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Review Article

PHARMACOLOGICAL ACTIVITIES OF ANTI-HYPERTENSIVE DRUG DELIVERY THROUGH A TRANSDERMAL PATCH – A BRIEF REVIEW

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Abstract
One of the methods falling under the category of controlled drug delivery is the transdermal drug delivery system (TDDS), which is designed to distribute the medicine via the skin at a predefined and regulated pace. Hypertension is one of the largest death-causing diseases in mankind. Since it is a chronic disease, it required continuous treatment. The disadvantages of antihypertensive drugs such as more frequent administration, extensive first-pass metabolism and variable bioavailability, making them an ideal candidate for transdermal drug delivery systems. This article is dedicated to reviewing antihypertensive transdermal patches from the perspective of enhancing bioavailability and improving patient compliance. The various antihypertensive drugs considered in the review include timolol maleate, nicardipine hydrochloride, captopril, verapamil hydrochloride, nifedipine, propranolol hydrochloride, diltiazem hydrochloride, amlodipine besilate and carvedilol. Clonidine was the first antihypertensive drug developed in the transdermal form. Recently, various antihypertensive transdermal patches are available in the pharmaceutical market. Most of the reported methods in the literature employed the solvent evaporation method or solvent casting method for the preparation of transdermal patches. Depending on the release required over some time, the concentrations of polymer, plasticizer and penetrant were varied.

INTRODUCTION

Nowadays, transdermal delivery of drugs is one of the most beneficial methods for drug application. New drugs are being added to the list of therapeutic agents given to the systemic circulation through the skin. The transdermal route offers several advantages over conventional dosage forms such as tablets and injections, including avoidance of first-pass metabolism by the liver, minimization of pain, minimising of side effects, increasing the duration of action, more stable drug concentration in the blood and continuous sustained release of drug [1].

With minimum fluctuation between and among patients, the transdermal drug delivery system's goal is to deliver medications into systemic circulation via the skin at a predefined rate [2]. The presence of barrier qualities displayed by the top layer of skin, the stratum corneum, and the transdermal medication delivery method has long been a difficult subject for researchers to study. Especially in the past twenty years, the transdermal drug delivery system has become a more focused technology that offers significant clinical benefits over other dosage forms, because transdermal drug delivery offers controlled also offers state blood concentration [3]. Hypertension, a cardiovascular disease, accounts for many deaths and disability worldwide. As per the Global Burden of Disease research, cardiovascular illnesses were the cause of 5.2 million deaths in economically developed nations and 9.1 million deaths in underdeveloped nations [4]. An estimated 1 billion people have hypertension and approximately 7.1 million deaths per year because of hypertension [5]. Hypertensive causes 57% of all stroke death and 24% of coronary heart diseases in India. The transdermal system is ideally suited for the disease that demands chronic treatment. In this project, TDDS is also utilised for the delivery of antihypertensive drugs from transdermal patches [4].

Hypertension is defined conventionally as a sustained increase in blood pressure 140/90 mm Hg, a criterion that characterizes a group of patients whose risk of hypertension-related cardiovascular disease is high enough to merit medical attention. The risk of both fatal and nonfatal cardiovascular disease in adults is lowest with systolic blood pressures of less than 120 mm Hg and diastolic BP of less than 80 mm Hg; these risks increase progressively with higher systolic and diastolic blood pressures [6]. Antihypertensive patches with defined dose forms decreased the frequency of hospitalisation and diagnostic expenses despite the high cost of patches applied transdermally to treat high blood pressure. For instance, a study based on Medicaid claims in two American states, Florida and South Carolina, found that although patients using the patch spent much more on prescription drugs, it prevented them from having to pay for hospitalisation and diagnostic procedures. These benefits let the target audience adopt antihypertensive patches as a more expensive alternative to standard medication. This acceptability factor encouraged both academicians and research scientists to take up various challenging projects in this particular arena.

In order to alleviate motion sickness and nausea brought on by travel, the FDA approved the first transdermal device, Transderm SCOP, in 1979. Most transdermal patches are designed to release the active ingredient at a zero-order rate over several hours to days after being placed on the skin. This is especially advantageous for prophylactic therapy in chronic conditions [7]. Measurable blood levels of the medication, the presence

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of the drug and its metabolites in the urine, and the patient's clinical reaction to the pharmacological therapy are all possible indicators of percutaneous drug absorption [8].

Anatomy and Physiology of Human Skin

The adult surface area of skin is 1.5 to 2 square metres and contains glands, hair, and nails. It is the biggest organ in the body. Dermis and epidermis are the two major skin layers.

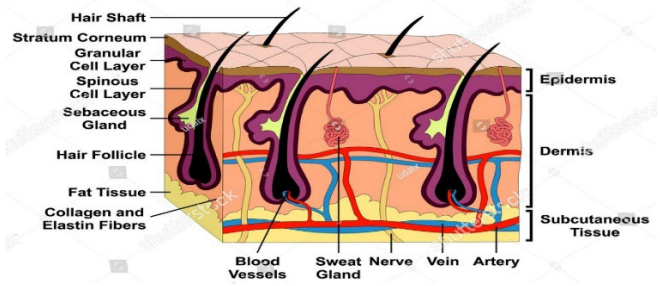

Fig. 1: Anatomy of human skin [9]

Epidermis

The skin's topmost layer is called the epidermis and is composed of stratified keratin squamous epithelium which varied in thickness in different parts of the body. It is thickest on the palms of the hands and soles of the feet. Blood vessels or nerves are ending in the epidermis, but its different layers are bathed in interstitial fluid from the dermis, providing oxygen and nutrients and draining away as lymph. The maintenance of a healthy epidermis depends upon three processes:

- keratinized cells are removed from the surface by desquamation.
- Keratinization of the cell effectively when it approaches the surface
- Continual cell division in the dipper layers with newly formed cells being pushed to the surface [10].

Dermis

Durable and elastic, the dermis. It is made of connective tissue and has an elastic fibre and collagen fibre matrix. Stretch marks are permanent striae that can appear during pregnancy and obesity due to ruptured elastic fibres that occur when the skin is stretched beyond its normal capacity. The skin's tensile strength and capacity to bind water are both provided by collagen, but as we age, wrinkles appear because this ability deteriorates. Dermal cells include mast cells, macrophages, and fibroblasts. There are different quantities of adipose tissue and areolar tissue underneath its lowest layer. Structures noticeable in the dermis include blood vessels, lymph vessels, sensory nerve endings, sweat glands, and their ducts. Sebaceous glands, hairs, and arrector pili muscles [11].

Hypodermis

Support for the dermis and epidermis is provided by the hypodermis or subcutaneous fat tissue. This region is used to store fat. Along with providing mechanical and nutritional support and temperature regulation, this layer also helps regulate body temperature. It may also have pressure-sensing organs and major blood vessels carrying nerves to the skin. In contrast to topical drug delivery, which only requires stratum corneum penetration and then aims to retain the medication in the skin layers, transdermal drug administration requires the drug to pass through all three of these layers and enter systemic circulation [11].

Advantages of Transdermal Drug Delivery [12][13][14]

In TDDS, a patch-like device clings to the skin's surface to transport the medication into systemic circulation via the skin at a predetermined concentration for therapeutic benefits.

1. By using this approach, further limitations related to standard dose forms are avoided.
2. It provides continuous drug absorption through the skin, maintaining the serum drug level, the therapeutic aim.
3. It may be used as a substitute for the oral drug delivery method for individuals who have problems swallowing their drugs.
4. It can be used as an alternative for patients who are queasy or unconscious.
5. Since there would be no direct contact, medications can be administered to patients with gastrointestinal issues using TDDS.
6. Adverse drug-to-gut interactions.
7. It provides a consistent plasma level, similar to intravenous infusion.
8. The patch can be simply removed if toxicity results from TDDS.
9. It is incredibly practical due to how simple it is to apply the medication.
10. It does away with the first pass system.
11. It lessens medication interactions throughout the body.
12. It provides an action that lasts a long time.
13. It is possible to self-administrate.

Disadvantages of Transdermal Drug Delivery System [15]

The skin can only be penetrated by many hydrophilic medications very slowly or not at all. The effectiveness of the medicine as a treatment will be impacted by this.

1. Patches may lead to a variety of issues, including itchiness, oedema, erythema, and more.
2. The skin's ability to act as a barrier can vary depending on the individual, their age, or the location of their skin.
3. The area where the medicine was administered may become irritated.
4. A drug delivery system with poor economics.
5. The only conditions for which it is utilised are chronic ones; it is not used for acute ones.
6. Ionic medications and TDDS do not mix well. 8. Dosage dumps could happen.
7. Drugs that have a preference for both lipophilic and hydrophilic phases are employed.
8. It is impossible to reach high drug blood levels.

Routes of drug penetration through the skin

As seen in Figure 2, a drug molecule may diffuse through shunts provided by the more widely dispersed hair follicles and eccrine glands during the percutaneous penetration process rather than passing through the epidermis itself. Before being absorbed by the follicular epithelium and sebaceous glands, drug molecules might enter the skin through perspiration or hair follicles in the initial transient diffusion stage. The main channel for transdermal penetration changes after a steady state has been attained and diffusion via the intact stratum corneum [16].

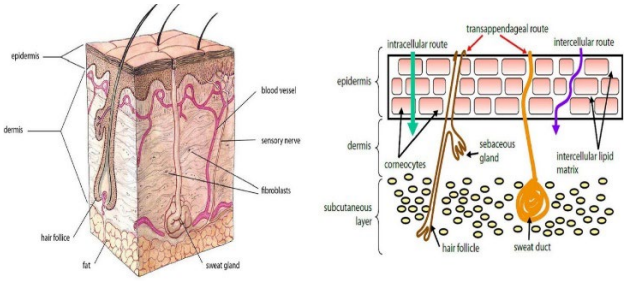

Fig. 2: Micro Routes Drug Penetration Through Skin

There are two primary pathways for chemicals to penetrate the skin after application:

✓ Transepidermal route ✓ Transfollicular route

Transepidermal route

In transepidermal transport, molecules cross the intact horny layer. Two potential micro-routes of entry exist, the transcellular (or intracellular) and the intercellular pathway as shown in Fig.3

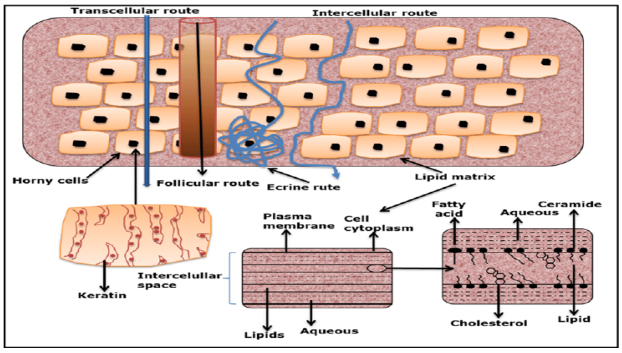

Fig 3: Possible micro routes for drug penetration across human skin intercellular or transcellular

Molecules go through the horny layer unharmed during transepidermal transfer. There are two possible micro-entry points: the transcellular (or intracellular) pathway and the intercellular pathway, as depicted in Fig.3. Different methods allow polar and non-polar compounds to diffuse via transcellular and intercellular pathways. In contrast to the non-polar molecules, which dissolve and diffuse through the stratum corneum's non-aqueous lipid matrix, polar molecules mostly diffuse through the polar channel made up of "bound water" in the hydrated stratum corneum. As a result, the partition coefficient (log K) plays a major role in determining a penetrant's primary route. When compared to lipophilic permeants (octanol/water log K > 2), hydrophilic medicines preferentially partition into intracellular domains while lipophilic permeants go through the stratum corneum through the intercellular pathway. Most molecules go through both pathways to reach the stratum corneum [17].

Transfollicular route (Shunt pathway)

The associated sebaceous glands, hair follicles, and sweat glands must be passed through on this path. The fact that these pathways only make up a small portion of the skin, or around 0.1% of it, despite having great permeability, makes them of secondary importance. This pathway appears to be particularly significant for ions and big polar compounds, which barely pass through the stratum corneum [17].

Barrier functions of the skin

The most critical component in preserving the barrier's efficacy is the top layer of skin. The skin's ability to retain water is preserved because the individual cells are closely packed and overlie one another in this area [18]. Stratum corneum is mostly made up of keratinized dead skin cells, and it contains less water than other skin layers [19]. Cells secrete lipids from the topmost layer of the skin to the bottom layer. These lipid molecules combining to form a robust connective network is what makes up the mortar in between bricks of a construction.

Basic Principle of Transdermal permeation

Passive diffusion is the foundation for transdermal permeation [20]. The skin is the body's most active and accessible organ due to the little amount of tissue that separates its surface from the capillary network below [21]. When applied to the skin, a medication is liberated from its formulation and gradually absorbed into the bloodstream [20], including

1) Drug diffusion from the drug to the membrane that regulates flow rates.
2) The composition dissolves both inside and externally.
3) Passing via a healthy epidermis and sorption in the stratum corneum.
4) Drug absorption by the dermal papillary layer's capillary network.
5) The target organ's reaction.
6) Separating into the skin's uppermost layer, the stratum corneum.
7) A lipidic intercellular route is the main means of achieving diffusion across the stratum corneum.

ANTIHYPERTENSIVE DRUGS

Timolol maleate

A beta adreno receptor blocker called timolol maleate is used to treat hypertension, myocardial infarction, and other cardiovascular conditions. Propranolol is 8–10 times less powerful than it. It requires frequent administration of doses to maintain therapeutic drug levels since it rapidly absorbs from the gastrointestinal tract with a peak plasma concentration of 5–10 ng/mL after 1 h and is metabolised up to 80% in the liver with a mean half-life of 2.0–2.5 h [4]

Swarnlata et al. [22] two different kinds of polymer patches were created: one using polyvinyl alcohol (PVA) alone and the other combining hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC). HPMC 10% and EC 10% polymer solutions were made using a 1:1 combination of methanol and chloroform. Various mixtures of the two liquids were used. A 0.5% glycerin plasticizer and polymer concentrations of 5, 10, and 15% are used in the manufacture of PVA matrix patches. According to the investigations, transdermal distribution of timolol maleate using both reservoirs and a matrix system is feasible. In contrast to the matrix system, which used a first-order release profile, the reservoir system operated in zero order. The permeability of the PVA (10%) patch is greater than that of HPMC: EC (2:8) in both matrix systems.

Hanan et al. [23] examined the viability of a matrix-controlled transdermal patch containing timolol maleate based on a sugar fatty acid ester as a penetration and absorption booster. The effects of fatty acid type, chain length, hydrophilic-lipophilic balance, and permeability over hairless rat skin were investigated and compared in order to choose a patch formulation for clinical performance. According to the findings, among the several acid esters tested, the laureate acid ester with shorter fatty acid

chain length & greater hydrophilic-lipophilic balancing value considerably boosted the quantity of timolol maleate freed from the patch (992.1%) and its permeability across rat skin (864.3%). Comparing the overall drug permeation and flow results to the acid ester-free patch, they were around times higher. All of the individuals tolerated the created patch well, except for a little amount of mild skin sensitivity that subsided within 24 hours of patch removal. The outcomes are very positive and provide a different strategy for sustaining a higher, more sustained, and tightly regulated blood level profile of the medication over the course of 18–24 hours.

Nicardipine hydrochloride

Chronic stable angina and hypertension are both treated with nicotine hydrochloride, a calcium channel blocker. The medicine takes five to ten minutes to start working, and it lasts for fifteen to thirty minutes [24]. The medication 19 has a bioavailability of 20–40% and a half-life of 2-4 hours [25]. Aboofazeli et al. [26] It is possible to clarify the mechanistic impacts of formulation ingredients on the transdermal penetration of medicine via the skin by preparing and evaluating flux and its effects. Based on the solubility results, vehicles, such as pure solvents alone and their preferred combinations, are chosen and examined. In comparison to PG, PG/OA, polyethylene glycol 300, ethanol/PG (70:30 w/w), transistor, DMI, ethanol, water and buffer 4.7, and 2-propanol, it was discovered that the medication was better soluble in ethanol/propylene glycol/oleic acid/dimethyl isosorbide (DMI) (80:10:10 v/v). The creation of a transdermal product then chose PG as its primary delivery system. As a first step in developing a transdermal delivery system, the vehicle impact on nicardipine hydrochloride's percutaneous absorption was determined using the excised skin of a hairless guinea pig. PG/OA/DMI ternary and binary mixtures both demonstrated outstanding flow among the systems under study. According to the findings, no one solvent could increase the penetration of nicardipine hydrochloride.

Krishnaiah et al. [27] developed a membrane-moderated transdermal therapeutic system of nicardipine hydrochloride using 2% w/w hydroxyl propyl cellulose (HPC) gel as a reservoir system containing 4% w/w of limonene as a penetration enhancer. The permeability flux of nicardipine hydrochloride across the membrane constructed of ethylene vinyl acetate was found to rise as the amount of vinyl acetate in the copolymer increased. It was also investigated how different pressure-sensitive adhesives, such as MA-31 (a moderate acrylic pressure-sensitive adhesive), MA-38 (a mild acrylic pressure-sensitive adhesive), or TACKWHITE A4MED (a water-based pressure-sensitive acrylic emulsion), affected the permeability of nicardipine hydrochloride through ethylene vinyl acetate membrane 2825 (28% w/w vinyl acetate) or membrane/skin composite. The results showed that nicardipine hydrochloride permeability was higher in TACKWHITE 4A MED/skin composite-coated EVA membranes than in MA-31 or MA-38-coated membranes.

Captopril

Both hypertension and congestive heart failure are commonly treated with captopril, an angiotensin-converting enzyme inhibitor that is orally active. The medication's efficacy and minimal toxicity make it a preferred option for antihypertensive therapy [28]. Although its activity lasts for 6–12 h, its typical half-life is 2–3 h [18]. Captopril has a bioavailability of 75%, although food lowers oral absorption by 30% to 50%. Because the oxidative product of captopril, a captopril disulfide, has poor intestinal absorption [29], earlier studies have found that the oxidation rate of captopril in dermal homogenates is much lower than the intestinal homogenate.

Jain et al. developed a matrix diffusion transdermal administration system for captopril using varied polymer ratios of EC and HPMC, such as (3:1) and (2:2). According to research on both in vitro skin penetration and in vitro dissolution, the release of captopril was higher in matrices with an EC: HPMC ratio of 2:1 as opposed to 3:1. The rabbit abdominal skin was permeable to captopril from a matrix having EC: HPMC ratio 2:2. The produced matrices were stable for three months and devoid of any irritative effects [30].

Nifedipine

A powerful medication with a long history of usage in the management of hypertension is nifedipine. Its bioavailability is poor because of substantial first-pass metabolism. Sankar et al. [31] made and assessed nifedipine transdermal patches. Plasticizers such as castor oil (30% w/w) and glycerol (40% w/w) were added to the drug-free polymeric films of EC produced for the experiment to determine their appropriateness for transdermal application as regulating membranes. EC, a material with good film-forming properties, was employed in the study for fabrication. The results of the physicochemical assessment research indicate that room temperature storage of the films did not result in any physical alterations to their appearance, colour, or flexibility. Comparing films with castor oil to films with glycerol, the folding durability was greater in films with castor oil. A regulated in vivo distribution of nifedipine via patches is achievable, according to tests on the drug's release in rabbits. The maximal percentage release was obtained within 24 hours, even though the drug release from the EC patches containing 40% glycerol as a plasticizer was delayed in the first few hours (up to 4 h). After 24 hours, 82.6% of the medicine that was placed into the delivery was discovered.

Carvedilol

The gastrointestinal system quickly and thoroughly absorbs carvedilol, a non-selective beta-adrenergic blocker used to treat hypertension. Carvedilol has an absolute bioavailability of between 25% and 35%, however due to considerable first-pass metabolism, the apparent mean terminal elimination half-life after oral dosing typically ranges from 6 to 10 hours.

Barhate et al. [4] By combining PVA and PVP K30 with glycerine, PEG 400, and PG as plasticizers, carvedilol patches were made utilising the solvent casting process. It was found that the patch containing utilised plasticizers and a PVA: PVP ratio of 8:6 was a promising controlled-release transdermal medication delivery device for carvedilol. According to research on the in vitro drug skin penetration of transdermal patches, drug permeability from formulations comprising 20% and 40% by weight of PEG 400 was 91.50% and 94.21%, respectively. The results show that

PEG 400, which is primarily employed as a plasticizer, also improves carvedilol's in vitro absorption. The transdermal carvingilol patches that have been created have zero-order release kinetics.

Amlodipine besilate

A calcium ion antagonist or slow-channel blocker, amlodipine is a dihydropyridine calcium antagonist that stops calcium ions from entering cardiac muscle and smooth muscle in the vascular system through transmembrane pathways. With a terminal elimination half-life of around 30–50 h and a bioavailability of 60–65%, plasma elimination is biphasic [4]. The first-pass metabolism it passes through is substantial.

Patel et al. Amlodipine besylate was created as a matrix-type transdermal drug delivery system employing several polymers, including Carbopol 934, 940, HPMC, and Eudragit L100 in varying ratios. According to the permeability studies, the medication is appropriate for TDDS. After 24 hours, 84% of the medication was released from the improved formulation, which contained Carbopol 934: Eudragit L100 (3:7) and hyaluronidase as an enhancer. Models by Higuchi and Peppa were utilised to enhance the formulation.

Diltiazem hydrochloride

Angina pectoris, hypertension, and arrhythmia can all be treated with diltiazem hydrochloride, a calcium channel blocker. Its first-pass metabolism, which varies with species and is diverse and vast, is revealed by a review of the literature.

Rama et al. [32] The polymeric films (8:2:2 and 8:2:3) comprising EC, PVP, and medication were produced. According to in vitro skin permeation experiments, diltiazem's ability to penetrate the skin rises with both starting drug concentration and PVP content in the film, reaching its maximum at the aforementioned ratio. The mercury substrate approach was used to create the EC: PVP: drug (8:2:2 and 8:2:3) polymeric films. As a plasticizer, dibutyl phthalate was added to the dry weight of the polymers at a concentration of 30% w/w. In a nutshell, the procedure required pouring a chloroform solution comprising chemicals, plasticizers, and polymers over a mercury surface inside a petri dish.

Satturwar et al. [33] Transdermal patches with a matrix structure are created by utilising a solvent evaporation technique in a glass ring with varying ratios of polymerized rosin, PVP, and diltiazem hydrochloride. After being cast onto a PVA backing membrane, the uniform dispersion was dried at 60°C for 8 hours. The current study's findings show that, although film thickness is unaffected by drug and PVP loading, both the rate of drug release from films and its penetration through the skin increase. For the examination of pharmacokinetic and pharmacodynamic performance in an appropriate animal model, patches comprising polymerized rosin: PVP (7:3) show potential.

Propranolol hydrochloride

Propranolol hydrochloride is a beta-blocker that lowers blood pressure. Due to its short biological half-life (3.9 h), it requires controlled distribution. [34].

Murthy et al. [35] To assess how the solvent affected the mechanical and permeability characteristics of the films, rate-controlling membranes for TDDS were created using cellulose acetate and EC with a variety of solvents. A variety of solvents were used to make cellulose acetate and ethyl cellulose films, including acetone: methanol (8:2), dichloro methane: methanol (8:2), chloroform: methanol (8:2), and ethyl acetate: methanol (8:2). Plasticizers like dibutyl phthalate and propylene glycol are utilised when the polymer makes up 40% of the total weight of the mixture. In both situations, the rate of water vapour transfer reduced when the sequence of the films in the different solvents changed as follows: Dichloromethane: methanol (8:2), chloroform: methanol (8:2), ethyl acetate: methanol (8:2), etc.

Murthy et al. [4] cellulose acetate, EC, and eudragit RS100 were used to create and assess rate-controlling membranes for TDDS.The films were created using the following solvents: dichloro methane: methanol (8:2), acetone: methanol (8:2), and ethyl acetate: methanol (8:2). Dibutyl phthalate, or PG, makes up 40% of the weight of the polymer used to make cellulose acetate and EC film. 15% of the polymer in Eudragit RS100 was made up of dibutyl phthalate as a plasticizer. The Peppas model controlled how much medication was released. According to the study's findings, a film's permeability, capacity to transmit water vapour, and ability to diffuse drugs are all significantly influenced by the polymer and solvents employed in its manufacture.

Verapamil hydrochloride

Verapamil hydrochloride acts as an inhibitor of calcium ion influx. The therapy of angina, hypertension, and supraventricular tachyarrhythmias all include its frequent usage. Verapamil hydrochloride has a 2–7 h plasma half-life, hence it requires several doses. Although it is vulnerable to significant first-pass metabolism and only absorbs around 90% of the way through the digestive system, its bioavailability is only about 20–30%.

Devi et al. [36] Verapamil hydrochloride transdermal patches were created employing four distinct (single and combination) polymers, including HPMC 15 cps, Eudragit RL100, Eudragit RS100, and EC. Eudragit RL100 3 was used as the parent polymer, and factorial designs were used to optimise the formulations. Due to its hydrophilicity, the patch made from Eudragit RL 100 demonstrated a maximal water vapour transfer rate, moisture absorption, and moisture loss. All of the following values were dropped when Eudragit RS100, HPMC, and EC were substituted due to their lower hydrophilicity levels. By taking into account technical features, the patch that had 8 parts of Eudragit RL 100 and 2 parts of HPMC with plasticizer, i.e., dibutyl phthalate (30% 1 of the polymer weight), emerged as the most effective formulation.

CONCLUSION

TDDS, also known as transdermal drug delivery systems, are topically applied medications that are administered via the skin for systemic effects at a predefined and regulated pace. Antihypertensive medicines can be delivered transdermally to give the ideal dosage while minimising negative effects to treat the illness condition. The delivery of medications by this route enhances bioavailability as well as patient compliance,

according to this analysis of several antihypertensive medications. Additionally, it may result in the long-term management of hypertension being cost-effective for medical care. The key restriction, however, is that not all antihypertensive medications may be administered by this route since the substance must have particular physicochemical qualities that are suitable for permeating through the skin. The market for transdermal medication delivery is expanding, and during the next years, there is a likelihood that this industry may expand even more. Antihypertensive medication transdermal administration is anticipated to have a significant effect on patient treatment.

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CONSENT FOR PUBLICATION

The authors declare no conflict of interest.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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