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ROLE OF TRANSDERMAL PATCHES IN MANAGEMENT OF HYPERTENTION: A REVIEW

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Abstract

Medications are applied topically using transdermal drug delivery methods. Transdermal patches are pharmacological preparations that come in different sizes and are designed to be placed to intact skin. The purpose of the patches is to enable the active component to penetrate the skin's barriers and reach the systemic circulation, hence preventing the first pass effect. The ability to administer medication to a patient in a controlled manner via a transdermal patch is one advantage over other methods, such as oral, topical, intravenous, intramuscular, etc. Typically, this is accomplished by either a porous membrane enclosing a medication reservoir or by body heat melting thin layers of medication embedded in the adhesive. In this review article author revealed the advantages, disadvantages, skin structure and commonly drugs available in patch form for the hypertension treatment.

Keywords: Transdermal Patches, Hypertension, Antihypertensive drugs, Skin

INTRODUCTION

The World Health Organization has recognized hypertension as one of the leading global risk factors for morbidity and mortality, accounting for over nine million deaths per year. [1]

The illness known as hypertension is defined by consistently elevated blood pressure. One heart condition that is linked to many deaths and disabilities globally is hypertension. High blood pressure is one of the leading causes of death in humans. As a chronic illness, it necessitates ongoing care. [2]

Conventionally, hypertension is defined as a persistent rise in blood pressure of 140/90 mm Hg. This threshold is used to identify a subset of patients whose risk of cardiovascular disease associated with hypertension is significant enough to require medical attention. In India, hypertension is directly to blame for 24% of deaths from coronary heart disease and 57% of fatalities from stroke. Hospitalization rates and diagnostic expenses were decreased when antihypertensive patches were used in accordance with recommended dose forms. These benefits helped the target customer accept antihypertensive patches as a more expensive treatment option than traditional medication. They are preferred in antihypertensive therapy due to the potential for controlled zero order absorption, their ease of administration, and their option for simple dose withdrawal in the event of adverse symptoms. [3]

When Indian epidemiological data are combined, 25% of respondents in urban areas and 10% in rural areas have hypertension. [4].Thus, there is a great need for affordable methods to effectively control blood pressure in Indians. Although TDDS is a suitable treatment for chronic diseases such as hypertension, target patients may reconsider due to the higher cost of antihypertensive patches compared to conventional solutions. [5]

Numerous classes of antihypertensive drugs reduce blood pressure by various methods; the most significant and commonly utilized antihypertensive drugs include thiazide diuretics, β-blockers, ACE inhibitors, calcium channel blockers, and angiotensin II receptor antagonists. [6,7]

Classification of drugs used in hypertension

Classification of antihypertensive drugs are shown in figure 1.

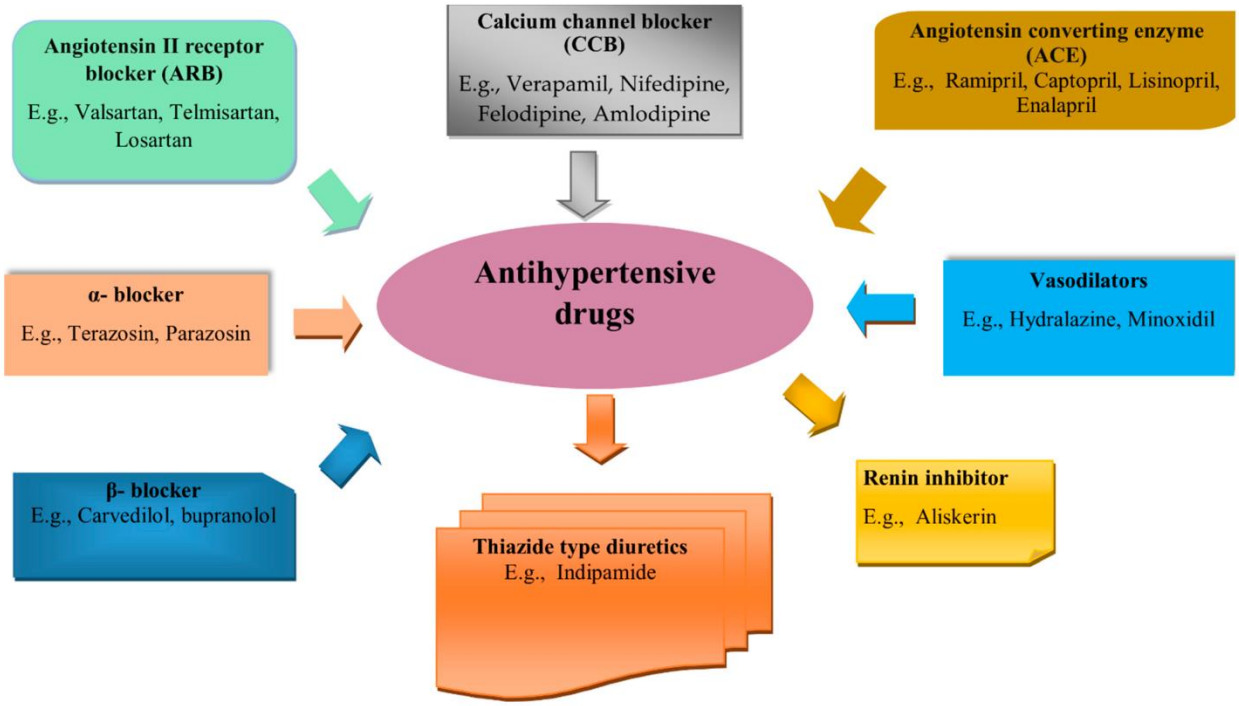

Figure 1: Classification of drugs used in hypertension [8]

When applied to intact skin, transdermal drug delivery systems (TDDSs) are discrete, self-contained dosage forms that gradually release the drug(s) into the systemic circulation through the skin portal at a predetermined and consistent pace over an extended period of time. [9]

Drugs delivered topically are provided via transdermal delivery systems. Transdermal patches are pharmaceutical preparations that come in different sizes and include one or more active ingredients. They are designed to be applied topically to intact skin, where they will pass through the skin's barriers and into the systemic circulation, preventing the first pass effect. Drugs for systemic effects are delivered by transdermal patches at a set and regulated rate. [10]

It is thought to be preferable to deliver medication to the general circulation through the skin as opposed to ingesting it orally. Patients frequently neglect to take their medications, and even the most obedient patients become weary of swallowing pills—especially if they have to take many doses every day. Furthermore, avoiding partial first-pass activation via the liver and avoiding the commonly occurring gastrointestinal (GI) irritation would result from bypassing the GI system. Furthermore, the blood level spikes and troughs caused by oral dosing forms are typically undesirable to the gradual absorption of the medication over hours or days. The transdermal products that are now on the market provide these benefits. [11]

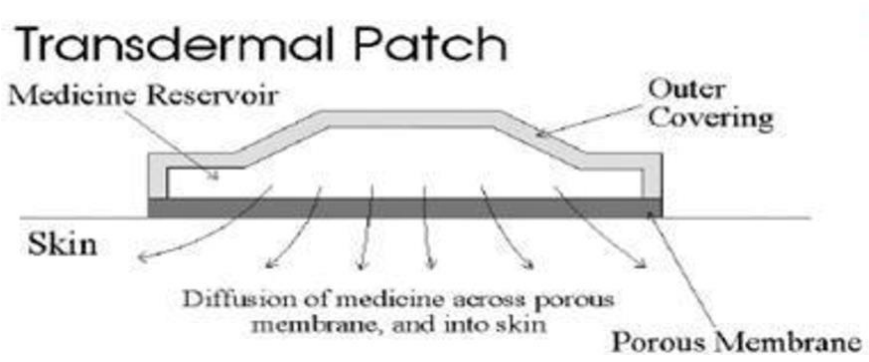

Figure 2: Mechanism of drug release from transdermal patch [12]

In 1979, the US Food and Drug Administration (FDA) approved the first transdermal system containing scopolamine; in 1984, the FDA approved nicotine patches. Ten years later, the FDA approved and sold transdermal patches for analgesic activity, contraception, and hormone replacement treatment. Developments in this area are still ongoing. In 1981, the FDA gave its approval to prevent motion sickness-related nausea and vomiting. Up until 2003, the FDA had approved over 35 transdermal patches that crossed 13 molecules. Targeting drug administration and preventing the first pass impact are two benefits of using transdermal patches. [13]

With at least 13 authorized compounds, more than 35 medications are used as transdermal patches nowadays. Transdermal patches are increasingly being used for hormone replacement, analgesics, heart disease alleviation from chest pain, quitting smoking, and neurologic conditions. Comparing transdermal patches to oral and hypodermic injections reveals a variety of benefits. In the first stage of hepatic metabolism, it offers improved biocompatibility. Other benefits include greater flexibility in drug administration through patch removal, painless application, and one-week extended use. However, this drug delivery system has not completely achieved its potential due to few. [14]

Minimizing medication retention and metabolism in the skin while optimizing medicine flux through the skin and into the systemic circulation is the aim of transdermal product dose design. Transdermal administration is preferred over injectables and oral methods because it improves patient compliance and inhibits first-pass metabolism. [15]

Components of Transdermal Drug Delivery System [16**]**

1) Polymer matrix/ Drug reservoir
2) Drug
3) Permeation enhancers.
4) Pressure sensitive adhesive (PSA).
5) Backing laminate.
6) Release liner.
7) Other excipients like plasticizers and solve

ADVANTAGES OF TDDS [17]

a. Topical patches are apainless, non-invasive way to deliver substances directly into the blood.
b. Topical patches can bypass first-pass hepatic metabolism
c. Termination of medicament can be possible by removing the patch from skin.
d. Drug which is, stomach irritant can modify to topical delivery.
e. Topical patches have fewer side effects than oral medications.
f. Topical patches are easier to use and remember.
g. Topical patches are cost-effective.
h. Topical patch can release the drug at steady state over the long period of time.
i. Topical patch can bypass the enzymes action on it.

DISADVANTAGE OF TDDS [18]

a. Local irritation possible at site of action.
b. Some time itching and edema can cause by drug.
c. Some time may cause allergic reaction.
d. Some time not require high blood levels to drug administration.
e. Molecular weight less than 500 Da.
f. Drug not suitable, not possess o/w partition coefficient.
g. The barrier functions of skin of change to one site to another site and person. to person.

LIMITATION OF TDDS [19]

i. Limited skin permeability.
ii. Significant lag time.
iii. Cannot be used for large molecule
iv. Restricted to potent drug.
v. Skin irritation and allergic response
vi. Tolerance inducing drugs or those (eg. Hormones) requiring chronopharmacological management are not suitable candidates.
vii. Skin structure poses a barrier on the mw of the drug (<500Da>)

Anatomy and Physiology of skin

The skin is the easiest organ in the body to reach and serves as a barrier against environmental micro- and macromolecules due to its low permeability. The average adult's skin is about 2 m^2 in surface area and receives one-third of the blood that circulates throughout the body as shown in the figure 3. [20]

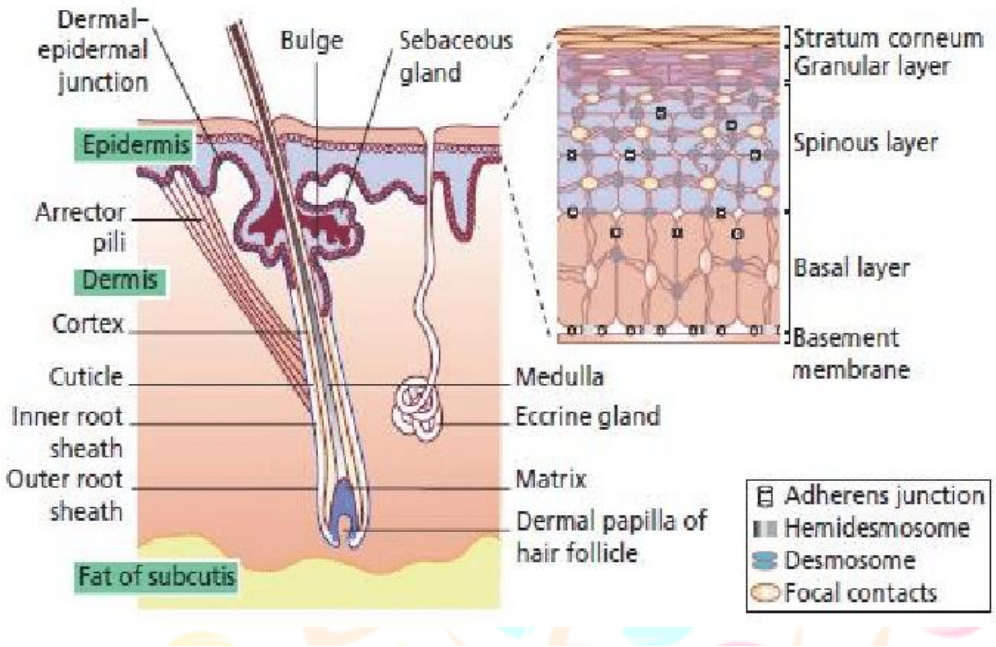

Figure 3: Structure of Skin [21]

Factors affecting transdermal permeability [22,23**]**

1. **Physiochemical properties of drug**
   - Skin physiology and pathology
   - Partition coefficient & solubility
   - Drug concentration
   - pH conditions
2. **Formulation characteristics**
   - Skin physiology and pathology
   - Release rate of drug
   - Ingredients of formulation
   - Presence of permeation enhancers
3. **Skin physiology and pathology**
   - Skin condition
   - Skin age
   - Blood flow
   - Regional skin site
   - Skin metabolism
   - Species difference

TDDS FOR THE TREATMENT OF HYPERTENSION

In the pharmaceutical sector, creating regulated medication delivery is becoming more and more important. The majority of drugs taken today—roughly 75%—are not as effective as intended when taken orally. Transdermal

drug delivery systems, or novel drug delivery systems, were developed to enhance such characteristics. Because transdermal drug delivery circumvents the drawbacks of oral hypertension medications, it is one of the innovative drug delivery technologies that is developing the fastest. [24]

DRUGS USED AS ANTIHYPERTENSIVE PATCHES

1. Propranolol

PP is a β-adrenergic blocking drug that is nonselective. By competitively inhibiting β-adrenergic receptors in the heart, bronchial smooth muscle, and vascular smooth muscle, it decreases the response to adrenergic stimulation. It has been extensively utilized to treat numerous other cardiovascular conditions in addition to hypertension. After oral treatment, PP undergoes a prolonged and extremely variable hepatic first-pass metabolism, with a reported systemic bioavailability of 23 percent. [25]

2. Carvedilol

A non-selective β-blocker is CVD. Together with the α-1 adrenergic receptors, it also inhibits β-1 and β-2 adrenergic receptors. It is the medication that is most frequently used for the long-term management of hypertension. It is clinically indicated not only for the treatment of hypertension but also for the treatment of congestive heart failure and myocardial infarction. Even though CVD is effectively absorbed, it is quickly absorbed after oral administration; in humans, these results in an oral bioavailability of approximately 20% because of a substantial amount of first-pass metabolism. CVD has a short plasma half-life of six hours, a low molecular weight of 406.5, and a favorable logP of 4.115. [26]

3. Atenolol

Atenolol has limited lipid solubility and is a relatively selective β1 blocker. Although it is entirely absorbed orally, there is little first-pass metabolism. It is among the beta blockers that is most frequently used to treat angina and hypertension. By optimizing various ratios of cellulose acetate phthalate (CAP) and polyvinyl pyrrolidone (PVP) and incorporating 15% w/w dibutyl phthalate as a plasticizer with varying concentrations of oleic acid and isopropyl myristate as a permeation enhancer by the solvent evaporation technique. [27]

4. Amlodipine

Among the class of calcium channel blockers is amlodipine (AD). Their delayed and consistent binding to target receptors results in a smooth commencement of action and 24-hour blood pressure management. These longer-acting calcium channel blockers have a lower incidence of side effects and enhance patient compliance when taken once daily. Many different types of hypertensive individuals, such as the elderly, people of color, and those with coexisting conditions that make it impossible to use other antihypertensive, can benefit from using calcium channel blockers. [28].

5. Indapamide

Long-acting hypertensive with diuretic and vasodilator properties is indapamide. The dose of 2.5 mg/day is the maximum for this anti-hypertensive action, and the diuretic impact is minimal

and typically not clinically noticeable. The diuretic impact is more pronounced at higher doses. Reductions in total peripheral and arteriolar resistance as well as vascular hyperactivity are two ways that 2.5 mg/day's extra-renal anti-hypertensive impact is established. The ability of functionally anephric patients to maintain the anti-hypertensive effect is another indication of the extra-renal mechanism of action. .[29]

6. Telmisartan

The medication telmisartan is used to treat hypertension. With a high affinity, TS binds to the angiotensin II type 1 (AT1) receptors, inhibiting the effects of angiotensin II on vascular smooth muscle and thereby lowering arterial blood pressure. It is used to treat hypertension either by itself or in conjunction with other kinds of anti-hypertensives. [30,31]

Although transdermal drug delivery faces difficulties in expressing the therapeutic action of the drug molecules due to the complexity of the skin, it offers benefits over the oral route of administration, such as avoiding first-pass metabolism, good patient compliance, and smaller plasma fluctuations levels for repeated dosing. The stratum corneum, dermis, adipose tissue, and epidermis are the layers that make up the skin. The stratum corneum (SC), the topmost layer of the epidermis with a thickness of 10–15 μm, is thought to be the primary barrier to drug flux. [32]

7. Clonidine

The US Food and Drug Administration authorized transdermal clonidine in 1984 as a transcutaneous antihypertensive medication. [33] For seven days, a clonidine transdermal patch is a transdermo-therapeutic device that delivers medications at a steady pace. A clonidine transdermal patch can achieve complete efficacy and minimize side effects since it lacks a peak or valley plasma concentration when compared to standard preparation. [34]

The transdermal treatment system for clonidine is comprised of an adhesive patch measuring 0.2 mm that contains a drug reservoir, a membrane that regulates the distribution rate, and a flexible backing (Figure). Because transdermal clonidine is released from the patch at a steady rate, it absorbs with zero-order kinetics, simulating the conditions of a continuous infusion. As long as the reservoir is at least 40% wet, the clonidine suspension within guarantees continuous delivery. It has been demonstrated that the transdermal system can hold this percentage of clonidine (at least) for up to nine days. [35]

Transdermal Patch Design

A number of variables, including skin permeability, the area and length of the application, and the skin's metabolic activity (i.e., first pass metabolism), influence how well a drug travels through the skin. Actually, each medication has distinct qualities that can influence transdermal delivery. The medication needs to be non-ionic and somewhat lipophilic in order to penetrate the epidermal barrier and achieve sufficient absorption and penetration. It is more difficult for molecules bigger than 500 Daltons to get through the stratum corneum, and the drug's therapeutic dose should preferably be less than 10 mg daily. [36]

Pharmacokinetics of Transdermal Patches

The medication is either impregnated into the patch's fabric or kept in a reservoir within the TDDS. A drug concentration gradient forms on the skin upon application of TDDS, and the drug begins to migrate down the gradient. The stratum corneum serves as the establishment of a second drug reservoir. The medication enters the systemic circulation after being absorbed into the local capillary vasculature as it penetrates deeper into the skin. [37-39]

Marketed Transdermal Patch [40]

List of marketed formulations are given in table 1.

Table 1: List of Marketed Transdermal Patch

Drug	Product name	Clinical use
Scopolamine	Transderm-Scop	Motion sickness
Nitroglycerin	Transderm-Nitro	Angina pectoris
Clonidine	Catapres-TTS	High blood pressure
Estradiol	Estraderm	Menopause
Fentanyl	Duragesic	Chronic pain
Nicotine	Nicoderm	Smoking cessation
Testosterone	Testoderm	Testosterone low level
Lidocaine/epinephrine	Iontocaine	Pain relief
Estradiol/norethidrone	Combipatch	Menopause
Lidocaine	Lidoderm	Pain relief
Norelgestromin	Ortho Evra	Contraception
Estradiol/levonorgestrel	Climara Pro	Menopause
Oxybutynin	Oxytrol	Overactive bladder
Lidocaine (ultrasound)	SonoPrep	Pain relief
Lidocaine/tetracaine	Synera	Pain relief
Fentanyl HCl	Ionsys	Postoperative pain
Methylphenidate	Daytrana	ADHD
Selegiline	Emsam	Depression
Rotigotine	Neupro	Parkinson's disease
Rivastigmine	Exelon	Dementia

Future Prospective of Transdermal Patches

TDD is a non-invasive delivery method that avoids some bioavailability issues that come with oral drug delivery because of poor absorbability and metabolism issues. It is generally thought to be easy to administer, even in more vulnerable age groups, such as pediatric and geriatric patients. Because of its large surface area and accessibility, the skin is a handy and patient-friendly target for medication delivery. Key benefits of transdermal delivery include decreased systemic medication interactions, prolonged drug release, enhanced patient compliance, minimizing first-pass metabolism, steady distribution, and typically higher therapeutic efficacy. [41,42]

Conclusion

Due to its benefits, including noninvasiveness, self-administration, and the ability to distribute drugs consistently at predetermined and controlled rates, transdermal drug delivery is currently becoming more and

more popular as a delivery method for a range of disorders. TDD technology is consequently gaining traction in the pharmaceutical sector. Nevertheless, the stratum corneum, which prevents hydrophilic molecules and macromolecules from entering intact skin, occasionally comes into contact with these delivery platforms. It has been demonstrated that the use of physical enhancement techniques can improve the delivery of medications to the systemic circulation. This makes it possible to administer a variety of drugs, particularly those that are sometimes challenging to administer by chemical penetration augmentation ways.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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