TDDS (Transdermal Drug Delivery System): A Updated Review

Rajesh Kumar[1*], Richa Mishra[2], Manmeet Singh saluja[3]

[1*]Research Scholar, SunRise University, Alwar, Rajasthan
[2]Professor, SunRise University, Alwar, Rajasthan
[3]Professor, Saint Solider College of Pharmacy, Tonk, Rajasthan

[*]**Corresponding Author:** Rajesh Kumar
[*]Research Scholar, SunRise University, Alwar, Rajasthan

Abstract
The use of chemicals on the face for aesthetic and therapeutic purposes dates back thousands of years. It wasn't until the 20th century that topical medication became common practise. According to Merriam-Webster, the term "transdermal" was coined in 1944. This exemplifies the novelty of the concept in the medical and pharmaceutical communities. Self-contained dosing types of transdermal medicines are available. Drugs may be applied topically to have a systemic impact without affecting the drug's blood concentration. This review article provides a concise discussion of the advantages, cutaneous routes, fundamental clinical concerns, and limitations of TDDS. The effectiveness of the patches has been shown, and this is especially so when compared to the alternatives for administering restricted substances.

Keywords: Transdermal, Drug delivery, Advantages, Limitation

INTRODUCTION

In order to effectively treat a patient, transdermal drug delivery systems (TDDS), sometimes referred to as "patches," are used. All of the skin's physical, biochemical, and physicochemical qualities must be taken into consideration if medications are to be absorbed via the skin and distributed throughout the body. Because of its convenience and lack of first-pass metabolism, transdermal injection is preferable to intramuscular or oral administration of a drug. Transdermal drug delivery allows for the continuous administration of drugs having short biological half-lives. It also eliminates the potentially harmful consequences of the drug's fast entrance into the systemic circulation and instead delivers it gradually over time. This resulted in the creation of novel routes of drug administration such transdermal, controlled release, and transmucosal delivery. The liver's first-pass processing is reduced, therapy is enhanced, and the medication concentration in the circulation is maintained when transdermal drug delivery is used. The first transdermal device, Transderm-SCOP, for treating motion sickness and nausea due to travel, particularly sea travel, was authorised by the Food and Drug Administration in 1979. How much of the medication is in the blood, how much of the drug and its metabolites are in the urine, and how well the patient reacts to medical therapy are all indicators of direct drug absorption.

The Food and Drug Administration (FDA) gave its blessing to the first transdermal patch, scopolamine, in 1981. Angina pectoris due to coronary artery disease (Treated with Transderm Nitro) and motion sickness (Treated with TransdermScop, ALZA Corp.) are two examples of diseases treated with topical applications of nitroglycerine and scopolamine. Products that distribute medication transdermally aid patients in their recovery. There are around 35 transdermal medication delivery alternatives available for purchase in the United States and elsewhere, and each one contains roughly 16 active components.

LITERATURE REVIEW

According to K. Purushotham et al. Sometimes referred to as "patches," transdermal drug delivery systems (TDDS) are dosage forms developed to transport a therapeutically effective amount of medicine over a patient's skin for systemic effects. Topical drugs may be provided using transdermal drug delivery devices. These pharmacological preparations comprise one or more active components and are available in a range of sizes to provide equal distribution of the active ingredient after it has penetrated the skin and avoided first-pass digestion. They are meant to be used on intact skin. About 74% of all drugs prescribed today are given orally, and most of them do not work as well as hoped. In order to improve the efficacy of medications, transdermal drug delivery methods were created. In TDDS, the drug gets where it needs to go rapidly and penetrates the skin. To get around the drawbacks of oral medicine administration, transdermal medication delivery systems were developed. These systems have been utilised for reliable and secure drug delivery since 1981.

Citation: Woo Yeup Jeong et al., 2021 Several non-invasive alternatives to needle-based injections have emerged in recent years. Transdermal drug delivery systems (TDDS) are the least objectionable option because of their low rejection rate, excellent simplicity of administration, and great patient convenience and persistence. TDDS has potential use in the cosmetics and pharmaceutical industries for treating skin conditions. Because of the emphasis on local administration, this method may prevent unwanted side effects and drug accumulation in certain areas. However, there

are a number of barriers and restrictions to transdermal dispersion due to the skin's physicochemical features, and a lot of research have been conducted to overcome these obstacles. In this research, we introduce the various TDDS methods now in use, discuss their advantages and disadvantages, characterise them, and assess their potential. Studies have progressed on these other methods, proving the high efficiency of TDDS, which is expected to be used in many fields.
In Merugu Rajashekar et al. Drug reactivity and breakdown under acidic circumstances, dosage variations, and epithelial duct irritation are all potential side effects of orally administered drugs that may be avoided using transdermal patches. Various types, structural components, chemical compound functionalities, and appropriate assessment procedures for the wide variety of transcutaneous patches on the market are covered in this study. Although transdermal patches have been used for a wide variety of medical purposes, including smoking cessation, pain management, pathology, birth control, illness, angina, and diseases of the internal organs, new formulation research is allowing for the development of transcutaneous patches that can deliver more potent medication. Long-term use and the chemical scientific properties of both active and inert components will be considered in the design and development of transdermal patches. As a result, research is being conducted on a wide variety of chemical processes and physical procedures for creating skin patches.
Said Maryam Shabbir in 2018 The present study's objectives were to develop a transdermal patch formulation of tizanidine HCl, evaluate the effect of polymers on the drug's in vitro release pattern, and investigate the effect of permeation enhancers on the drug's uptake by rabbit skin. Hydrophilic polymers (HPMC) and hydrophobic polymers (Eudragit L-100) were mixed with PEG 400 as a film-forming agent, and Span 20 or DMSO was used as a permeation enhancer. The formulations were tested for their physicochemical qualities and in vitro drug release using the USP paddle over disc procedure in phosphate buffered saline (pH 7.4) at 32°C. Based on in vitro testing and physicochemical evaluations, Eudragit: HPMC ratios of 8: 2 and 7: 3 were selected for further ex vivo study of samples S03-A and S04-A, respectively. Different concentrations of Span 20 and DMSO were tested on rabbit skin that had been surgically removed using a Franz diffusion cell. It was compared to a control formulation in terms of drug flow, permeation, permeability, target flux, and enhancement ratio. Both kinetic models and Tukey's multiple comparison test were employed to analyse the drug release profiles. Formulation SB03-PE, which used a zero-order kinetic model with a super case-II drug release mechanism, created the greatest increase in drug permeability by combining Span 20 (15% w/w) with Eudragit L-100: HPMC (7:3).

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

Transdermal distribution has many advantages over more traditional administration routes.

- Medicines that are able to avoid the first pass metabolism in the intestines, saliva, and liver have improved bioavailability and efficacy.
- It is possible to self-manage.
- In an emergency, the patch may be removed from the skin's surface at any time during treatment to immediately cease the absorption of the active substance.
- little intra- and inter-patient variation; skin structure and biochemistry are universally conserved among species.
- Maintaining digestive compatibility.
- Because of its simplicity of administration, it lessens the discomfort and potential for infection associated with parenteral treatment and boosts patient adherence.
- Negative effects are kept to a minimum by preserving optimum temporal patterns of blood concentrations.
- Long-acting medication is one whose effects continue to be felt after the patient has stopped taking it.
- Medicines with short biological half-lives and treatment windows are used.
- stabilising plasma concentrations of the medication.
- The plasma concentration of very potent drugs is maintained at all times.
- The treatment might be abruptly terminated if necessary.
- Patient compliance may be enhanced by doing away with the standard multiple-dosing profile.
- When side effects from the oral route, including nausea and stomach pain, make it difficult to give the drug candidate, the transdermal route is used instead.

LIMITATIONS FOR SELECTION OF TDDS:

However, only drugs with certain physicochemical properties may be administered in this manner.

- Unacceptable for drugs that need to be in the bloodstream often.
- Incompatible with drugs that trigger allergic skin reactions.
- Drugs having a high molecular weight are incompatible with it.
- Those drugs that are metabolised in the skin should not use this method.
- Since the skin is such a formidable barrier to drug entry, a wide range of treatments are inaccessible by transdermal delivery. Dosing must be kept to a minimum.

PHYSIOLOGY OF THE SKIN:

The skin covers around 2 square metres on a normal adult, and it receives about a third of the body's total blood supply. There are four distinct sections inside the epidermis, which is the outermost layer of skin. These include the basal layer, the spiny layer, the stratum granulosum, and the stratum corneum, the outermost layer. The epidermis is a continuous

layer of cornified (dead) cells wrapped in a lipid membrane matrix. The unique composition of these extracellular membranes includes ceramides, cholesterol, and free fatty acids. On average, a human being has between 10 and 70 hair follicles and 200 to 250 sweat ducts per square centimetre of skin. One of the most accessible human organs.

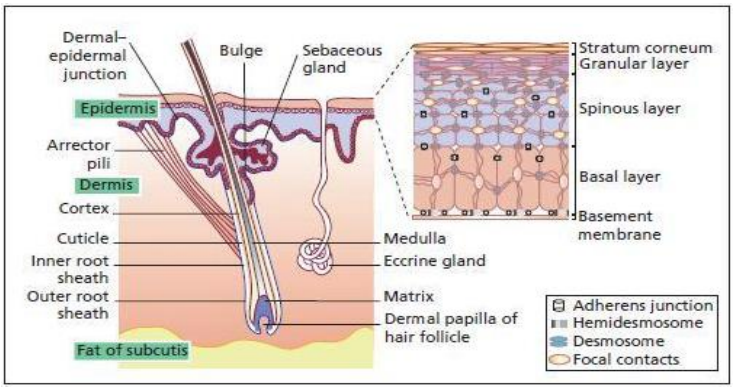

Figure 1: Anatomical and physiological Structure of skin

SKIN PATHWAYS FOR TRANSDERMAL DRUG DELIVERY SYSTEMS:

Drugs applied to the skin's surface may enter the body in a variety of ways. Figure 2 depicts the two possible routes of drug administration: transepidermal and transappendageal. The stratum corneum may be breached in two different ways: (1) by passing back and forth between the corneocytes and the lipid lamellae (the "trans cellular route"), and (2) by following the twisting channel between the lipid lamellae (the "intercellular route").

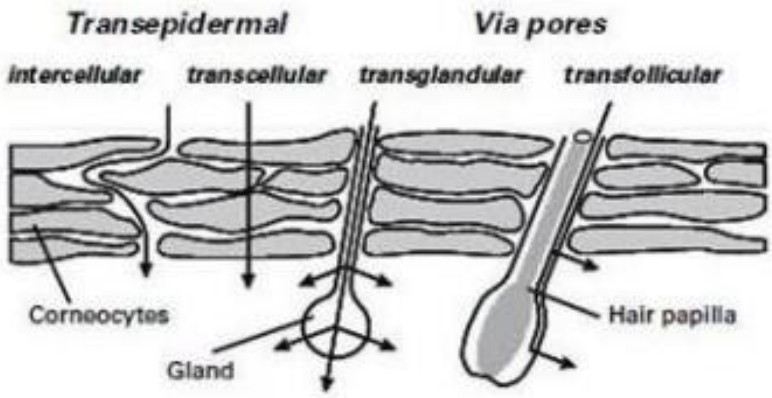

Figure 2: Possible pathways for permeation of drug across the skin barrier

Penetration of the stratum corneum most often occurs through the intercellular channel. This is mostly due to the keratinocytes' cross-linked cornified membrane. However, there is still some water and other small hydrophilic molecules that make it across the trans cellular pathway. Appendage routes and shunt routes include the follicular duct and the eccrine sweat gland duct. Eccrine sweat glands produce largely hydrophilic sweat, whereas the follicular duct mostly secretes lipophilic substance. This is mostly caused by sebum that is secreted into the opening of the follicular duct. The intact stratum corneum, with its massive surface area, is widely recognised as the major channel for passive skin permeation.

FACTORS INFLUENCING TRANSDERMAL DRUG DELIVERY:

Transdermal drug delivery systems have three components: the medicine, the skin, and the delivery vehicles. Therefore, the components that play a role may be broken down into two categories: biological and physicochemical.

A. Biological factors:

Acids, alkalis, and a number of solvents, including chloroform and methanol, damage skin cells and promote penetration, leading to a variety of skin conditions. The health of a patient's skin reflects their inside state. Undamaged skin provides a greater barrier, although the aforementioned conditions still reduce vulnerability.

When comparing skin of different ages, younger skin is more permeable. When it comes to skin absorption of toxins, kids are especially vulnerable. Therefore, skin ageing is a factor in TDDS that affects the effectiveness of medicine absorption.

Changes in peripheral circulation may affect transdermal absorption. Targeted area of skin: Depending on the location, one's skin's thickness, kind of stratum corneum, and number of appendages may vary. These factors significantly affect the depth of penetration.

The skin is involved in the metabolism of a wide variety of substances, including steroids, hormones, chemical carcinogens, and even certain medications. Therefore, the effectiveness of a drug's skin absorption is affected by the skin's metabolic rate.
Variation across species: skin thickness, density, and keratinization all influence penetration to varying degrees.

B. Physicochemical factors:
When skin is properly hydrated, its permeability drastically increases upon contact with water. Hydration is the single most important factor in increasing skin permeability. Transdermal delivery necessitates the use of humectants. Temperature and pH: Medication absorption rises by a factor of ten with temperature change. The coefficient of diffusion decreases as the temperature drops. Weak acids and bases are often separated by pH and pKa or pKb values. The fraction of a medication that is unionised determines its concentration in the skin. Therefore, temperature and pH are critical factors affecting medicine absorption.
Drug penetration is affected by a property known as the diffusion coefficient. The diffusion coefficient of a drug at a constant temperature is a function of the properties of the drug, the diffusion medium, and the interactions between the two.
The Potency of the Drug: If the drug concentration is greater across the barrier, then the concentration gradient will be larger, and the flow will be smaller.
Coefficient of partitioning: for maximum efficiency, the value of K should be as high as possible. Substances with a high K value are not yet able to penetrate the skin's lipid layer. Furthermore, low-K drugs will not be absorbed by the body.
Size and form of molecules: Small molecules enter more rapidly than large ones, hence there is a negative correlation between molecular weight and medication absorption. Due to the dominance of the partition coefficient, the effect of molecule size is mostly hypothetical.

TYPES OF TRANSDERMAL PATCHES

The medication is integrated into the adhesive layer of this single-layer drug delivery system. The adhesive layer's dual purpose is to keep everything in place while also delivering the medicament to the skin. The adhesive layer is protected by a backer and a short-term liner.
Similar to the single-layer version, the multi-layer drug in adhesive consists of a layer for fast drug release, a layer for regulated drug release, and an adhesive layer. The release of the medicine is controlled by the sticky layer. This patch has both a permanent backing and a removable lining.
The adhesive layer's role in a vapour patch extends beyond just keeping everything in place. It's also a marketplace, where people go to unload their bottled-up stress-relieving essential oils. Vapour patches come in a variety of formulations, some of which are intended to improve sleep quality while reducing the negative effects of smoking.
The reservoir system involves a drug reservoir, an impermeable backing layer, and a membrane that regulates the medication's flow rate. The drug is only released through the membrane that controls the release rate, which may or may not be microporous. The drug reservoir compartment may contain the medicine in a liquid, a suspension, a gel, or a solid polymer matrix. It is possible to utilise a polymeric membrane with a drug-compatible and hypoallergenic outer surface.

CONCLUSION

Transdermal drug administration is a noninvasive, practical, and potentially effective method for administering several medications at regular intervals. Better pharmaceutical absorption and distribution with few side effects, low cost, and easy use for a broad range of medications. To avoid first-pass metabolism, an approved medicinal substance that is now taken orally might instead be given trans dermally. Transdermal medicine delivery through patches has becoming more common. However, transdermal technologies are limited by the thick, protective outer stratum corneum layer. There have also been major developments in transdermal patches. Research in this area is difficult because of the many barriers to broad use of TDDS and its assured efficacy. When it comes to medicine absorption and distribution, the skin is a particularly complicated and formidable barrier.

REFERENCE

1. Merugu Rajashekar et.al “Design and Study of Transdermal Drug Delivery System in Humans” DOI: 10.36648/2471-853X.7.10.62
2. Zhao, Z., Li, M., Zheng, L., Yang, Y., Cui, X., Xu, T., Zhang, W. and Wang, C., (2022) Non-invasive transdermal delivery of mesoporous silica nanoparticles using deep eutectic solvent. Journal of Controlled Release, 343, pp.43-56.
3. Maryam Shabbir **“**Influence of different formulation variables on the performance of transdermal drug delivery system containing tizanidine hydrochloride: in vitro and ex vivo evaluations” Brazilian Journal of Pharmaceutical Sciences http://dx.doi.org/10.1590/s2175-97902018000400130
4. K Purushotham et.al “A review on transdermal drug delivery system” DOI: https://doi.org/10.30574/gscbps.2023.22.2.0053
5. Jeong, W.Y., Kwon, M., Choi, H.E. et al. Recent advances in transdermal drug delivery systems: a review. Biomater Res **25**, 24 (2021). https://doi.org/10.1186/s40824-021-00226-6

6. Ahn, J. S. (2017). Transdermal buprenorphine and fentanyl patches in cancer pain: A network systematic review. Journal of Pain Research, **10**, 1963–1972
7. Chee, A., & Chenga, C. (2017). Transdermal patch simulation using the lattice Boltzmann method with active diffusion in the cell and lipid pathways. Stony Brook, NY: Stony Brook University.
8. Cilurzo, F., Gennari, C. G. M., & Minghetti, P. (2012). Adhesive properties: a critical issue in transdermal patch development. Expert Opinion on Drug Delivery, **9**(1), 33–45. https://doi.org/10.1517/17425247.2012.637107
9. Di Stefano, A., Sozio, P., Cerasa, L. S., & Marinelli, L. (2012). Transdermal donepezil on the treatment of Alzheimer's disease. Neuropsychiatric Disease and Treatment, **8**, 361–369.
10. Economidou, S. N., Lamprou, D. A., & Douroumis, D. (2018). 3D printing applications for transdermal drug delivery. International Journal of Pharmaceutics, **544**(2), 415– 24. https://doi.org/10.1016/j.ijpharm.2018.01.031
11. Falcone, R., Jaffe, M., & Ravindra, N. M. (2013). New screening methodology for selection of polymeric matrices for transdermal drug delivery devices. Bioinspired, Biomimetic and Nanobiomaterials, **2**(2), 66–75.
12. Kaye, R., Goldstein, T., Zeltsman, D., Grande, D. A., & Smith, L. P. (2016). Three-dimensional printing: A review on the utility within medicine and otolaryngology. International Journal of Pediatric Otorhinolaryngology, **89**, 145–148.
13. Lim, D. (2018). Microneedles: A versatile strategy for transdermal delivery of biological molecules. International Journal of Biological Macromolecules, **110**, 30–38.
14. Margetts, L. (2007). Transdermal drug delivery: Principles and opioid therapy. Continuing Education in Anaesthesia, Critical Care & Pain, **7**(5), 171–176.
15. Pastore, M. N., Kalia, Y. N., Horstmann, M., & Roberts, M. S. (2015). Review Transdermal patches: History, development and pharmacology. British Journal of Pharmacology, **172**, 2179–2209.