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A REVIEW ON TRANSDERMAL DRUG DELIVERY FOR CARDIOVASCULAR DISEASES

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ABSTRACT:

Cardiovascular diseases (CVDs) remain a leading cause of morbidity and mortality worldwide, necessitating innovative drug delivery systems for effective management. Transdermal drug delivery (TDD) has emerged as a promising alternative to conventional oral and parenteral routes due to its advantages, including sustained drug release, improved bioavailability, reduced systemic side effects, and enhanced patient compliance. This review explores the potential of transdermal drug delivery systems (TDDS) for cardiovascular therapeutics, focusing on their mechanisms, formulations, permeation enhancers, and recent advancements. Various transdermal formulations, such as patches, nano-based carriers, and microneedle-assisted systems, have demonstrated efficacy in delivering cardiovascular drugs like nitroglycerin, clonidine, and beta-blockers. Furthermore, challenges such as skin barrier limitations, drug physicochemical constraints, and formulation stability are discussed alongside novel strategies to overcome these barriers. The review highlights the current landscape of transdermal drug delivery for CVDs and future prospects for optimizing these systems for enhanced therapeutic outcomes.

Keywords: Transdermal drug delivery, cardiovascular diseases, transdermal patches, permeation enhancers, bioavailability, sustained release, nanocarriers, microneedles, drug delivery systems, patient compliance.

INTRODUCRION:

Transdermal Drug Delivery Systems (TDDS) are a type of controlled drug delivery that allows the administration of drugs through the skin at a controlled rate, offering advantages over oral and injectable methods. These adhesive, drug-containing devices deliver a precise amount of medication through intact skin into the bloodstream, bypassing the first-pass metabolism seen with oral drugs. This results in more stable drug concentrations and fewer adverse effects compared to the fluctuating levels seen with oral

administration.

TDDS are advantageous for chronic conditions because they provide sustained drug release, improved patient compliance, reduced side effects, and eliminate the need for frequent doses. The transdermal route is especially beneficial for patients who require constant therapeutic levels without the risks associated with oral medications, such as fluctuations in drug concentration.

Hypertension, a leading cause of cardiovascular disease-related deaths worldwide, affects over a billion people and results in millions of deaths annually. In India, it contributes to a significant percentage of stroke and heart disease fatalities. With 25% of urban and 10% of rural populations affected, cost-effective treatments are crucial for managing blood pressure. Although transdermal patches for hypertension are more expensive than oral medications, their benefits, such as reducing hospitalization and diagnostic costs, make them an appealing option. Studies show that despite the higher prescription costs, antihypertensive patches save on other healthcare expenses.

Clonidine was the first antihypertensive drug formulated into a transdermal patch, and now several other patches are available. These patches offer controlled, zero-order absorption, ease of administration, and the ability to quickly discontinue treatment if adverse effects occur, making them increasingly popular in hypertension management.

1. **Anatomy of Skin:** The structure of human skin can be categorized into four main layers:

- The epidermis.
- The viable epidermis.
- A non-viable epidermis (Stratum corneum).
- The overlying dermis. The innermost subcutaneous fat layer (Hypodermic).

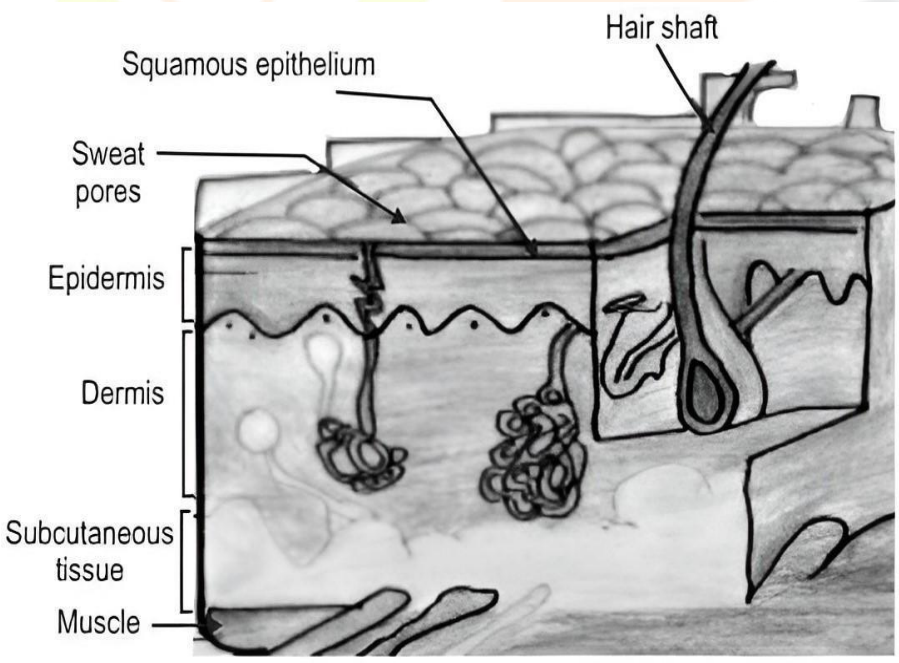


Fig. Anatomy of Skin

The Epidermis: The Epidermis is a continuasally self-renewing, stratified squamous epithelium covering the entire outer surface of the body and primarily composed of two parts: the living or viable cells of the Malpighian layer (viable epidermis) and the dead cells of the stratum corneum commonly referred to the horny layer. Viable epidermis is further classified into four distinct layers.

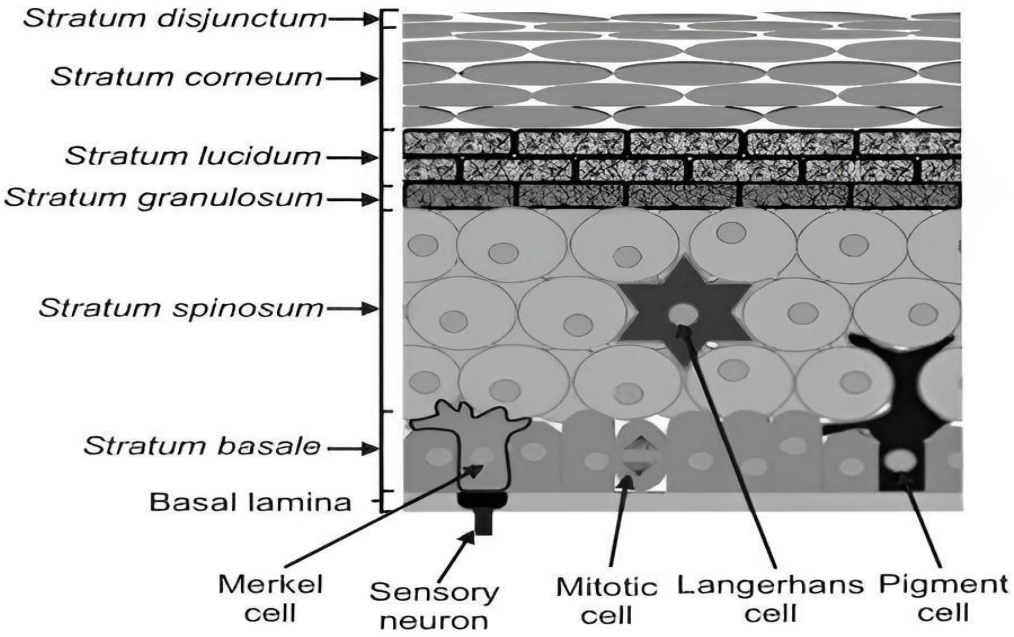


Fig. Anatomy of Epidermis

Stratum Corneum: The stratum corneum, also known as the horny layer, is the outermost layer of the skin and serves as the primary barrier, regulating the movement of substances in and out of the body. Its composition is about 75-80% proteins, 5-15% lipids, and 5-10% other materials, on a dry weight basis. While it is roughly 10 micrometers thick when dry, it swells significantly when hydrated. This layer is flexible yet largely impermeable, structured like a wall with protein "bricks" and lipid "mortar." The corneocytes, or skin cells, are linked by desmosomes and embedded in a lipid matrix that significantly influences the skin's permeability.

Viable Epidermis: Located beneath the stratum corneum, the epidermis varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. It includes layers such as the stratum lucidum, granulosum, spinosum, and basale. The basale layer constantly renews the skin through cell mitosis, compensating for the loss of dead skin cells. As these cells move upward, they undergo keratinization, forming the stratum corneum.

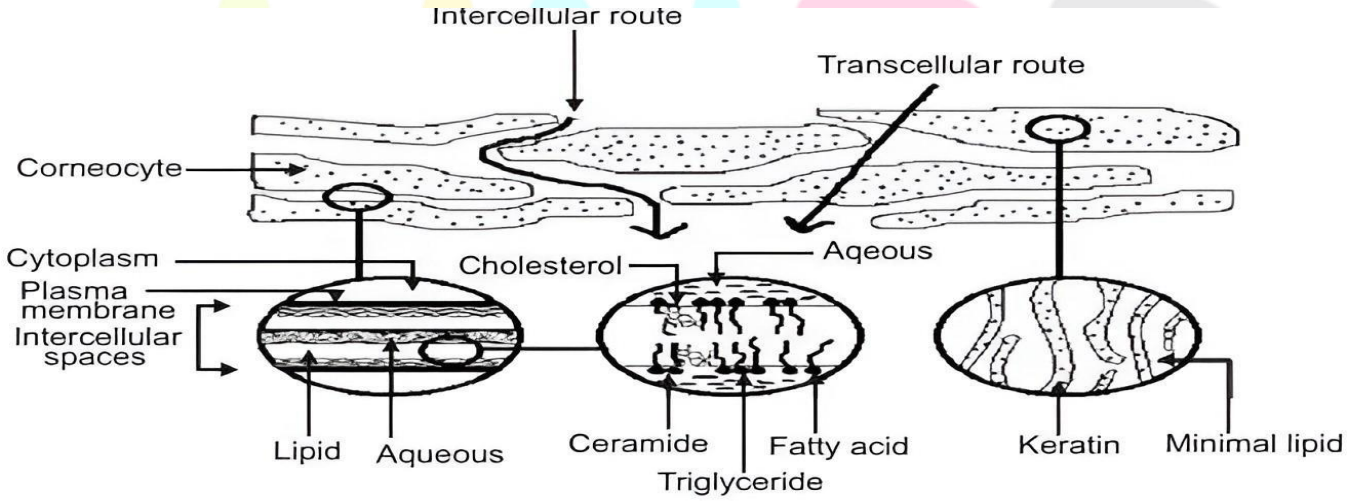


Fig. Different layers of Epidermis

Dermis: The dermis, a connective tissue layer beneath the epidermis, supports blood vessels, lymphatics, and nerves, playing a key role in temperature regulation and nutrient delivery. Its vascular system aids transdermal drug delivery by maintaining a low permeate concentration, with minimal resistance for polar drugs, though it can hinder highly lipophilic molecules.

Hypodermis: The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery drug has to penetrate through all three layers and reach in systemic circulation

Routes of Drug Penetration Through Skin: In percutaneous permeation, drug molecules must pass through the epidermis, dermis, and hypodermis to reach systemic circulation. Initially, drugs can diffuse through hair follicles or sweat ducts, while in the steady state, the primary pathway is the intact stratum corneum. Permeation occurs via trans-epidermal absorption, trans-follicular (shunt) absorption, and clearance by local circulation.

Trans epidermal Absorption: The stratum corneum provides the main barrier for absorption, with drug permeation depending on its ability to partition into this layer. Lipophilic drugs diffuse more easily due to their affinity for the skin's lipid-rich environment, while permeation through the dermis occurs via interlocking channels in the ground substance.

Trans follicular Absorption: The skin appendages are considered as shunts for by passing the stratum corneum. Follicular route is important for permeation because the opening of the follicular pore is relatively large and sebum aids in the diffusion of the penetrant.

Clearance by local circulation: The earliest point of entry of drugs into the systemic circulation is within the papillary plexus in the upper epidermis. The process is thus regarded as the end points.

BASIC COMPONENTS OF TDDS: The basic components are as like this polymer matrix, membrane, drug, permeation enhancers, pressure-sensitive adhesives, backing laminates, realease liner.

VARIOUS APPROACHES TO TRANSDERMAL DEVICES:

1. Membrane permeation controlled TDDS
2. Adhesive dispersion type TDDS
3. Polymer matrix diffusion controlled TDDS
4. Micro reservoir type TDDS.

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM:

1. Suitable for drug candidates with short half-life and low therapeutic index.
2. No first pass effect.
3. Reduction in dosing frequency.
4. Minimization of daily intake of drug.

DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM:

1. The transdermal route of administration is unsuitable for drugs that irritate or sensitize the skin.
2. Only relatively potent drugs are suitable for transdermal delivery due to the natural limits of drug entry by the skin's permeability.
3. Technical difficulties with the adhesion of the systems to different skin types and under various environmental conditions.
4. A constant concentration gradient is difficult to maintain

FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY SYSTEM:

A) Physicochemical Properties of Drug:

1. Partition coefficient
2. Molecular size
3. Solubility/Melting point
4. Ionization
5. Diffusion Coefficient

B) Physiological factor:

1. Skin age
2. Lipid film
3. Skin hydration
4. Skin temperature

EVALUATION TEST OF TRANSDERMAL PATCH:

Studies on Drug Excipient Interactions: It's crucial for the medicine and excipients to interact well for stability, requiring thorough defect detection. Interaction studies, including thermal analysis, FT-IR, UV, and chromatographic techniques, help assess their compatibility by comparing physicochemical properties.

Drug Content: A specific volume of solvent dissolves a patch section, which is then filtered. The drug composition is determined using appropriate technologies like UV, X-rays, or HPLC, with each sample value being an average of three readings.

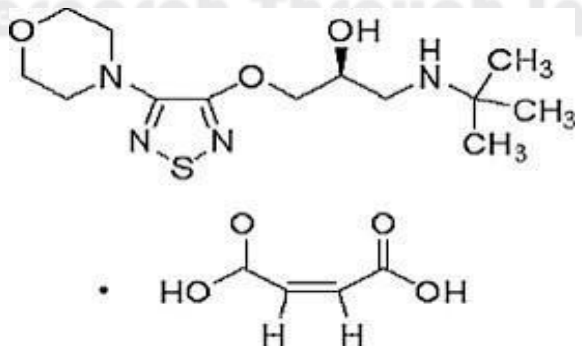
Patch Thickness: By using a digital micrometre to measure the patch's thickness at multiple locations, the average thickness and width of the drug-loaded patch are found. To confirm the thickness of the constructed patch, find the standard deviation for the same.

Moisture loss: Each of the generated films then store them in a calcium chloride-filled desiccator at 40˚C. The movies will be screened the next day. Utilizing the procedure below, reweigh and determine the percentage of moisture loss. % Moisture Loss = [Start weight–End weight] × 100.

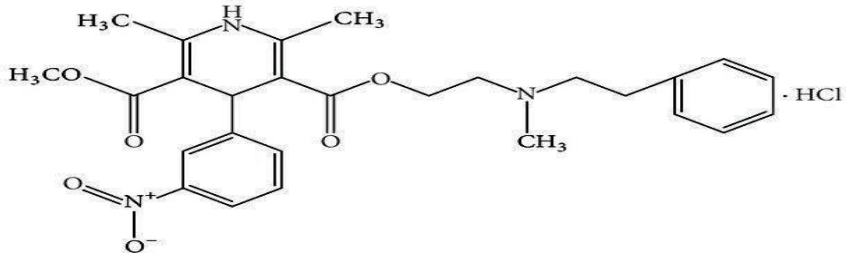
Swellability: The 3.14 cm^2 patches were soaked in 10 ml of double-distilled water, and weight changes were monitored at set intervals until no further change occurred. The swelling degree (S) was calculated using the formula S (%) = (Wt - Wo) / Wo × 100, where Wt is the weight at time t and Wo is the initial weight.

CARDIOVASCULAR DISEASES TREATING DRUGS:

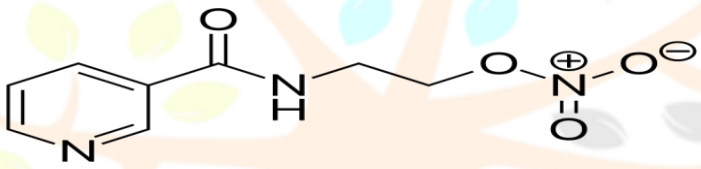
1) Timolol maleate: Timolol maleate is a potent beta-blocker used for cardiovascular conditions, with rapid absorption and a short half-life, requiring frequent dosing. Swarnlata S et al. developed two types of polymer patches—HPMC/EC and PVA—for transdermal delivery, showing the PVA (10%) patch had better permeability than the HPMC:EC system. Hanan M et al. studied matrix-controlled patches with sugar fatty acid esters, finding that laurate acid ester significantly increased drug release and permeation across rat skin. These patches showed five times greater drug flux compared to those without the ester. This approach could offer prolonged and controlled drug release over 18-24 hours.



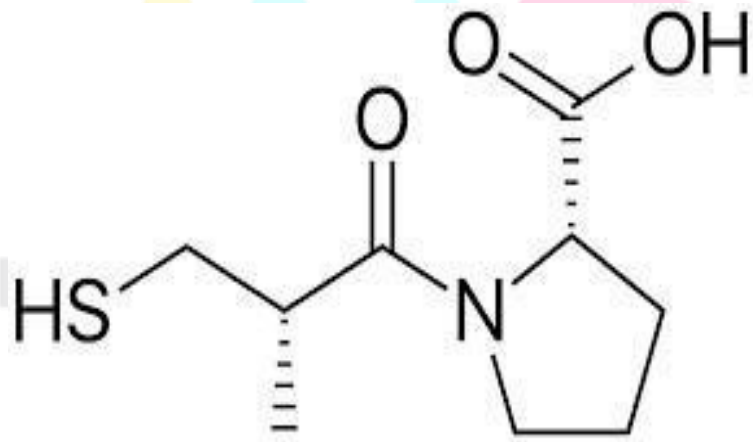
2) **Nicardipine hydrochloride:** Nicardipine hydrochloride, a calcium channel blocker used for angina and hypertension, has a rapid onset (5-10 min) and a short duration (15-30 min). Aboofazeli Reza et al. studied the effect of various solvent systems on the transdermal permeation of the drug, finding that a mixture of PG/OA/DMI showed the best flux. PG was chosen as the primary vehicle for the transdermal formulation. The study concluded that no individual solvent alone could effectively promote drug penetration through the skin.



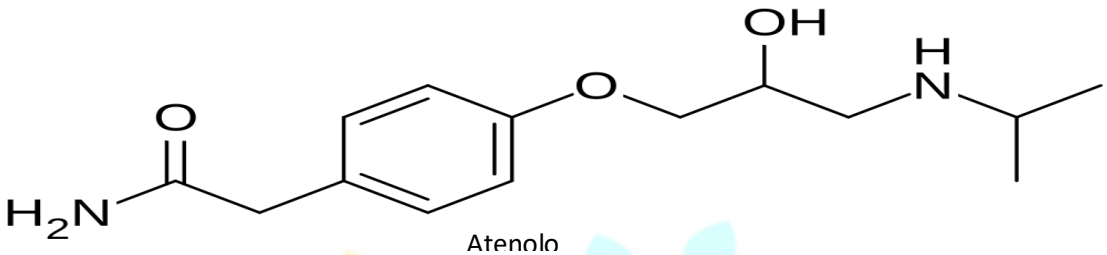
3) **Nicorandil:** Nicorandil belongs to the class of compounds known as potassium channel activators, which exert their action by arteriodilating and venodilating properties, and represents a novel type of compound for use in the treatment of angina pectoris. It has a short half-life and the usual oral dosage regimen is 5 to 40 mg taken two to four times a day. Hence, to reduce the frequency of administration and improve patient compliance, once a day TDDS of nicorandilis desirable.



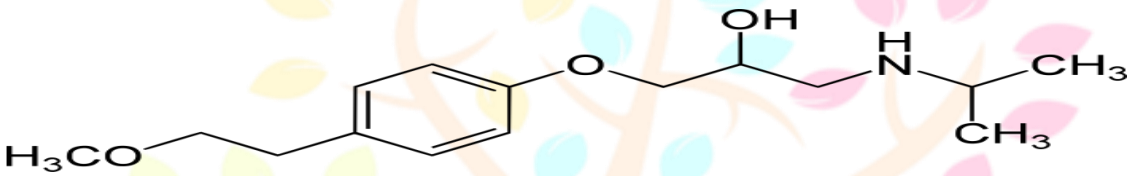
4) **Captopril:** Captopril, an effective and low-toxicity angiotensin-converting enzyme inhibitor, is commonly used for hypertension and heart failure treatment. It has a short half-life of 2 to 3 hours, but its effects last 6-12 hours, with 75% bioavailability, reduced by food. Studies show that captopril's oxidation rate is lower in dermal homogenates than in intestinal ones, leading to poor intestinal absorption of its disulfide product. Sunita Jain et al. developed a transdermal drug delivery system (TDDS) with different EC: HPMC ratios, finding better release and skin permeation at a 2:2 ratio. In vivo studies confirmed stability and non-irritant properties for 3 months.



5) **Atenolol and metoprolol tartrate**: Atenolol and metoprolol tartrate, β1 blockers with half-lives of 6-7 hours, have limited gastrointestinal absorption. Agrawal SS et al. developed matrix-type transdermal patches using polymers like polyvinylpyrrolidone, cellulose acetate phthalate, HPMC, and EC, with PG as a plasticizer and 1,8-cineole as a penetration enhancer. In vitro permeation studies showed maximum drug release after 48 hours (85% for atenolol, 44% for metoprolol), with reduced release when cadaver skin was used. Aqil M et al. formulated metoprolol tartrate matrix patches with varying Eudragit RL100 and PVA ratios. The best formulation (Eudragit:PVA 8:2) released 95.04% of the drug in 48 hours and had superior skin permeation (90.38%). This formulation was selected as the optimal one.

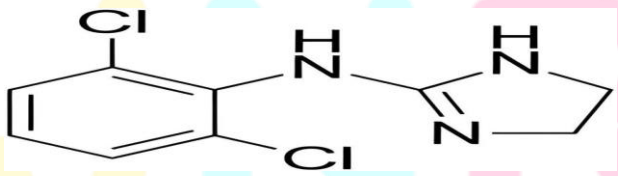


Atenolo

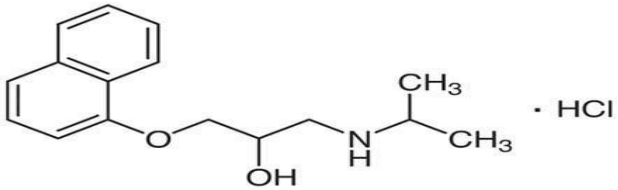


Metoprolol

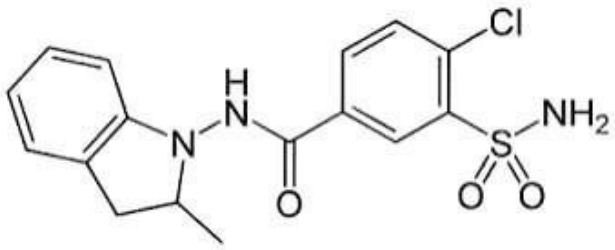
6) **Clonidine**: Clonidine is a centrally acting antihypertensive drug with a plasma half-life of 8-12 hours, peaking in 2-4 hours, and effectively reduces blood pressure in mild-to-moderate hypertension. Studies comparing transdermal and oral clonidine showed similar efficacy, but fewer side effects like drowsiness and dry mouth with the transdermal form. Mao Zhenmin et al. developed a new polyacrylate polymer for membrane-controlled drug release, synthesized via UV curing using three acrylate monomers and a photo initiator. They investigated the effects of monomer ratios, membrane thickness, and clonidine concentration on permeation rates. The membranes, characterized by FTIR, DSC, and SEM, demonstrated controlled clonidine release in transdermal delivery systems.



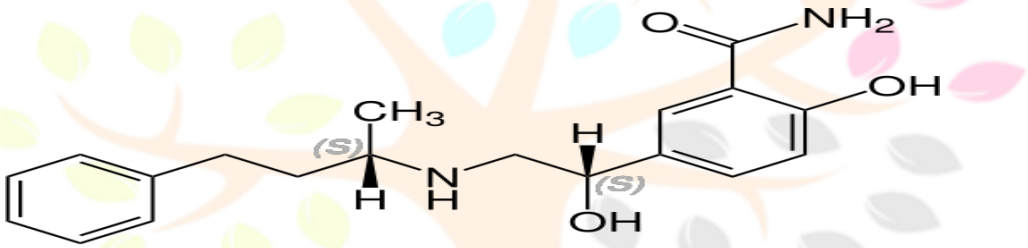
7) **Propranolol hydrochloride:** Propranolol hydrochloride is a beta blocker which is used in management of hypertension.



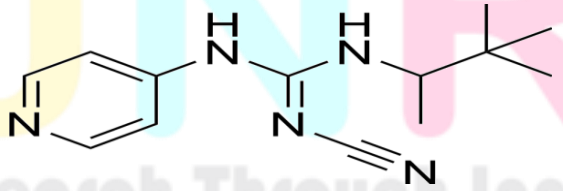
8) Indapamide: Indapamide is a long -acting hypertensive with both diuretic and vasodilative action and is defined by the 1999 WHO/ISH Hypertension Guidelines and JNC VII as a first -line drug for the treatment of hypertension. This anti -hypertensive action is maximal at a dose of 2.5 mg/day, and the diuretic effect is slight, usually without clinical manifestation. The oral delivery of this drug has certain disadvantages such as frequent administration and adverse drug reactions. Additionally, since indapamide is usually intended to be taken for a long period, patient compliance is also very important.



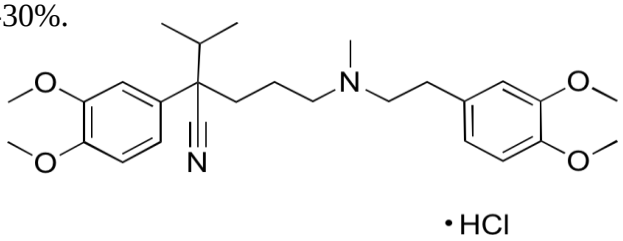
9) Labetalol: Labetalol is a non-selective α and β adrenergic receptor blocker that helps manage hypertension by competitively binding to these receptors. It undergoes significant hepatic first-pass metabolism (60-75%), reducing its oral bioavailability. Aqil M et al. developed a transdermal drug delivery system (TDDS) using solvent evaporation, with different combinations of Eudragit RL 100, Eudragit RS 100, and PVP K30. Dimethyl sulfoxide (10-12%) was used as an enhancer, and PEG 400 (2.5-7.5%) as a plasticizer. The TDDS formulations showed a maximum drug release of 90.26% in 48 hours for the Eudragit RL100: Eudragit RS100 (7.5:4.5) formulation.



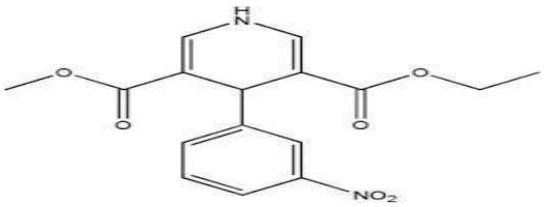
10) Pinacidil: Pinacidil, a potassium channel opener used for hypertension, has low oral bioavailability (57%) due to hepatic first-pass metabolism and a short half-life of 1.6 to 2.9 hours. Aqil Mohd et al. used the film casting technique to develop a transdermal drug delivery system (TDDS) for pinacidil monohydrate, aimed at effective hypertension management for up to 48 hours. The formulation contained Eudragit RL100, PVP K30, PEG 400 as a plasticizer, and DMSO as a penetration enhancer. In vitro studies using a rat skin model showed that the best formulation was made with a 6:4 ratio of Eudragit RL100 to PVP K30. The TDDS demonstrated effective drug release and skin permeation.



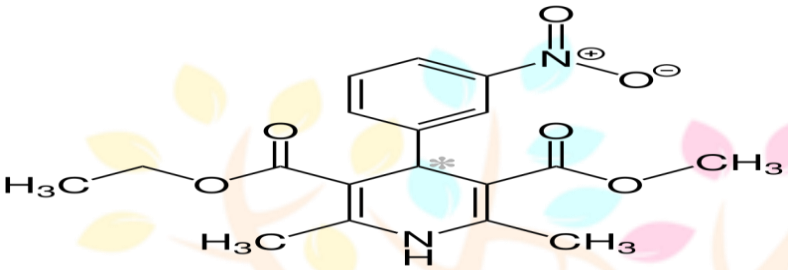
11) Verapamil hydrochloride: Verapamil hydrochloride is a calcium ion influx inhibitor. It is widely used in the treatment of angina, hypertension, and supraventricular tachyarrhythmia. The plasma half-life of verapamil hydrochloride is 2-7 h, which necessitates multiple dosing. It is approximately 90% absorbed from the gastrointestinal tract but is subject to considerable first pass metabolism and its bioavailability is around 20-30%.



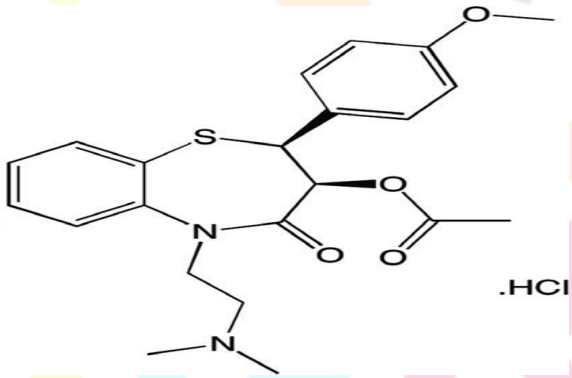
12) Nitrendipine: Nitredipine a potent antihypertensive molecule which is a calcium entry blocker and potent peripheral vasodilator, reported to be well absorbed following oral administration, but undergoes extensive first pass metabolism and oral bioavailabilty in the range from 10% to 20%.



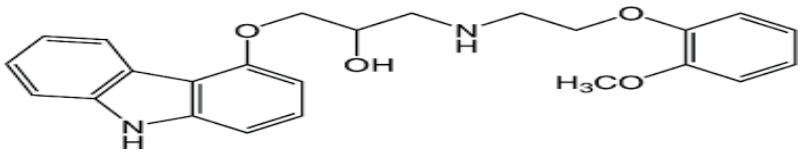
13) Nifedipine: Nifedipine is a potent drug which is widely used for the treatment of hypertension. Due to extensive first pass metabolism its bioavailability is low.



14) Diltiazem hydrochloride: Diltiazem hydrochloride is a calcium channel blocker used in the treatment of arrhythmia, angina pectoris and hypertension. The literature survey reveals that it undergoes variable and extensive first pass metabolism before entering into systemic circulation and varies with species.



15)Carvedilol; Carvedilol, a non-selective β-adrenergic blocker used in hypertension, it is rapidly and extensively absorbed from the gastrointestinal tract. Following oral administration, the apparent mean terminal elimination half-life of carvedilol generally ranges from 6 to 10 h, the absolute bioavailability is approximately 25% to 35% due to a significant degree of first pass metabolism.



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