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The Study of Various Approaches for the Transdermal Patches Possess Therapeutic Potential

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ABSTRACT

A non-invasive method of administering drugs through the skin's surface, transdermal delivery allows for the drug to be delivered across the dermis at a predefined rate, either locally or systemically. It might be used in place of hypodermic injections and the oral medication delivery system. Despite being more expensive than traditional formulations, transdermal dosage forms are gaining traction due to their distinct benefits. Transdermal systems have been used to formulate many medications, and more are being tested to see if this is a feasible way to administer them such as beta-blockers, calcium channel blockers, non-steroidal anti-inflammatory drugs, contraceptives, anti-arrhythmic drugs, insulin, antivirals, hormones, alpha-interferon, and cancer chemotherapeutic agents. Additionally, studies on several chemical penetration enhancers that can facilitate the delivery of medicinal compounds are still ongoing. This review article discusses personalized patch designs, transdermal patches' range of therapeutic uses in addition in-vitro and in-vivo studies.

Keywords: Transdermal Patch, Skin, In-vivo, In-vitro, Customized Patches

1. Introduction

Transdermal drug delivery systems, which are commonly referred to as patches, are a non-invasive method of distributing drugs throughout the skin's surface or dermis. It may be used as a substitute for giving hypodermic injections and medications orally. With the use of this drug delivery technology, an analgesic can be applied topically at a predetermined pace to provide either a local or systemic impact [1]

Transdermal drug delivery systems (TDDSs) are self-contained, discrete dose forms that enter the systemic circulation over an extended period at a predetermined, predictable rate through the skin portal when applied to intact skin [2-4]. For transdermal products, the aim of dosage design is to limit drug metabolism and retention in the skin while optimizing the amount of medicine that is absorbed through the skin and enters the systemic circulation. Transdermal administration offers a significant advantage over oral and injectable methods due to its ability to prevent first pass metabolism and increase patient compliance, respectively [5] The nitroglycerin patch was one of the earliest transdermal patches created

in 1985. The patch is based on a rate-controlling ethylene vinyl acetate membrane that was created by Gale and Berggren. Many medications are currently offered as transdermal patches, such as nicotine, fentanyl, clonidine, scopolamine (hyoscine), and estradiol combined with norethisterone acetate. The application site may change based on the drug's therapeutic category [6] Transdermal medications will keep becoming more and more popular as their efficacy and safety are enhanced. The development of patches that administer peptide and even protein molecules, such as insulin, growth hormone, and vaccinations, will represent yet another significant advancement [7].

1.1 Dominance of Transdermal Patches

For several valid reasons, they are favored over the oral route of medication administration to the systemic circulation.

- There is an improvement and increase in bioavailability.
- Some patients are tempted to smash tablets to facilitate swallowing, which eliminates the tablets-controlled release properties. Patients have trouble swallowing tablets and capsules.
- Hypodermic injections are not as good as these since they cause greater discomfort, waste medical resources, and increase the chance of spreading disease [8].
- More flexibility in stopping medication by removing patches, together with non-invasive, easy, and comfortable therapy, all contribute to improved patient compliance.
- When medications are administered subcutaneously, there can be less variation and a decrease in the concentration of the drug spike that occurs after oral administration [9].

1.2 Custom Designs of Transdermal Patches

Iontopatch - Iontophoresis technology has been used in physical therapy for over 20 years, but it has gained popularity recently because it is non-invasive, has fewer side effects than traditional treatments, and can accommodate more customized treatment plans. The IontoPatch is an iontophoresis patch that uses a low electric current to deliver medication through the skin, hair follicles, and sebaceous glands to the underlying tissue. The IontoPatch, in contrast to other iontophoresis patches available on the market, is intended exclusively for usage on body parts such as the elbows, knees, and shoulders that need a lot of motion. It is weight-bearing, can be splinted, wrapped, or braced, and patients with pacemakers can use it without risk.

Macroperm -It is now possible to distribute molecules that were previously too big for transdermal distribution to work with the help of the MacroPerm patch. APIs up to 25,000 daltons can be sent using the MacroPerm patch. New transdermal patch medications to benefit people worldwide will be the end product. The MacroPerm patch not only increases in size but also in variety of compounds that can be absorbed via the skin. For instance, the scientists at Tapemark were the first to show that big hydrophilic compounds—molecular substances that are soluble in water and attracted to it—could be applied topically.

Microderm -Patients can get a variety of medications via the MicroDerm patch due to the utilization of microneedle technology. The patch contains small microneedles that pierce the skin just enough to allow the medication to reach the bloodstream, without causing the discomfort or pain that is associated with using hypodermic needles. In the future, large molecule delivery, protein and peptide administration, biologics, diabetes control, and vaccinations are among the many uses for MicroDerm patches that offer safe, efficient substitutes for needles and injections

2. Review for Therapeutic applications of Transdermal Patch

As technology and research have advanced, numerous potential application areas for transdermal patches have been explored, as described below.

2.1 Based on Viral Infectious disease

The herpes simplex virus is the source of the viral infection known as herpes simplex (HSV). Based on the site of infection, the two most prevalent forms are genital herpes and herpes labialis. Cold sores, commonly known as herpes labialis, are characterized by blistering pain, ulcers, and vesicles on the lips or perioral region. Typically, herpes simplex virus type 1 (HSV-1) causes it, while type 2 (HSV-2) can also infrequently cause it. On the other hand, HSV-2, rather than HSV-1, is typically responsible for genital herpes, which develops in or around the genital area [10] Following the first attack, HSV travels retrogradely via axons that link the body's entry site to sensory neuron nuclei [11] The virus might occasionally reactivate to cause another outbreak of excruciating vesicles or ulcers [12] Acyclovir, a small molecule medication, is the mainstay treatment for HSV infection. An artificial counterpart of acyclic purine nucleoside is called acyclovir [10]; It can prevent the replication of HSV DNA at the basale stratum [13].

Dissolving polymeric microneedle arrays loaded with acyclovir have been developed to overcome the limitations of poor skin permeation for topical acyclovir formulations. These microneedle arrays break the skin barrier and improve acyclovir delivery to the stratum basale, resulting in enhanced site-specific acyclovir delivery [14] According to in vitro research, after 24 hours, the proportion of total acyclovir loading in the skin given by microneedle arrays was 45 times higher than that of acyclovir cream bought in outlets. Additionally, five times as much acyclovir was accumulated at the stratum basale as was needed to treat HSV infections. Intradermal acyclovir administration using microneedle arrays was also significantly higher in one in vivo investigation than it was for a cream formulation that existed commercially [14] According to these studies, acyclovir-loaded dissolving microneedle arrays are a potentially effective treatment for topical HSV infections. They are particularly helpful in avoiding major side effects related to systemic drug delivery after oral or intravenous drug administration.

Human papillomavirus (HPV) is the source of cutaneous viral infections that manifest as warts or verrucae. Salicylic acid applied topically is another popular wart therapy. Over time, salicylic acid can be used to partially eliminate warts and epidermal tissue because of its chemical peeling effect on the skin. Early transdermal administration of salicylic acid-containing Karaya gum patches has been utilized to treat verruca vulgaris, with a good rate of wart resolution [16]. Recently, bleomycin microneedle patches have been created to treat warts. Global assessment scores from patients as well as healthcare professionals indicated that the bleomycin microneedle patch was as effective as cryotherapy. However, assessments of much reduced visual analogue scale pain from patients in the microneedle group indicate that treatment with the bleomycin microneedle patch was significantly less unpleasant than cryotherapy. Reduction of pain is one of the main benefits of TDDS. In comparison to traditional injection drug delivery, encapsulated drug delivery using microneedles is more efficient, practical, and painless. It is particularly well-suited for treating cutaneous lesions [17].

2.2 Based on Vaccination

A pandemic outbreak has resulted from the newly discovered contagious respiratory disease known as COVID-19, which is brought on by the SARS-CoV-2 virus. Most COVID-19 patients have mild to severe symptoms when they first show up. Safe vaccinations that quickly elicit strong and enduring coronavirus-specific immune responses are desperately needed to stop the spread of COVID-19. One distinctive structural element of the viral envelope, the coronavirus spike (S) protein, is thought to be a major target

for vaccinations. Delivery systems for the COVID-19 vaccination have been developed using microneedle arrays. Dissolving microneedle arrays with embedded SARS-CoV-2-S1 subunits have been used to create novel vaccinations [15]. According to this study, skin-targeted delivery of SARS-CoV-2 S1 subunit vaccines was more immunogenic than traditional subcutaneous needle injection, as evidenced by the effective immune responses seen two weeks after vaccination and the significantly stronger responses observed. A promising vaccination approach to prevent coronavirus infection is the use of microneedle vaccinations. Because of their higher capacity for self-administration, which could boost vaccination coverage and aid in the disease's elimination, as well as their ease of use, pain reduction, and noninvasive nature, they may even be more advantageous than previously thought [15].

In order to provide a more comfortable and painless option to injections, researchers are working on transdermal patches that can administer vaccines via the skin. A prime example is the smallpox vaccine patch made with microneedles. Neutralizing antibodies were generated three weeks after inoculation when this vaccine patch was administered to mice. The transdermal patch may offer an alternate method of immunization and preservation because levels were sustained for 12 weeks and IFN-γ secreting cells significantly increased [18].

A lytic microneedle patch that targets skin antigen-presenting cells was created by another research team for use in influenza vaccinations. A biocompatible polymer was used to manufacture microneedles, which contain an inactivated influenza virus vaccine and dissolve into the skin in a matter of minutes. The patch completely protected the mice against a fatal threat by inducing robust antibody and cell-mediated immune responses. The findings offer a novel method for enhanced immunogenicity and simplicity of administration of vaccination using a transdermal patch, which may lead to a rise in immunization rates [19].

2.3 Based on Motion-Sickness

Most frequently, a 1 mg transdermal patch is put to the mastoid on a clean, hairless area behind the ear [20-21]. The patch's effects persist for around 72 hours, thus it should be applied at least 4 hours, preferably 8 hours, before being exposed to motion [20], [22-23], at that time, if needed, the patch can be changed. [20];[24]. Hands should be well cleaned before handling the transdermal patch as well as afterward. [26] Nonoral modes of administration, such the transdermal route, are beneficial because they enable the maintenance of therapeutic blood levels of a drug with a short half-life for extended periods of time. Additionally, since motion sickness frequently causes stomach stasis, the transdermal route is favorable. [26] Transdermal scopolamine is generally well tolerated [20]. Short-term use often has little effect on performance. [23] Dry lips, dry eyes, impaired vision, mydriasis, photosensitivity, and application-site dermatitis are a few such adverse effects. [27]; [20]; [22];[25]. Headache, sleepiness, disorientation, palpitations, tachycardia, bloating, constipation, and urine retention are less frequent side effects. [29] Rarely have reports of ipsilateral mydriasis, cycloplegia, toxic psychosis, hallucinations, restlessness, and acute angle glaucoma been documented. [23];[25]. Since its safety in children under the age of ten has not been proved, transdermal scopolamine should not be used in that age group. It should also be used cautiously in older adults.[21] It is not advisable to cut the transdermal scopolamine in half since this may impact the medication's release time. [27] Scopolamine users should refrain from operating heavy machinery or driving. Patients with prostatic hypertrophy or glaucoma should not use scopolamine. [20] Transdermal scopolamine has been shown in a randomized, double-blind crossover research involving 76 members of the naval crew to be more efficacious than cinnarizine in preventing motion sickness, and it also has less side effects [28].

2.4 Based on Analgesic

NSAIDs are widely used medications for the treatment of musculoskeletal disorders, both acute and chronic [30]. Their advantage is that they function locally without causing negative effects on the central nervous system or cognitive impairments. Ketoprofen, diclofenac, flurbiprofen, and piroxicam patches are among the various NSAIDs that are accessible commercially [31]. The purpose of topical NSAIDs is to promote adherence and reduce systemic side effects. After reviewing 3455 cases in a comprehensive analysis, topical NSAIDs for acute musculoskeletal problems (such strains and overuse injuries) can effectively relieve pain without having the systemic side effects linked to oral NSAIDs [32].

A typical NSAID patch used to treat acute pain in epicondylitis and ankle sprains is 1% diclofenacepolamine. Its application to aid in topical and systemic effects is supported by a recent review [33]. Patients with ankle sprains showed a decrease in pain levels after three hours. It is believed that the patch must provide analgesia by a local action because diclofenac first manifests in the plasma at a mean of 4.5 hours following topical application. Due to a local reservoir effect, the half-life of plasma diclofenac after patch removal is approximately 9–12 hours, as opposed to 1-2 hours after oral ingestion. Systemic adverse effects are extremely rare since systemic transfer after patch removal is only approximately 2% when compared to oral versions of diclofenac.

High potency, short-acting narcotic analgesic fentanyl is commonly used as a transdermal patch for chronic pain management and as an anesthetic during surgery. Additionally, they are employed in the management of cancerous discomfort. The low molecular weight and strong lipophilicity of this substance allow it to permeate the skin and disperse throughout the body. Over the course of a 72-hour application, each patch is made to keep the plasma fentanyl levels constant, with maximal plasma concentrations occurring between 12 and 24 hours. The anatomical site of application and blood flow have no bearing on the drug delivery rate. Fentanyl administration can increase by up to one-third when exposed to heat or when body temperature rises. Under the brand names duragesic/durogesic, fentanyl patches are sold commercially in doses of 12 µg/h, 25 µg/h, 50 µg/h, 75 µg/h, and 100 µg/h.

Patients with osteoarthritis or rheumatoid arthritis who have chronic pain benefit from these patches in terms of pain management and quality of life [34]. They are helpful when vomiting or trouble swallowing prevents the oral route from being utilized, or when severe renal impairment prevents oral morphine from being used [35]. According to several research, fentanyl patches are thought to be superior to oral morphine in the treatment of cancer.

2.5 Based on Migraine

A particular type of headache condition that mostly affects the head is called a migraine. Its severity can vary from mild to severe, and it is frequently accompanied by additional symptoms such as nausea, vomiting, sickness, vertigo that worsens with movement, photophobia, sonophobia, severe impairment, or other natural phenomena. Both migraines and inflamed injection sites can be treated with intravenous triptans. Transdermal delivery refers to the precise, controlled administration of pharmaceuticals through the skin. The goal of our research is to determine every potential transdermal patch application and combination for the management of migraines. Rizatriptan is a medication that is categorized as a selective serotonin receptor agonist. It works by narrowing blood arteries in the brain, blocking the brain's ability to receive pain signals, and stopping the synthesis of a number of naturally occurring substances that cause pain, nausea, and other migraine symptoms. Verapamil is a member of the calcium-channel blocker medication class. It functions by letting the blood arteries relax, which lessens the heart's workload. Verapamil and Rizatriptan have respective lambda maxima of 228 and 278.9 nm. In the majority of

solvents, they dissolve. The transdermal patch for rizatriptan increases patient compliance in hypertensive patients when administered in conjunction with verapamil. P2 patch displays the ideal outcomes.

2.6 Based on Cardiovascular

In a heart failure scenario, pharmacokinetics (PK) and pharmacodynamics (PD) are frequently altered to accommodate hypoperfusion systemic conditions due to reduced cardiac ejection fraction [36]. In addition, drug metabolism and metabolite clearance are reduced in the renal failure [37]. Moreover, hypoalbuminemia and hepatic congestion due to heart failure impair drug absorption [38]. Therefore, transdermal patch delivery systems provide a drug delivery solution. For example, propranolol is a nonselective beta-adrenergic blocker. Its hepatic first-pass metabolism is highly altered when taken orally, with a bioavailability of approximately 23% [39-40]. A result of a previous animal study with rabbits showed that oral propranolol gave a Cmax of 56.4 ng/mL within 13.2 min. However, due to liver metabolism involvement, its bioavailability was 12.3% [40]. On the other hand, the transdermal propranolol patch achieved a steady-state plasma concentration (Css) of 9.3 ng/mL after 8 h of initial lag time, recording a bioavailability of 74.8% higher than oral propranolol [40].

Nitroglycerin is another drug worth mentioning in cardiovascular therapy. Lauder Blanton used nitroglycerin to relieve angina pectoris and first noted drug resistance after repeated doses in 1867 [41]. Ferid Murad found that nitric oxide (NO) from nitroglycerin acts on vascular smooth muscle by activating cyclic guanosine monophosphate (cGMP), resulting in vasodilation [42]. The first transdermal nitroglycerin patch was developed by Gale and Berggren (Patent access US-4615699-A) in 1985. A year later, a two-way crossover study was performed on twenty-five healthy males with Nitro-Dur and another type of nitroglycerin transdermal patch, Nitro-Dur II, which showed an average Cmax of 0.383 ng/mL and 0.432 ng/mL, respectively [43].

3. Review for the In-vitro Studies

3.1 Based on study of drug release In vitro

The drug release from the produced patches was evaluated using the paddle over disc method (USP, 1995). Dry films with a surface area of 4.906 cm^2 were cut, weighed, and adhered to a glass disc using an adhesive. After that, the disk was put in the dissolving medium, which had been adjusted to 32 ± 0.5 °C. Samples (10 ml aliquots) were taken out of 900 mL of phosphate buffer (pH 7.4) at the required intervals for up to 24 hours, and the drug concentration was measured at 236 nm using a Shimadzu double beam UV-visible spectrophotometer. To keep the sink condition, 10 mL of newly heated buffer solution was added to the dissolving vessel (Mundada A.S & Avari J.G; 2011).

3.2 Based on Study of In vitro penetration

In the current investigations, a diffusion cell with a diffusional area of 4.906 cm^2 that was constructed along the lines of the Franz diffusion cell was used. The entire thickness of skin from the human cadaver's chest was utilized. The barrier in the diffusion cell was made of epidermis that had been isolated using the heat separation method [45]. It was positioned between the donor and receiver compartments with the stratum corneum facing upward in the donor compartment. The entire assembly was placed in an oven pre-set at 32 ± 0.5°C, with the skin in situ and in close contact with the receptor medium. The oven was left there until no UV absorbance was noticed [48]. The stratum corneum was covered with the test patch. As the receptor media, PBS pH 7.4 solution was mixed at 50 rpm using a magnetic stirrer. The absorbance of the sample was measured spectrophotometrically at 236 nm against a blank (PBS pH 7.4) after samples

(1 ml each time) were removed from the sampling port every 2 hours [47]; [49]. Using acquired data, flux and permeability coefficients were calculated [46], [44].

4. Review on Invivo

By monitoring the drug's pharmacological reaction after transdermal administration, the effectiveness of the created transdermal patch can be examined. Male adult Dawley rats weighing between 230 and 250 grams were employed in the current study's in vivo investigations. They were obtained from the animal house of our department. Standard laboratory settings were maintained for the animals, including a 12-hour light/dark cycle, 25 ± 1°C and 55 ± 5% RH. The animals were kept in individual polypropylene cages, each holding one animal. They had unlimited access to water and a standard laboratory feed provided by Lipton Feed, Mumbai, India.

After a cursory assessment of the skin's surface for anomalies, the animals were chosen. For the investigation, only rats weighing between 230 and 250g were chosen. The dorsal side of the skin was shaved down to about 10 cm^2. Rats were fasted for a full day prior to the patches being applied to monitor any negative effects of shaving. For this trial, a total of six rats were selected, and using conventional adhesive tape, a transdermal patch from the optimized transdermal formulation was applied to each rat's shaved skin (Johnson & Johnson). After dosage, food and liquids were avoided for at least two hours. Different times were used to obtain blood samples (2, 4, 6, 8, 12, 24 and 28 hours). After immediately centrifuging the blood samples at 5000 rpm, the plasma was separated and kept at -40 °C until it was analyzed using HPLC [53].

4.1 HPLC-based quantitative assessment of DH in plasma

Utilizing the Reverse Phase High Performance Liquid Chromatography (RP-HPLC) method, the quantitative analysis of DH was carried out. A variable wavelength programmable UV/VIS detector with a model LC-10A liquid chromatograph (Shimadzu Corporation, Kyoto, Japan) made up the chromatographic assembly. Reversed-phase C-18 Inertsil ODS 3V (250 mm × 4.6 mm ID, particle size 5 µm) (Shimadzu) was the column employed. The software from Shimadzu's Class-VP series, version 5.03, was installed on the HPLC system.

A precise 0.5 mL aliquot of plasma was transferred into a 10 mL glass tube featuring a Teflon-lined cover. 3.0 mL of cyclohexane: diethylether (2:1), 0.25 mL of 1.0 M dipotassium hydrogen phosphate, and 0.2 mL of water were added to it. A reciprocating test tube shaker was used to shake the samples for 15 minutes. After that, the organic phase was removed from the test tube and placed into a new test tube with 0.5 mL of 0.01 M hydrochloric acid. To release the medication into the aqueous phase, these tubes were shaken. Following extraction, the aqueous phase was fed into the HPLC column in 20 µL volumes. A 37:63 ratio of acetonitrile to water was utilized as the mobile phase, and 0.35 percent w/v of triethylamine was added. The pH was then corrected to 3.0 using 5% orthophosphoric acid. At a flow rate of 1 mL/min, the filtered mobile phase components were pumped out of the corresponding reservoirs. The temperature of the column was kept constant at 40˚C. The eluent was identified at 240 nm using a UV detector, and the data were collected, archived, examined, and utilized to calculate the DH plasma concentration using a standard graph. To create the standard graph, drug-free plasma was treated as previously mentioned and spiked with different concentrations of DH to span the concentration range from 10 to 200 ng/0.5 ml.

4.2 Studies on Drug Carrier Interactions and Skin Irritation

To determine whether the polymer under examination was suitable for transdermal application, its propensity to cause skin irritation was assessed [52].The cutaneous irritation of the rats was studied using

the [51] technique of grading. Based on UV, IR, and TLC analysis, drug carrier interaction experiments were carried out on the optimized formulation by contrasting it with pure drug and placebo formulation [50].

5. Conclusion

The low bioavailability of many oral medications and the discomfort and inconvenience of injections can both be addressed with transdermal drug delivery. Studies are being conducted to improve efficacy and safety. To improve practical concerns such as the experience for the wearer of the patch, and also to provide more precise medication delivery coupled with extended duration of action. Other possible advancements include enhanced transdermal technology, which raises the energy of the drug molecules or modifies the skin barrier to increase drug flux through the skin by using mechanical energy. Many "active" transdermal technologies are being researched for a variety of medications following the successful establishment of patches utilizing iontophoresis.

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