

A DETAIL REVIEW OF ANTI-FUNGAL TRANSDERMAL PATCH OF LULICONAZOLE

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ABSTRACT

Topical dose forms are designed to make it easy to administer medication across a specific region of skin. In order to create the optimal dosage form, considerations such as drug flux through the skin, dosage form retention on the skin's surface, dosage form reservoir capacity, and patient acceptance of the formulation must be made. Because of its shorter medication duration, increased effectiveness, and improved tolerance, luliconazolean optically active R-enantiomer of laniconazolehas superior patient compliance.The substance retains the wide antifungal range of an imidazole while having strong efficacy against filamentous fungi, including dermatophytes. The produced luliconazole transdermal patch.

Transdermal patches are a non-invasive way of medication delivery. It is an adhesive patch that is intended to penetrate the skin and enter the bloodstream, distributing a precise dosage of medicine throughout the body. Compared to other administration methods, transdermal medication delivery is less intrusive, more patient-friendly, and able to avoid first-pass metabolism and the harmful acidic environment of the stomach that arises from oral drug absorption.

For decades, transdermal patches have drawn interest and were used to administer medications such as nicotine, fentanyl, nitro glycerine , and clonidine to treat various diseases or disorders. This approach has also been investigated recently for the delivery of biologics in several applications. The design and application of medical patches for transdermal drug administration are reviewed here, with particular attention paid to current technological and innovative developments that have resulted in the development of smart, biodegradable/soluble, high-loading/release, and 3D-printed patches.

Keyword: luliconazole, transdermal patch ,drug delivery .

1. INTRODUCTION

Nowadays, a lot of topical, cosmetic, and transdermal delivery methods employ transdermal patches. Transdermal delivery systems, sometimes known as "patching," are medical procedures designed to disperse a very advantageous amount of medication across a patient's epidermis. Transdermal patches are often composed of many layers that cooperate to deliver the medication through the skin and into the circulatory system.

The term "transdermal patch" refers to a medical patch that has been surgically medicated and adheres to the skin's epidermis to allow the prescribed dosage of medication to penetrate the skin and reach the bloodstream.

Transdermal medication delivery is an alternate means of administering pharmaceuticals via the skin layer . The medication enters the bloodstream through the epidermis and travels across the body's systems before arriving at the intended location . Compared to alternative administration methods, the transdermal medication delivery approach offers a number of advantages. Some examples are the capacity to escape first-pass metabolism in the liver, the ability to avoid the digestive tract, and the capacity to provide continuous dosages of medications over a prolonged length of time . Other methods of administering drugs, such intravenous, may hurt and raise the risk of infection. However, the oral route is ineffective, and it is challenging to regulate the amount when using the inhalation approach.Transdermal administration is frequently used to administer medications for ailments like chronic pain, motion sickness, smoking cessation, and hormone replacement treatment because of its benefits over conventional delivery methods.

Transdermal drug delivery systems (TDDSs) are discrete, self-contained dosage forms that, when placed to skin that is not injured, release one or more medications over an extended period of time at a consistent, predetermined rate through the skin portal. Dosage design for transdermal medicines aims to maximize the amount of medication that is absorbed through the skin and reaches the systemic circulation while minimizing drug metabolism and retention in the skin. Because transdermal delivery may avoid first pass metabolism and improve patient compliance, respectively, it presents a considerable benefit over oral and injectable approaches.Modern pharmacology requires novel pharmacological forms to be produced in order to achieve appropriate therapeutic outcomes. These forms must be safe to deliver, have a suitable bioavailability, and promote patient compliance.

Transdermal patch :-

The first transdermal patch, Transderm-Scop (scopolamine), was initially authorized by the FDA in 1981 to treat motion sickness. Transderm-Nitro, a nitroglycerine patch, was then authorized in 1982 for the treatment of angina pectoris. Mountain View, California-based ALZA Corp. is the creator of both patches. In recent years, one of the most innovative concepts in medicine distribution has been TDDS. Currently, the USA has authorized over 35 transdermal medication

delivery devices for a variety of pathophysiological disorders, such as motion sickness, angina pectoris, hypertension, female menopause, and male hypogonadism.

Currently, over 40% of medications are being studied to see if transdermal drug administration is a practical solution. This demonstrates the transdermal delivery methods' effectiveness in the drug industry. In 2005, the market share of transdermal delivery was valued at \$12.7 billion; by 2010, it had increased to \$21.5 billion, and by 2015, it is expected to reach \$31.5 billion. In an attempt to enhance transdermal drug delivery for therapeutic and diagnostic purposes and target the distribution of the drugs to specific tissues, a number of state-of-the-art technologies have lately surfaced. One method of delivering medications locally or into the bloodstream is the transdermal patch. It can be applied at high doses and stays on the skin for a long period, which gives it an edge over other dermal drug delivery methods. There are four main varieties of transdermal patches, and each one is made up of three parts: the adhesive, backing layer, and patch matrix

1) Drug in a matrix type: The active pharmaceutical ingredients are directly loaded into the film patch material and the matrix is covered with adhesive and a backing layer.

2) Drug in adhesive type: The drug is loaded in a selfadhesive polymer and covered with a backing layer.

3) Drug in reservoir type: This type combines the drug in a matrix dispersion with a porous polymeric membrane for release rate control.

4) Multilamellar type: There are several layers of a drug-loaded matrix with a membrane in between the layers. This type could provide an initial burst drug release followed by sustained release. Therefore, it is suitable to relieve pain or swelling of muscles.

Advantages

- 1) Patches provide a range of medication delivery methods.
- 2) Easy to use
- 3) Transdermal delivery system is bypass for first pass metabolism effect
- 4) Reduce risk of high and low dose
- 5) No limitations on the patient's action
- 6) simply stopped by taking off the patch
- 7) Patches are in a single formulation, but give many dosages.

Disadvantages

- 1) Irritating the skin while attached.
- 2) Low quality patches falls off early when attached.
- 3) IMPAIRING THE MEDICINE'S DELIVERY

Transdermal patch design :-

A number of variables, including skin permeability, the area and length of the application, and the skin's metabolic activity (i.e., first pass metabolism), influence how well a medication travels through the skin. Actually, each medication has distinct qualities that might influence transdermal delivery. The medication has to be non-ionic and somewhat lipophilic in order to penetrate the epidermal barrier and achieve sufficient absorption and penetration. It is more difficult for molecules bigger than 500 Daltons to get through the stratum corneum, and the drug's therapeutic dosage should preferably be less than 10 mg daily.

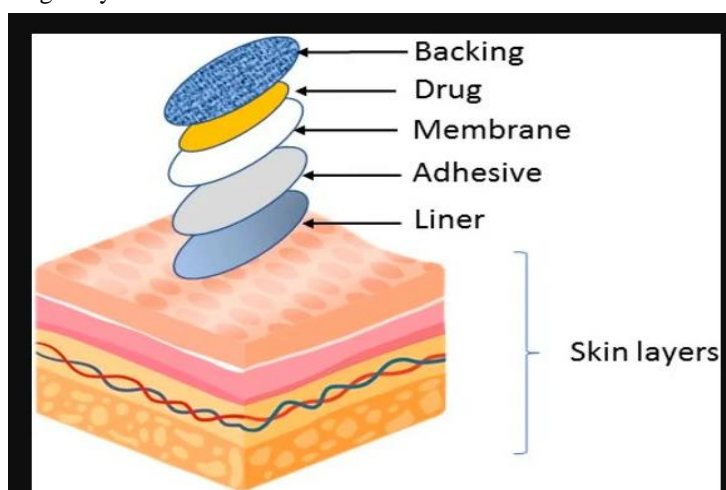


FIG -1

Transdermal patchetypes :-

1) Adhesive System Drug

The most basic type of membrane permeability control system is this one. This system's adhesive layer, which holds the many layers together, is drug-containing. The backing and liner are positioned between the medication combination.

2) System of Reservoirs

The medicine is delivered through the microporous rate-controlling membrane of this device, which is sandwiched between the backing layer and the drug reservoir. Within the reservoir chamber, the medicine may be disseminated in a solid polymer matrix or exist in the forms of a gel, suspension, or solution.

3) Matrix System

Drugs in the Matrix System are evenly distributed within hydrophilic or lipophilic polymer matrices. Affixed to drug-containing discs with regulated thickness and surface area is the resultant drug-containing polymer.

4) Small-Storage Device

This system combines a matrix dispersion system with a reservoir. In order to construct thousands of non-leaching tiny drug reservoirs, the drug is synthesized here by first suspending drug solids in an aqueous solution of a water-soluble liquid polymer and then evenly distributing the solution in a lipophilic polymer.

Recent Progress in Transdermal Patch Technology:

There are just two uses for conventional transdermal patches: medication release and storage. While there are several benefits to this approach, conventional patching has numerous difficulties and disadvantages, such as low release or restricted dose. Transdermal medication delivery has seen a number of advancements to date. Among these include the creation of innovative patches with improved drug penetration and release, increased loading, and precise drug sensing and release capabilities. All things considered, transdermal medication administration is a burgeoning field of study and research, with a plethora of fascinating new advancements to come, as will be covered below.

A smart Patches :

Sensors and other technologies are included into smart patches so that they may monitor patient circumstances and modify medicine administration as necessary. A team of scientists created a smart patch sensor technology in 2014 that uses microneedles to provide diabetics with continuous, painless intradermal glucose monitoring. The glucose-specific c-enzyme glucose oxidase (GOx) is immobilized by this patch, which employs a conducting polymer like poly (3,4-ethylenedioxythiophene) (PEDOT) as an electrical mediator for glucose sensing [72]. Subsequent investigation and advancement led to the creation of an intelligent insulin-releasing patch with 121 nanoparticle-containing microneedles. The patch enters the interstitial fluid between subcutaneous skin cells painlessly. Insulin and the glucose-sensing enzyme glucose oxidase, which changes glucose into gluconate, are both found in the nanoparticles that make up each needle. Polymers that respond to hypoxia envelop these molecules. Figure 4 illustrates how elevated glucose oxidase activity in response to elevated glucose produces an oxygen-depleted environment inside the nanoparticles, which is detected by the hypoxia-responsive polymer and causes the breakdown of the nanoparticles and the release of insulin.

The regeneration process of wound healing is intricate and dynamic, with physical and chemical characteristics that are always shifting. There are several advantages to its administration and observation, particularly for patients who are bedridden. A low-cost, flexible, completely printed smart patch was used to assess changes in wound pH and fluid volume on the skin, according to Iversen et al. Wound dressings may also be simply made with such flexible sensors. For measuring pH and humidity, the sensor is made up of different electrodes printed on a polydimethylsiloxane (PDMS) substrate. The resulting sensor patch is sensitive to the pH of the wound at a rate of 7.1 ohm/pH. The results of the hydration sensor demonstrated that the change in resistivity may be used to quantify the water content of a semi-porous surface.

In addition to mending wounds, researchers have created a smart patch that may be used to track and manage diabetic foot ulcers (DFU). Conductive hydrogel patches with an ultra-high transparency polymer network are used to construct this system. Significantly, the use of extremely transparent conductive hydrogel patches can include visual monitoring of the state of wound healing, haemostasis promotion, enhanced cell-to-cell communication, wound infection prevention, collagen deposition promotion, and vascularity improvement. It successfully encourages the repair of DFU by fostering angiogenesis. The adaptable intelligent patch can also promptly detect movements of different body proportions and do indirect blood glucose monitoring by measuring the amount of glucose present in wounds. It's interesting to note that this smart patch can both cure wounds and monitor chronic wound dressings.

Additionally, curcumin and other natural substances are delivered via smart patches. Paraffin wax and polypropylene glycol, a phase-change material (PCM), make up the substance. PCM was mixed with heating components made of

graphene, which were produced by laser-scribing polyimide sheets. With this setup, smart patches with electronically controlled release and repeatable dosage are given a new lease of life. Rather than depending on passive diffusion, emission is initiated and halted by carefully regulated heating of the PCM, and penetration only happens when the PCM changes from a solid to a liquid state. The results showed that the curcumin delivery yields were acceptable and good.

Three dimensional (3D) printed patch:-

Researchers are creating transdermal patches that are personalized to each patient's unique needs through the use of 3D printing technology [83]. The usage of a 3D-printed patch to aid with wound healing is one such example. Gelatin methacrylate, or GelMA, was investigated as a potential solution with adjustable physical characteristics in a research by Jang et al. Because hydrogel inks are shear-thinning, it was possible to print GelMA hydrogel with a peptide that mimics vascular endothelial growth factor (VEGF) using a 3D bio-printer. The hydrogel patch's three-dimensional structure was very porous and capable of absorbing water. It is possible to employ the 3D Gel-MA-VEGF hydrogel patch for wound healing because the VEGF peptide, which is gradually released from hydrogel patches, may encourage cell survival, proliferation, and tubular structure creation.

Transdermal patches, on the other hand, were designed and made using a three-dimensional (3D) printing method known as continuous liquid interface production (CLIP). When compared to the smooth square pyramid shape, the multifunctional microneedle design increased surface area, which enhanced the surface coating of the model vaccine components (ovalbumin and CpG). The study evaluated in vivo charge retention and bioavailability in mice as a function of delivery route using fluorescent tags and live animal imaging. Transdermal delivery of soluble components produced better skin charge retention than subcutaneous bolus injection, and it also increased the activation of immune cells in draining lymph nodes.

Furthermore, the administered vaccination produced dose sparing due to a robust humoral immune response with increased total IgG (immunoglobulin G) and a more balanced IgG1/IgG2a repertoire. Additionally, it triggered a T-cell response that was demonstrated by Th1 (T helper type 1) cytokine-secreting CD4⁺ T-cells and functionally lethal CD8⁺ T-cells. To sum up, CLIP 3D-printed microneedles loaded with vaccine ingredients offer a practical platform for self-administered, non-invasive immunization.

Using a class I resin that was exclusive to them, another team of researchers used stereolithography (SLA) technology to design and print the patch. They demonstrated the potential of these patches for transdermal administration of antibiotics with large molecular weights, as rifampicin (M(w) 822.94 g/mol). This medication has significant hepatotoxicity, decreased bioavailability, and stomach chemical instability. To improve the mechanical strength and integrity of the patch array, the patch was built with sub-apical holes located at one-quarter of the needle tip. To assess print quality and uniformity throughout the array, optical and electron microscopy were used to characterize the tips.

Additionally, the system was mechanically characterized for penetration and failure analysis. The ex vivo penetration and subsequent transport of rifampicin through swine epidermis were methodically assessed by the authors. Additionally, an in vivo trial using a 3D-printed patch to administer rifampicin showed effective penetration and acceptable bioavailability.

High load releasing patch:-

High drug loading and regulated drug release are necessary for long-acting transdermal medication administration. A new pressure-sensitive adhesive (PSA) modified with hydroxyphenyl (HP) was developed [89] to enable regulated drug release and increase drug-polymer miscibility. The findings demonstrate that, in contrast to ionic and neutral H-bonds, the dual-ionic H-bonds between R(3)N and R(2)NH-type medications and HP-PSA are reversible and quite strong. This allowed patches to greatly increase the drug loading from 1.5- to 7-fold and regulate the drug release rate from 1/5 to 1/2 without affecting the overall release profile. The HP-PSA-based high-load patch has the potential to deliver drugs for a long time since, according to pharmacokinetic data, it prevented abrupt release, raised the area under the concentration-time curve (AUC), and extended the average dwell time by more than six times. Its mechanical and safety requirements are also satisfied. Mechanistic investigations have demonstrated that relatively strong contacts may also govern drug release, and that repulsion of ionic pharmaceuticals in HP-PSA promotes drug loading. Its reversibility was evaluated by incomplete hydrogen bond transfer, which made the medication release percentage comparable to that of non-functional PSA. In summary, the development of long-acting transdermal drug delivery systems will be aided by HP-PSA's unique interactions, high drug loading efficiency, and regulated drug release capabilities. Furthermore, the synthesis of double-ionic H-bonds offers further motivation for diverse drug delivery schemes in non-polar settings. Strong intermolecular hydrogen and ionic bonding in pharmaceutical polymers is a common technique to prevent drug recrystallization; however, this comes at the price of the drug's release rates in transdermal patches. Researchers devised

a novel drug IL (drug ionic liquid) technique to boost drug loading in order to get around this problem [90]. The model polymer selected was a pressure-sensitive adhesive (PSA) based on carboxyl.

Application of transdermal patch:-

1)Transdermal Gene Therapy Patches :-

Transdermal patches have been the subject of recent research with gene therapy delivery of genetic material to damaged cells [94]. Innovative research aimed to concurrently transfer photothermic chemicals and genes to cancer cells. Transdermal patches co-loaded with p53 DNA and IR820, a near-infrared dye, were made for this purpose using a two-step casting process. Before p53 DNA and IR820 were mostly put onto the patches, hyaluronic acid was originally created as the matrix. The patches released p53 DNA and IR820 at subcutaneous tumor locations with efficiency, penetrating the stratum corneum and dissolving quickly. The patch demonstrated an excellent anti-tumor impact in vivo due to the synergistic effect of gene therapy and photothermal agents.

2)Transdermal patch of patch of vaccination:-

Patches for transdermal gene therapy

Recent studies have explored the transfer of genetic material to damaged cells via transdermal patches as a means of gene therapy [94]. The goal of this creative research was to introduce genes and photothermic substances into cancer cells at the same time. For this reason, transdermal patches containing both p53 DNA and the near-infrared dye IR820 were created by a two-step casting procedure. Hyaluronic acid was first developed as the matrix before p53 DNA and IR820 were primarily applied to the patches. The patches penetrated the stratum corneum and promptly disintegrated, releasing p53 DNA and IR820 to subcutaneous tumor areas with efficiency. The patch's outstanding anti-tumor efficacy in vivo was caused by the combination of photothermal agents and gene therapy working in concert. A different research team created a lytic microneedle patch that targets skin antigen-presenting cells in order to immunize against influenza. A biocompatible polymer that contains an inactivated influenza virus vaccine for quick skin disintegration was used to make microneedles. In mice, the patch produced robust antibody and cell-mediated immune responses that offered total defense against deadly challenge. The findings offer a novel method for more easily administered, safer immunization with enhanced immunogenicity through the use of a transdermal patch, which may allow for higher vaccination rates.

3) Transdermal Infectious Disease Patches :-

Novel medication delivery strategies are made possible by developments in transdermal drug delivery techniques. Currently, attempts are underway to test the transdermal administration of more medications, including vaccinations and antibiotics. Regarding transdermal antibiotics, a transdermal cephalexin patch was created by combining the zwitterionic characteristic cephalexin with solid lipid nanoparticles (SLNs). This demonstrated a consistent antimicrobial action while using little antibiotics. An alternative method is to put amoxicillin, ampicillin, and kanamycin onto bacterial cellulose/polycaprolactone (BC/PCL) patches for the development of transdermal administration. Such approaches can create a good bactericidal effect against *Staphylococcus aureus* and *E. coli* [154]. Tetracyclines have also been added to hydrogel-forming microarray patches intended for transdermal administration. Rats were used in an in vivo investigation to evaluate the C_{max} of this method, which was 7.40 µg/mL at 24 hours as opposed to 5.86 µg/mL at 1 hour for oral tetracycline [155]. Vancomycin was treated similarly, with the C_{max} of the hydrogel-forming microarray patch rodent model being 3.29 µg/mL at 48 h post-treatment and the dissolving microarray patch rodent model showing 1.58 µg/mL at 24 h post-treatment, compared to oral with C_{max} 3.37 µg/mL and intravenous with C_{max} 50.34 µg/mL.

4) Contraception transdermal patch :-

Another estrogenic medication used for contraception is ethylestradiol [130]. The FDA authorized Ortho Evra™, the first transdermal ethinyl estradiol contraceptive, in November 2001. It consists of ethinyl estradiol and norelgestromin together [131]. According to a similar pharmacokinetic research, transdermal ethinylestradiol had a minimum half-life of 16.1 and a C_{max} of 58.7 to 71.2 pg/mL at various application field locations [131]. Early research on the effectiveness of transdermal ethinylestradiol patches revealed statistically significantly higher medication compliance than oral tablets.

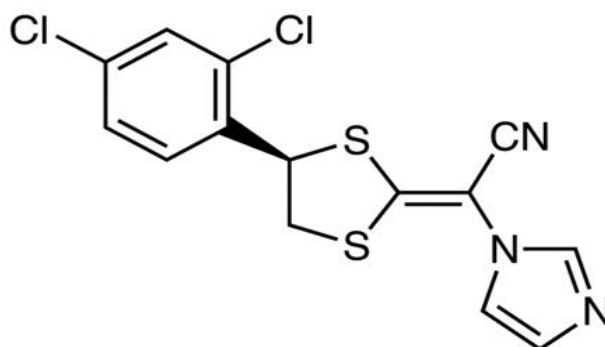
However, male hypogonadism has been treated with testosterone. Testosterone can be administered in a number of methods, such as intravenous testosterone enanthate and transdermal testosterone patches (both matrix and reservoir forms). With a lengthy half-life of 7-9 days, intravenous treatment produced a C_{max} of over 1200 ng/L (1.2 ng/mL) 24 hours after dosage (Drugbank access: DB13944). At 16 weeks of therapy, the C_{max} for reservoir testosterone transdermal patches, like Androderm, was 765 ng/L (0.765 ng/mL), with a mean T_{max} of 8 hours. However, after 15–19.5 hours, greater testosterone concentrations were seen for administration using novel matrix-type testosterone

transdermal patches (mean Cmax varied from 4.33 to 6.18 ng/mL). The average half-life of testosterone after removal of the patch from the skin is 1.3 hours.

4) Transdermal Patches for Disorders of the Central Nervous System (CNS)

5) Hormone Deficiencies Transdermal Patches

Luliconazole structure :-



Evaluation tests for luliconazole :-

- 1)pH
- 2) Outward appearance
- 3)Drug content
- 4) Absorption of moisture
- 5)Melting point

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