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Advances in Transdermal Patch Technology: Design Principles, Optimization Strategies, and Therapeutic Potential in Hypertension

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Abstract

Hypertension is a chronic heart disease that requires a course of therapeutic drugs; however, traditional oral antihypertensive agents often face constraints related to non optimal adherence to medication, variable pharmacokinetics, and strong first pass hepatic bio-transformation. Transdermal drug delivery systems (TDDS) have become a patient centric option that is able to provide a sustained and controlled delivery of drugs, as well as maintain stable plasma levels, and reduce the number of doses. This review states the latest advances in transdermal patches technology which are specifically designed to control hypertension and it focuses on history of the advancement, design principle of the core, the polymer used, the modes of permeability promotion, and optimization of the formulations. Modern technologies such as microneedle delivery, incorporation of nanocarriers into matrices and stimuli responsive polymers have significantly extended the range of antihypertensive drugs to which transdermal delivery can be applied. *In vitro* and *in vivo* techniques of analyzing mechanical integrity, release kinetics, dermal permeation and therapeutic efficacy are discussed. In addition, it discusses some of the new directions like combinatory patches, biosensor based intelligent systems, and AI assisted formulation design, thus showing how TDDS can enable patient specific, effective, and efficient treatment of hypertension.

Keywords: Smart drug delivery systems; controlled drug delivery; hypertension; Transdermal patches; permeation enhancers

Introduction

Hypertension is one of the most common non communicable diseases in the world. Among adults, its prevalence is estimated at approximately 1.3 billion, thereby representing a principal risk factor for the morbidity of cardiovascular diseases. However, despite the wide range of antihypertensive agents on the market, including diuretics, beta blockers, and angiotensin converting enzyme inhibitors, a balance between blood pressure and optimal patient adherence, partial and intermittent changes in plasma levels, and interval first pass hepatic metabolism that is represented by oral administration make good blood pressure control often difficult. These challenges have led to interest in alternative strategies for delivering drugs that will increase the consistency of the therapy while minimizing the systemic side effects. Among such strategies, transdermal drug delivery systems (TDDS) have attracted more and more interest as a patient friendly controlled release system of hypertension for long term treatment [1].

The idea of skin delivery of drugs was first achieved in the 1970s with the creation of reservoir type nitroglycerin patches. These early systems proved the possibility of long term release of drug through the stratum corneum, and brought new opportunities to the management of chronic diseases. Traditional oral or parenteral treatments, contrastingly, tend to suffer from dose dumping, varying pharmacokinetics and compliance problems especially in hypertensive elderly populations who need to be on medication for the rest of their lives. Transdermal patches do not encounter the gastrointestinal degradation and hepatic metabolism, which leads to better bioavailability, constant plasma levels, and a diminished dosing frequency. In the last 30 years the field has experienced great technological development. The first generation patches have been based primarily on mechanisms of passive diffusion; the second and third generations have added chemical enhancers, iontophoresis, and microneedle array to overcome the formidable barrier function of the stratum corneum. The advent of nanotechnology improved these systems further by adding polymeric nanoparticles, lipid vesicles and nano emulsions, which can improve the permeability and stability of drugs [2].

Most recently, AI/ML-driven formulation optimization and biosensor integrated patches are designed in a new stage of “smart” TDDS with the ability of real time feedback control of drug delivery according to physiological parameters such as blood pressure or heart rate. In particular relation to hypertension, transdermal patches are particularly useful for drugs such as clonidine, amiloride, losartan and verapamil, where over time, therapeutic action and better compliance become paramount. The combination of computational modelling, responsive polymers and biodegradable materials is now overturning the design norms for safer, more efficient and personalized antihypertensive treatment [3]. This review is intended to give an overall account of the design principles, formulation strategies, *in vitro*/*in vivo* characterization techniques and therapeutic implications of transdermal patches in hypertension. Emphasis is laid on the interconversion between traditional diffusion based systems and the latest intelligent drug delivery architectures, as well as the future trend towards the integration of TDDS with digital health and precision medicine-based architecture.

Historical Evolution of Transdermal Technology

The evolution of transdermal delivery of drug systems (TDDS) revolutionized nowadays pharmaceutics by providing a possibility to deliver medication sustainably, non mainstream and patient compliant. Historically, it can be recalled that the idea of delivering therapeutics via the skin originated in ancient civilizations in which herbal drugs and ointments were applied to skin, respectively, to deliver medicinal extracts transcutaneous. However, this changed only in the second half of the 20th century, when transdermal systems received scientific validation. The breakthrough was made with the discovery of the understanding and ability to cross the stratum corneum in controlled conditions by small lipophilic and potent drugs. This realization resulted in development of first generation transdermal patches which initiated a paradigm shift from conventional oral and parenteral routes to a transdermal system that can be controlled from site specific and is able to bypass the first pass effect through the liver [4]. Since, in 1979, the approval by the U.S. Food and Drug Administration (FDA) of the scopolamine patch for motion sickness and, in 1980, the nitroglycerin patch for angina pectoris, TDDS have been remarkably refined from a scientific and technical standpoint. The artificial system journey from traditional passive systems to the smart drug delivery advanced architectures are observed in the following subsections.

Traditional Systems

Traditional or first generation transdermal systems were designed to have the primary function of passive diffusion of drugs through the skin. These systems were generally made from either reservoir or matrix systems composed of four basic layers: a backing membrane, drug containing layer, rate controlling membrane, and adhesive layer. Drug transport followed Fick's laws of diffusion in which the concentration gradient was the driving force behind permeation. The scopolamine patch provided proof of concept of the feasibility of achieving sustained transdermal delivery followed by other successful products like nitroglycerin, clonidine and fentanyl transdermal patches [5]. These early systems showed a number of therapeutic benefits constant plasma concentrations, fewer injections and better patient compliance.

However, their applicability was restricted by physicochemical limitations set by the drug molecule as per the requirement of a molecular weight of less than 500 Da, moderate lipophilicity (log P 1-3), and a low dose (a low dose, in the order of 10 mg/day). Hydrophilic or macromolecular drugs were unable to pass efficiently through the stratum corneum, which was the key rate limiting step. In addition, reservoir systems were at risk of dose dumping (in case of membrane rupture); and matrix patches of drug crystallization at storage [6]. In spite of these limitations, first generation systems were able to set the grounding for controlled release research and validated the skin as a drug administration route which in turn inspired subsequent generations to overcome the skin's physiology through material and engineering innovations.

Modernization of Patch Systems

The second and third generations of transdermal technologies were characterized by active enhancement strategies and advances in polymeric materials with the purpose of drug permeation and patient safety. These systems had introduced chemical enhancers, physical enhancement methods and novel carrier technologies to enhance drug flux across the stratum corneum.

Chemical enhancers like oleic acid, ethanol, propylene glycol and menthol temporarily disrupted lipid bilayer and provided enhanced permeability for hydrophilic drugs and ionic drugs [7]. However, to ensure reproducibility and reduce irritation, some physical enhancement methods such as iontophoresis, sonophoresis, and electroporation, which rely on the use of electrical or ultrasonic energy to transiently increase skin permeability, were developed by researchers.

Next Generation and Future Systems

The entering of microneedle technology was a revolutionary innovation during this phase. Since microneedles are fabricated out of bio compatible materials like silicon, metal or biodegradable polymers, creating microscopic channels allows the effective delivery of drugs without causing any pain and bleeding. For the treatment of hypertension, microneedle assisted patches showed an improved delivery mode of delivery of therapeutic agents, such as atenolol and lisinopril, and increased bioavailability with decreased dosing frequency [8].

In parallel, nanotechnology started to play an important leading role in patch modernization. Nanocarriers, such as liposomes, solid lipid nanoparticles, and polymeric nanospheres, were used in the patch matrices in order to increase solubility, stability, and controlled release of non permeable drugs. This multidisciplinary combination of materials, nanotechnology and pharmaceutical engineering was the step from the traditional transdermal system towards the smart, hybrid delivery systems.

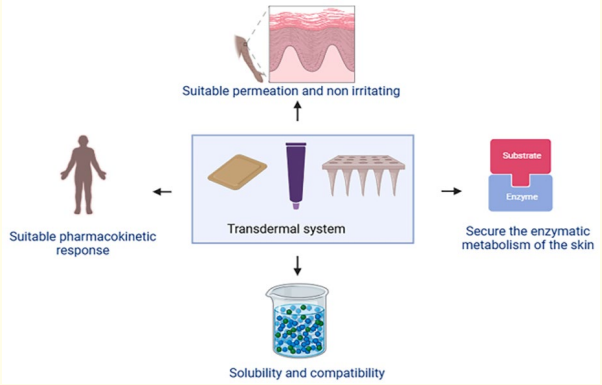

Figure 1: Modernization of Patch system.

Design Principles and Formulation Approaches

Selection of Drug

The choice of an appropriate medication is the most important parameter in the design of an effective transdermal patch. The drug itself must have physicochemical and pharmacokinetic properties that enable it to pass efficiently across the skin barrier with therapeutic concentrations in the plasma without causing irritation and toxicity to the skin barrier. Ideal candidates for transdermal delivery are generally molecules with a molecular weight of less than 500 Da with moderate lipophilicity within the 1-3 log P range and a daily dose requirement which is ideally less than 10 mg per day [9]. These qualities provide for sufficient dividing into both lipophilic and hydrophilic skin layers without making the patch impractical in size. The melting point of the drug is usually high; these drugs are poorly soluble and their diffusion is not good; so the melting point of the drug lies below 200°C. In addition, the drugs should be potent, eliminate in the half-life range of 6-24 hours, and have small potential for skin irritation. Antihypertensive agents, such as clonidine, losartan, atenolol, and amiloride, meet these criteria and represent the ideal candidates for transdermal formulations to maintain a steady state plasma concentration and improve patient compliance in the treatment of chronic hypertension.

Selection of Polymers

The polymer matrix is the basis of a transdermal patch and has both the role of a drug reservoir and rate controlling structure, controlling release kinetics. The key properties required from the polymer are excellent film forming ability, flexibility, biocompatibility, compatibility with the drug and excipients. Commonly used synthetic polymers include ethylene vinyl acetate (EVA), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP) and Eudragit RS/RL while natural polymers like hydroxypropyl methylcellulose (HPMC), chitosan and sodium alginate have attained increased prominence as they are biodegradable and have a safe profile. The selection of polymer depends on the solubility properties of the active pharmaceutical ingredient; depending on the drug, a more or less rapid drug release may be desired, being more easily supported by hydrophilic matrices or polymers that are more liable to produce a sustained drug diffusion, such as matrices based on Eudragit or ethyl cellulose [10, 11]. The molecular weight and cross linking density of the polymer affect the diffusivity of the drug, the strength of the polymer, and the absorption of moisture. Recent advances have comprised the development of stimuli responsive polymers that regulate drug delivery in response to temperature, pH or the concentration of ions in sweat, thus being ideally suited for responsive antihypertensive treatment. For ensuring the compatibility of polymer drug through spectroscopic and thermal analysis to prevent crystallization and ensure stability in storage [12].

Drug and Permeation Enhancer Optimization

The human stratum corneum poses as the main challenge to transdermal delivery and the use of permeation enhancers is required to support the diffusion process of drugs. More recently, non cosmetic agents have emerged that work via the transient modification of the lipid bilayers or protein domains of the skin, to increase the permeability without permanent damage to the skin. Chemical enhancers like oleic acid, menthol, ethanol and propylene glycol have been widely used because of their synergistic effect in enhancing drug flux and hydration. Their concentration must be optimized to maximize permeability and at the same time prevent irritation [13-15]. Physical approaches, in the form of iontophoresis, sonophoresis, microneedle arrays can be combined for drugs with poor skin permeability. Novel enhancer systems such as nanoemulsions, liposomes, and solid lipid nanoparticles can further enhance solubilization, stability and controlled diffusion of drugs. For antihypertensive molecules such as losartan and amiloride, optimized enhancer systems have shown significantly better transdermal absorption and plasma maintenance, and their therapeutic relevance.

Backing Laminates

The backing laminate serves as a protection for the drug polymer matrix from environmental exposure, such as moisture ingress, drug loss and mechanical damage. It has to be impermeable to the action of both drug and enhancer vapors and at the same time flexible and comfortable to wear. Common materials are polyethylene (PE), polyethylene terephthalate (PET), laminates of aluminum foils and polyurethane films. The laminate should also possess sufficient tensile strength to resist handling but be thin enough (50-100 μm) to retain flexibility. It was shown in the Figure.2 It must also be chemically inert to avoid absorption or migration of the formulation components [16-18]. In more modern transdermal systems, backing layers would be designed to be lightweight, hypoallergenic, and aesthetically acceptable, which will act to achieve prolonged patient compliance.

Adhesive Layers

The adhesive layer ensures intimate contact of the patch to the skin, and more or less constant drug diffusion at an area of contact. The most widely used type of adhesive in modern research in the area of adhesives are pressure sensitive adhesives (PSAs) which include acrylics, silicones, and polyisobutylene. A perfect PSA needs to have sufficient tack, peel, and shear resistance properties to prevent delamination or unwanted separation during physiological usage, but to also be easy to remove, leaving no residual depositions or epidermal discomfort. It should also be permeable enough to permit the diffusion of the drug over it and at the same time tenacious enough to make sure that the active ingredient is not degraded [19, 20]. Adhesive selection has a direct bearing on wear time, comfort to the wearer, and the overall reliability of the therapeutic use of the patch. Hypoallergenic and moisture resistant adhesives are the ones of choice for long term applications in hypertensive patients requiring 24-72 hours of continuous delivery.

Release Liners

The release liner is used as a protective cover for the adhesive surface during the manufacturing and storage of the patch to ensure that it is not contaminated or difficult to handle. It must be coated with non sticky materials such as silicone, fluoropolymer or Teflon to ensure a smooth release before its use. The liner should have a low peel force and be chemically inert so as to have no interaction with the drug or adhesive constituents. Some common materials are polyethylene terephthalate (PET), polypropylene (PP) or paper with a laminated silicone [21-23]. It must be able to withstand processing temperatures while being moisture impermeable and thus provide patch stability. In essence, the release liner maintains the integrity of the product from fabrication to the point of application to the patient that plays a part in the overall performance and safety of the transdermal system.

In Vitro and *In Vivo* Characterization

Comprehensive characterization of transdermal patches is a critical step in the evaluation of mechanical integrity, uniformity of drug content, release performance, and therapeutic efficacy of transdermal patches [24]. Both *in vitro* and *in vivo* analysis ensure that the system delivers the drug in a controlled, reproducible and biocompatible manner during the intended time of application.

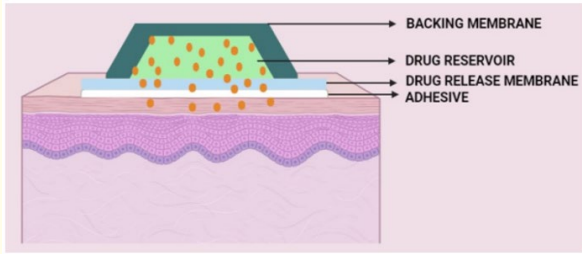

Figure 2: Transdermal Patch.

Physical Characterization

Physicochemical evaluation is needed to assure the uniformity, mechanical integrity, and reliability of transdermal patches. Some important parameters are thickness, weight uniformity, folding endurance, moisture content, and content uniformity. Patch thickness and weight count is taken to ensure uniform drug loading and distribution [25, 26]. Folding endurance is an assessment of the flexibility and resistance to mechanical stress and the moisture content for stability which can be lost by becoming brittle or by microbial growth. Content uniformity, based on spectrophotometry or reverse phase high performance can be used to verify homogeneous drug dispersion throughout patches. Adhesion properties are tested using shear, tack and peel adhesion tests to determine the strength, stickiness and ease of removal of the patch. Ideal formulations have a balance of adhesion, they have enough adhesion to last, but they are not so strong that they cause a painful experience of removal [27]. Collectively, these physicochemical tests assure structural integrity, consistent drug dosage and adequate adhesion of the patch to ensure optimal performance of the patch and patient compliance during transdermal therapy.

In Vitro Characterization

In vitro characterization assesses the drug release and permeation behavior of the transdermal patch in controlled conditions in the laboratory in order to predict their behavior in vivo. The Franz diffusion cell is the most commonly used cell in which the patch is embedded on a synthetic or biological membrane of the patch between a donor and a receptor compartment. Receptor medium which is maintained in a temperature of 32 ± 5 degree Celsius in order to simulate the skin temperature and it is continuously stirred to provide uniform diffusion [28]. Samples are withdrawn at predetermined intervals and are analyzed using UV spectrophotometry or using high performance liquid chromatography (HPLC) to obtain the cumulative drug release. The data are fitted to kinetic models such as zero order, first order, Higuchi or Korsmeyer Peppas in order to interpret the release mechanism. In addition, flux, permeability coefficient and lag time are calculated to assess the efficiency of membrane transport [29, 30]. These studies offer insight into the rate, extent and mechanism of drug delivery, providing for consistent, sustained release to provide effective transdermal therapy.

In Vivo Characterization

In vivo characterization is important to ensure the performance of the patch as a therapeutic, pharmacological, and safety (under physiological conditions). Studies done on animal models (e.g., rats, rabbits, or pigs) or human volunteers to assess the concentration of the pharmaceutical in the blood as a function of time after the patch is applied [31, 32]. Key pharmacokinetic parameters like Cmax, Tmax, Area under the plasma concentration-time curve (AUC) and bio-availability values are compared to the conventional oral formulations and it is used to check improvement in sustained drug delivery and systemic absorption. Skin irritation and sensitization tests are done (e.g. Draize Method) to assess the amount of erythema and edema or allergic response after extended contact time. Histopathological examination of treated skin can also be used as a further means of confirming tissue safety [33, 34]. The results of the *in vivo* studies confirm the efficacy, compatibility and stability of the patch, leading to a sustained level of therapy, minimal side effects

and better patient compliance important for chronic conditions such as hypertension, which require long term care.

Therapeutic Applications in Hypertension

Transdermal drug delivery systems have been proposed as a promising alternative for hypertension management providing many benefits for patients in addition to controlled release of the drug, prevention of hepatic first pass effect, and better compliance of patients, exposed particularly for chronic therapy [35]. By maintaining constant concentrations in the plasma, the transdermal patches limit fluctuations seen with oral dosing and limit the adverse effects, and therefore they are applicable for long term blood pressure control.

Traditional Molecules

Among the first antihypertensive agents used in the transdermal therapy, clonidine, nitroglycerin and verapamil have demonstrated clinical success [36, 37]. One drug, the clonidine patch, which has been approved by the FDA, releases the drug in a continuous manner for up to 7 days and provides a consistent level of plasma and a reduced risk of rebound hypertension. Similarly, nitroglycerin patches have been extensively utilized to treat both high blood pressure and angina while verapamil preparations are of interest with stable once daily transdermal administration [38, 39]. These different established molecules indicate the feasibility and the clinical utility of transdermal systems in cardiovascular management.

Emerging Molecules

New generation antihypertensive drugs like losartan potassium, amiloride hydrochloride, atenolol, nifedipine etc. are undergoing wide research for transdermal use. These agents have good molecular weight, lipophilicity and potency for good dermal absorption. Studies have showed that the use of losartan patches can improve bioavailability as well as maintain therapeutic plasma concentrations for 24-48 hours, while amiloride transdermal systems, optimized using exception based modeling supported by artificial intelligence, develop better diffusion and controlled release profiles [40]. These advances help decrease dosing frequency and improve adherence which seems to be a problem among hypertensive patients needing long term treatment.

Combination and Personalized Patches

The future of antihypertensive therapy are combination and personalized transdermal patches. Multi drug matrix systems with combination agents such as losartan, amlodipine or clonidine hydrochlorothiazide offer synergistic blood pressure control. Meanwhile, smart patches embedded with biosensors and microcontrollers making it possible for the real time monitoring of blood pressure and dynamic adjusting of drug release [41, 42]. Table 1 shows the combination of personalized patches. With the merging of information algorithms and pharmacogenomic information, these intelligent systems have become the next frontier of individual hypertension management with the promise of precision dosing, improving compliance, and achieving the best possible therapeutic results.

Future Perspectives

The future of antihypertensive therapy are combination and personalized transdermal patches. Multi drug matrix systems with combination agents such as losartan, amlodipine or clonidine hydrochlorothiazide offer synergistic blood pressure control. Meanwhile, smart patches embedded with biosensors and microcontrollers making it possible for the real time monitoring of blood pressure and dynamic adjusting of drug release [48, 49]. With the merging of information algorithms and pharmacogenomic information, these intelligent systems have become the next generation of individual hypertension management with the promise of precision dosing, improving compliance, and achieving the best possible therapeutic results [50-52].

Category	*Drug / Example*	*Mechanism / Function*	*Key Advantages*
Traditional Molecules	Clonidine	acts with alpha 2 adrenergic receptors, suppressing effect on the sympathetic outflow, reduces the arterial pressure [43].	Long lasting effect, fewer doses, and stable plasma levels.
	Nitroglycerin	By releasing nitric oxide and bringing vasodilation and improved perfusion.	The time of onset is rapid, and the prolonged action of the drug makes it useful both for hypertensive crisis as well as anginal relief [44].
	Verapamil	reduces myocardial contractility and peripheral vascular resistance reducing the cardiac workload.	Its first phase metabolism avoidance helps in a smoother blood pressure control.
Emerging Molecules	Losartan Potassium	The antagonist works by selective receptor blocking that works against vasoconstriction [45].	Sustained release preparations enhance absorption and supplement the systemic bioavailability.
	Amiloride Hydrochloride	Potassium sparing diuretic and retains serum potassium concentration.	Controlled release decreases the dosing frequency and the systemic adverse effects.
	Atenolol	A selective antagonist of the beta1-adrenergic receptors reduces heart rate and decreases cardiac output.	steady plasma concentration helps improve consistency of therapy and patient adherence to therapy [46].
Combination/ Personalized Patches	Losartan + Amlodipine	combines an ARB with a calcium channel blocker offer dual modulation of pathways.	Synergistic engagement in higher efficacy and simplified therapeutic regimen.
	Clonidine + Hydrochlorothiazide	combined presence of central sympatholytic and diuretic strategies enhances the control of hypertension.	The combination enables side effects burden reduction, blood pressure stability, and is amenable to once daily administration.
	Smart / Biosensor Patches	wearable devices include sensors and automatically adjust the release of a drug [47].	Personalized dosing, real time doses, and increased safety culminate to further increased medication adherence.

Table 1: Combination of Personalized patch.

Conclusion

Transdermal patch technology has emerged as a revolution in the way we treat high blood pressure, bringing together the benefits of controlled release of the medication, improved bioavailability and better patient compliance. Beyond the role of the passive delivery system, functional patches in the modern era even incorporate smart material, nanotechnology and biosensing functionality, marking the dawn of the era of individualized and adaptive therapy. The evolution of systems of artificial intelligence aided formulation design

and real time feedback controlled drug delivery has transformed the precision, reliability of the drug delivery. In addition, the progress in the biocompatible and biodegradable polymers guarantees long term safety and sustainability. As the global healthcare paradigm continues to be patient centric, technology driven, transdermal systems are destined to become next generation therapeutic interfaces the intersection of pharmaceuticals, digital health and biomedical engineering. Ultimately, then, the future of the control of hypertension is not only in drug innovation, but in the way that medicines are intelligently and efficiently delivered to provide a controlled and consistent efficacy with minimal burden on the patient.

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