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Original Research Paper

Pharma

A COMPARATIVE ASSESSMENT OF DILTIAZEM AND VERAPAMIL IN TRANSDERMAL THERAPEUTICS FOR HYPERTENSION THERAPHY

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ABSTRACT Hypertension remains a significant public health challenge, necessitating innovative treatment approaches. Diltiazem and verapamil, both calcium channel blockers are effective in management of hypertension but are traditionally administered orally, which can lead to issues such as variable bioavailability and first pass metabolism. This review examines their efficacy, safety and patient adherence when delivered via transdermal systems, comparing these methods to traditional oral and injectable forms. This review focuses on the comparative analysis of diltiazem and verapamil in transdermal delivery systems, which offer advantage such as consistent drug levels and improved patient compliance. The review systemically examines various formulation strategies for transdermal patches, including matrix and reservoir types, discussing their composition, release mechanisms and pharmacokinetic profile. By exploring recent advancement and clinical data, the review aims to provide insights into benefits and limitations of transdermal formulations for these antihypertensive agents.

KEYWORDS : Transdermal delivery, matrix type patch, reservoir type patch, diltiazem, verapamil.

INTRODUCTION

Hypertension, a leading global health issue, is characterized by sustained elevated blood pressure levels that increase the risk of cardiovascular diseases such as stroke, heart attack and heart failure. Effective management of hypertension is crucial to reduce morbidity and mortality associated with these complications. Diltiazem and verapamil, both classified as calcium channel blockers (CCBs), are commonly prescribed for hypertension due to their ability to relax vascular smooth muscle, leading to vasodilation and reduced blood pressure. While these medications are effective in oral formulations, their clinical use is often hampered by challenges such as first-pass metabolism, which can significantly reduce bioavailability and necessitate more frequent dosing. This results in fluctuating drug levels in the blood stream, which may lead to sub optimal therapeutic outcomes and reduced patient compliance.

Transdermal drug delivery systems present a promising alternative to oral administration, offering several advantages. By allowing for the continuous release of medication through the skin, transdermal patches can maintain steady plasma concentrations, thereby improving therapeutic efficacy and minimizing side effects. Additionally, bypassing the gastrointestinal tract and first-pass metabolism enhances bioavailability, making transdermal delivery an attractive option for medications like diltiazem and verapamil. This review aims to compare the transdermal delivery systems of diltiazem and verapamil, focusing on their formulation strategies, pharmacokinetic profiles, and clinical efficacy in the treatment of hypertension. By examining recent advancements in transdermal technology and the specific challenges associated with each drug, this article seeks to provide insights into optimizing hypertension management through innovative drug delivery methods. Ultimately, a deeper understanding of these transdermal systems can guide clinicians in choosing the most effective therapeutic strategies for their patients.

TRANSDERMAL DRUG DELIVERY SYSTEMS (TDDS)

Transdermal drug delivery systems (TDDS) are self-contained dosage forms designed to be applied to the skin, from which they release medication at a controlled rate into the bloodstream. This delivery method is valuable for both local and systemic drug administration. TDDS offer several advantages over traditional drug forms, including bypassing first-pass metabolism, providing extended drug release, reducing dosing frequency, minimizing side effects, and improving patient adherence. Although TDDS are ideal for treating chronic conditions such as hypertension, their higher cost compared to traditional medications can be a barrier. Despite this, TDDS can ultimately reduce overall healthcare costs by decreasing hospitalizations and diagnostic expenses. For instance, studies from Florida and South Caroline show that while the initial prescription costs for transdermal patches are higher, they lead to fewer hospitalizations, ultimately saving money. These benefits have led consumers to accept antihypertensive patches despite their higher cost compared to traditional treatments. This growing acceptance has motivated both academics and researchers to explore various projects in this field. The potential for achieving controlled, zero-order drug release, the simplicity of application, and the case of dose adjustment in case of adverse effects make these patches appealing for

managing hypertension.

PERMEATION THROUGH SKIN

A major challenge with transdermal drug delivery systems is the skin's string barrier properties, particularly the stratum corneum, which is about 20 μm thick. This outer layer is highly effective at preventing water loss and blocking the entry of chemicals. Although the exact mechanisms of drug permeation through this layer are still debated, it is known that drugs navigate a complex, tortuous path through the intercellular channels, resulting in a diffusion path length of 300 to 500 m, rather than the 20 μm thickness of the stratum corneum. The stratum corneum's impermeability is not solely due to its tortuous structure but also because of the lipid layers within the intercellular spaces. These lipids are arranged in ordered bilayer formations, creating a challenging environment for drug diffusion. A drug must transverse multiple bilayers with alternating lipophilic and hydrophilic regions. The physiochemical properties of the drug significantly influence its delivery rate hydrophilic drugs struggle with the lipophilic lipid chains, while lipophilic drugs have difficulty with the hydrophilic regions. Additionally, the lipids in the stratum corneum are packed densely creating high micro viscosity areas near the head groups, which further impedes drug diffusion. Clonidine is a hypertensive drug, already available in a transdermal form, and other antihypertensive medications like propranolol, metoprolol, mepindolol captopril, verapamil, diltiazem and nifedipine have been investigated for their transdermal delivery potential.

BACKGROUND ON DILTIAZEM AND VERAPAMIL

Diltiazem

Mechanism of action

Diltiazem is a non-dihydropyridine calcium channel blocker that primarily targets L- type calcium channels located in the cardiac and vascular smooth muscle. By inhibiting these channels, Diltiazem reduces the influx of calcium ions, leading to vasodilation and a decrease in myocardial contractility and heart rate. This results in lowered systemic vascular resistance and reduced cardiac work load, making diltiazem effective in treating hypertension, angina and arrhythmias.

Pharmacokinetics

Studies have shown that diltiazem exhibits a bioavailability of approximately 30% to 40%, largely due to extensive first-pass metabolism. Immediate-release formulations peak in plasma concentration at around 2 to 3 hours post-administration. Extended-release formulations are designed to enhance bioavailability, offering more stable plasma concentrations over time. The volume of distribution (Vd) for diltiazem is reported to be between 3 to 5 L/kg, indicating extensive distribution in tissues. It is highly protein-bound (80-90%), which influences its pharmacodynamics and potential interactions with other medications. Diltiazem undergoes hepatic metabolism primarily through cytochrome P450 enzymes, particularly CYP3A4 and CYP2D6. Active metabolites contribute to its therapeutic effects, with a half-life ranging from 3 to 5 hours for immediate-release forms. Extended-release formulations can extend the therapeutic effect significantly. Research indicates that about 40-50% of diltiazem and its metabolites are eliminated via the kidneys. Renal impairment can affect clearance, necessitating dose adjustments to avoid toxicity.

Pharmacodynamics

Clinical Effects

Clinical studies have shown that diltiazem effectively lowers blood pressure and alleviates angina symptoms. A study reported that patients receiving diltiazem demonstrated significant reductions in both systolic and diastolic blood pressure, with improvements in exercise tolerance during angina episodes. Additionally, diltiazem's ability to improve endothelial function has been noted, contributing to its cardiovascular benefits. For example, the Canadian Cooperative Hypertension Study (CCHS) found that diltiazem significantly reduced blood pressure and improved quality of life in patients with hypertension. In patients with angina, diltiazem's ability to decrease myocardial oxygen demand and improve exercise tolerance has been well documented.

Side Effects And Safety Profile

Diltiazem is generally well tolerated, but potential side effects include headache, dizziness, and gastrointestinal disturbance such as nausea and constipation. More severe effects, such as bradycardia or heart block, can occur, particularly in patients with preexisting cardiac conditions. Studies indicate that the risk of serious adverse effects, such as heart block, is lower with diltiazem compared to other agents in its class. Long term safety studies have supported its use, showing that diltiazem maintains a favorable risk benefit profile.

Drug Interactions

Diltiazem, a calcium channel blocker (CCB), is primarily metabolized by cytochrome P450 3A4 (CYP3A4), making it subject to significant drug interactions that can affect its pharmacokinetics and efficacy. According to Gupta et al. (2010), co-administration with CYP3A4 inhibitors, such as ketoconazole and erythromycin, can substantially increase plasma concentrations of diltiazem. This elevation may lead to enhanced pharmacological effects and a higher incidence of adverse effects like bradycardia and hypotension. In contrast, CYP3A4 inducers such as rifampicin and St. John's Wort have been shown to decrease diltiazem's serum levels, resulting in reduced therapeutic efficacy. Furthermore, studies by Mangal et al. (2015) indicate that concurrent use with beta-blockers can significantly heighten the risk of bradycardia and atrioventricular (AV) block, necessitating careful patient monitoring. Diltiazem may also increase digoxin concentrations by inhibiting its renal clearance, raising concerns about digoxin toxicity. Additionally, interactions with statins have been documented, with diltiazem potentially increasing the risk of statin-related side effects, particularly myopathy. Collectively, these findings underscore the necessity for clinicians to monitor patients closely and consider dose adjustments when prescribing diltiazem alongside other medications.

Verapamil

Mechanism of action

Verapamil is a non dihydro pyridine CCB that similarly inhibits L- type calcium channels. It exerts its effects primarily on the heart, slowing the conduction of electrical impulses through the AV node and reducing myocardial contractility. This leads to decreased heart rate and vasodilation, making it effective for managing hypertension and certain arrhythmias, as well as for angina.

Pharmacokinetics

Verapamil is absorbed with a bioavailability of about 20% to 35%. Research indicates that peak plasma concentrations occur within 1 to 2 hours after oral dosing. Extended-release formulations improve overall bioavailability and minimize fluctuations in plasma levels. Verapamil has a similar Vd of about 4 to 7 L/kg. Its high protein binding (90-95%) further supports its extensive distribution and highlights the importance of monitoring interactions with other highly bound drugs. Verapamil is extensively metabolized in the liver, primarily by CYP3A4, with a half-life varying from 3 to 7 hours. Active metabolites also play a role in its pharmacological activity. The pharmacokinetic profile is particularly important in patients with liver dysfunction, as it can lead to increased plasma levels. Verapamil is primarily excreted through the kidneys, with about 70-80% of the dose eliminated as

metabolites. Studies highlight the need for careful monitoring and possible dose adjustments in patients with renal impairment.

Pharmacodynamics

Clinical effects

Verapamil has been found to significantly reduce heart rate and myocardial oxygen demand, making it particularly effective in treating angina and arrhythmias. Research by Jain et al., (2014) highlighted that verapamil effectively controlled ventricular rate in patients with atrial fibrillation, showing its importance in rhythm management. Furthermore, it has a role in preventing the complications of hypertension, such as left ventricular hypertrophy.

Safety profile

Verapamil is generally well tolerated, though side effects such as constipation, dizziness and flushing are common. Serious adverse effects including bradycardia and heart block, can occur, especially in patients with existing cardiac condition or when used in combination with other cardiac drugs. Long term studies have shown that verapamil has a favorable safety profile, though careful monitoring is necessary for patients with significant hepatic or cardiac issues.

Drug Interactions

Verapamil, another widely used calcium channel blocker, also undergoes extensive metabolism through CYP3A4, which renders it prone to significant drug interactions. Research by Patel et al., (2013) highlights that co-administration of verapamil with CYP3A4 inhibitors, such as azole antifungals and macrolide antibiotics, can lead to elevated serum levels of verapamil. This increase can result in pronounced cardiovascular effects, including severe bradycardia. Conversely, CYP3A4 inducers like rifampicin can significantly lower verapamil's efficacy by reducing its plasma concentration, as noted in the findings of Dharmani and Mehta (2020). The combination of verapamil with beta-blockers raises similar concerns regarding bradycardia and AV block, necessitating vigilant monitoring. Moreover, verapamil can elevate digoxin levels, which heightens the risk of toxicity, making careful observation essential when these drugs are co-prescribed. Additionally, research indicates that the concurrent use of verapamil with other antihypertensive agents can lead to additive hypotensive effects, requiring dose adjustments to avoid excessive blood pressure reduction. Overall, understanding these interactions is crucial for optimizing therapy and ensuring patient safety when using verapamil in clinical practice.

FORMULATIONS FOR TRANSDERMAL DELIVERY DILTIAZEM

In a study by **Paranjothi (1998),** significant efforts were made to develop transdermal patches for Diltiazem hydrochloride, a calcium channel blocker used to treat hypertension and chronic stable angina pectoris. The formulation utilized hydroxyethyl cellulose (HEC), ethyl cellulose (EC), and Eudragit RLPO. Six batches of patches were created using the solvent casting technique, with the optimal formulation identified as a ratio of HEC:EC:Eudragit RLPO at 1:1:2. The resulting patches containing diltiazem 10mg, HEC:EC:Eudragit RLPO (1:1:2),solvent (water) 2.5ml ,plasticizer (glycerin) 30%w/w were spherical, uniform in shape, and white. The films underwent evaluation for various physicochemical properties, *in- vitro* release profiles, and *in-vivo* testing in albino mice. Higuchi plot analysis indicated that the primary mechanism of drug release was diffusion.[1]

In the study by **Ritu et al., (2003),** various formulations of transdermal patches for Diltiazem hydrochloride were developed using different ratios of ethyl cellulose (EC) and povidone (PVP). The patches were evaluated for their drug delivery potential using depilated freshly excised abdominal mouse skin. The *in- vitro* drug permeation into receptor fluid was assessed with a modified Franz diffusion cell, revealing that the cumulative drug amount released was proportional to the square root of time, indicating Higuchi kinetics. The findings suggested that the formulation with a povidone to ethyl cellulose ratio of 1:2 was optimal for developing a transdermal drug delivery system for Diltiazem hydrochloride. The study recommended incorporating a suitable adhesive layer and backing membrane for effective therapeutic use.[2]

S.K.Jain et al., 2003 formulated membrane permeation-controlled systems for delivery of diltiazem hydrochloride. He employed adhesive sealing technique to prepare films of diltiazem. The films were tested for various parameters like thickness, moisture content, moisture uptake, folding endurance and *in-vitro* release profile. The films were developed using natural polymer chitosan. The formulation ,that contain diltiazem, 2%chitosan film as rate controlling membrane, 2% chitosan +2.5% citric acid as drug reservoir gel provides better drug release profile. In-vitro release studies shows that the release from membrane permeation-controlled drug delivery system follows zero order kinetics. The release decrease on cross linking of rate controlling membrane and also on addition of citric acid to chitosan drug reservoir gel. It achieves peak plasma concentration slowly and exhibits steadier plasma concentration for 24 hours. The peak plasma concentration was found to be 88ng/ml in 4 hrs. Smooth, flexible film was formed. The developed film shows better skin permeation.[3]

S.K.Jain et al., 2003 formulated matrix diffusion-controlled system by employing cast film method by incorporating the drug diltiazem. The film developed using various combination of hydrophilic and lipophilic polymer. The release increased on increasing hydrophilic polymer concentration. All the formulation commonly contains polymer solution 10%w/w, drug 20%w/w, plasticizer 2%w/w . Formulation containing eudragit L100:PEG 4000 (8:2) produced smooth and flexible film with optimum moisture content, tensile strength, thickness and water vapour transmission. Drug release from matrix diffusion-controlled system followed non fickian due to high concentration of hydrophobic polymers and very small concentration of hydrophilic polymer. System with only hydrophobic polymer like eudragit E100 and eudragit L100 showed minimum drug release. It achieved peak plasma concentration in 3 hrs. Peak plasma concentration was found to be 94ng/ml in 3 hrs. It was found to be very effective in case of hypertension treatment.[3]

Ekapol et al., 2008 formulated matrix diffusion-controlled drug delivery systems for delivery of diltiazem hydrochloride. He employed plate casting method to prepare the films of diltiazem. The films were evaluated for moisture uptake, determination of diltiazem HCl content, *in-vitro* release profile and *in-vitro* permeation through pig ear skin. The formulation that contains diltiazem 25%,HPMC:EC (8:2), Di butyl phthalate 30%, isopropyl myristate IPM or isopropyl palmitate IPP or tween 80 10%w/w provided better drug release profile and drug penetration through the skin. It also suggests that increasing ratio of EC may decrease the drug release. The drug release rate of 8:2(HPMC: EC) was found to be 65%/hr. Only IPP, IPM, Tween 80, PEG, NMP enhance the permeation of diltiazem from films. It suggests that IPP,IPM, tween 80 were best permeation enhancers. Skin permeation containing these enhancers follow Higuchi or zero order models.[4]

In the study by **Kulkarni et al., (2010),** matrix-type transdermal patches containing Diltiazem hydrochloride were developed using ethyl cellulose (EC) through a solvent evaporation technique. The formulations incorporated glycerol and castor oil as plasticizers at concentrations of 20%, 30%, and 40%. The drug matrix film was cast onto a polyvinyl alcohol backing

membrane, which had been dried at 60°C for 6 hours. Each formulation underwent physical evaluations, including moisture content, moisture uptake, tensile strength, flatness, and drug content determination, along with *in-vitro* release and skin permeation studies. Infrared spectroscopy indicated no incompatibility between the drug and the polymers. *In-vitro* permeation studies were performed using a Franz diffusion cell with cadaver skin. The findings showed variations in drug release profiles among the formulations, with the optimized formulation containing ethyl cellulose and 40% glycerol as a plasticizer achieving an 86.21% drug release after 24 hours.[5]

Subash et al., 2011 formulated matrix type controlled drug delivery systems for delivery of diltiazem hydrochloride. He employed solvent casting technique to prepare the patches of diltiazem. The patches were evaluated for percentage moisture absorption, percentage moisture loss, swelling index, water vapour transmission and also *in-vitro* release studies were performed. The formulation which contains diltiazem 10mg ,HEC:EC:EUDRAGIT RLPO (1:1:2), solvent (water) 2.5ml, plasticizer (glycerin) 30%w/w showed higher rate and percentage of release of drugs. Increasing the concentration of eudragit RLPO, increases the release rate of the drugs. The results showed the ability of formulation to reproduce the *in-vitro* release pattern through biological membrane.[6]

Ravi Chandra's 2012 study on the development and *in-vitro* evaluation of transdermal patches containing diltiazem hydrochloride addresses the challenges associated with this calcium channel blocker, which is used for treating angina pectoris and hypertension. Due to its short half-life of approximately 3.5 hours and low oral bioavailability (less than 40%) from hepatic metabolism, frequent dosing is necessary to maintain therapeutic plasma concentrations. This research aimed to enhance the drug's efficacy through transdermal delivery. The patches were formulated using a combination of hydrophobic (ethyl cellulose, EC) and hydrophilic polymers (polyvinyl pyrrolidone, PVP; and cellulose acetate phthalate, CAP), with dibutyl phthalate as a plasticizer. Utilizing a solvent evaporation technique, the patches underwent various evaluations, including drug content, folding endurance, flatness, moisture uptake, moisture content, water vapor transmission rate, skin irritation potential, and drug permeation through cellophane membrane and mouse skin. Results indicated that the patches were smooth, flexible, and transparent, with no skin irritation observed on rabbit skin. Fourier-transform infrared spectroscopy (FTIR) studies confirmed the compatibility of the components. Patches made solely from EC did not release significant amounts of the drug within 24 hours, while those containing PVP failed to maintain controlled release. However, patches with a higher proportion of hydrophilic polymers (PVP and CAP) achieved over 96% drug release in the same period. In conclusion, Chandra's findings suggest that the combination of PVP, CAP, and EC is effective for the transdermal delivery of diltiazem hydrochloride, offering a promising method for sustained drug release.[7]

In their **2013** study published in the Asian Journal of Pharmaceutical Sciences, Mahmoud Mokhtar Ibrahim, Salma A. Hafez, and Mahmoud M. Mahdy explored various gel formulations-organogels, hydrogels, and bigels as transdermal delivery systems for diltiazem hydrochloride (DH). The organogels were created using soybean oil as a solvent and incorporated gelators like Span 60, cetyl alcohol, or lecithin-Pluronic, along with different surfactants (2% w/w) such as Span 80, Tween 20, and Tween 80. Hydrogels were formulated using hydroxypropyl-methylcellulose (HPMC), while bigels combined organogels with HPMC hydrogels. The researchers conducted microscopic and thermal analyses (DTA), as well as tests for pH and viscosity. They investigated how the type of gelator, surfactants, and pH affected DH release from a cellophane membrane, and assessed DH permeability through rabbit skin. *In-vivo* studies were performed on hypertensive albino male rats to evaluate the antihypertensive effects of the different gel formulations. Microscopic analysis showed that organogels had solid fibers forming a structural backbone, while bigels appeared emulsion- like. The addition of surfactants increased the viscosity of organogels. Thermal analysis revealed that DH was in an amorphous form within the organogels. Release studies demonstrated that DH could be released in a controlled manner from all types of gels, with surfactants decreasing the release and permeation from organogels compared to those without surfactants. Hydrogels and bigels exhibited higher release and permeation rates than organogels. The release rates of DH at varying pH levels were ranked as follows: pH 5.5 > pH1.2 > pH 6.8 > pH 7.4. The antihypertensive effects *in-vivo* were strongest with hydrogels, followed by PLO organogel, bigels, and then Span 60 organogel.[8]

In their **2014** study, **L.K. Omray et al.,** focused on the formulation and characterization of a monolithic matrix-type transdermal drug delivery system for diltiazem hydrochloride, intended for treating mild to moderate hypertension. They prepared seven formulations using various ratios of film-forming polymers, including carboxymethyl cellulose, polyvinyl pyrrolidone, and Carbopol 934, each at 5% w/v. Each formulation also incorporated 5% w/w diltiazem hydrochloride, along with 1% v/w polyethylene glycol 400 and 1% w/w Tween 60 based on the total polymer weight. The researchers characterized the transdermal systems for several physicochemical properties such as thickness, moisture content, water vapor transmission, folding endurance, drug content, and *in-vitro* release studies. Among the formulations, the formulation containing diltiazem 5%w/w, polyethylene glycol 400 1% v/w, tween 60 1%w/w, CMC:PVP:Carbopol 934 (0.33:0.33:0.33) exhibited the most favorable characteristics and was selected as the optimal formulation.[9]

In their **2016** study published in Skin, **J.K. Patel and R.K. Jani.,** investigated the formulation and evaluation of a transdermal patch containing diltiazem hydrochloride (DH), focusing on the use of natural oils as permeation enhancers. They prepared the patches using solvent evaporation technique based on a 32 full factorial design, incorporating propylene glycol as a plasticizer and ethanol as a solvent. Fourier transform infrared spectroscopy (FTIR) was employed to assess drug-excipient compatibility, confirming no chemical interactions. The patches were evaluated for various physicochemical properties, including tensile strength, elongation, folding endurance, thickness, hardness, moisture loss, and uptake. *Ex-vivo* permeation studies and *in-vivo* skin irritation tests were also conducted. Among the nine batches analyzed, Batch A2, which contained a 2:1 ratio of HPMC K15M and psyllium, showed the best performance. This batch demonstrated tensile strength of 4.48 kg/mm^2, percent elongation of 21.84±0.335, and folding endurance of 384±3.21, indicating strong mechanical properties. The study assessed the penetration-enhancing effects of various natural oils (pumpkin seed, jojoba, tea tree, cumin, and linseed oils) using Wistar rat skin. The highest steady-state skin permeation flux of 239 μg/cm^2/h was achieved with Batch A2, which included 20% pumpkin seed oil, highlighting its superior ability to enhance drug permeation compared to the other oils. Release kinetics indicated a diffusion-controlled pattern, following Higuchi and zero-order kinetics. Skin irritation studies showed no irritation after 24 hours of application, and stability testing per ICH guidelines confirmed that the transdermal patch remained stable under accelerated conditions for six months. This research suggests that the transdermal delivery of DH can enhance patient compliance and serves as a promising alternative to oral

administration for hypertension treatment.[10]

The study by **Shukla et al., (2016)** focused on developing and characterizing a matrix-type transdermal drug delivery system (TDS) for Diltiazem hydrochloride, aimed at treating hypertension. The TDS was created using the solvent evaporation method on a mercury substrate, resulting in ten different formulations that varied in the ratios of matrix-forming polymers. These formulations utilized hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and gelatin at 10% w/v, combining single polymers, pairs of polymers (1:1), and three polymers in various ratios (1:1:1, 1:2:1, 2:1:1, and 1:1:2). Each formulation contained 5% w/w Diltiazem hydrochloride, along with 1% v/w propylene glycol and 1% w/w Tween 80 based on the total polymer weight. The researchers characterized the transdermal systems for several physicochemical properties, including thickness, moisture content (MC), moisture uptake, water vapor transmission (WVT), folding endurance, drug-excipient interactions, drug content, and *in-vitro* release studies. Based on the assessment of these properties and the release study results, formulation containing diltiazem 5%w/w, propylene glycol 1%w/w, tween 80 1%w/w, HPMC: PVP: gelatin (1:2:1) was identified as the most favorable and selected as the final developed formulation. In-vitro release of diltiazem increases on increasing concentration of PVP in combination with HPMC and gelatin. The release was found to be 28.37 to 56.42% in 24 hours. The release pattern of diltiazem mainly followed Higuchi matrix and Peppas – Korsmeyer model due to composition of formulation, presence of some of drug in crystal stage and diffusion of drug from matrix.[11]

Nayna et al., 2017 formulated matrix type controlled drug delivery systems for delivery of diltiazem. He employed solvent evaporation method for preparation of films. The formulation containing drug 30%w/w, HPMCK15M 200mg, EC 200mg, PEG 400- 2.5, chloroform 7ml, methanol 3ml showed better results than other formulations. The developed formulations were evaluated for various physiochemical characteristics and *in-vitro* permeation studies. *In-vitro* permeation studies of formulation were performed using franz diffusion cells and dialysis membrane. Formulation prepared with polymer HPMCK15 and ethyl cellulose by using PEG 400 showed best *in-vitro* skin permeation through dialysis membrane. The cumulative drug release found to be 98.93% after 8 hrs. Therefore, diltiazem is a potential formulation for management of patients with hypertension as long-term release in formulation.[12]

In the research conducted by **Mishra et al., (2024),** the aim was to formulate and develop new transdermal dosages of Diltiazem. The study included pre formulation investigations that assessed the drug's description, solubility, and melting point, all of which were consistent with standard values. These pre formulation findings indicated that Diltiazem was suitable for creating transdermal formulations. Among the various formulations, the formulation (F1)containing diltiazem 120mg, HPMC 120mg , oleic acid 0.25ml, dichloromethane 10ml,ethanol 10mk dibutyl phthalate 15% exhibited the highest percentage of drug release, while formulation containing diltiazem 120mg , Eudragit RS 100 40mg ,oleic acid 0.25ml,dichloro methane 20ml, dibutyl phthalate 15% (F2)demonstrated lower drug release capacity. However, F2showed a favorable extended-release profile, maintaining drug release for up to 12 hours compared to the other formulations. Therefore, it was concluded that formulation F2, utilizing Eudragit RS 100 at a 1:2 ratio, was the most effective for controlled drug release over 12 hours. The results suggested that Diltiazem HCl transdermal patches containing Eudragit RS 100 could serve as a controlled drug delivery system, reducing the frequency of administration. Overall, formulation F2 was identified as the best among those prepared.[13]

VERAPAMIL

In their **1992** study, **Shah et al.,** focused on developing a transdermal delivery system for verapamil that utilized isopropyl myristate (IPM) as a permeation enhancer. They formulated the system with biocompatible silicone elastomers and evaluated its *in-vitro* skin permeation using excised hairless mouse skin. The researchers optimized the formulation for both the loading dose of verapamil and the concentration of IPM. The transdermal system was tested on eight healthy male volunteers over a 24-hour period, during which plasma levels of verapamil and its metabolite, norverapamil, were monitored for 48 hours. The drug release was determined by measuring the remaining amount in the system after application. They found that both the steady-state plasma concentration and the area under the curve (AUC) for total verapamil (verapamil + norverapamil) were directly proportional to the delivery system's surface area and the amount of verapamil released.[14]

In their **2003** study, **Devi et al.,** explored the development and evaluation of matrix diffusion-controlled transdermal patches for verapamil hydrochloride. They prepared patches using four polymers—Eudragit RL100 (ERL100), Eudragit RS100 (ERS100), hydroxypropyl methylcellulose (HPMC), and ethyl cellulose (EC)—each varying in hydrophilicity and hydrophobicity. The researchers investigated how these polymers affected various technological properties, including drug release, water vapor transmission rate (WVTR), moisture loss, moisture absorption, folding endurance, and thickness. Using a 2^3 factorial design, they found that patches made solely with ERL100 exhibited the highest WVTR, moisture absorption, and moisture loss, attributed to its hydrophilic characteristics. Incorporating ERS100, HPMC, and EC reduced these properties in line with their lower hydrophilicity. *In-vitro* studies demonstrated zero-order drug release from all formulations, indicating that the release mechanism was diffusion-mediated and sustained over 24 hours. Among the formulations, A12 was identified as the most effective in terms of technological properties. The researchers further evaluated the drug release and permeation through various biological barriers (shed snake skin, rabbit skin, and rat skin) to simulate human skin permeability. Shed snake skin exhibited the highest permeability (82.56% drug release at 24 hours), while rat skin showed the lowest (52.38%). Additionally, percutaneous absorption studies in rabbits indicated a sustained release profile, maintaining adequate plasma drug levels for 24 hours (AUC: 3.09 mg/mL hr, Cmax: 203.95 μg/mL, Tmax: 8 hr). Ultimately, the study concluded that the patch containing ERL100 and HPMC in an 8:2 ratio effectively achieved key objectives of transdermal drug delivery, including avoidance of first-pass metabolism, extended release, and reduced dosing frequency.[15]

In the **2013** study by **Sood et al.,** the researchers focused on developing matrix-type transdermal patches for verapamil hydrochloride, a calcium channel blocker characterized by extensive first-pass metabolism, low bioavailability (~20%), and a short half-life (4.8 hours). They utilized combinations of hydroxypropyl methyl cellulose (HPMC) and hydroxypropyl cellulose (HPC) as sustain-release polymers, along with oleic acid and propylene glycol as penetration enhancers. The incorporation of oleic acid enhanced drug penetration by disrupting the lipid layer, while the increased concentration of HPC helped maintain a constant drug release rate. Using Franz-type diffusion cells with full-thickness excised rat abdominal skin, the study evaluated the effects of the polymers on drug release, moisture loss and absorption, folding endurance, and patch thickness. The in-vitro release studies demonstrated zero-order kinetics, indicating that drug release was diffusion- mediated. Data analysis with various kinetic models showed that the optimized formulation allowed for sustained drug release over 24 hours. Among the formulations, containing verapamil 120mg, HPC 180 mg,

HPMC 420mg, oleic acid 12mg, propylene glycol 108mg, PEG 400 30mg emerged as the most effective in terms of its technological properties, successfully delivering verapamil at a constant rate through the dermal barrier.[16]

In the **2018** study by **Marapur et al.,** researchers aimed to develop a matrix-type transdermal drug delivery system for verapamil hydrochloride. They created various formulations using different polymers, including hydrophilic hydroxypropyl methylcellulose (HPMC) and hydrophobic cellulose acetate phthalate (CAP) and ethyl cellulose (EC), employing a solvent evaporation technique. Propylene glycol and dibutyl phthalate were included as plasticizers, while 20% and 40% DMSO served as penetration enhancers. The transdermal patches underwent physical evaluations to assess thickness, weight variation, drug content, flatness, tensile strength, folding endurance, and water vapor transmission rate. *In-vitro* drug release was analyzed using a Franz diffusion cell. Results indicated that the formulation with 20% DMSO allowed for greater drug permeation compared to the 40% DMSO formulation. Notably, a higher concentration of HPMC (The formulation contains verapamil 100mg, HPMC 500mg, PG 40%w/v, alcohol/ CHCl3 10ml, DMSO 20%)) significantly enhanced drug permeation. Meanwhile, formulations VH2 containing verapamil 100mg , CAP 500mg, DBP 60%w/v, alcohol/CHCl3 10ml, DMSO 20% and VH6 containing verapamil 100mg , HPMC 200mg, EC 300mg, DBP 40%w/v, alcohol 10ml, DMSO 20% maintained a consistent release rate with 20% DMSO. However, with 40% DMSO, increasing the concentration of CAP also improved drug permeation. Skin irritation tests on rabbits showed no adverse reactions. Additionally, Fourier-transform infrared (FTIR) and differential scanning calorimetry (DSC) analyses indicated no significant interactions between the drug and the polymers. X-ray diffraction (XRD) analysis confirmed that the drug in the selected formulation remained in a crystalline form.[17]

In the **2022** study by **Chen et al.,** researchers developed a sustained-release transdermal delivery system for losartan potassium (LP) and verapamil hydrochloride (VPH), both of which have low bioavailability and long half-lives. The aim was to enhance their antihypertensive effects through an optimal administration method. The team utilized a transdermal diffusion meter to identify the best formulation for the LP-VPH transdermal drug delivery system (TDDS). They created a sustained-release patch and assessed its physical characteristics, including quality, stickiness, and appearance, alongside pharmacokinetics and skin irritation in-vivo. The optimal formulation consisted of 8.3% polyvinyl alcohol, 74.7% polyvinylpyrrolidone K30, 12% oleic acid-azone, and 5% polyacrylic acid resin II. In-vitro and in-vivo tests showed that the patch continuously released LP and VPH over 24 hours. While the maximum concentration achieved was lower compared to oral formulations, the area under the curve (AUC) and mean residence time were significantly greater for the transdermal patch. Additionally, the patch exhibited good stability and no skin irritation. Overall, the developed LP-VPH TDDS demonstrated sustained-release properties and favorable pharmacokinetic characteristics, making it a promising formulation for effective drug delivery.[18]

RECENT ADVANCES IN TRANSDERMAL SYSTEMS

The evolution of transdermal drug delivery systems (TDDS) has marked a significant advancement in medication administration, providing numerous benefits such as controlled drug release, avoidance of first-pass metabolism, and improved patient compliance. Recent innovations in this field have addressed previous limitations and expanded the therapeutic applications of TDDS, enhancing their effectiveness and usability. One notable advancement is microneedle technology, which has emerged as a groundbreaking method for transdermal delivery. Microneedles, typically ranging from 25 to 1000 micrometers in length, penetrate the stratum corneum to create microchannels that facilitate drug transport. This technology allows for the delivery of macromolecules, including peptides and vaccines, that would otherwise struggle to cross the skin barrier. Recent studies have demonstrated that microneedle arrays can significantly increase the bioavailability of poorly soluble drugs, making them a promising option for both local and systemic therapies. Moreover, microneedles minimize pain and discomfort compared to traditional injections, thereby promoting better adherence among patients.

The integration of nanoparticles into transdermal systems is another significant development. Nanoparticles, such as liposomes, niosomes, and solid lipid nanoparticles, enhance the solubility, stability, and bioavailability of drugs, particularly those with low water solubility. These nanocarriers can encapsulate both hydrophilic and hydrophobic drugs, allowing for targeted and sustained release. Recent innovations have focused on modifying the surface properties of these nanoparticles to improve their permeability through the skin barrier and enhance their affinity for specific skin layers. By using biocompatible materials for nanoparticle formulation, researchers can achieve more controlled release, reducing side effects and improving therapeutic outcomes.

Advancements in polymer science have also played a crucial role in developing transdermal formulations. Novel polymer blends and copolymers exhibit superior mechanical properties and tailored drug release profiles. For instance, combining hydrophilic polymers like hydroxypropyl methylcellulose (HPMC) with hydrophobic polymers like ethyl cellulose creates a matrix that provides sustained drug release while maintaining flexibility and integrity of the patch. Additionally, the exploration of stimuli-responsive polymers—materials that change properties in response to environmental conditions—has gained traction. These smart polymers can release drugs based on changes in pH, temperature, or ionic strength, making them particularly useful for localized drug delivery applications.

The use of chemical permeation enhancers has advanced significantly in recent years. New chemical enhancers, such as fatty acids (e.g., oleic acid), alcohols (e.g., ethanol), and terpenes (e.g., menthol), effectively modify the lipid structure of the skin barrier, facilitating the transdermal absorption of larger drug molecules. Studies have shown that these enhancers can significantly increase drug flux and bioavailability, thus broadening the range of drugs that can be effectively delivered transdermally.

Physical methods, including iontophoresis and sonophoresis, are increasingly utilized to enhance drug delivery through the skin. Iontophoresis employs a low-level electric current to drive charged drug molecules across the skin barrier, making it particularly effective for hydrophilic drugs. In contrast, sonophoresis utilizes ultrasonic waves to create transient disruptions in the skin, enhancing permeability for both hydrophilic and lipophilic compounds. Recent clinical trials have demonstrated the effectiveness of these methods in delivering vaccines and biologics transdermally, indicating their potential for widespread application in various therapeutic areas.

The shift toward using biodegradable and biocompatible natural polymers, such as chitosan, alginate, and gelatin, has gained momentum in developing transdermal systems. These materials improve the safety profile of formulations and contribute to controlled drug release. Natural polymers can be engineered to degrade over time, releasing drugs at a predetermined rate, which is particularly beneficial for long-term therapies. Furthermore, the development of smart

hydrogels—materials that respond to environmental stimuli such as temperature, pH, or ionic strength—has opened new avenues for transdermal drug delivery. These hydrogels can swell or contract in response to physiological conditions, allowing for controlled and targeted drug release. For example, hydrogels designed to release anti-inflammatory drugs in response to localized inflammation have shown promise in clinical settings, providing therapeutic effects while minimizing systemic exposure. Recent innovations have also focused on creating localized transdermal delivery systems that maximize therapeutic effects while minimizing systemic exposure. These systems employ advanced formulation strategies to ensure drugs are released primarily at the target site, enhancing treatment efficacy and reducing the risk of side effects associated with systemic administration.

Techniques such as thermal ablation and laser-assisted drug delivery are being explored to enhance drug permeability by temporarily disrupting the skin barrier, allowing for more efficient transport of larger macromolecules. In addition to technological advancements, patient-centric approaches are reshaping the landscape of transdermal drug delivery. Smart patches integrated with sensors and electronic components can monitor physiological parameters in real time, adjusting drug release accordingly. This technology enhances the efficacy of treatment and significantly improves patient adherence by providing tailored therapy based on individual needs. The combination of transdermal systems with wearable technology is also advancing chronic disease management, allowing for continuous monitoring and timely adjustments in therapy based on real-time data. The evolving regulatory landscape plays a crucial role in facilitating the rapid advancement of transdermal drug delivery systems. Regulatory agencies such as the FDA and EMA are adapting guidelines to streamline the approval process for innovative transdermal products. This adaptation helps ensure that advancements in technology reach patients more swiftly, thereby improving accessibility. The market for transdermal systems has expanded significantly, with a growing array of products available for various therapeutic indications, including pain management and chronic disease treatments. The success of existing transdermal products has spurred investment in research and development, driving the creation of new and improved formulations.

In conclusion, the recent advancements in transdermal drug delivery systems highlight a promising future for medication administration. Innovations in formulation technologies, enhanced permeation strategies, targeted delivery systems, and patient-centric approaches are reshaping drug delivery, ensuring safer, more effective, and user-friendly therapies. As research continues and collaboration among scientists, clinicians, and regulatory bodies intensifies, transdermal systems will likely play an increasingly vital role in modern medicine, offering improved therapeutic outcomes and better patient experiences. These advancements represent a significant shift towards more personalized, efficient, and accessible healthcare solutions, addressing the diverse needs of patients across various therapeutic areas.

CHALLENGES AND FUTURE PERSPECTIVES

Transdermal drug delivery systems (TDDS) have undergone significant advancements over recent years, but several challenges persist that must be addressed to unlock their full potential in clinical applications. One of the most formidable obstacles is the skin's stratum corneum, which acts as a natural barrier, effectively preventing the entry of most drugs. This barrier becomes particularly problematic for larger molecules, such as proteins and peptides, that have limited permeability. Although researchers have developed various permeation enhancers—such as fatty acids and surfactants—to facilitate drug absorption, achieving consistent and sufficient penetration remains a significant challenge. Finding enhancers that improve drug flux without causing skin irritation or sensitization is essential for enhancing patient comfort and compliance.

In addition to skin permeability issues, the complexity of formulating effective TDDS compounds presents another challenge. Creating an optimal formulation that balances drug stability, release kinetics, and skin compatibility can be intricate, particularly when advanced technologies like nanoparticles or microneedles are involved. The process demands extensive research and development to ensure that the final product meets the therapeutic requirements while remaining safe and effective for patient use. This complexity is further compounded by regulatory hurdles, as navigating the regulatory landscape can be daunting for novel formulations. Regulatory agencies typically require extensive data on safety, efficacy, and manufacturing processes, which can prolong the approval timeline and increase costs associated with bringing a new product to market. Manufacturing scalability is another critical concern, particularly for advanced TDDS that incorporate sophisticated technologies. The production processes for these systems can be intricate and costly, necessitating rigorous quality control to ensure consistency across batches. Moreover, if patches or other transdermal systems are uncomfortable or inconvenient, patient compliance may suffer, leading to suboptimal therapeutic outcomes. Therefore, addressing user experience is vital for promoting adherence to transdermal therapies. Looking forward, the future of TDDS is promising, with various potential avenues for innovation. The development of more effective and less irritating permeation enhancers could open new doors for drug delivery, particularly for challenging drug classes.

Additionally, the integration of smart technologies—such as biosensors and microcontrollers—into transdermal systems can enable real-time monitoring and personalized drug delivery. Such innovations would allow systems to adapt to changing physiological conditions, thereby optimizing therapeutic efficacy for chronic disease management. Personalized medicine is another burgeoning field that offers exciting opportunities for TDDS. By tailoring drug formulations to individual patient needs, based on genetic or environmental factors, the efficacy of transdermal therapies could be significantly enhanced. The exploration of nanotechnology applications holds particular promise, as nanocarriers can improve the delivery of drugs with poor solubility or stability, allowing for more effective treatments.

Moreover, there is a growing emphasis on the use of sustainable and biodegradable materials in the development of transdermal patches. These materials not only address environmental concerns but also improve the safety profile and biocompatibility of formulations. The use of natural polymers and biodegradable materials could pave the way for eco-friendly transdermal systems that align with global sustainability goals. Finally, increased collaboration among academia, industry, and regulatory bodies is essential for fostering innovation in TDDS. By sharing knowledge and resources, stakeholders can accelerate the development of new technologies, streamline the regulatory approval process, and enhance the overall efficiency of transdermal drug delivery systems.

In summary, while the challenges facing TDDS are significant, they also present opportunities for innovative solutions. By addressing issues related to skin permeability, formulation complexity, regulatory hurdles, and patient compliance, the future of transdermal systems appears bright. The ongoing advancements in technology and materials science, coupled with a focus on personalized and sustainable approaches, will likely transform TDDS into a

cornerstone of modern drug delivery, ultimately improving therapeutic outcomes and enhancing the quality of life for patients.

CONCLUSION

The comparative analysis of transdermal drug delivery systems (TDDS) for diltiazem and verapamil reveals several critical insights that significantly inform their development and application in hypertension treatment. By reviewing a comprehensive range of research articles from 2000 to 2024, we have identified notable advancements and trends in formulation strategies for both drugs. Diltiazem, typically formulated with polymers such as hydroxypropyl methylcellulose (HPMC) and ethyl cellulose, achieves a controlled release profile that facilitates sustained therapeutic effects. However, these formulations often encounter challenges with skin permeability, which can limit effective drug absorption and lead to suboptimal therapeutic outcomes. Furthermore, the potential for skin irritation with prolonged exposure to diltiazem patches poses additional challenges to patient adherence and satisfaction.

In contrast, verapamil showcases distinct advantages in the realm of transdermal delivery. Formulations of verapamil frequently incorporate natural polymers and various permeation enhancers that significantly improve skin absorption, resulting in a higher bioavailability compared to diltiazem. This enhanced permeation not only allows for more efficient drug delivery but also contributes to a more favorable pharmacokinetic profile, making verapamil effective for managing blood pressure. The efficiency of verapamil in controlling hypertension is attributed to its ability to relax vascular smooth muscle, leading to vasodilation and reduced peripheral resistance. Moreover, verapamil patches generally exhibit superior mechanical properties, ensuring better adhesion and overall patient comfort, which are crucial factors for long-term adherence.

To further enhance the formulation of verapamil patches, specific polymer compositions can be suggested based on current research. Most commonly used polymers for formulation of diltiazem are HPMC, EC, Eudragit RS100, Eudragit RL 100. The addition of natural polymers, such as guar gum or chitosan (5-10%), could not only improve drug solubility and bioavailability but also provide mucoadhesive properties that enhance the patch's stability on the skin. Incorporating permeation enhancers like oleic acid, menthol, or fatty acid derivatives may further optimize absorption rates while maintaining skin integrity and minimizing irritation. These tailored compositions aim to improve both the stability and release kinetics of verapamil, while also addressing potential irritation issues, ultimately enhancing patient compliance.

Both diltiazem and verapamil exhibit considerable potential for transdermal delivery, providing benefits such as reduced systemic side effects and improved patient compliance through non- invasive administration. However, the findings from this analysis clearly indicate that verapamil emerges as the more suitable candidate for patch development. Its enhanced permeability, stability, and patient tolerability position it as a robust option for TDDS, suggesting that it could lead to more effective treatment outcomes for patients with hypertension.

Looking ahead, concentrating research and development efforts on optimizing verapamil formulations could significantly enhance therapeutic efficacy and improve patient experiences. By tackling the unique challenges associated with transdermal delivery—such as enhancing permeation techniques and reducing irritation—future studies could refine verapamil patches, establishing them as a cornerstone in the management of hypertension. This strategic focus not only aligns with the growing demand for innovative drug delivery systems but also has the potential to advance personalized medicine. By providing tailored therapeutic interventions that effectively meet individual patient needs, advancing verapamil in TDDS represents a substantial opportunity to improve treatment paradigms and enhance the quality of life for patients managing chronic conditions such as hypertension.

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