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Original Article

Development and In-Vitro Evaluation of a Sustained-Release Transdermal Patch for Improved Patient Adherence

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Abstract: *Transdermal drug delivery systems (TDDS) are a new, patient-friendly way to treat long-term chronic illnesses compared to traditional systemic dose types of medicine administration. TDDS can decrease the dosing schedule and increase the regularity of therapy by avoiding first-pass metabolism and allowing patients to control drug delivery. Nevertheless, a significant number of commercially current transdermal preparations continue to be high drug loaded and demand high frequency of application that can potentially adversely affect patient compliance and safety. In that regard, sustained-release transdermal patches provide a valid approach in overcoming these constraints. This paper is a review of concepts of drug delivery through transdermal patches, special focus is given to the sustained-release systems and how they can help increase patient compliance. Evaluation techniques, both in vitro and ex vivo, such as skin deposition study using Franz diffusion cells and drug-excipient compatibility are discussed alongside important formulation considerations like polymer choice. In addition, the effect of the sustained-release transdermal patches on patient compliance is examined through the comparison of the benefits of the patches over oral and injectable treatments with respect to convenience, non-invasiveness, and controlled drug delivery. In general, sustained-release transdermal systems show a lot of potential to enhance the adherence level, reduce dose-related adverse effects, and maximize long-term therapeutic effects, which could be considered important in the future development of patient-centric drug delivery platforms.*

Keywords: *Transdermal Drug Delivery Systems (TDDS), Sustained-Release Transdermal Patches, Patient Compliance, Chronic Disease Management, Controlled Drug Delivery, Polymer Selection.*

I. INTRODUCTION

Transdermal drug delivery system (TDDS) has gotten a lot of attention as a possible new way to get drugs into the body, especially small, powerful molecules that stick to fat. TDDS increase patient adherence through direct delivery of drugs bypassing the first-pass metabolism and prolonging their release into the bloodstream. Consequently, multiple transdermal medications, including buprenorphine, clonidine, oestradiol, fentanyl, nicotine, rivastigmine, rotigotine, scopolamine, or testosterone, are now available for sale in the US market.

Amongst them, testosterone-impregnated transdermal systems are extensively popular because of the vitality of the hormone in the male physiology. The testes contain a majority of the testosterone, which helps in supporting bone strength, body mass and strength, fat distribution, erythropoiesis, libido, and sperm production [1]. As people age, the amount of testosterone drop substantially, and the serum below 200-300 ng/dL is a clinical diagnosis of hypogonadism, especially in men aged over 60 years of age hence requiring long-term testosterone replacement therapy (TRT).

In order to meet this clinical requirement, several types of TRT dosage forms have been produced such as transdermal gels, metered-dose gels, transdermal solutions, nasal gels, extended-release films, and implantation pellets transdermal gels being the most prevalent in the market [2]. Nonetheless, these formulations tend to be high drug loaded (70120 mg) and have to be applied multiple times a day which may affect adherence and cause dose related adverse effects as a result of inappropriate usage [3]. Based on these shortcomings, transdermal patch development is a feasible approach that the strategy of controlled and sustained testosterone delivery and enhancement of patient adherence. The effectiveness of such a system can be determined by the proper choice of polymers and excipients, so the pre-formulation drug-polymer compatibility studies are vital.

The rationale behind these experiments was to study the drug's interaction with the dialysis membrane's permeation rate and release in a controlled laboratory setting using a modified Franz diffusion cell. Additionally, used Fourier transform infrared (FTIR) spectroscopy to look for possible drug-excipient interactions [4].

A. Structured of the Paper

The paper is organized as follows: Section II discusses drug delivery, Section III focuses on sustained-release transdermal systems and their role, Section IV examines the impact of sustained-release transdermal patches on patient adherence, Section V presents a summary of the relevant literature, and Section VI outlines potential directions for future research in this area.

II. DRUG DELIVERY VIA TRANSDERMAL PATCHES

A multitude of factors influence the effectiveness of transdermal medication delivery, including skin permeability, application area, exposure duration, and epidermal metabolic activity (i.e., first-pass metabolism). In reality, transdermal administration may be affected by certain peculiarities of the medicine in question, as is the case with all medicines. It is important for drugs to not be ionic and to be relatively lipophilic so that they can penetrate the epidermal barrier and be absorbed and used effectively. Subcutaneous medication delivery becomes more difficult with molecules larger than 500 Dalton, and 10 mg of the medicine daily is the ideal therapeutic dosage.

A multi-layered transdermal patch is used to administer the medicine into the bloodstream through the skin [5]. A medicated patch is much the same as seen in Figure 1. The composition and form of the patch can be modified to suit the treatment and the rate of drug release that is desired.

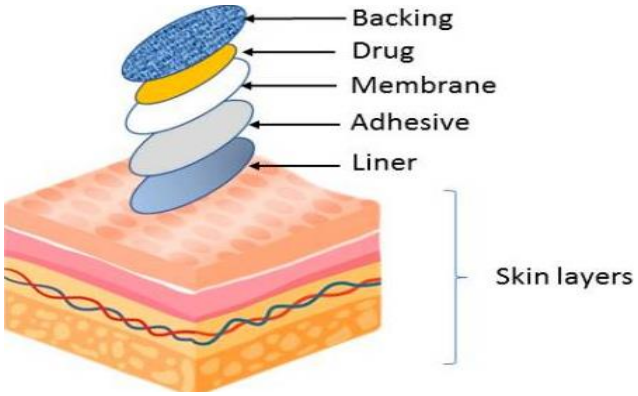

Figure 1 : Basic Component of a Transdermal Medical Patch.

The backing layer protects the patch's inner layers from environmental hazards; it is the outermost layer. Waterproof and pliable materials, such as polyethylene or polypropylene, make up the bulk of this coating. The patch is secured to the skin and not come off thanks to the adhesive coating. The adhesive that comes with it is typically mild yet effective, and it is both skin-and allergen-safe [6]. Medications are delivered through the skin and are contained in the drug layer. The medication is designed to be released gradually over time.

The rate-controlling membrane allows the user to modify the dosage of medication given by the patch. Typically, semi-permeable materials are used to control the rate of drug transport over a membrane. The linen shields the glue and patch from damage and take the patch off first before put it on skin. The results are in Table I.

Table 1 : A Summary of Transdermal Patches/Products and their Unique Features.

Drugs	Indication	Product Name	Duration of Application
Asenapine	Mania, bipolar disorder	Secuado	24 h
Bisoprolol	Atrial fibrillation	Bisono	24 h
Buprenorphine	Management of pain	Butrans	7 days
Dextroamphetamine	ADHD	Xelstrym	Up to 9 h
Donepezil	Alzheimer disease	Adlarity	7 days

A. Types of Transdermal Patches

a) Drug-in-Adhesive System

This controls the most fundamental aspect of a membrane's permeability. In this method, the adhesive layer serves to both bind the different components and also includes medicinal ingredients [7]. The liner and backing are placed on top of the medication mixture.

b) Reservoir System

The microporous rate-controlling membrane, located between the backing layer and the system, is responsible for regulating the release of the substance from the drug reservoir. There are a variety of possible drug delivery systems that can be used in the reservoir chamber, including solid polymer matrices, solutions, suspensions, gels, and more.

c) Matrix System

A polymer matrix that is either hydrophilic or lipophilic is used to disseminate drugs evenly. The drug-containing polymer is bonded to discs with defined thickness and surface area.

d) Micro-Reservoir System

A matrix dispersion system and a reservoir have merged into one. Using a water-soluble liquid polymer solution to suspend drug solids and a lipophilic polymer to equally distribute the combination, this approach can produce thousands of tiny, leak-proof drug reservoirs.

B. Mechanism of Drug Absorption through Skin

The three primary pathways for medication delivery through the skin are the intercellular, transcellular, and appendageal channels [8]. Most of the time, it's the intercellular route. Here, the medicinal compounds enter the bloodstream via the stratum corneum's intercellular gaps between corneocytes. This method allows for the delivery of hydrophilic molecules and relatively big drug molecules. By skipping the cell membrane's lipid bilayers and going straight through the stratum corneum, drug molecules can be transported via the transcellular system.

a) Chemically-Enhanced Methods

Chemically-enhanced skin-mediated drug transport is a diffusion-based approach that modifies the stratum corneum layer to enable the transdermal delivery of medications rather than their intravenous injection. To improve medication permeability, this method employs chemical enhancers. By decreasing the skin barrier function, absorption enhancers raise skin permeability [9]. Absorption enhancers often contain solvents, such as organic solvents that dissolve in water (such as propylene glycol and ethanol). Lipophilic compounds are more soluble in certain solvents, which allows them to penetrate the skin more easily.

b) Physically-Enhanced Methods

Physically boosting skin-mediated drug delivery technologies improve drug permeability in the skin by removing or penetrating the stratum corneum. The stratum corneum has sparked research into methods to bypass or directly penetrate this layer in order to administer medications to the inner layer. In addition, physically upgraded techniques of drug delivery have been developed, which include a triggering system that can release medications as needed.

C. Factors Affecting Skin Permeation

Partition coefficient, pH conditions, and penetrating concentration, as shown in Figure 2.

a) Formulation Factor

- The transport's physical chemistry.
- Transporters and membranes in usage.
- Additives that increase penetration.
- Approach to implementation.
- Device used.

b) Physiological Factors

- This is the stratum corneum, the top layer of skin.
- Application location on the body's anatomy.
- Skin condition and disease.
- Patients' ages.
- Physiology of the skin.
- Desquamation is the process by which the outer layer of skin peels or flakes.
- Skin redness, inflammation, and sensitivity.

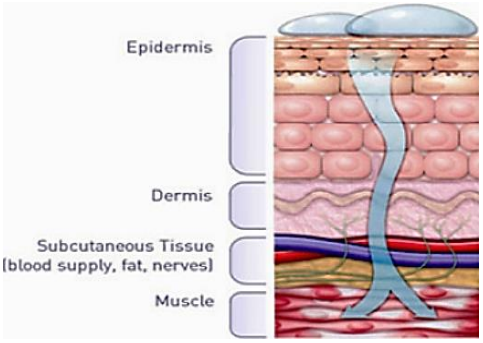

Figure 2 : Permeation Through Skin

D. Advantages of Transdermal Drug Delivery Systems.

The transdermal route is a fascinating alternative to traditional distribution methods because of the ease and security it provides [10]. A number of benefits are associated with drug delivery via the skin to attain systemic effects, including:

- Skipping the first-pass metabolic process.
- Symptoms of gastric intolerance.
- Activity duration that is both predictable and prolonged.
- Reducing potentially harmful side effects.
- Uses medications with limited therapeutic windows and short biological half-lives.

E. Disadvantages of Transdermal Drug Delivery Systems

- The existing delivery system is limited to just very tiny, lipophilic medicines.
- There can be no slack in the medication molecule due to the small patch size.
- The blood circulation does not receive drugs that have extremely low or high partition coefficients.
- Simple toxicity-related medication delivery elimination.
- The poor solubility of the drug in both water and fat makes this route ideal for administering highly soluble drugs.

III. SUSTAINED-RELEASE TRANSDERMAL SYSTEMS

Sustained-release transdermal systems (SR-TDS) are the result of technological advancement in the pharmaceutical industry in the last few decades [11]. Theoretical basis of controlled drug delivery was provided by early pioneering works by Higuchi in 1963, covering the release of drugs out of a solid matrix. The development of matrix-based systems in the 1980s and 1990s further developed rate-controlled formulations, which were then applied to transdermal patches to release drugs over extended periods via the skin [12].

The appreciation of the effects of drug properties, such as solubility and molecular weight, led to the continued development of efficient sustained-release systems. SR-TDS provide today, good reproducibility of plasma drug concentrations, increased compliance in patients, and a diminished dose frequency in most therapeutic indications, a major advancement in non-invasive, controlled drug delivery.

A. Formulation Strategies for Sustained Release

Sustained release and trigger-responsive release are two types of controlled medication release. For example, stimuli-responsive release can lessen systemic toxicity in chemotherapy, but the medications' short half-life in tumours still limits their widespread use. In addition to avoiding potentially dangerous burst drug releases, sustained drug release allows for longer medication release, which in turn reduces dosage frequency and increases patient compliance. To build a compressed structure out of HA-derived hydrogels and crosslink them is one way to make HA-DDSs that release drugs continuously; the rate of drug release is directly related to the rate of structure disintegration. Modulating the crosslinking, swelling, or hydrogel concentration levels allows one to control the breakdown rate [13]. Hydrogels for wound healing were created by crosslinking HA that had been treated with both methacrylate and dopamine with arginine derivatives (refer to Figure 3). Because of the strong electrostatic connection between the arginine derivatives and the HA in the hydrogels, the arginine derivatives were able to be released gradually over time.

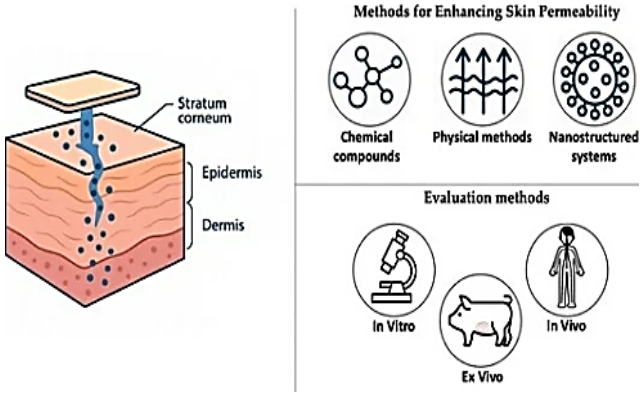

Figure 3 : Sustained Release Thermal Strategies

Pharmacologically encapsulating nanogels with drugs inside hydrogels is another way to provide sustained drug release without the need for bursts. A more progressive and prolonged release of the drug was achieved by combining nanogels loaded with chlorhexidine diacetate (CHX) with a hybrid hydrogel composed of aminoethyl methacrylate HA and methacrylate PEG. The sustained drug release was observed in microspheres loaded with micelles containing DOX, as compared to those without

the micelles. After 7 days, the former released 25% of the medication, while the latter released 38%. Microspheres made of poly (lactic-co-glycolic acid) (PLGA) were modified in a similar way to incorporate DOX-based micelles.

B. In-Vitro and Ex-Vivo Evaluation

The described method was used with Franz diffusion cells to study drug permeation and deposition in vitro. The optimized formulation (KOF1) has been tested and compared and contrasted with a suspension formulation (KTZ-SUS) and a commercially available product (Nizral 2% w/v; Janssen Pharmaceuticals). The belly skin of the rat was shaved carefully with the electric trimmer and not cut or damaged in any way [14]. The excisional skin was introduced into the Franz diffusion cell's donor and receptor compartments. With one side of the skin in touch with the formulation-holding donor compartment and the other side in touch with the phosphate-buffered saline (PBS, pH 7.4) receptor medium. The enhancement ratio, cumulative drug permeation quantity, and permeation flux were measured. All experiments were repeated six times (n = 6), and the average plus standard deviation were used to represent the results.

C. Drug Deposition (Skin Retention) Study

- The epidermis samples were removed and thoroughly rinsed with running water to eliminate any remaining formulation at the conclusion of the permeation trial.
- The skin that was used was washed with surgical scissors in very small pieces.
- Skin samples: The skin samples were dipped into 2:1 v/v methanol-chloroform mixture to extract drugs.
- The process was extracted at room temperature and stirred without interruption taking 12 h.
- The extract was filtered and centrifuged at 9000 rpm over a 15-min period in order to achieve a clear supernatant.
- A determination of the number of medicines retained in the skin was made by examining the supernatant using high-performance liquid chromatography (HPLC).

IV. IMPACT ON PATIENT ADHERENCE

The primary responsibility of the attending physician or medical examiner is to review the patient's medical history and to provide a suitable, individualised treatment plan when a person seeks medical assistance. Medication prescription is just the beginning of the process when dealing with infectious infections, chronic ailments, or metabolic disorders. Patients have just as much responsibility as doctors and other healthcare providers to follow their treatment plans and schedule follow-up appointments as directed [15][16]. What this means in scientific words is that the patient needs to be diligent and follow all of the instructions. A growing concern in the current era is the correlation between non-compliance and non-adherence and the occurrence of resistance, disease, and mortality.

Adherence: The term "adherence" describes how well a patient cooperates with their healthcare provider to take their medication as prescribed, when and how often, and to get refills when needed; these factors all add up to a better therapeutic result, as shown in Table II:

Table 2 : Factors Influencing Medication Adherence in Patients with Chronic Diseases.

OM-B model	Specific factors	Descriptions
Capacity factor	Physical capacity factor	Physical health, functional capacity, and cognitive capacity
	Psychological capacity factor	Mental condition Medications routines Personal Style Situation regarding mental health
Opportunity factor	Physical opportunity factor	Medication availability Access to healthcare services Tools and assistance from technical experts
	Social opportunity factor	Mutual aid and participation in communities Cultural standards The patient's ability to pay
Motivation factor	Reflective motivation factor	confidence in one's own abilities Literacy in health The perception of disease
	Automatic motivation factor	Pharmaceutical faith Optimal health and its pursuit

A. Importance of Adherence in Chronic Therapy

A patient is engaging in intentional non-adherence when they wilfully change or skip treatment as prescribed. This is why they pay close attention to patients' adherence to their drug regimen and the circumstances that may be contributing to

their deliberate deviation from their prescribed dosage schedule [17]. The fact that non-prescribed components, which are crucial for disease control, are also subject to adherence is a noteworthy development. When individuals intentionally disregard treatment recommendations, including those for cardiovascular disease, renal disease (such as food restrictions and fluid intake guidelines), and device use (such as urine catheterization for bladder control), adherence concerns arise.

a) Underestimating Consequences of a Chronic Condition

Patients may think they have control of their disease if they are getting good treatment or don't have any symptoms. The latter is mostly linked to the start of treatment after an early or accidental diagnosis in chronic illnesses. For instance, hypertension often causes no symptoms until problems arise, and studies have shown that only half of people on antihypertensive medication actually take it as prescribed [18]. In spite of the hazards associated with UTIs, preventive antibiotic adherence is poor (40%) in children with UTI abnormalities.

b) Inadequate Disease Awareness and Education

One major reason patients don't take their medication as prescribed is because they don't understand the gravity of their illness or the repercussions of untreated chronic diseases. The incorrect management of newly diagnosed hypertension, which is frequently asymptomatic, can lead to a variety of serious health consequences such as vascular dementia, chronic renal disease, heart failure, stroke, and coronary artery disease. Despite this, 20% of patients skip taking their medication because they think it is unneeded. Despite the critical importance of patient education, healthcare resources are sometimes insufficient to satisfy the expectations. Patients with uncommon diseases face an even bigger uphill battle when it comes to medication adherence due to low disease awareness and limited drug availability.

c) Societal Attitudes Towards Health Information-Seeking Behaviors

Traditional doctor-patient interactions are seeing a decline as patients turn to alternative sources for advice due to healthcare systems' limits caused by things like time and resource restrictions and the widespread adoption of patient-centered medicine [19]. When compared to patients who depended on HCPs directly, patients who relied only on digital sources had lower medication adherence and more negative impressions of drugs, according to retrospective research of over 16,000 patients. Accordingly, it appears that online health forums and social media are becoming increasingly influential, which may significantly affect adherence.

B. Benefits of Sustained-Release Patches

Medication can be introduced to the bloodstream directly into the skin by use of transdermal patches, which are sticky strips. These patches enable for increased bioavailability of medication by avoiding its degradation in the stomach and liver by navigating the digestive system bypass. How Transdermal Patches Help Patients are:

Patients, particularly those dealing with long-term health issues or looking for easier, more accessible alternatives to conventional medicine, can reap several benefits from transdermal patches. The efficacy and convenience of these patches enhance treatment regimens and their results.

a) Ease of Use

A transdermal patch requires zero effort to apply. The glue can be applied straight to the skin when the protective lining is peeled off. This method is simple enough to employ at home without the need for expensive or complicated machinery. Some people have trouble moving around because of arthritis or other dexterity issues, and they can benefit from transdermal patches [20]. Patients are able to take an active role in their own therapy with little to no support needed.

b) Continuous Medication Delivery

Transdermal patches' capacity to furnish a continuous flow of medicine over a long time is a major benefit. Consistent pharmaceutical release is provided by transdermal patches, in contrast to oral pills or injections, which necessitate frequent doctor visits. Controlled release ensures that patients receive the correct dosage of medication throughout time while minimising the risk of side effects and maintaining sustained therapeutic effects.

c) Non-Invasive and Pain-Free

Transdermal patches offer a non-invasive, painless alternative for people who are afraid of needles or have trouble swallowing medications. Skin absorption eliminates the need for needles or oral delivery of the medicine. Because of this, it is a great alternative for people who want a controlled and consistent way to get the benefits of medication but still value discretion and comfort throughout treatment.

d) Improved Medication Adherence

The constant adherence to the specified treatment regimen is a major difficulty in the management of chronic illnesses. Less medication is needed since transdermal patches make this procedure easier. For up to seven days, and make sure to keep some patches on. Less frequent reminders increase the likelihood that patients adhere to their treatment regimens, leading to

better health outcomes. Better condition management and fewer problems occur when patients continuously follow their treatment recommendations.

C. Comparison with Oral and Injectable Therapies

This study aims to determine the long-term efficacy of injectable and oral first-line disease-modifying therapies (DMTs), such as interferons and glatiramer acetate, in individuals without RRMS using measures such as time to first relapse, time to confirmed disability progression (CDP) [21], and time to interruption. The study compares these two groups with dimethyl fumarate and teriflunomide.

An additional selection was done from the original pool of 39 trials in order to clearly separate patient-reported opinions regarding oral tablets against long-acting injectables (LAIs). Studies were only considered for inclusion in the analysis if they provided a clear definition of the specifically mentioned formulation type [22]. Table III displays the results, and the discussion follows:

Table 3 : Comparative Thematic Analysis : Oral Versus Long-Acting Injectable Antipsychotics.

Analytical theme	Descriptive theme	Antipsychotic formulation	Codes	%
Perception and Experience of antipsychotics	Factors influencing antipsychotic adherence	LAI	10	11.8%
		Oral	2	5.8%
	Perceived effectiveness of antipsychotics	LAI	20	23.5%
		Oral	7	20.6%
Social Dynamics and Influence	Improvement in social, working and daily life	LAI	15	17.6%
		Oral	8	23.5%
	Social and family influence on antipsychotics	LAI	3	3.5%
		Oral	0	0.0%
Trust and communication with healthcare providers	Relationship with healthcare professionals	LAI	6	7.1%
		Oral	1	2.9%

V. LITERATURE REVIEW

The literature reviewed has proven that transdermal patches are superior in delivering drugs with better adherence to the patient since it allows the drug to be given in controlled doses over a period of time. The summary of literature as shown in Table IV.

Alissa et al. (2023) develop and test a Treprostinil transdermal patch that sticks to the skin and assess its efficacy in living organisms. X1: drug amount and X2: enhancer concentration were chosen as independent variables to optimise the effect of Y1: drug release and Y2: transdermal flux in a 3^3-factorial design. Rats were used to assess the optimised patch's pharmacokinetics, skin irritation, and other pharmacological characteristics. The optimisation findings show that X1 has a significantly greater impact ($p < 0.0001$) on Y1 and Y2 than X2. There is no drug crystallisation, an appropriate surface shape, and a greater drug content (>95%) in the optimised patch [23].

Sharma and Tailang et al. (2022) This study aimed to examine the efficacy of a transdermal patch containing primaquine in treating malaria. The transdermal patch was made using a number of components. Polymers were selected through the development of placebo patches. Utilizing response surface methodologies, development teams optimized polymer ratios and evaluated their effects on tensile strength, in vitro drug release, in vitro drug permeation, and ex vivo drug permeation. These data-driven conclusions led to the selection of the F5 formulation as the gold standard. Tested the F5 formulation's stability [24].

Hassam et al. (2022) shows that the gel was put into the transdermal patch's reservoir compartment. Tested the skin's permeability and in vitro release with USP V equipment. Based on the findings of the in vitro drug release and penetration assessments, the ideal formulation was derived. Following formulation optimization (F3) and a reduction in surface area to 1 cm 2, the drug's penetration was evaluated using a Franz diffusion cell and a Strat-M transdermal diffusion membrane. The donor compartment was used to install the nimesulide reservoir patch. Five milliliters of permeation medium was allowed to be

mixed into the receptor compartment using a magnetic stirrer. The solution was a pH 7.4 normal saline solution that also contained 20% v/v PEG-400. The optimized patch's reactivity to skin sensitivity was evaluated using the Draize method [25].

Tadhi, Chopra and Sharma et al. (2021) create a transdermal matrix-type patch of Methimazole that releases the drug slowly and steadily. Solvent casting was used to produce the matrix patch with varying concentrations of hydrophilic (HPMC), hydrophobic (Eudragit RL100), and hydrophobic (Ethyl cellulose) polymers. The nine prototype formulations were put through a battery of tests to determine their efficacy. The following were included in the list of tests: in-vitro drug release examination utilizing a Franz diffusion cell, weight uniformity, folding durability, thickness, drug content, percent moisture content, and percent moisture absorption. Using a kinetics model to fit the in-vitro CDR% data allowed us to evaluate the release kinetics of the patches. [26].

Verma et al. (2020) The purpose of this research was to test different polymer ratios and combinations using Glipalamide transdermal patches in order to determine their impact on physicochemical parameters, such as the in-vitro drug release profile. The transdermal patches containing glipalamide were made utilising a variety of ratios of chitosan, the primary natural polymer, and hydroxypropyl methyl cellulose (HPMC). A plasticiser called dibutyl phthalate and a permeation enhancer called oleic acid were both made using the solvent casting approach. In vitro tests were performed on the produced formulations to determine their drug content, drug penetration, folding durability, thickness, weight fluctuation, moisture absorption, and loss. Drug release tests in vitro were conducted using Franz diffusion cells [27].

Qiang et al. (2019) created a drospirenone (DRSP) and ethinylestradiol (EE) long-acting contraceptive patch and studied its transdermal penetration and degree of release in vitro; this laid the groundwork for clinical trials and in vivo evaluations. Methods: The in vitro determination of DRSP and EE was accomplished using an HPLC technique. In order to make the birth control patches, the solvent evaporation method was employed. Prescription optimisation was achieved by screening adhesive matrices, medication loadings, and penetration enhancers using in vitro transdermal qualities as indicators [28]

Table 4 : Summary of Transdermal Patch Formulations and their Pharmaceutical Evaluation for Improved Patient Adherence

Authors (Year)	Focus Area	Key Findings	Approaches	Objectives	Future Work
Alissa et al. (2023)	Transdermal Treprostinil Adhesive Patch	To formulate and optimize a sustained-release transdermal patch and evaluate in vitro and in vivo performance	investigations on pharmacokinetics, skin irritation, pharmacodynamics, FTIR, DSC, in vitro and in vivo optimization of drug dose and enhancer concentration; 3^2 factorial design	Drug amount significantly influenced drug release and flux; optimized patch showed >95% drug content, amorphous drug state, good adhesion, no skin irritation, and enhanced pharmacokinetics	Clinical evaluation in humans and long-term stability studies
Sharma & Tailang et al., (2022)	Primaquine transdermal patch for malaria	To develop and optimize a safe and effective transdermal system for primaquine delivery	Polymer screening; response surface methodology; in vitro, ex vivo permeation; tensile strength; skin irritation studies	Optimized formulation (F5) showed good mechanical strength, sustained drug release, high permeation, and no skin irritation	In vivo pharmacokinetic and therapeutic efficacy studies
Hassam et al., (2022)	Reservoir-type transdermal patch of nimesulide	To evaluate in vitro drug release, permeation, and skin safety	USP apparatus V; Franz diffusion cell with Strat-M membrane; Draize skin irritation test	Optimized formulation (F3) showed effective drug release, good permeation, and absence of skin sensitivity	Evaluation using human skin models and clinical trials
Tadhi, Chopra & Sharma	Matrix-type transdermal patch of methimazole	In order to create a transdermal system that is both regulated	Using hydrophilic and hydrophobic polymers in a solvent casting process; doing in vitro	Formulation F5 showed optimal sustained release, uniformity, and	In vivo performance and long-term

et al., (2021)		and sustained-release	evaluations and kinetic modelling	favorable physicochemical properties	stability assessment
Verma et al., (2020)	Glibenclamide transdermal patch	For the purpose of researching how different polymer blends influence medication release characteristics	Solvent casting; chitosan–HPMC polymers; in vitro drug release and permeation studies	Sustained drug release up to 8 hours; no drug-polymer interaction; suitable physicochemical properties	Enhancement of release duration and in vivo studies
Qiang et al., (2019)	Prolonged-release contraceptive transdermal patch	To develop and optimize a long-acting contraceptive patch and assess transdermal permeation	Solvent evaporation; HPLC analysis; screening of adhesives, drug loading, penetration enhancers	Optimized formulation achieved steady drug permeation for 7 days with >90% cumulative release	Clinical application studies and large-scale manufacturing evaluation

VI. CONCLUSION AND FUTURE WORK

Transdermal drug delivery regimes are an innovative and patient-focused method of the controlled deliverance of treatment agent, especially in chronic illnesses that need prolonged treatment. In this research, the sustained-release transdermal patch was effectively designed and thoroughly tested to overcome the shortcomings of traditional dosage routes, including the high dosing frequency and lack of compliance in patients. The formulation exhibited good in-vitro permeation characteristics and useful drug retention as established using Franz diffusion cells and skin deposition examination. The sustained-release properties of the designed patch allow sustained delivery of the drug, which is likely to keep plasma drug concentrations constant without causing dosage-related adverse reactions in the body. The created system has great potential to increase adherence and treatment responses among patients by minimizing the dosing schedule and providing an alternative route of administration that does not require any intrusion equipment. Future research should aim to undertake in-vivo pharmacokinetic and pharmacodynamics research aimed at providing a clear in-vitro-in-vivo correlation and confirming clinical performance. There must also be long term stability studies and skin irritation tests to make sure that the products are safe and strong. Moreover, optimization of polymer mixtures and the use of superior permeation enhancers can also enhance the drug flux and control drug release. Patient-centric design and scalability of large-scale manufacturing will be essential to the success in clinical translation of the sustained-release transdermal patch.

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