International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 2033-2040 www.ijprajournal.com ISSN: 2249-7781

# A Comprehensive Review of Transdermal Drug Delivery Systems - Mechanisms, Advancements, and Future Frontiers

Mayur R. Najan*, Proff. Rani M. Deokar And Dr. Megha T. Salve
*Department of Bachelor in Pharmacy*
*Shivajirao Pawar College of Pharmacy, Pachegaon, Ahmednagar-413725.*
**Corresponding Author- Mayur R. Najan*

Submitted: 10-15-2023 Accepted: 20-12-2023

**ABSTRACT:** Currently, approximately 74% of medications are administered orally, but they often fall short of achieving optimal effectiveness. To address these limitations, the transdermal drug delivery system has emerged as a promising solution. This method involves delivering drugs through the skin to achieve systemic effects, distinguishing it from traditional topical drug delivery. This approach offers several advantages, such as prolonged therapeutic effects, minimized side effects, enhanced bioavailability, improved patient compliance, and convenient termination of drug therapy. The stratum corneum is recognized as the primary barrier affecting the transdermal permeation of most molecules. The process of transdermal drug delivery involves three main routes of drug penetration: appendageal, transcellular, and intercellular. Factors like skin age, condition, physicochemical properties, and environmental influences must be considered when delivering drugs through this route. Key components of transdermal drug delivery systems (TDDS) include a polymer matrix membrane, the drug itself, penetration enhancers, pressure-sensitive adhesives, backing laminates, and a release liner. Transdermal patches are categorized into reservoir systems, matrix systems, and micro-reservoir systems, each designed to introduce active ingredients into the circulatory system through the skin.

**Keywords:**transdermal drug delivery, transdermal patches, systemic blood circulation, skin.

## I. INTRODUCTION:

Conventional dosage forms often result in significant fluctuations in plasma drug concentrations, leading to undesirable outcomes such as toxicity or diminished effectiveness. These issues, coupled with challenges like repetitive dosing and unpredictable absorption, spurred the development of controlled drug delivery systems. Such systems release one or more drugs continuously in a predetermined pattern over a fixed period, either systemically or targeting a specific organ. The primary goals of controlled drug delivery are to enhance drug safety, improve efficacy, and ensure patient compliance by achieving better control over plasma drug levels and reducing dosing frequency. One prominent example of controlled drug delivery is the Transdermal Therapeutic System (TTS), which refers to self-contained discrete dosage forms applied to intact skin. These systems deliver drugs at a controlled rate through the skin to the systemic circulation. The pioneering Transdermal Drug Delivery (TDD) system, Transdermal-Scop, was developed in 1980 to treat motion sickness using scopolamine. Employing a membrane-moderated approach, this system features a microporous polypropylene film as the membrane and a drug reservoir containing a solution of the drug in a mixture of mineral oil and polyisobutylene. The controlled release is maintained over a three-day period, showcasing the potential of this innovative drug delivery technology. [1]

The Transdermal Drug Delivery System presents several advantages:

- The frequency of dosing can be significantly reduced.
- Improved bioavailability allows for a reduction in drug concentration.
- Escaping first-pass metabolism by the liver enhances drug effectiveness.
- Issues related to gastrointestinal medication absorption, such as those arising from stomach pH, enzymatic activity, and interactions with food or other orally administered pharmaceuticals, can be avoided.
- Lowering plasma concentration levels of drugs leads to decreased side effects.
- Non-invasive nature eliminates the need for parenteral therapy, streamlining the drug administration process.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 2033-2040 www.ijprajournal.com ISSN: 2249-7781

- Enhanced compliance is achieved compared to previous dosage forms, as longer therapy is provided with a single application.
- Rapid termination of drug therapy is possible by simply removing the application from the skin's surface.
- Self-administration is facilitated by these systems.
- Systemic drug interactions are reduced.
- Extended duration of action is a key feature of transdermal drug delivery, offering prolonged therapeutic effects. [2]

**Anatomy and physiology of skin-**

The skin is primarily made up of three layers. The upper layer is the epidermis, the layer below the epidermis is the dermis, and the third and deepest layer is the subcutaneous tissue.

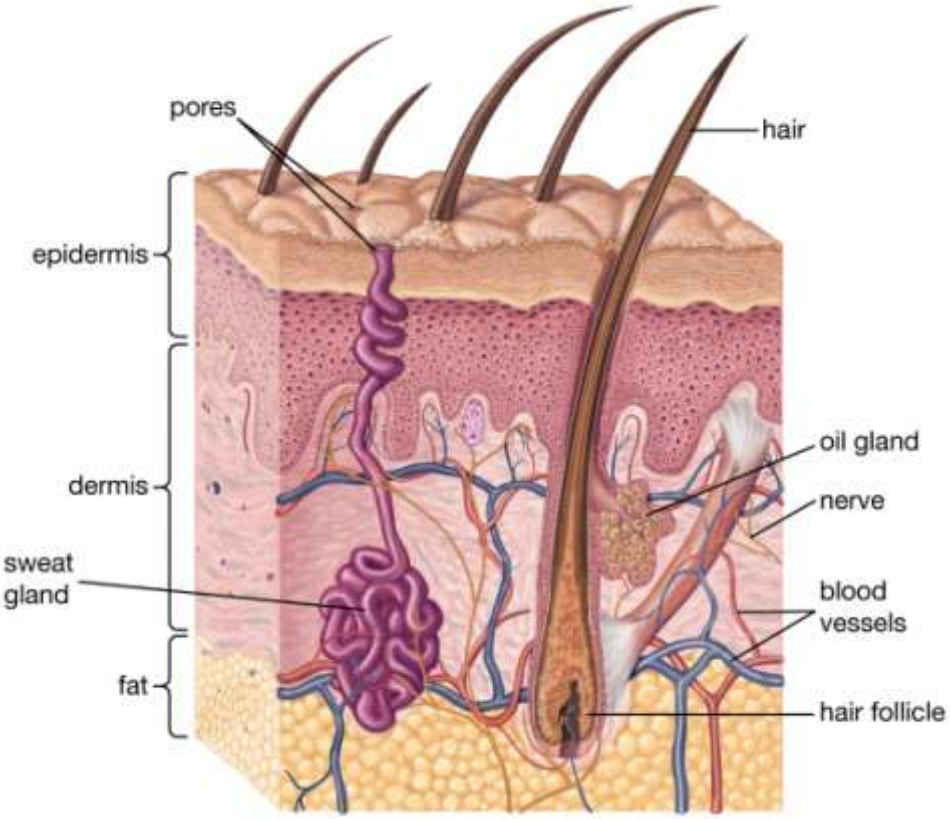


**Fig 1. Structure of skin [3]**

- The epidermis, the outermost layer of skin, provides a waterproof barrier and contributes to skin tone.
- The dermis, found beneath the epidermis, contains connective tissue, hair follicles, blood vessels, lymphatic vessels, and sweat glands.
- The deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue.

The epidermis is further divided into five layers on thick skin like the palms and soles (stratum basal, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum, while in other places, the epidermis only has four layers, lacking the stratum lucidum).

The dermis is divided into two layers, the papillary dermis (the upper layer) and the reticular dermis (the lower layer). [4]

**The functions of the skin include:**

- Protection against microorganisms, dehydration, ultraviolet light, and mechanical damage; the skin is the first physical barrier that the human body has against the external environment.
- Sensation of pain, temperature, touch, and deep pressure starts with the skin.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 2033-2040 www.ijprajournal.com ISSN: 2249-7781

- Mobility: The skin allows smooth movement of the body.
- Endocrine activity: The skin initiates the biochemical processes involved in Vitamin D production, which is essential for calcium absorption and normal bone metabolism.
- Exocrine activity: This occurs by the release of water, urea, and ammonia. Skin secretes products like sebum, sweat, and pheromones and exerts important immunologic functions by secreting bioactive substances such as cytokines.
- Immunity development against pathogens.
- Regulation of Temperature. Skin participates in thermal regulation by conserving or releasing heat and helps maintain the body's water and homeostatic balance. [4]

**Classification of Transdermal Drug Delivery System-**

Classification of transdermal drug delivery Systems has proceeded through three generation on the basis of drug molecule Size andthe presence of penetration enhances material.

**1. First-generation transdermal delivery systems-** The majority of transdermal patches currently in clinical use belong to the first generation of transdermal delivery systems. Recent advancements and increased public acceptance have led to a surge in the market availability of these first-generation patches. However, this trend is expected to slow down as drugs suitable for these systems become less available. First-generation candidates are typically low-molecular weight, lipophilic, and effective at low doses. Transdermal delivery is preferred when oral bioavailability is low, there's a preference for less frequent dosing, a need for steady delivery profiles, or other relevant factors.[5]

**2. Second-generation transdermal delivery systems-**The second generation of transdermal delivery systems acknowledges the importance of enhancing skin permeability to broaden the range of transdermal drugs. An ideal enhancer in this generation should (i) temporarily disrupt the stratum corneum structure to increase skin permeability, (ii) provide an additional force for transport into the skin, and (iii) avoid causing harm to deeper living tissues. However, methods developed in this generation, like conventional chemical enhancers, iontophoresis, and non-cavitational ultrasound, have faced challenges in finding the right balanceincreasing delivery across the stratum corneum while safeguarding deeper tissues from damage.[6]

**Basic Components of Transdermal Drug Delivery Systems-**

1. Polymer matrix or matrices.
2. The drug
3. Permeation enhancers
4. Other excipients

**1. Polymer Matrix:** The Polymer controls the releaseof the drug from the device. Possible usefulpolymers for transdermal devices are:

- Natural Polymers: e.g., cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.
- Synthetic Elastomers: e.g., polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber,Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.
- Synthetic Polymers: e.g., polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinyl pyrrolidone, Polymethylmethacrylate, Epoxy etc.[7]

**2. Drug:** For successfully developing a transdermaldrug delivery system, the drug should be chosenwith great care. The following are some of thedesirable properties of a drug for transdermaldelivery.

**3. Permeation Enhancers:** These are compoundswhich promote skin permeability by altering theskin as a barrier to the flux of a desired penetrant.These may conveniently be classified under thefollowing main headings:

- Solvents: These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolid-ones- 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone), miscellaneous solvents-propylene glycol, glycerol, silicone fluids, isopropyl palmitate.
- Surfactants; These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length. Anionic Surfactants: e.g. Dioctyl sulpho-

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 2033-2040 www.ijprajournal.com ISSN: 2249-7781

succinate, Sodium lauryl sulphate, Decodecyl-methyl sulphoxide etc. Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc. Bile Salts: e.g. Sodium ms taurocholate, Sodium deoxycholate, Sodium tauroglycocholate. Binary system:

- Miscellaneous chemicals: These include urea, ahydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Some potential permeationenhancers have recently been described butthe available data on their effectiveness sparse.These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein.[8]

**4. Other Excipients:**

**a. Adhesives:** The fastening of all transdermaldevices to the skin have so far been done byusing a pressure sensitive adhesive which canbe positioned on the face of the device and inthe back of the device and extendingperipherally. Both adhesive systems shouldfulfill the following criteria

- Should adhere to the skin aggressively, should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should not irritate or sensitize the skin.

The face adhesive system should also fulfill thefollowing criteria;

- Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
- Permeation of drug should not be affected.
- The delivery of simple or blended permeationenhancers should not be affected.

**Role of adhesion in drug delivery-** In TDDS, main principle is it selectively adhere the skin and providedrug release. Drug delivery is varied in age and gender function.Because in this system drug release is through the skin and alsoyounger and older patient having different skin nature. Younger skinis greater dehydrated while aged skin has less moisture content soyounger skin have more elastic than aged skin so we carefully selectthe adhering material for the drug release. This type of condition roleof adhesion is very important. Here, drug absorption based on thedrug partition between TDDS and skin. Good permeation and actionis depending on the proper adhesion of patch. After the application ofpatch, the adhesion covers the particular effective area, that area onlyprovides greater action. And also, so many factors are affectingthe drug absorption such as thickness of skin, skin temperature, bloodflow, no. of hair follicles, skin cleansing, sweat gland function, pH of skin surface, and body temperature. After the application of patch, itwarms the sin temperature that lead to increase the flow of drug to skin.During the gradually increasing of skin temperature swells the polymerand sustained release of drug to stratum corneum. [9]

**b. Backing membrane:** Backing membranes areflexible and they provide a good bond to thedrug reservoir, prevent drug from leaving thedosage form through the top, and acceptprinting. It is impermeable substance thatprotects the product during use on the skin e.g.metallic plastic laminate, plastic backing withabsorbent pad and occlusive base plate(aluminum foil), adhesive foam pad (flexiblepolyurethane) with occlusive base plate(aluminum foil disc).[10]

**Transdermal patch-**

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. An advantage of a transdermal drug delivery route over other types of medication delivery (such as oral, topical, intravenous, or intramuscular) is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.[11]

Types of transdermal patches:[12,13,14]

**a) Single layer drug in adhesive:**In this type the adhesive layer contains the drug. Theadhesive layer not only serves to adhere the various layerstogether and also responsible for the releasing the drug tothe skin. The adhesive layer is surrounded by a temporaryliner and a backing.

**b) Multi -layer drug in adhesive:**This type is also similar to the single layer but it contains aimmediate drug release layer and other layer will be acontrolled release along with the adhesive layer. Theadhesive layer is responsible for the releasing of the drug.This patch also has a temporary liner-layer and apermanent backing.

**c) Vapour patch:**In this type of patch the role of adhesive layer not onlyserves to adhere the various layers together but also serves as release vapour. The vapour patches are new to themarket,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 2033-2040 www.ijprajournal.com ISSN: 2249-7781

commonly used for releasing of essential oils indecongestion. Various other types of vapor patches arealso available in the market which are used to improve thequality of sleep and reduces the cigarette smoking conditions.

**d) Reservoir system:**In this system the drug reservoir is embedded between animpervious backing layer and a rate controllingmembrane. The drug releases only through the rate-controlling membrane, which can be micro porous or non-porous. In the drug reservoir compartment, the drug can bein the form of a solution, suspension, gel or dispersed in asolid polymer matrix. Hypoallergenic adhesive polymercan be applied as outer surface polymeric membranewhich is compatible with drug.

**e) Matrix system:**

i. Drug-in-adhesive system:In this type the drug reservoir is formed by dispersing thedrug in an adhesive polymer and then spreading themedicated adhesive polymer by solvent casting or melting(in the case of hot-melt adhesives) on an imperviousbacking layer. On top of the reservoir, unmediatedadhesive polymer layers are applied for protectionpurpose.

ii. Matrix-dispersion system:In this type the drug is dispersed homogenously in ahydrophilic or lipophilic polymer matrix. This drugcontaining polymer disk is fixed on to an occlusive baseplate in a compartment fabricated from a drugimpermeable backing layer.

**f) Micro reservoir system:**In this type the drug delivery system is a combination ofreservoir and matrix-dispersion system. The drug reservoiris formed by first suspending the drug in an aqueoussolution of water-soluble polymer and then dispersing thesolution homogeneously in a lipophilic polymer to formthousands of unreachable, microscopic spheres of drugreservoirs. This thermodynamically unstable dispersion isstabilized quickly by immediately cross-linking thepolymer in situ by using cross linking agents.

**Factors affecting transdermal drug delivery-** (15,16,17)

**1. Skin condition-** The intact skin itself acts as a barrier, but many agents like acids and alkali cross the barrier cells and penetrate through the skin. Many solvents open the complex dense structure of the horny layer: solvents like methanol and chloroform remove the lipid fraction, forming artificial shunts through which drug molecules can pass easily.

**2. Skin age-**It is seen that the skin of adults and young ones is morepermeable than that of the older ones. but there is no dramaticdifference. Children show toxic effects because of the greatersurface area per unit body weight. Thus, potent steroids, boricacid andhexachlorophene have produced severe side-effects.

**3. Physicochemical factors-**

- Hydration of skin- Generally, when water saturates the skin, it swells tissues, softens wrinkles on the skin and its permeability increases for the drug molecules that penetrate through the skin.
- Temperature and pH of the skin- The penetration rate varies if the temperature varies and the diffusion coefficient decreases as the temperature falls; however adequate clothing on the body prevents wide fluctuations in temperature and penetration rates. According to pH, only unionized molecules pass readily across the lipid membrane, and weak acids and bases dissociate to different degrees according to their pH and pKa or pKb values.

**4. Environmental factors-**

- Sunlight- Because of to sunlight, the walls of blood vessels become thinner, leading to bruising, with only minor trauma in the sun-exposed areas. Also, pigmentation, the most noticeable sun-induced pigment change, is a freckle or solar lentigo.
- Cold season- The cold season often results in itchy and dry skin. The skin responds by increasing oil production to compensate for the weather's drying effects. A good moisturizer will help ease symptoms of dry skin.
- Air pollution- Dust can clog pores and increase bacteria on the face and the surface of skin, both of which lead to acne or spots, which affects drug delivery through the skin. Invisible chemical pollutants in the air can interfere with the skin's natural protection system, breaking down the skin's natural oils that normally trap moisture in the skin and keep it supple.

**US FDA approved transdermal drugs.**

This list includes transdermal patches and delivery systems approved by the FDA. Only the first approved product for a given drug or drug combination administered by a given delivery

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 2033-2040 www.ijprajournal.com ISSN: 2249-7781

method is shown. Topical creams, ointments, gels and sprays are not included.[18]

Table No. 1 US FDA approved transdermal drugs- [19]

| Approval year | Drug | Indication | Product Name | Marketing company |
|---|---|---|---|---|
| **1979** | Scopolamine | Motion sickness | Transderm-Scop | Novartis Consumer Health (Parsippany, NJ) |
| **1981** | Nitroglycerin | Angina pectoris | Transderm-Nitro | Novartis (East Hannover, NJ) |
| **1984** | Clonidine | Hypertension | Catapres-TTS | Boehringer Ingelheim (Ridgefield, CT) |
| **1986** | Estradiol | Menopausal symptoms | Estraderm | Novartis (East Hannover, NJ) |
| **1990** | Fentanyl | Chronic pain | Duragesic | Janssen Pharmaceutica (Titusville, NJ) |
| **1991** | nicotine | Smoking cessation | Nicoderm, Habitrol, ProStep | GlaxoSmithKline (Philadelphia, PA), Novartis Consumer Health (Parsippany, NJ) Elan (Gainesville, GA) |
| **1993** | Testosterone | Testosterone deficiency | Testoderm | Alza, Mountain View, CA |
| **1995** | Lidocaine/epinephrine (iontophoresis) | Local dermal analgesia | Iontocaine | Iomed (Salt Lake City, UT) |
| **1998** | Estradiol/norethindrone | Menopausal symptoms | Combipatch | Novartis (East Hannover, NJ) |
| **1999** | Lidocaine | Post-herpetic neuralgia pain | Lidoderm | Endo Pharmaceuticals (Chadds Ford, PA) |

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 2033-2040 www.ijprajournal.com ISSN: 2249-7781

| | | | | |
|---|---|---|---|---|
| **2001** | Ethinyl estradiol/norelgestromin | Contraception | Ortho Evra | Ortho-McNeil Pharmaceutical (Raritan, NJ) |
| **2003** | Estradiol/levonorgestrel | Menopausal symptoms | Climara Pro | Bayer Healthcare Pharmaceuticals (Wayne, NJ) |
| **2003** | Oxybutynin | Overactive bladder | Oxytrol | Watson Pharma (Corona, CA) |
| **2004** | Lidocaine (ultrasound) | Local dermal anesthesia | SonoPrep | Echo Therapeutics (Franklin, MA) |
| **2005** | Lidocaine/tetracaine | Local dermal analgesia | Synera | Endo Pharmaceuticals (Chadds Ford, PA) |
| **2006** | Fentanyl HCl (iontophoresis) | Acute postoperative pain | Ionsys | Alza, Mountain View, CA |
| **2006** | Methylphenidate | Attention deficit hyperactivity disorder | Daytrana | Shire (Wayne, PA) |
| **2006** | Selegiline | Major depressive disorder | Emsam | Bristol-Myers Squibb (Princeton, NJ) |
| **2007** | Rotigotine | Parkinson's disease | Neupro | Schwarz Pharma (Mequon, WI) |
| **2007** | Rivastigmine | Dementia | Exelon | Novartis (East Hannover, NJ) |

## II. CONCLUSION-

The transdermal drug delivery system (TDDS) review articles offer useful insights on the transdermal drug deliverysystems and its evaluation procedure as a handy reference for the research scientist working on TDDS. The informationabove demonstrates that TDDS have significant potentials, since they can be used to create promising deliverablemedications from both hydrophobic and hydrophilic active substances. More knowledge of the various biologicalinteractions and polymer mechanisms is needed to optimize this drug delivery technology. The next generation of drugdelivery systems, TDDS, has a realistic, practical use.

**ACKNOWLEDGEMENT-**

The author extends their heartfelt gratitude to Proff. Rani M. Deokar and Dr. Megha T. Salve for their invaluable guidance, unwavering support, and significant contributions during the creation of this review article.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 2033-2040 www.ijprajournal.com ISSN: 2249-7781

## REFERENCE-

[1]. Prabhakar, D., Sreekanth, J., & Jayaveera, K. N. (2013). TRANSDERMAL DRUG DELIVERY PATCHES: a REVIEW. Journal of Drug Delivery and Therapeutics, 3(4). https://doi.org/10.22270/jddt.v3i4.590

[2]. Purushotham, K., & Vijetha, K. A. (2023). A review on transdermal drug delivery system. GSC Biological and Pharmaceutical Sciences, 22(2), 245–255. https://doi.org/10.30574/gscbps.2023.22.2.0053

[3]. Ebling, F. J. G., & Montagna, W. (2023, November 30). Human skin | Definition, Layers, Types, & Facts. Encyclopedia Britannica. https://www.britannica.com/science/human-skin

[4]. Lopez-Ojeda, W. (2022, October 17). Anatomy, skin (Integument). StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK441980/

[5]. Bedre Ashwini, Bhoge Durga, Pradyumna Ige (2023) Review on transdermal drug delivery system-Focus on innovativetransdermal dosage forms. J Pharma Drug Develop 10(2): 204

[6]. Prausnitz, M. R., & Langer, R. (2008b). Transdermal drug delivery. Nature Biotechnology, 26(11), 1261–1268. https://doi.org/10.1038/nbt.1504

[7]. Yewale, C., Tandel, H., Patel, A., & Misra, A. (2021). Polymers in transdermal drug delivery. In Elsevier eBooks (pp. 131–158). https://doi.org/10.1016/b978-0-12-819659-5.00005-7

[8]. Jain.N.K. K, Controlled and novel drug delivery, first edition, CBSpublishers and distributors, New Delhi.1997.

[9]. Jayaprakash, R., Hameed, J., & Anupriya, A. (2017). AN OVERVIEW OF TRANSDERMAL DELIVERY SYSTEM. Asian Journal of Pharmaceutical and Clinical Research, 10(10), 36. https://doi.org/10.22159/ajpcr.2017.v10i10.19909

[10]. Bioadhesive Drug Delivery Systems: fundamentals, novel approaches, and development. (2019, June 10). Routledge & CRC Press. https://www.routledge.com/Bioadhesive-Drug-Delivery-Systems-Fundamentals-Novel-Approaches-and-Development/Mathiowitz-III-Lehr/p/book/9780367399603

[11]. Wikipedia contributors. (2023h, December 1). Transdermal patch. Wikipedia. https://en.wikipedia.org/wiki/Transdermal_patch

[12]. House, L. K. (n.d.). What are Transdermal Patches and their Different Types? Strouse. https://www.strouse.com/blog/what-are-transdermal-patches-types

[13]. Drug delivery systems. (2015). In Elsevier eBooks (pp. 87–194). https://doi.org/10.1016/b978-0-08-100092-2.00006-0

[14]. Admin. (2012, February 7). TRANSDERMAL PATCHES. PharmaTutor. https://www.pharmatutor.org/articles/detail-information-on-transdermal-patches

[15]. Rastogi, V., & Yadav, P. (2012). Transdermal drug delivery system: An overview. Asian Journal of Pharmaceutics, 6(3), 161. https://doi.org/10.4103/0973-8398.104828

[16]. Shabbir, M., Ali, S., Shahid, M. N., & Raza, M. (2014). Formulation Considerations and Factors Affecting Transdermal Drug Delivery System-A Review. ResearchGate. https://www.researchgate.net/publication/308802974_Formulation_Considerations_And_Factors_Affecting_Transdermal_Drug_Delivery_System-A_Review

[17]. Vanbever, R., & Préat, V. (1995). Factors affecting transdermal delivery of metoprolol by electroporation. Bioelectrochemistry and Bioenergetics, 38(1), 223–228. https://doi.org/10.1016/0302-4598(95)01830-8

[18]. Bird, D., & Ravindra, N. M. (2020). Transdermal drug delivery and patches—An overview. Medical Devices & Sensors, 3(6). https://doi.org/10.1002/mds3.10069

[19]. Prausnitz, M. R., & Langer, R. (2008). Transdermal drug delivery. Nature Biotechnology, 26(11), 1261–1268. https://doi.org/10.1038/nbt.1504