systems: an overview. Int J Pharm Biol Arch. 2011;2(6):1581–1587.

38. Kavitha K, More MR. Design and evaluation of transdermal films of lornoxicam. Int J Pharm Biol Sci. 2011;2(2):54–62.

39. Rani S, Saroha K, Syan N, Mathur P. Transdermal patches: a successful tool in transdermal drug delivery system – an overview. Der Pharm Sin. 2011;2(5):17–29.

40. Saroha K, Yadav B, Sharma B. Transdermal patch: a discrete dosage form. Int J Curr Pharm Res. 2011;3(3):98–108.

41. Bharkatiya M, Nema RK, Bhatnagar M. Designing and characterization of drug-free patches for transdermal application. Int J Pharm Sci Drug Res. 2010;2(1):35–39.

42. U.S. Food and Drug Administration. Assessing adhesion with transdermal delivery systems and topical patches for ANDAs. Silver Spring (MD): FDA; 2016. Available from: https://www.fda.gov/media/99546/download

43. U.S. Food and Drug Administration. Transdermal and topical delivery systems – product quality tests. Silver Spring (MD): FDA; 2020. Available from: https://www.fda.gov/media/140795/download

44. European Medicines Agency. Guideline on quality of transdermal patches. EMA/CHMP/QWP/608924/2014. London: EMA; 2023. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-transdermal-patches_en.pdf

45. Indian Pharmacopoeia Commission. Indian Pharmacopoeia. Vol. II. Ghaziabad: IPC; 2022.

46. Markets and Markets. Transdermal drug delivery system market by type and application – global forecast to 2030. 2024.

47. Ita KB. Transdermal delivery of drugs with microneedles – potential and challenges. Pharmaceutics. 2018;10(4):203.

48. Al-Jarsha HYM, Ghareeb MM, Hussein AA. A review on film forming drug delivery systems. Res J Pharm Technol. 2021;14(10):5579–5588.

49. Cevc G, Vierl U. Nanotechnology and the transdermal route: a state of the art review and critical appraisal. J Control Release. 2010;141(3):277–299.

50. Lusina A, Cegłowski M. Molecularly imprinted polymers as state-of-the-art drug carriers in hydrogel transdermal drug delivery applications. Polymers. 2022;14(3):640.

51. Larrañeta E, Lutton RE, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: materials science, manufacture and commercial development. Mater Sci Eng R Rep. 2016;104:1–32.

52. Chien YW. Transdermal therapeutic system. 2nd ed. New York: Marcel Dekker; 1987.

53. Nishida N, Taniyama K, Sawabe T, Manome Y. Development and evaluation of a monolithic drug-in-adhesive patch for valsartan. Int J Pharm. 2010;402:103–109.

54. Dubey BK, Katare OP, Singh R, Jain SK. Lyophilized aqueous based polymer matrices for transdermal delivery of captopril. J Dermatol Sci. 1995;10:191–195.

55. Yan G, Li SK, Higuchi WI. Evaluation of constant current alternating current iontophoresis for transdermal drug delivery. J Control Release. 2005;110:141–150.

56. Marashi AYM, Shoeibi G, Bakhshandeh H, Yazdanifard P. The analgesic effect of intravenous neostigmine and transdermal nitroglycerine added to lidocaine on intravenous regional

anesthesia (Bier's block): a randomized, controlled study in hand surgery. Int J Pharmacol. 2008;4:218–222.

57. Tojo K, Chien YW. Release and permeation kinetics of matrix-type transdermal delivery systems for verapamil. J Chem Eng Jpn. 1989;22:689–691.

58. Marashi AYS, Shoeibi G, Bakhshandeh H, Yazdanifard P. The analgesic effect of intravenous neostigmine and transdermal nitroglycerine added to lidocaine on intravenous regional anesthesia (Bier's block): a randomized, controlled study in hand surgery. Int J Pharmacol. 2008;4(3):218–222.

59. Tojo K, Chien YW. Release and permeation kinetics of matrix-type transdermal delivery systems for verapamil. J Chem Eng Jpn. 1989;22(6):689–691.

60. Alexander A, Dwivedi S, Giri TK, Saraf S, Saraf S, Tripathi DK. Approaches for breaking the barriers of drug permeation through transdermal drug delivery. J Control Release. 2012;164(1):26–40.

61. Chien YW. Microsealed drug delivery system: theoretical aspects and biomedical assessments. New York: Plenum Press; 1984.