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Review Article

Transdermal Patches For The Treatment Of Hypertension

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ABSTRACT

One of the crucial diseases that kills people worldwide is hypertension. As a chronic illness, therapy must be given over an extended period of time. Antihypertension medications are a great fit for transdermal drug delivery systems due to their drawbacks, which include larger frequency of administration, significant first-pass metabolism, and variable bioavailability. The present article aims to study transdermal antihypertensive patches with the goal of increasing bioavailability and patient compliance. Among the several medications are indapamide, furosemide, eplerenone, captopril, enalapril maleate, valsartan, Olmesartan, telmisartan, atenolol, propranolol, carvedilol, diltiazem hydrochloride, azelnidipine, verapamil.

INTRODUCTION

Transdermal treatment has taken over oral therapy as the most successful field for new drug development delivery. Transdermal drug delivery has grown in significance in recent years due to its potential benefits, which include preventing hepatic first-pass metabolism, sustaining blood levels for an extended length of time, reducing the need for frequent doses, improving doses, improving bioavailability, reducing gastrointestinal irritation brought on by local contact with the stomach mucosa, and enhancing patient compliance[1]. Transdermal therapy systems are defined as distinct, self-sufficient dosage forms that enable controlled delivery of the drugs to the systemic circulation by means of surface when placed over intact skin. A controlled drug delivery system is made up of a dosage form that may be administered systemically or to a specific target organ, continuously delivering several medications in a predetermined sequence for a certain period of time. Transdermal drug administration provides a simple, painless, and potentially effective way to provide different medications at regular intervals. A wide variety of pharmaceuticals are accessible with better drug

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absorption and fewer side effects and issues. affordable and easy to use transdermal drug administration provides a simple, painless, and potentially effective way to provide different medications at regular intervals. A wide variety of pharmaceuticals are accessible with better drug absorption and fewer side effects and issues. affordable and easy to use[2]. TDDS has many advantages over traditional antihypertensive drug administration. For example: non-invasive, easy to use, avoid withdrawal (increased side effects), first-pass metabolism, best compliance, no need for hospitalization, avoid gastric irritation, reduce the frequency of administration. Therefore, TDDS was chosen to treat hypertension[3]. A persistent rise in blood pressure of 140/90 mm Hg is considered hypertension. This threshold is used to identify a subset of patients whose risk of cardiovascular disease associated with hypertension is significant enough to require medical intervention. In India, hypertension is the direct cause of 24 % of deaths from coronary heart disease and 57% of fatalities from stroke. Hospitalization and diagnostic expenses were decreased when antihypertensive patches were used in accordance with prescribed dose forms. These benefits made it easier for the intended customer to accept antihypertensive patches as a more expensive treatment option than traditional medication. They are appealing in antihypertensive therapy because of the potential for regulated zero order absorption, their ease of administration, and their option for simple dosage withdrawal in the event of adverse symptoms. Antihypertensive patches with the recommended dose forms decreased the incidence of hospitalization and diagnostic expenses despite the high cost of transdermal patches for the treatment of hypertension. These benefits helped the target market accept antihypertensive patches as a more expensive treatment option than traditional medication. This acceptance factor has inspired researchers and academics to embark on a number of difficult initiatives in this specific field. They are also preferred in hypertension therapy because to the potential for regulated zero order absorption, an uncomplicated method of administration and the opportunity of a simple dosage withdrawal in the event of adverse symptoms[4,5].

Types of transdermal patches

- Single layer drug in matrix
- Multi-layer drug in matrix
- Reservoir types patches
- Matrix type patches
- Vapour type patches6.

Advantages

- Prevent the variations in metabolism and absorption brought on by taking drugs orally.
- Eliminate the risk and trouble associated with intravenous treatment.
- Permits the continuous administration of drugs with a biological half-life of zero and the use of drugs
- Science it avoids the hepatic first -pass elimination process, it increases the bioavailability and effectiveness of medicines
- Establish a simple therapy plan that encourages patient compliance and can be quickly discontinued by removing the patch
- Transdermal medicine provides a continuous, long-lasting infusion of a medicament. It is also possible to prevent side effects or treatment failures that are commonly linked to sporadic dosage.
- It’s feasible to self -medicate.

Disadvantage

- The transdermal route of administration is not recommended to be used for drugs that irritate or sensitize skin.

- Due to the skin's permeability, which naturally limits drug entry, only strong medications are appropriate candidates for transdermal delivery.
- The main technical difficulties include the systems' adhesion to different skin types, varying environmental circumstances, and the developing factors that regulate the rate.
- It can be difficult to load drugs into a transdermal device that require high blood levels to be effective due to the substantial physical volume of material required7,8.

BASIC COMPONENTS OF TRANSDERMAL DELIVERY SYSTEM

Transdermal drug delivery devices facilitate the transfer of medication from the skin's surface through its different layers and into the bloodstream. The fundamental elements of a transdermal dosing system regulate the speed at which medication is delivered to the skin. The parts of the system consist of

1.The drug substance
2.Polymer matrix
3.Permeation enhancer
4.Adhesives
5.Backing membrane

1.The drug substance

The effective creation of a transdermal product depends on the wise selection of medication. Important pharmacological characteristics that influence how quickly the substance diffuses through the skin and from the device include its molecular weight, solubility, physical characteristics, and melting point. The drug's structure has an impact on skin penetration as well. It is crucial that the medicine diffuses in sufficient amounts to have a positive therapeutic impact. Prior to selecting a medication, other factors such skin irritation and therapeutic need should be taken into account. The drug should have molecular weight less than 1000 Daltons. The drug should have affinity for both lipophilic and hydrophilic phases.

The drug should have a low melting point.

The half-life of drug should be short.

The drug must not induce a cutaneous or allergic response.

The drugs, which degrade in gastrointestinal tract or inactivated by hepatic first pass effect are suitable candidates for transdermal drug delivery system

2. Polymer matrix

Polymers are important components of transdermal medication delivery systems. Only through the rate-controlling polymeric membrane are the drugs molecules permitted to release. Polymers are also utilized in matrix devices, where a drug is placed in a polymer matrix to regulate how long the drug releases. The polymer's molecular weight, physical properties, and chemical functionality must allow the medicinal ingredients to diffuse at a desired rate. The polymer should be an inert drug carrier, non-reactive, or chemically non-toxic. To create the intended result, the polymer needs to be simple to make and shape. It should enable the addition of a significant quantity of active agent.The polymer regulates the medication's release from the system. The polymer that is utilized has to be stable, non-reactive with the medication, and allow the medication to diffuse and release through it. Some of the useful polymers are as follows

Natural polymers Cellulose derivatives: Zein, gelatine, gums and their derivatives etc.

Synthetic elastomers: Polybutadiene, polysiloxane, acrylonitrile, butyl rubber, neoprene etc.

Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polyacrylate, polymethylmethacrylate etc.

3. Penetration enhancers

Penetration enhancers are chemicals that change the stratum corneum's barrier characteristics in a reversible manner. They facilitate the drug's easier penetration of living tissues, which helps with systemic administration. They can be included in transdermal formulations to gain systemic distribution, to distribute medications to the skin's 13 deeper layers, or to create a specific therapeutic effect while using a lower concentration of the active ingredients.

- The substance must be non-toxic, non-irritating, and have a low index of sensitization.
- It must also be pharmacologically inactive.
- The activity aimed at improving penetration need to be executed promptly and possess an appropriate duration of action.
- The enhancer should to be compatible both physically and chemically with a variety of medications and pharmacological adjuncts.
- The substance needs to evenly distribute throughout the skin. It ought to be tasteless, colourless, and odourless.

4. Adhesives

All transdermal devices must be adhered to the skin with a pressure-sensitive adhesive. An adhesive system needs to meet these specifications.

- It should stick to the skin tenaciously; it shouldn't irritate, sensitize, or alter the natural flora of the skin while in touch with it.
- It must be effortlessly removed without creating an unusable residue.
- It must be compatible both chemically and physically with the medicine, enhancers, and excipients.
- It shouldn't have an impact on the medication's penetration.
- The types of adhesives commonly used in transdermal drug delivery system are:

  Rubber based adhesives: Natural gum (Karaya gum), olylisoprene, polybutene, and polyisobutylene.

  Polyacrylic based: Ethyl acrylate, 2-ethylhexylacrylate, iso-octyl acrylate.

  Polysiloxane based: Polymethyl siloxane, polyciliate resins, sufloxane blends.

5. Backing membrane

During the application phase, it offers protection from outside influences. The backing layer is often impervious to water vapor as it needs to be impermeable to the medications and enhancers. The most often utilized backing materials are Alupoly polyester, metalized polyester laminated with polyethylene, and polyester9.

HYPERTENSION

The most commonly seen cardiovascular disease in the world is hypertension. Further, since long-term hypertension care necessitates frequent administration of drugs, patients may not comply well with standard dose forms. Since the beginning, transdermal drug administration has provided several benefits, such as non-invasiveness, extended therapeutic effect, less adverse effects, enhanced bioavailability, increased patient compliance, and simple drug therapy termination. The etiology of this progressive cardiovascular disease is diverse and interconnected. Functional and structural cardiac and vascular problems that harm the heart, kidneys, brain, vasculature, and other organs and cause early illness and death are closely linked to progression. Antihypertensive medicines come in several categories and reduce blood pressure by diverse methods. The most often used and significant antihypertensive medications include ACE inhibitors, β-blockers, thiazide diuretics, calcium channel blockers, and angiotensin II receptor antagonists[10].

Research on the administration of hypertensive drugs via the surface of the skin has consistently proven difficult since due to the barrier properties that the stratum corneum, the skin's outermost layer, exhibits. With considerable therapeutic advantages over alternative dosage forms, the transdermal drug delivery system has evolved into a proven technology throughout the past 20 years. Transdermal treatment can maintain steady state blood concentration because it provides a patient with a regulated and expected rate of drug release. Its clear benefits, such as patient convenience and painlessness in self-administration and the avoidance of hepatic first-pass metabolism and the GI tract for medications with low bioavailability as compared to alternative delivery methods, make it a preferred method of drug delivery. The demand for TDD is expected to increase tremendously in the future. Although it has significantly improved medical practice, transdermal drug delivery still hasn't reached its full potential as a substitute for oral medication administration and hypodermic injections[11]. Transdermal drug administration going to be the most effective choice for hypertensive drugs.

ANTIHYPERTENSIVE DRUGS

INDAPAMIDE

As a Thiazide type diuretic indapamide increases the volume of urine excreted causing the body to lose salt and water one medication that helps manages hypertensin is indapamide it also lessens the edema and retention of water on by a number of illnesses including reneal, hepatic, cardiac, problem. One prescription medication used to treat high blood pressure and fluid retention is indapamide. Long-acting hypertensive indapamide has vasodilator and diuretic properties. indapamide is a novel antihypertensive diuretic drug that is prescribed to treat edema and hypertension. The vascular reactivity of indapamide to calcium and other agonists is altered, indicating the potential for a direct vascular action. Doses of 2.5 to 5 mg of the medication should be taken once day. It is quickly and entirely absorbed from the digestive system, reaching maximum blood levels in about 2.3 hours[12]. G S. Sanap et al., stated that the solvent casting process was used to create the indapamide transdermal medication delivery devices. Glycerine and dibutyl phthalate were used as plasticizers to create monolithic systems employing hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) polymers. Regarding the assessment using scanning electron microscopy (SEM) and physicochemical analysis, every patch was identical. The results of the in vitro drug release assays showed that films containing HPMC had superior release compared to films containing EC and no permeation enhancer. Using a drug polymer ratio of 1:4, eight monolithic systems were created, and various vegetable oils were added in varying amounts to improve penetration. The medication was released by the ready systems in the subsequent order: A > B > C > D > E > F7 > F5 > F8 > F6 > F1 > F2. For each formulation, the different permeation parameters such as flux, permeability coefficient, enhancement ratio, and diffusion rate constants were ascertained. With an HPMC monolithic system containing 30% w/w olive oil, the highest flux of 9.08 × 102 mg/cm2 h was recorded. The following oil combinations showed much better flux: olive oil, sunflower oil, coconut oil, cottonseed oil, linseed oil, and castor oil. When 30% w/w olive oil was applied immediately to the skin before the trials, further improvement in flux was seen. The results of the in vitro release investigations showed that the release followed zero-order kinetics and might last for up to 24 hours. Regarding their physical characteristics and drug content, all the films were determined to be stable at 37°C and 45°C[13].

FUROSEMIDE

Furosemide is a loop diuretic that is used to treat diseases of the liver, kidney disorders such nephrotic syndrome, and congestive heart failure in patients who have fluid retention (edema). In addition, furosemide is used to treat hypertension, or elevated blood pressure. Furosemide lowers high blood pressure and helps minimize edema and symptoms of fluid retention by increasing the volume of urine the body produces. Based on the clinical pharmacokinetics of furosemide, it was shown that 50% of the drug's bioavailability and 65% of the drug's excretion are through the urine, with an approximate half-life of one hour. With ongoing infusion of the medication, furosemide's natriuretic and diuretic effects can be more potent. Controlled release mechanisms, such as transdermal drug delivery systems, are non-invasive methods that minimize medication-related adverse effects while enabling a continuous drug infusion[14]. Indira Muzaib Yallamali et al., The study investigates the impact of penetration enhancers on the release kinetics of a novel drug in the adhesive transdermal system of furosemide. The adhesive systems were evaluated for their pharmacotechnical properties and in vitro permeation through the excised rat epidermis. The optimized drug was tested in vivo using New Zealand male rabbits and tested for tack properties and skin irritation. The results showed that DURO-TAK 2510 had the best permeation profile, while a combination of penetration enhancers was more efficient. The maximum permeation of the drug was observed with a flux of 9.2052±0.33 μg/cm2/h in the case of F9. The controlled release of the drug for a prolonged duration with an extended AUC and MRT decreased Cmax in adhesive systems compared to the oral route, suggesting a promising pharmacological effect in the DIA system. The findings confirm that drugs in adhesive systems can enhance bioavailability and patient compliance with a combination of penetration enhancers[15].

EPLERENONE

Eplerenone is used to treat edema and hypertension, or elevated blood pressure. It cures edema, or fluid excess, linked to lung, liver, kidney, or cardiac conditions. Eplerenone is a diuretic that spares potassium. By eliminating excess water and electrolytes from the body without depleting potassium, it reduces blood pressure and edema. Similar to spironolactone, eplerenone is an antagonist of the aldosterone receptor that has been shown to promote increases in serum and plasma renin levels while blocking the negative regulatory effect of aldosterone on renin emission. The effects of eplerenone are greater than those of the subsequent increased plasma renin action and aldosterone circulating levels[16].

Ramesh Shiding et al., The study aimed to optimize, formulate, and characterize transdermal patches of eplerenone for efficient transdermal drug delivery. The log P estimation of eplerenone was 1.34, indicating higher permeation through the skin. A FTIIR study was conducted to compare eplerenone and FTIR spectra of pure drug and polymer. The calibration curve of eplerenone in Phosphate buffer pH 6.8 was analysed. The selected range of eplerenone was linear, with a regression coefficient (R2) at 245 nm of 0.994. Drug content outcomes were uniform in all clusters, with batches arranged with ERS 100 showing great mechanical properties compared to different polymers. The flatness of 4 cm2 patches ranged from 348±0.087 mg to 387±0.527 mg. Skin irritation was produced, with minimal erythema and obvious edema after 12 days. The in vivo skin irritation study recommended that advanced batch S9 did not show significant disturbance on rodent skin for up to 14 days and was safely used for 24 hours. The optimized batch S9 was continuously released through Wistar rodent skin for up to 16 hours[17].

CAPTOPRIL

Hypertension and congestive heart failure are conditions that individuals with captopril alone or in conjunction with other drugs are treated for. Additionally, individuals with left ventricular hypertrophy enlargement of the left side of the heart who take captopril after a heart attack are more likely to survive and have a lower chance of developing heart failure. In individuals with type 1 diabetes, captopril is also used to treat retinopathy, an eye condition, and kidney illness (nephropathy). Oral bioavailability of captopril is 70%; however, oral absorption is reduced by 25–40% when food is present. Captopril has a brief half-life of elimination in plasma and is easily soluble in water[18]. The class of drugs known as angiotensin-converting enzyme (ACE) inhibitors includes captopril. Blood flows more easily and the heart can pump blood more effectively because it reduces some of the substances that restrict blood vessels. Treatments for hypertension, congestive heart failure, and myocardial infarction include the angiotensin converting enzyme inhibitor (ACE) captopril. It requires a large oral dosage because to its very short elimination half-life, which ranges from 1.6 to 1.9 hours. Five A significant issue that has to be resolved for the therapeutic application of TDDS is the skin's impermeability. The most promising method for overcoming the challenges of getting the medication to pass through the resistant stratum corneum layers has been demonstrated to be chemical permeation enhancers[19]. M S Sonali Angadrao Gore et al., The study aimed to develop a transdermal patch of Captopril using various penetration enhancers. The patch was prepared using HPMC E15 as a film forming agent and Eudragit RS100 as a rate controlling polymer propylene glycol as a plasticizer. DMSO, DMF, and Oleic acid were used as penetration enhancers. The patch was prepared using solvent casting method and stability studies were performed according to the ICH guideline. The best batch was selected for an in vivo pharmacokinetic study in an Albino rat model. The drug and excipients were characterized using FT-IR. The films underwent physicochemical characterization, and the optimized batch passed accelerated stability studies without significant changes in dissolution profile. The formulation was characterized with FTIR studies and found no chemical interactions between the drug and polymer. The transdermal patch of Captopril could be a better alternative for tablets and capsules, achieving rapid oral bioavailability in treating allergic rhinitis[20].

ENALAPRIL MALEATE

Enalapril is utilized for the treatment of elevated blood pressure, or excessive blood pressure, as well as heart failure and the prevention of heart attacks and strokes. An ACE (angiotensin converting enzyme) inhibitor) is enalapril. In order to improve blood flow and the heart's ability to pump blood more effectively, it works by relaxing blood vessels and lowering cardiac strain. Enalapril maleate, a prodrug that is part of the ACE inhibitor family, is digested to release the active inhibitor of the covering enzyme, enalaprilat, when taken orally. As the drug, enalapril maleate is 40% accessible and 60% absorbed. Both symptomatic congestive heart failure and hypertension can be treated with it. Controlled release mechanisms, such transdermal drug delivery systems, are non-invasive techniques that reduce side effects associated with treatment while allowing a continuous drug release[21]. Keerthana devi N S et al., stated that Transdermal drug delivery has been a significant advancement in medical practice, but its full potential as an alternative to oral delivery remains untapped. A study involving polymers like HPMC K100 and EC was conducted to create transdermal patches for Enalapril maleate, which was found to be effective in controlling hypertension, angina pectoris, and congestive heart failure. The study evaluated various physiochemical properties,

including film thickness, weight variation, folding endurance, moisture content, and drug content22.

VALSARTAN

Valsartan is utilized for the management of hypertension, or high blood pressure, as well as to prevent strokes and heart attacks. One angiotensin receptor blocker (ARB) is valsartan. By obstructing the chemical that often causes blood vessels to constrict, it relaxes the blood vessel. This reduces blood pressure, which facilitates better blood flow to various organs and enhances the heart's pumping action. The physiological effects of valsartan include decreased blood pressure, decreased aldosterone levels, decreased cardiac activity, and enhanced salt excretion. The renin-angiotensin aldosterone system (RAAS), which is crucial for hemostasias and the control of renal, vascular, and cardiac processes, is similarly impacted by valsartan. When AT1 receptors are blocked pharmacologically, RAAS's negative regulatory feedback is inhibited. Pooja Sahu et al., reviewed that considering the perspective of developing processes and scale-up, the preparation of matrix type transdermal patch seems to be the most efficient method. An effort was attempted to formulate valsartan patch utilizing HPMC, ethylene glycol 600, glycerol, methanol, ethylene cellulose, eudragit RLPO, and eudragit RLSO. description of transdermal patches made from prepared matrix. to create a patch form for the medication in order to lower the frequency of dosage and extend the drug's plasma concentration. Especially in long-term therapy, the development of a Valsartan patch formulation would be a major benefit for patient compliance and minimize medication side effects due to a decrease in drug blood concentration fluctuations[23].

OLMESARTAN

After entering the digestive system, the prodrug olmesartan medoxomil hydrolysed to become olmesartan. Angiotensin receptor blockers are a class of drugs that includes olmesartan medoxomil. In addition to helping to prevent heart attacks, it helps manage hypertension. By specifically inhibiting angiotensin II's binding to the AT1 receptors in vascular smooth muscle, olmesartan blocks the vasoconstrictor activity of angiotensin II. The oral bioavailability of olmesartan medoxomil is 100%; however, due to substantial first pass metabolism, its bioavailability is lowered to 26%. Due to its biological and physicochemical characteristics, including its high lipid solubility, potency, extensive first pass metabolism, and bioavailability, olmesartan medoxomil is a great option for transdermal patch formulation. In order to enhance bioavailability and overcome substantial first pass metabolism Olmesartan medoxomil is designed as transdermal patches, which allows for regulated medication delivery into the bloodstream. Naga Anusha Nadimpalli et al., The primary objective of this work was to synthesize matrix-type Olmesartan medoxomil transdermal patches using several polymer ratios (HPMC 15 cps, HPMC 5 cps, and Eudragit S 100) using the solvent evaporation technique. Solvents like methanol and chloroform are utilized, along with plasticizers such glycerine, propylene glycol, and PEG 200. FT-IR studies indicate that excipients and pure pharmaceuticals work well together. The thickness, weight fluctuation, folding durability, moisture content, drug content, surface pH, and in vitro diffusion investigations of the produced patches are evaluated. F6 had the best in vitro drug diffusion and characteristic features of all the formulations[24].

TELMISARTAN

Telmisartan is employed for the treatment of hypertension, or high blood pressure, as well as for preventing heart attacks and strokes and to cure fever. Angiotensin II receptor antagonist (ARB) telmisartan is used to treat hypertension. Generally speaking, angiotensin II receptor blockers (ARBs),

like telmisartan, bind highly affinity to the angiotensin II type 1 (AT1) receptors. This suppression of angiotensin II's effect on vascular smooth muscle results in a drop in arterial blood pressure. According to recent research, telmisartan may also exhibit PPAR-gamma agonistic qualities, which may have positive metabolic consequences. Telmisartan binds reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland, preventing angiotensin II from attaching to the angiotensin II AT1-receptor. Reduced systemic vascular resistance is the outcome of blocking the actions of angiotensin II, a vasoconstrictor that also promotes the production and release of aldosterone. The angiotensin converting enzyme, other hormone receptors, and ion channels are not inhibited by telmisartan.5. Research indicates that telmisartan functions as a partial agonist of PPARγ, a known target for medications that treat diabetes. This implies that telmisartan can regulate insulin resistance, enhance lipid and carbohydrate metabolism, and avoid the negative effects linked to complete PPARγ activators. The optimal delivery method for telmisartan is transdermal[25]. Pavan Kumar Yadav et al., investigated a controlled transdermal drug delivery system containing the medication telmisartan with varying ratios of hydrophilic (HPMC) and lipophilic (EC, Eudragit RS 100) polymeric systems by solvent casting technique on aluminium foil. The polymeric weight consisted of 20% w/v, 30% w/v dimethyl sulfoxide, which was used as a permeation enhancer for transdermal drug release, and 30% w/v dibutyl phthalate, which was incorporated as a plasticizer. Nine formulations in all were created utilizing the same medication but distinct polymeric ratios. The physicochemical evaluation of every transdermal patch included measurements of thickness, weight fluctuation, moisture uptake, moisture loss, folding endurance, flatness, drug content, and drug release percentage. Every transdermal patch that has been created shows high physical stability. the diffusion cell-based in vitro permeation investigation. Diffusion cell research on in vitro penetration. Formulation F8 having HPMC: EC: Eudragit RS 100 in a 5:0:1 ratio showed the greatest invitro% drug release for up to 48 hours[26].

ATENOLOL

Synthetic beta-1 selective blocker atenolol is used to treat hypertension, chronic angina, and lower mortality in individuals with hemodynamic stability who have a suspected or known myocardial infarction. In the heart, atenolol inhibits beta-1 receptors. Normally, these receptors bind to catecholamine hormones. Catecholamines induce your heart to beat more quickly and forcefully when they attach to these receptors. Your heart will beat more slowly if these receptors are blocked. These effects may lessen your chance of having a heart attack or stroke, as well as assist lessen chest discomfort and blood pressure. Heart cells have beta receptors on them. Blood pressure and heart rate increase when beta receptors are triggered by adrenaline. Beta blockers stop the effects of adrenaline on your heart and blood vessels' beta receptors. Blood vessels relax as a result of this. Beta blockers assist in lowering blood pressure and reducing chest discomfort by relaxing the arteries. They also aid in lowering the oxygen requirement of the heart. Chest discomfort and blood pressure are not permanently altered by beta blockers. Rather, they aid in the treatment of the symptoms. TDDS improvement in patient adherence and decrease in dosage frequency[27]. Pankaj Singh Negi et al., The goal of the current study was to create atenolol transdermal patches using a solvent casting process in various ratios of HPMC (hydroxyl propyl methyl cellulose), EC (ethyl cellulose), and PVP (polyvinyl pyrrolidine). Span 80 is utilized as a permeation enhancer and 3% propylene glycol as a plasticizer. FTIR spectroscopy was used to

analyse the drug's identity as well as potential interactions with other polymers. The physicochemical properties of the transdermal patches (thickness, folding durability, etc.) were assessed, and Franz diffusion cell in vitro permeation tests were carried out. To ascertain the transdermal patch formulations' release mechanism, a range of standard mathematical models, including zero order, first order, Higuchi, and Korsmeyer-Peppa's, were applied to the data gathered from in-vitro permeation investigations. The correlation coefficient (R2) and release constant (k) values found by curve fitting the release data were used to select an appropriate release model. It was discovered that the first order kinetics is followed by every formulation. It was discovered that the regression coefficients (R2) for all of the Higuchi plot formulations, F1 through F6, were almost linear[28].

PROPRANOLOL

The beta-adrenergic receptor antagonists' prototype, propranolol, is an activity. Racemic in nature, propranolol's l-isomer blocks adrenergic receptors, making it a competitive, non-selective beta-blocker without intrinsic sympathomimetic action. It is comparable to nadolol. As a beta (1)-adrenergic receptor in the heart, propranolol inhibits sympathetic activation by competing with sympathomimetic neurotransmitters such catechol amines for binding. The systolic and diastolic blood pressure, reflex orthostatic hypotension, cardiac output, and resting heart rate all decrease as a result. β-adrenergic receptor antagonists that are nonselective include propranolol.2 By inhibiting these receptors, vasoconstriction, endothelial cell death, downregulation of the renin-angiotensin-aldosterone pathway, and suppression of angiogenic factors such as vascular endothelial growth factor (VEGF) and basic growth factor of fibroblasts (bFGF) are all brought on. Propranolol benefits of TDDS include reduced dosing frequency and improved compliance among patients[29]. V.N.L Sirisha et al., The goal of this study was to create a matrix-type transdermal therapeutic system that would incorporate the medication propranolol hydrochloride in various ratios of hydrophobic (eudragit's) polymeric systems using the solvent evaporation technique. A plasticizer, 30% w/w di-butyl phthalate, was added to the polymer weight. The drug's physicochemical compatibility with the polymers examined using infrared spectroscopy indicated that there was no incompatibility. The transdermal films that were prepared were examined physically in terms of their thickness, weight fluctuation, drug content, flatness, and moisture resistance during folding. Excellent physical stability was shown by all developed formulations. Franz diffusion cells were used for formulation in-vitro permeation experiments. It was demonstrated that drug release is zero order, with diffusion from the polymer serving as the release mechanism[30].

CARVEDILOL

Carvedilol is a beta-blocker. Regulating blood flow through arteries and veins, or circulation, is impacted by beta-blockers. Both heart failure and hypertension (high blood pressure) are treated with carvedilol. It's also employed in the event of a heart attack that impairs cardiac pumping function. Alpha-1 and beta-1 receptors in your blood vessels and heart are both blocked by carvedilol. Normally, these receptors bind to catecholamine hormones. Catecholamines constrict blood vessels and cause your heart to beat more quickly and forcefully when they attach to these receptors. Your blood arteries relax and your heart beats more slowly when these receptors are blocked. These effects can lower blood pressure, improve heart function, and perhaps minimize your risk of stroke and heart attack. For transdermal patch formulation, carvedilol is an ideal choice. Transdermal patches are a means of delivering carvedilol into the circulation in a controlled

manner, improving its bioavailability and overcoming significant first pass metabolism[31].

Vilegave K et al., The goal of this study was to assess transdermal formulations containing carvedilol that were plasticized using triethyl citrate and dibutyl phthalate using solvent evaporation techniques. The formulations included varying ratios of hydrophilic (Eudragit RL100, HPMC) and hydrophobic (Eudragit RS100, ethyl cellulose) polymeric combinations. The physicochemical properties of the produced patches, including their thickness, weight and drug content homogeneity, folding durability, water vapour transfer, and tensile strength, were examined. Research on the in vitro release of patches loaded with carvedilol in 30% v/v Methanolic Isotonic Phosphate Buffer (MIPB) at a pH of 7.4. Rats with hypertension produced by methylprednisolone acetate were used to test the antihypertensive efficacy of the patches. This article outlines many techniques for assessing the transdermal dose form that contains the antihypertensive medication carvedilol[32].

DILTIAZEM HYDROCHLORIDE

Diltiazem hydrochloride belongs to the family of calcium channel blocking antihypertensive medications. It is frequently recommended to treat angina and mild to severe hypertension. Hepatic metabolism of diltiazem hydrochloride is substantial and mostly occurs via cytochrome P-450. Diltiazem hydrochloride has an oral bioavailability of between 30% and 40% as a result of biotransformation. It has an absorption window from the upper gastrointestinal tract and an elimination half-life of 3.5 hours. When using traditional dosage forms, inadequate medication release from the absorption site may reduce the effectiveness of the oral dose. It takes many oral administrations of diltiazem each day to keep therapeutic plasma concentrations stable. Diltiazem hydrochloride is therefore a good medication for transdermal formulation, which provides regulated drug delivery.

L.K Omray et al., conducted a study that, seven formulations with varying ratios of film-forming polymers were developed. Polyvinyl pyrrolidone, carboxy methyl cellulose, and Carbopol 934 were the ingredients of formulations TDDS1 through TDDS7, varying in their w/v ratios of 5%. Based on total polymer weight, formulations additionally included 1% (v/w) of Polyethylene glycol 400, 1% (w/w) of Tween 60, and 5% (w/w) of Diltiazem hydrochloride. The developed transdermal drug delivery system was described based on a number of physicochemical factors, including drug content, in vitro release research, folding durability, moisture content, and water vapor transmission. After it was discovered that formulation TDDS7 outperformed the others, it was chosen to be the developed formulation[33].

AZELNIDIPINE

Azelnidipine is an L-typed calcium channel blocker that works by blocking calcium channels for a prolonged period of time using dihydropyridine. has been authorized lately and is used to treat myocardial infarction-related cardiac remodelling as well as ischemic heart disease. can lower blood pressure in those with hypertension without raising heart rate. When taking azelnidipine orally, the medication goes through a lengthy first pass metabolism. When Azelnidipine (AZP) is administered transdermally, some of the drawbacks of oral administration are reduced, and the drug's bioavailability is raised. Azelnidipine for the purpose of controlled release medicine and to boost bioavailability by preventing drug degradation in GIT fluids and hepatic first-pass metabolism. For this reason, azelnidipine makes an ideal treatment for transdermal formulation, which offers controlled drug administration[34].

Tejashree Chavan et al., developed a matrix-type transdermal treatment system employing the medication Azelnidipine and varying ratios of

Eudragit RL100 and HPMC E5 through the use of solvent evaporation and the addition of dibutyl phthalate as a plasticizer. When taken orally, the long-acting calcium channel blocker azelnidipine undergoes significant first-pass metabolism based on dihydropyridine. Transdermal distribution of azelnidipine may improve the medication's bioavailability and reduce some of the drawbacks of oral administration. Physical characteristics of the transdermal films that were prepared were assessed, including surface pH, water vapour transfer rate, percentage of moisture content, drug content, tensile strength, and folding endurance. The thickness varied from 0.17 ± 0.02 to 0.23 ± 0.01 mm. The medication content showed excellent consistency across all batches and ranged from 96.3 ± 0.2% to 98.9 ± 0.4%. Franz diffusion cells were used in in vitro drug release experiments. Out of all the formulations, formulation no. F6 showed the highest in vitro drug release (70.56 mg) during a 10-hour period. The cumulative percentage of drug permeation in that time was determined to be F6>F5>F4>F3>F2>F1[35].

VERAPAMIL

Verapamil Hydrochloride (VPH) is a class IV antiarrhythmic drug and phenylalkylamine derivative which belongs to a member of the heterogeneous class IV calcium channel blocker group of chemicals. It is frequently used to treat myocardial infarction, angina pectoris, and supraventricular tachyarrhythmia. One calcium channel blocker is verapamil hydrochloride. It functions by letting your heart and blood vessel muscles relax, which reduces the force of your heart's pumping action. In order to regulate heart rate, verapamil also improves blood and oxygen flow to the heart and decreases cardiac electrical activity. Its poor bioavailability of 20% is caused by substantial first pass metabolism upon oral ingestion. Since it must be taken three times a day due to its brief biological half-life of only 4.8 hours, patient compliance is negatively impacted. Verapamil hydrochloride is an ideal option for transdermal medication delivery because of its short half-life, rapid hepatic clearance, limited bioavailability, and low dosage required[36].

Jatin Sood et al., The main objective of this work was to create matrix-type transdermal patches of verapamil hydrochloride (VPL) using hydroxypropyl methyl cellulose (HPMC) and hydroxy propyl cellulose (HPC) combinations as matrix polymers. Additionally, oleic acid (OA) was investigated in relation to the in vitro penetration of VPL through rat skin. Franz-type diffusion cells and full-thickness excised abdominal rat skin were used in the permeation experiments. An analysis was conducted to determine how the polymers affected the drug release, thickness, folding endurance, moisture absorption, and loss percentages. According to in vitro release assays, all of the patches had zero-order drug release, with diffusion mediating the release process. Various release kinetic models were used to analyse the data. According to in vitro release profiles, the drug's release was prolonged and sustained from the optimal combination throughout a 24-hour period. In terms of its technical qualities, VPM 006 was found to be the most satisfactory formulation[37].

CONCLUSION

An assessment of the various antihypertensive medications showed that transdermal delivery enhances both bioavailability and patient outcomes by a large factor of compliance. On the other hand, not all antihypertensive medications may be administered transdermally since these medications need to have certain physicochemical properties in order to penetrate the skin. The right choice of medication, polymer, and other additives is essential for the formation of successful TDDS.

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