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Advancements in Transdermal Drug Delivery Systems: Innovations, Applications, and Future Directions

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Abstract:

Transdermal patches offer a convenient and non-invasive method for drug delivery through the skin, directly into the bloodstream. They provide several advantages such as bypassing first-pass metabolism, avoiding the digestive system, and allowing for continuous dosing over extended periods. Transdermal patches come in various types, including matrix, reservoir, drug-in-adhesive, and micro-reservoir systems, each with distinct mechanisms for controlling drug release. Recent advancements include smart patches with sensors for monitoring and adjusting drug delivery, dissolving patches that eliminate disposal concerns, three-dimensional printed patches for personalized medicine, and high-loading patches for increased drug efficacy. Potential applications extend beyond traditional drug delivery to include vaccination, gene therapy, insulin transport for diabetes management, and treatment for heart conditions. As research progresses, transdermal patches continue to evolve, offering promising solutions for a range of therapeutic needs. This article covers the creation and use of medical patches for transdermal medication transport, with a focus on recent technological and creative advancements that have led to the creation of intelligent, biodegradable/soluble, high-loading/release, and three dimensional-printed patches.

Keywords: Transdermal, Transdermal, Drug Delivery System, Transport, Innovation

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Introduction

1. Introduction

Transdermal drug transport is an additional technique for delivering medication through the cutaneous bed[1,2]. The medication enters the bloodstream through the epidermis and travels across the body's systems before arriving at the intended location[1,2]. Compared to alternative administration methods, the transdermal medication transport approach offers a number of advantages. Some examples are the capacity to prevent first-pass metabolism in the liver, the ability to prevent the digestive tract, and

the capacity to administer continuous dosages of medications over a prolonged length of time [3]. Other methods of administering drugs, such intravenous, may hurt and raise the hazard of infection. However, the oral way is ineffective, and it is challenging to regulate the amount when using the inhalation approach. Transdermal administration is a popular method of drug transport for chronic pain, motion sickness, smoking cessation, and hormone replacement treatment because of its advantages over other ways [4–6].

A transdermal patch is a medicated patch that can be applied topically to provide medication at a specified rate directly into the bloodstream via the beds of cutaneous. Actually, the most practical way to administer is via patches. They can be stopped at any time, and the course of treatment can last for several days because they are non-invasive (Table 1). They have various sizes and are made up of several substances. After the patch is applied to the cutaneous, diffusion processes allow it to release active ingredients into the bloodstream. Transdermal patches—like the 1985 nitroglycerin patch—use Gale and Berggren's rate-controlling ethylene vinyl acetate membrane as a paradigm to deliver long-lasting active ingredients to the skin. At the moment, a number of medications are offered as transdermal patches, including nicotine, scopolamine (hyoscine), fentanyl, clonidine, and estradiol combined with norethisterone acetate (Table 2). Depending on the drug's therapeutic category, the application location may change [7]. For instance, one can apply estradiol to the abdomen or buttocks and nitroglycerin to the chest. Moreover, the length of the drug's release is contingent upon usage, ranging from the shortest (up to 9 hours) to the longest (up to 9 days).

Table 1: Advantages and disadvantages of transdermal patches.

Advantages	**Disadvantages**
Continuous dosage during a few days of treatment	Restricted class of drugs
Escape the first-pass metabolism and the digestive system	Irritation of the cutaneous
Abrupt termination is possible	Variations in absorption
Not as intrusive	Patch malfunction
	Restricted choice for dosage

Table 2: An overview of the special qualities of transdermal patches and products.

Product Name	**Drugs**	**Duration of Application**	**Indication**	**Reference**
Secuado®	Asenapine	24 h	Mania, bipolar disorder	[8,9]
Catapres-TTS®	Clonidine	7 days	attention deficit hyperactivity disorder (ADHD), Hypertension, Tourette syndrome, Tic disorder.	[10–13]
Xelstrym®	Dextroampheta mine	Up to 9 h	ADHD	[14]
Bisono®	Bisoprolol	24 h	Atrial fibrillation	[15]
Butrans®	Buprenorphine	7 days	Management of pain	[16–18]
Daytrana®	Methylphenidate	Up to 9 days	ADHD	[19]

Nicorette®Habitrol®, CQ® Nicoderm® Nicoderm	Nicotine	24 h 16 h	Smoking cessation	[20,21]
Adlarity®	Donepezil	7 days	Alzheimer disease	[22,23]
Fematrix®	Estrogen	7 days	Postmenstrual syndrome	[24,25]
Ortho Evra®	Ethinyl Estradiol	7 days	Prevent pregnancy	[26,27]
Duragesic®	Fentanyl	72 hours	Moderate/severe pain	[28]
Sancuso®	Granisetron	Up to 7 days	Anti-emetic	[29–31]
Climara Pro®	Levonorgestrel, Estradiol	7 days	Postmenstrual syndrome	[32,33]
Lidoderm® Dermalid®	Lidocaine	up to 3 times daily for no more than 12 hours	Treatment of pain	[34,35]
Minitran® Nitro-dur®	Nitroglycerin	12–14 h	Angina pectoris Relieve pain after surgery	[36–39]
Combipatch®	Norethindrone Estradiol	3–4 days	Symptoms of menopause	[40]
Oxytrol®	Oxybutynin	3–4 days	Overactive bladder	[41,42]
Exelon®	Rivastigmine	24 h	Alzheimer disease	[43,44]
Neupro®	Rotigotine	24 h	Parkinson's disease	[45]
Emsam®	Selegiline	24 h	Depression	[45]
Transderm-scop®	Scopolamine	72 h	Motion sickness	[46,47]
Androderm®	Testosterone	24 h	Hypogonadism in males	[48,49]
Vivella® Menostar® Minivelle®Alora® Climara® Vivelle-Dot ® Estraderm®	17-β-Estradiol	3–4 days 3–4 days 7 days 3–4 days 3–4 days 3–4 days	Postmenstrual syndrome and osteoporosis	[50–52]

2. Transdermal Patch Creation

A number of variables, including cutaneous permeability, the area and length of the application, and the cutaneous metabolic activity (i.e., first pass metabolism), influence how well a drug travels through the cutaneous. Actually, each medication has distinct qualities that can influence transdermal transport. In order to effectively permeate and absorb through the epidermal barrier, the drug needs to be lipophilic and non-ionic. Greater than 500 Daltons in size may find it difficult to

pass through the stratum corneum, necessitating a therapeutic dose of less than 10 mg per day.

3. Fundamental Transdermal Patch Constituent

Transdermal patches are usually made up of many beds with the purpose of delivering the medication into the bloodstream through the cutaneous. A medicated patch's fundamental components are shown in Figure 1. Depending on the medication being administered and the intended rate of drug release, the patch's precise shape and composition may change.

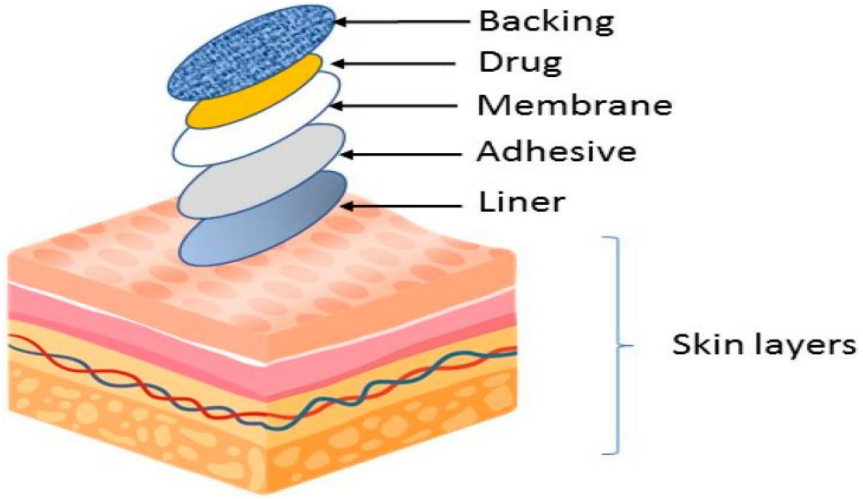

Fig. 1: Fundamental part of a medicinal transdermal patch.

The patch's outermost bed, known as the backing bed, shields the inner beds from the elements. Typically, a flexible, waterproof substance like polyethylene or polypropylene is used to create this bed. The purpose of the adhesive bed is to adhere and maintain the patch's position on the cutaneous. Usually, it is composed of a cutaneous-friendly, hypoallergenic adhesive that is robust. Drugs that are absorbed through the cutaneous are found in the drug bed. It is designed to release the medications gradually and at a steady pace. The rate at which the medications are released from the patch is managed by the rate-controlling membrane. Typically, semi-permeable materials are used to create membranes, which enable regulated medication passage through the membrane. The patch and adhesive are shielded by the linen. Prior to being placed to the cutaneous's surface, the patch needs to be taken off.

4. Transdermal Patch Types

Four main categories can be used to group transdermal medicinal patches: matrix, reservoir, drug-in adhesive, and micro-reservoir systems (Figure 2). Commercially available patches fall mostly into two categories: reservoir or matrix systems [53].

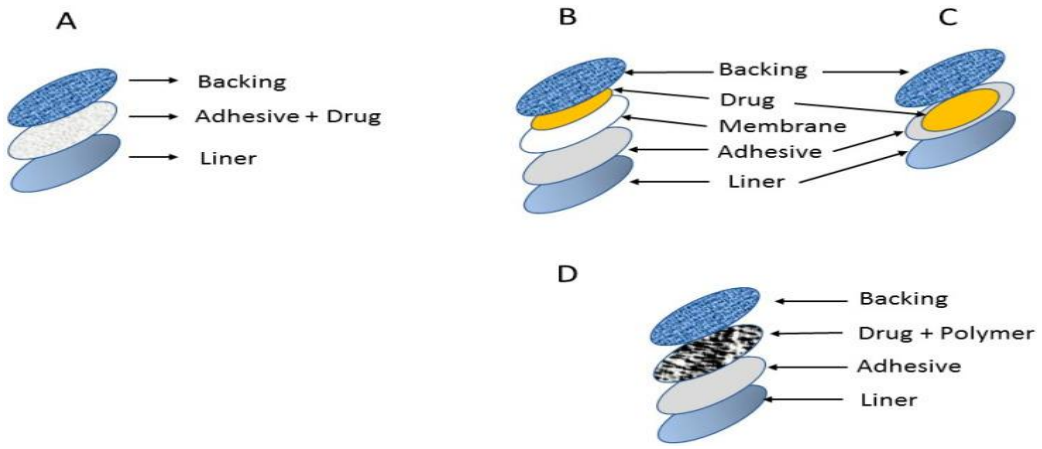

Fig. 2: Types of transdermal patches: (**A**) Adhesive System Drug; (**B**) System of Reservoirs; (**C**) matrix system; (**D**) Micro-reservoir system.

4.1. Adhesive System Drug

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

4.2. System of Reservoirs

This device's microporous rate-controlling membrane, which is positioned between the drug reservoir and the backing bed, is used to administer the medication. The medication may be distributed in a solid polymer matrix or take the form of a gel, suspension, or solution inside the reservoir chamber.

4.3. Matrix System

Drugs are evenly distributed throughout hydrophilic and hydrophobic polymer matrices in the Matrix System. The thereby formed polymer that contains drugs is affixed to plates that contain drugs and have a regulated surface area and thickness.

4.4. Micro-Reservoir System

To generate non-leaching drug reservoirs, the approach suspends pharmaceutical solids in a water-soluble polymer solution and uniformly disperses them in a lipophilic polymer.

5. Microneedle-Based Patches

Table 3 lists the several varieties of microneedles, each having special qualities and traits. To date, microneedle-based patches have been classified into four main categories: coated, hollow, solid, and dissolving microneedles (Figure 3). It will depend on the specific application and the user's requirements which type of microneedle works best.

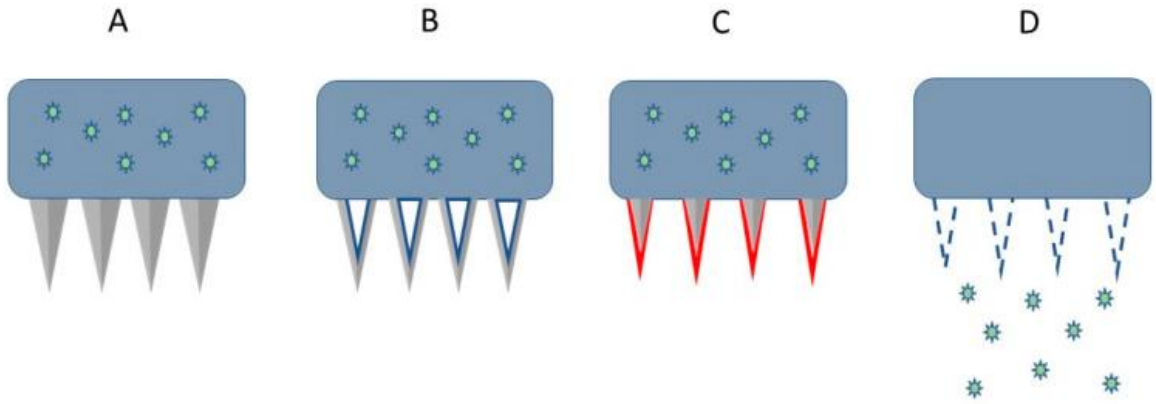

Fig. 3: The microneedle-based patch: (**A**) solid; (**B**) hollow; (**C**) coated; (**D**) dissolving.

Table 3: Varieties of microneedles and their distinctive characteristics.

Type	Construction	Material	Dose	Conveyance Rate	Application	References
Solid	Simple	Silicon, Metal, Polymer	Small dose	Fast	Can be reuse	[54–56]
Dissolving	Complex	Polymer	More precise dosing	Slow	Single	[57–60]
Coated	Complex	Polymer, Sugar, Lipids	More precise dosing	Fast	Single	[61–64]
Hollow	Simple	Silicon	Large dose	Fast	Can be reuse	[65–68]

5.1. Solid Microneedles:

The most basic kind of microneedles are solid ones, which are made up of solid needles that pierce the cutaneous to form microscopic channels. Solid microneedles are frequently employed in cosmetic and medication administration procedures.

5.2. Dissolving Microneedles:

These needles' composition includes elements that dissolves beneath the skin, allowing drugs or other chemicals to be released under control. In order to administer vaccines and other drugs, dissolving microneedles are frequently utilized.

5.3. Coated Microneedles:

When a coating on these microneedles penetrates the cutaneous, it dissolves, releasing medication or other substances. Transdermal medication transport frequently makes use of coated microneedles.

5.4. Hollow Microneedles:

These microneedles can transfer liquids or medications into the cutaneous because of their hollow cores. Hollow microneedles are frequently utilized for interstitial fluid collection and transdermal medication administration.

6. The Transdermal Patch's Latest Development

There are just two uses for conventional transdermal patches: medication release and storage. While there are several benefits to this approach, traditional patching has numerous difficulties and disadvantages, such as low release or restricted dosage. Several advancements have been made in the transport of transdermal medications thus far. Among these are novel patches with enhanced drug release and penetration, more loading, and accurate drug detection and release capabilities. All things considered, transdermal medicine transport is an area of study and research that is rapidly expanding, and as will be discussed below, there are many exciting new developments in store for this sector.

6.1. Smart Patches

In 2014, scientists created a smart patch sensor that use microneedles to provide diabetics with continuous, painless intradermal glucose monitoring. Using a conducting polymer such as PEDOT, the sensor immobilizes the glucose-specific c-enzyme glucose oxidase (GOx), enabling

glucose detection and adjusting drug delivery. This technology represents a major breakthrough in smart patch technology [69]. The interstitial fluid between subcutaneous skin cells can now be painlessly accessed thanks to the development of an intelligent insulin-releasing patch with 121 microneedles that contain nanoparticles. Insulin and glucose oxidase, two enzymes that sense glucose, are both present in hypoxia-responsive polymers in the patch. Figure 4 illustrates how the hypoxia-responsive polymer recognizes the oxygen-depleted environment caused by elevated glucose oxidase activity is recognized by the hypoxia-responsive polymer, which causes the disintegration of nanoparticles and the release of insulin [70,71].

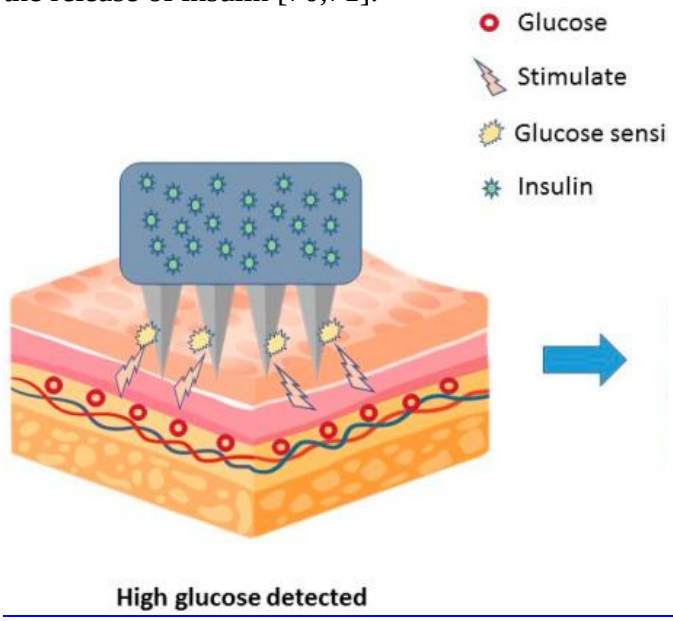

Fig. 4: The patch with microneedles pierces the epidermal layer and contains the enzymes glucose oxidase and insulin. Painless penetration of the skin is made possible by increased glucose oxidase activity, which also releases insulin and breaks down nanoparticles.

The process of healing a wound is dynamic, with physical and chemical aspects that are always shifting. A flexible, low-cost smart patch was created to monitor cutaneous surface changes in fluid volume and pH of the wound. The pH and humidity are measured by the sensor, which consists of electrodes printed on a polydimethylsiloxane substrate. With the addition of a hydration sensor, the patch can be used to measure the amount of water on a semi-porous surface, as it is sensitive to wound pH at 7.1 ohm/pH. This method has benefits for individuals who are bedridden [72]. A smart patch has been created by scientists to treat and track diabetic foot ulcers (DFU). Utilizing conductive hydrogel patches with an ultra-high transparency polymer network, the technique can monitor the healing process of wounds, facilitate hemostasis, improve communication between cells, ward off infections, encourage the deposition of collagen, and increase vascularity. The patch may detect changes in body proportion and promotes angiogenesis, which promotes wound healing. By determining the amount of glucose in wounds, it also carries out indirect blood glucose monitoring. This intelligent patch has the ability to monitor and heal open wounds [72].

Additionally, curcumin and other natural substances are delivered via smart patches. The material is made up of phase-change material (PCM) polypropylene glycol and paraffin wax. PCM and graphene heating elements made by laser-scribing polyimide sheets were coupled. This configuration gives fresh life to smart patches with electronically controlled release and reproducible dosing. Instead of relying on passive diffusion, the PCM is heated under carefully controlled conditions to start and stop emission, and penetration occurs only when the PCM transforms from a solid to a liquid state. It was discovered that the curcumin transport produced satisfactory and sufficient outcomes [73].

6.2. Three-Dimensional-Printed Patches

Scientists are creating transdermal patches that are customized to each client's unique needs through the use of three-dimensional printing techniques [74]. The application of GelMA, a three-dimensional printed patch, to aid in wound healing was investigated in a

study by Jang et al. The hydrogel patch was incredibly porous and water-absorbing, and it was printed with a peptide that resembled vascular endothelial growth factor (VEGF). The hydrogel patch is a promising treatment for wound repair because the VEGF peptide gradually seeps out of it and promotes cell survival, proliferation, and the development of tube-like structures [75].

Conversely, Continuous Liquid Interface Production (CLIP), a three-dimensional (three dimensional) printing technique, was used to develop and create transdermal patches. The enhanced surface area of the multifarious the microneedle design over the smooth square pyramid form led to an enhanced coating on the surface of the model vaccine components (ovalbumin and CpG). The in vivo charge accumulation and bioavailability in mice as a function of delivery method were evaluated in this work using tags with fluorescent tags and live animal imaging.

Compared to subcutaneous injection, transdermal delivery of soluble components resulted in higher epidermal charge retention and enhanced immune cell activation in draining lymph nodes. Dosage avoidance was made possible by the vaccine, which produced a strong humoral immune response with elevated total IgG and balanced IgG1/IgG2a repertoire. CLIP Vaccine-coated three-dimensional printed microneedles induce a T-cell response, exhibiting CD4+ T-cells that secrete Th1 cytokines and functionally lethal CD8+ T-cells [75].

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 high molecular weights, as rifampicin (M(w) 822.94 g/mol). This medication has been linked to significant hepatotoxicity, decreased bioavailability, and stomach chemical instability. To improve the mechanical strength and integrity of the patch array, sub-apical holes were incorporated into one-quarter of the needle tip when constructing the patch. To assess print quality and uniformity across the array, visual and scanning electron microscopy were used to characterize the tips. Additionally, the system underwent a mechanical evaluation for potential failures and intrusions. The ex-vivo penetration and subsequent transport of rifampicin through the swine epidermis were thoroughly assessed by the authors. Furthermore, an in vivo investigation using a three dimensional-printed patch to administer rifampicin showed effective penetration and acceptable bioavailability [75].

Powder extrusion (DPE) has emerged as the most practical approach because it can directly handle medications and excipients in a single step [76]. The purpose of the study was to ascertain whether various grades of ethylene-vinyl acetate (EVA) copolymers could be utilized as unique raw materials in the manufacturing of transdermal patches. To evaluate the flexibility of EVA in producing personalized transdermal treatment patches, two model drugs—ibuprofen and diclofenac sodium—were combined with 30% (w/w) EVA. The effective incorporation of the starting material into the final formulation was confirmed by Fourier transform infrared (FT-IR) spectra. Thermal analysis also revealed that the raw polymer's crystalline morphology was altered during the extrusion process, resulting in increased crystallization at smaller thicknesses. According to this study, direct powder extrusion and EVA technologies could be useful for creating transdermal patches. Drugs with varied melting points can be printed while retaining thermal stability if an EVA type with the right amount of VA is selected. Moreover, it is possible to obtain the required medication release and penetration characteristics. This is, in fact, a significant benefit when considering tailored therapy.

Acetyl-hexapeptide 3 (AHP-3) can be printed using personalized patches that fit the cutaneous surface, according to study by Lim

et al. Vinylpyrrolidone (VP) and polyethylene glycol diacrylate (PEGDA), two liquid monomers, were employed in the investigation to boost the swelling rate, mechanical strength, and polymerization rate of the polymer. Throughout the production process, AHP-3 stayed constant and had no impact on the physical properties of the finished polymer. CAD software and a three-dimensional digital light processing device were used to make a personalized patch. The patches showed negligible cytotoxic effects on human dermal fibroblasts and the capacity to puncture human cadaver skin and endure compression. This work presents personalized photopolymer patches for the first time, and it may present a new strategy for enhancing drug delivery through the skin for better wrinkle control [77].

6.3. Degradable/Dissolving Patches

There's no need to remove and discard these patches because they are meant to dissolve into the skin. These patches, which are often composed of biodegradable materials, are absorbed by the body following use. In a 2019 proof-of-concept study, scientists effectively used a dissolving patch to deliver the antibiotic gentamicin to a mouse model of bacterial infection [78] (Figure 5). The findings demonstrated the ability to manage Klebsiella pneumoniae infection with the application of a gentamicin-dissolving microarray patch to mouse ears. Furthermore, compared to the untreated control group, mice given lysing patches exhibited a lower bacterial burden in their lungs and lymphoid tissue connected to their noses.

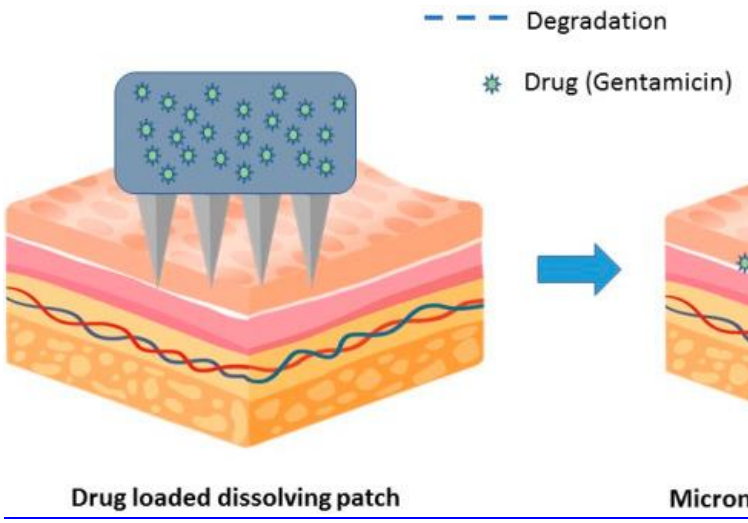

Fig. 5: These patches' microneedles are composed of biodegradable materials. Following the release of gentamicin from the patch, the microneedles on the cutaneous disintegrate.

Drugs and vaccinations that are not well absorbed by the body can be delivered with great efficiency using dissolving microneedles (MNs). By localizing insulin to the needle utilizing a two-step injection and centrifugation process, effective transdermal insulin transport was achieved. Insulin made from MN patches had relative pharmacological availability (RPA) of 95.6% and relative bioavailability (RBA) of 85.7%. In comparison to traditional subcutaneous injection, this study shows that dissolving patches are effective in treating diabetes because they provide enough relative bioavailability (RBA) when used for insulin administration [79].

Researchers have developed a biodegradable microneedle patch to prevent cancer immunotherapy by distributing hyaluronic acid (HA) antigen-peptide conjugates [80]. Biodegradable HA microneedle patches conjugated with the cytotoxic T-cell epitope peptide (SI-INFEKL) efficiently transfer antigens to the cutaneous immune system. A single transdermal immunization with an MN patch increased antigen-specific cytotoxic T-cells, which in

turn accelerated tumor growth in mice modelled by B16 melanoma.

An additional research team created sodium thiosulfate (ST) and sodium nitroprusside (SNP) transdermal administration via a hypotensive biodegradable patch [81]. The research created a biodegradable patch with soluble microneedles that contains SNPs and STs to treat hypertension. The antihypertensive microneedle treatment (aH-MN) met the clinical criterion for hypertension control by rapidly and efficiently lowering blood pressure. The patch's effectiveness and user-friendliness were further demonstrated when it prevented potential organ damage from continual SNP consumption.

In the cosmetics sector, transdermal patches are also frequently utilized. However, when carelessly disposed of in public spaces, the non-biodegradable polymers used in cosmetic patches constitute a hazard to the environment. Because biodegradable polylactic acid (PLA) is non-toxic, it was suggested in one study. The PLA/phycocyanin-alginate composite with the optimum film flexibility and release qualities was produced at 20 °C for 20 hours with a phycocyanin/alginate ratio of 40/60, according to the results [82]. While the overall results are encouraging, more in vivo or clinical study is needed before substantial improvements can be made.

6.4. Release/High Loading Patches

High drug loading and controlled release are necessary for long-acting transdermal drug delivery. A novel hydroxyphenyl (HP) treatment of pressure-sensitive adhesive (PSA) improves drug-polymer miscibility and permits controlled drug release. Because the reversible and reasonably strong dual-ionic H-bonds between drugs and HP-PSA enable patches to modify drug loading and release rate without changing the release profile overall [83].

It has been discovered that the HP-PSA-based high-load patch may administer drugs for longer periods of time by increasing the area under the concentration-time curve (AUC), preventing rapid release, and extending the average stay length by more than six times. It also satisfies all safety and mechanical criteria. Mechanistic investigations demonstrate that the repulsion of ionic pharmaceuticals facilitates drug loading in HP-PSA, which can be considerably controlled by strong contacts. More inspiration for non-polar drug delivery methods comes from the creation of double-ionic H-bonds. Strong intermolecular hydrogen and ionic bonding are frequently used by pharmaceutical polymers to avoid drug recrystallization, although this lowers the transdermal patch release rates of the medication. A novel drug IL strategy has been created by researchers to improve medicine loading [84].

The prototype polymer, a pressure-sensitive adhesive (PSA) produced from carboxyl, increased the drug load five times. Strong ionic and normal hydrogen connections were produced by the carbonyl groups of the medication and PSA, enabling the production of high-drug load, high-release patches. In a subsequent investigation, NSAIDs, specifically ibuprofen, were administered via COOH polyacrylate polymer (PA-1) and the drug concentration and epidermal uptake of PA-1 increased by 2.5 and 2.4 times, respectively. Using dielectric spectroscopy, EPR spectra, the four-point probe method, and molecular modeling, the improved conductivity of PA-1 was verified. According to the results, ion-ion repulsion via hydrogen bond reduction may be a workable method for developing large-capacity, high-emission patches [85].

7. Possible Usage of Transdermal Patches

A number of medicinally effective medications sold as transdermal patches were previously mentioned in Table 2. Numerous prospective applications for transdermal patches have been investigated as research and technology have progressed; some are outlined below.

7.1. Transdermal Patches for Heart Conditions

In a heart failure scenario, the reduced ventricular ejection fraction results in hypoperfusion systemic conditions, for which pharmacokinetics (PK) and pharmacodynamics (PD) are usually regulated [86]. Renal failure also results in decreased medication metabolism and metabolite clearance [87]. Furthermore, medication absorption is hampered by hypoalbuminemia and hepatic congestion brought on by heart failure [88]. Consequently, a drug transport option is offered by transdermal patch transport devices. One nonselective beta-adrenergic blocker is propranolol. With a bioavailability of roughly 23%, it dramatically affects the hepatic first-pass metabolism when taken orally [89,90]. Oral propranolol yielded a Cmax of 56.4 ng/mL in 13.2 minutes, according to a previous study on animals using rabbits. However, because liver metabolism was involved, its bioavailability was only 12.3% [90]. Nevertheless, during an 8-hour lag period, the transdermal propranolol patch did achieve a steady-state plasma concentration (Css) of 9.3 ng/mL, demonstrating a bioavailability that was 74.8% greater than that of oral propranolol [90].

In contrast, bisoprolol is the active ingredient in Bisono® Tape, a transdermal patch [91]. It is intended to treat atrial fibrillation [92], orthostatic hypotension resulting from heart failure [93], premature ventricular contraction [94], and aortic dissection [95]. Systemic edema did not influence the absorption of beta-blockers via topical patches, according to a study comparing edematous and non-edematous patients utilizing Bisono® Tape 4 mg patches. The non-oedematose group's Cmax was 17 ng/mL, whereas the oedematose groups were 13.3 ng/mL. The purpose of the study was to determine how systemic edema affects patient outcomes [96].

Another antihypertensive drug applied topically as transdermal patches is clonidine. First used to treat hypertension, clonidine is an α 2-adrenergic agonist [97]. It was utilized to treat conditions including drug withdrawal syndrome and attention-deficit hyperactivity disorder (ADHD) [98]. Introduced in 1983, the FDA approved the transdermal clonidine patch in 1984 [99]. Since then, a comparison of transdermal and oral clonidine has been carried out [100].

Transdermal clonidine had a longer half-life (31.9 h vs. 10.8 h) than oral clonidine (0.39 ng/mL) according to the results, although there was no difference in Cmax between the two. They also found no difference in the antihypertensive effect [100]. Additionally, research is being done on the transdermal delivery of losartan, an angiotensin II receptor blocker (ARB). Proniosome transdermal drug administration was previously developed and studied in a study conducted on the cutaneous of rats. When given orally, transdermal losartan has been identified to give rise to a Cmax of 152 ng/mL and 151 ng/mL. On the other hand, oral losartan has a bioavailability that is 1.93 times lower than transdermal losartan [101].

Another medication that is important to discuss in cardiovascular therapy is nitroglycerin. After administering nitroglycerin in multiple doses to treat angina pectoris, Lauder Blanton initially observed medication resistance in 1867 [102]. Ferid Murad discovered that cyclic guanosine monophosphate (cGMP), which is stimulated by nitric oxide (NO) from nitroglycerin, causes vasodilation in vascular smooth muscle [103]. Gale and Berggren invented the earliest transdermal nitroglycerin patch in 1985 (Patent access US-4615699-A). 25 men in good health were given Nitro-Dur and Nitro-Dur II transdermal patches in a two-way cross over study conducted a year later. The patches' corresponding average Cmax values were 0.383 ng/mL and 0.432 ng/mL [104].

7.2. Vaccination patches applied transdermally

Transdermal patches, which can administer vaccinations via the cutaneous and may be a more convenient and painless option than injections, are being developed by researchers. The smallpox vaccine patch made using microneedles is a prime example. Three weeks following inoculation, animals receiving this vaccine patch developed neutralizing antibodies. The transdermal patch may be used as an alternate method of immunization and maintenance because levels were sustained for 12 weeks and an important rise in IFN-secreting cells was observed [105].

To immunize against influenza, a different research team developed a patch with lytic microneedles that focuses on cell types that present antigen on the skin. A bio-compatible polymer containing a blocked virus from an influenza vaccine for quick cutaneous breakdown was used to make microneedles. The patch produced robust antibody and cell-mediated immunity responses in mice, offering total defense versus fatal challenge. According to the results, a transdermal patch can be used to administer vaccinations more easily, safely, and with better immunogenicity, which could lead to a higher immunization rate [106].

7.3. Transdermal Infectious Disease Patches

Advances in transdermal drug transport methods allow for the development of novel drug transport tactics. Currently, attempts are underway to test the transdermal transport of more medications, including vaccinations and antibiotics. Regarding transdermal antibiotics, solid lipid nanoparticles (SLNs) and the zwitterionic characteristic cephalexin were combined to develop a transdermal cephalexin patch.This demonstrated a consistent antimicrobial action while using little antibiotics [107].

An alternative method is to put amoxicillin, ampicillin, and kanamycin onto bacterial cellulose/polycaprolactone (BC/PCL) patches for the development of transdermal administration. These techniques have a strong bactericidal effect on E. coli and Staphylococcus aureus [107]. Additionally, hydrogel-forming microarray patches meant for transdermal application have tetracyclines added to them. The Cmax of this technique was assessed in an in vivo study using rats, and it was 7.40 μg/mL at 24 hours as contrasted to 5.86 μg/mL at 1 hour for oral tetracycline [108].

7.4. Transdermal Gene Therapy Patches

Recent studies have explored the transfer of genetic material to damaged cells via transdermal patches as a means of gene therapy [109]. The goal of this creative research was to introduce genes and photothermic substances into cancer cells at the same time. Because of this, a two-step technique known as casting was used to generate transdermal patches that included both p53 DNA and the near-infrared dye IR820. Before p53 DNA and IR820 were typically utilized to the patches, hyaluronic acid was originally created as the structure of the matrix. The patches effectively released p53 DNA and IR820 at subcutaneous tumor locations after penetrating the stratum corneum and quickly disintegrating. Because gene therapy and photothermal agents work well together, the patch demonstrated a strong anti-tumor impact in vivo. Based on these findings, a transdermal patch appears to be a viable therapy option for subcutaneous tumors [110].

7.5. Transdermal Insulin Transport Patches

For diabetics, who may have high blood sugar because they cannot use the insulin that their bodies make, transdermal insulin transfer patches are used to deliver insulin. To address the issue of insulin inadequate use, several delivery systems have been developed, including ionic liquids, liposomes, nanomaterials, choline bicarbonate, and geranic acid (CAGE) [111,112].

In place of more conventional insulin transport techniques like injections and insulin pumps, transdermal patches can offer a

discreet and practical option [113]. The patches are intended to release a steady quantity of insulin over a predetermined amount of time, and they are usually put to the cutaneous on the thigh, upper arm, or belly.

Notably, creating transdermal patches for insulin transport involves a number of obstacles. Large protein molecules like insulin are difficult for the cutaneous to absorb. In order to get around this, scientists have created a novel method of transdermal protein transport that uses a double-beded, spherical, the tip of a water-swellable microneedle (MN) patch. With this design, MNs can selectively enlarge distally after cutaneous insertion to mechanically engage soft tissue. Moreover, the loaded proteins were released over an extended period of time due to passive diffusion through the expanded tips. After 12 hours in saline, insulin-loaded MN patches released 60% of the insulin, and around 70% of the emitted insulin seemed to maintain its integrity as a structure. According to research on animals, swollen MN patches take longer to release insulin, which causes blood glucose levels to gradually drop [114]. All things considered, transdermal patches for insulin transport have promise as a practical and efficient way to give insulin to diabetic patients. To maximize the effectiveness and safety of these products, more investigation and development are yet required.

7.6. Transdermal patches for hormonal insufficiency and contraceptive

In 1938, castrated male guinea pigs were given testosterone ointment, which marked the beginning of transdermal hormone delivery. Research has looked into treating amenorrhea by using follicle-stimulating hormone and estrone topically. With a typical steady-state plasma estradiol level of 38 ng/L, the first transdermal patch containing estradiol was introduced in 1984.

A transdermal matrix transport technique was then used in the development of Menorest® [115,116]. Improved local tolerability, less plasma estradiol volatility, and a superior pharmacokinetic profile are all provided by the matrix transdermal administration system. At steady state, Menorest® 50 exhibited a Cmax of 51 pg/mL (0.051 ng/mL). Then, Climara, an updated version of the transdermal matrix patch for estradiol, was introduced. At a steady state, Menorest's Cmax was 87 pg/mL or 0.087 ng/mL, whereas Climara's Cmax was 98 pg/mL (0.098 ng/mL) at a nominal dose of 50 µg in 24 hours. Menorest, on the other hand, absorbs substances more quickly and takes less time to reach the maximum concentration (Tmax) [117–119].

Another estrogenic medication used for contraception is ethylestradiol. The FDA authorized Ortho EvraTM, the first transdermal ethinyl estradiol contraceptive, in November 2001. It consists of ethinyl estradiol and norelgestromin together. According to a related pharmacokinetic research, transdermal ethinylestradiol had a minimum half-life of 16.1 and a Cmax of 58.7 to 71.2 pg/mL at various application field sites. Early research on the effectiveness of transdermal ethinylestradiol patches revealed statistically significantly greater drug compliance than oral pills [120–122].

Conversely, male hypogonadism has been treated with testosterone. Numerous techniques are available for the administration of testosterone, including transdermal testosterone patches (both matrix and reservoir variants) and intravenous testosterone enanthate. Intravenous therapy resulted in a Cmax of more than 1200 ng/L (1.2 ng/mL) 24 hours after administration, with a long half-life of 7-9 days (Drugbank access: DB13944). The typical Tmax for reservoir testosterone transdermal patches, like Androderm, was eight hours, and the Cmax at 16 weeks of therapy was 765 ng/L (0.765 ng/mL). However, following 15–19.5 hours of therapy, novel matrix-type testosterone transdermal patches demonstrated increased testosterone

levels (mean Cmax ranging from 4.33 to 6.18 ng/mL). Testosterone normally has a half-life of 1.3 hours following cutaneous removal from the patch [123–125].

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

Creating transdermal drug transport systems for medications pertaining to the central nervous system has benefits. At plasma levels, it firstly provides a therapeutic dosage that is sustained. Secondly, the transdermal drug administration approach demonstrated a superior pharmacological pattern and bioavailability. Thirdly, clients tolerate it well, reducing systemic adverse reactions [126]. The pharmacokinetics of rivastigmine, donepezil, asenapine, rotigotine, methylphenidate, and asenapine using transdermal and nondermal methods are discussed here.

Ritalin, sometimes referred to as methylphenidate, inhibits dopamine reuptake and presynaptic NE, which activates precortex neurons in the treatment of ADHD. For chewed sustained-release tablets, the Cmax is 20.75 ng/mL, but the Tmax for immediate-release tablets is 2.36 hours. The elimination half-life of methylphenidate is 5.33–5.69 hours [127].

Depending on the size of the patches, the mean Cmax and mean Tmax of methylphenidate transdermal patches ranged from 20.0 to 46.5 ng/mL and 7.12 to 8.78 hours, respectively [128]. Nowadays, rogigotine-containing transdermal patches are used to treat Parkinson's disease [129]. Over the course of a period of one day, this medication exhibits proportional to the dose pharmacokinetics and constant plasma concentrations [130]. The terminal half-life of a single cutaneous dose of rotigotine (4 mg/24 h) administered in a pilot study was 5.3 h, and the mean Cmax was 0.56 ng/mL at 19 h [131].

Selegiline, also sold as the brand name Emsam, is a different medication indicated for treating Parkinson's disease. It is an irreversible blocker of monoamine oxidase that mainly works against monoamine oxidase B. At excessive doses, it can inhibit monoamine oxidase A, which raises serotonin and norepinephrine levels in the brain [132]. In a prior review, the pharmacokinetics of selegiline tablets in individuals with Parkinson's disease were examined. The Cmax for tablets weighing 2 × 5 mg is 0.9–2.2 ng/mL, measured 0.6–0.9 hours after oral administration [133,134].

One selegiline transdermal system (STS) patch, administered 16.5 to 17.3 hours after the first dose, has a Cmax of 2.1 ng/mL. The transdermal selegiline patch has an elimination half-life of between 27.6 and 36.6 hours [133,134]. The major depressive disorder group's Cmax for the pharmacokinetics of selegiline was 2.162 ng/mL following 18.4 hours of transdermal application of the 6 mg/24 h patch. 20.1 hours was the elimination half-life [135].

Asenapine is an additional medication intended for the treatment of schizophrenia and the manic phase of bipolar disorder. After 1.75 hours, in a steady state, the sublingual asenapine dosage of 5 mg BID resulted in a Cmax of 4.23 ng/mL. The 10 mg BID dose resulted in a Cmax of 6.56 ng/mL after 1.96 hours. Their half-lives were 17.7 hours for both. On the other hand, the transdermal asenapine patch's Cmax was 1.14 to 4.68 ng/mL following twelve to sixteen hours of use, as per the patch design. The transdermal asenapine patch has a half-life of 33.9 hours [8,9].

Cholinesterase inhibitors such as galantamine, rivastigmine, and doneezil are used to treat Alzheimer's disease [136]. These medications improve mild-to-moderate Alzheimer's disease by cholinergic transmission [137]. Oral donepezil has an elimination half-life of 53.8-82.8 hours and a Cmax of 3.2-11.6 ng/mL [138]. The half-life of transdermal donepezil's elimination is 63.77-94.07 hours, and its Cmax is 5.24-20.36 ng/mL [23].

Based on research, the rivastigmine patch has a Tmax that is 14 times longer and a Cmax that is 20% lower than the oral solution. In this investigation, the average Cmax achieved by rivastigmine 3 mg oral solution in an hour was 7.63 ng/mL. Moreover, 1.45 hours was the elimination half-life [43,44].

Alternatively, a transdermal patch with 9.5 mg of rivastigmine per 24 hours resulted in an elimination half-life of 3.02 hours and a Cmax of 5.84 ng/mL after an average of 14.1 hours [43,44]. A pill containing 10 mg of galantamine had an elimination half-life of 5.68 h and a Cmax of 49.2 ng/mL at 0.88 h [139,140]. While there aren't any transdermal galantamine patches available right now, there have been a number of attempts to create one. For example, TAHO Pharmaceuticals' innovative patch TAH-8801 is presently going through Phase III studies. Furthermore, a group of scientists is developing pressure-sensitive adhesive patches for continuous transdermal application of galantamine [141]. According to the study, the maximal level (Cmax) of vancomycin therapy in mouse models was 1.58 μg/mL at 24 hours, 3.29 μg/mL at 48 hours, 3.37 μg/mL when administered orally, and 50.34 μg/mL when administered intravenously [142].

8. Conclusions and Upcoming Difficulties

With numerous Transdermal patch technology is a practical medication transport approach with advantages over other administration techniques. Patches can deliver continuous drug dosing for a longer amount of time by preventing the first-pass metabolism and digestive system. Medication for a variety of ailments, including as motion sickness, chronic pain, and hormone replacement therapy, is commonly given to them. Transdermal patch technology has advanced significantly in recent years, with the creation of smart, biodegradable/solvent, high-loading/release, and three dimensional-printed patches among its numerous innovations. Transdermal patches hold promise as a convenient and efficient drug transport method for a range of conditions; But there are some challenges that must be overcome. These involve the potential for misdosing to cause self-inflicted toxicity, inadequate adhesion, insufficient drug penetration, cutaneous irritation, and patch failure. To maximize this transport mechanism's safety and effectiveness, more study and development are required.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Chien, Y.W.; Liu, J.-C. Transdermal Drug Delivery Systems. *J. Biomater. Appl.* **1986**, *1*, 183–206.
2. Lasagna, L.; Greenblatt, D.J. More than Skin Deep: Transdermal Drug-Delivery Systems. *N. Engl. J. Med.* 1986, *314*, 1638–1639.
3. Berner, B.; John, V.A. Pharmacokinetic Characterisation of Transdermal Delivery Systems. *Clin. Pharmacokinet.* **1994**, *26*, 121–134.
4. Thirunavukkarasu, A.; Nithya, R.; Jeyanthi, J. Transdermal Drug Delivery Systems for the Effective Management of Type 2 Diabetes Mellitus: A Review. *Diabetes Res. Clin. Pract.* **2022**, *194*, 109996.
5. Kumar, L.; Verma, S.; Singh, M.; Chalotra, T.; Utreja, P. Advanced Drug Delivery Systems for Transdermal Delivery of Non-Steroidal Anti-Inflammatory Drugs: A Review. *Curr. Drug Deliv.* **2018**, *15*, 1087–1099.
6. Kopper, N.W.; Gudeman, J.; Thompson, D.J. Transdermal Hormone Therapy in Postmenopausal Women: A Review of Metabolic Effects and Drug Delivery Technologies. *Drug Des. Devel. Ther.* **2009**, 193–202.
7. Al Hanbali, O.A.; Khan, H.M.S.; Sarfraz, M.; Arafat, M.; Ijaz, S.; Hameed, A. Transdermal Patches:

Design and Current Approaches to Painless Drug Delivery. *Acta Pharm.* **2019**, *69*, 197–215.
8. Suzuki, K.; Castelli, M.; Komaroff, M.; Starling, B.; Terahara, T.; Citrome, L. Pharmacokinetic Profile of the Asenapine Transdermal System (HP-3070). *J. Clin. Psychopharmacol.* **2021**, *41*, 286–294.
9. Musselman, M.; Faden, J.; Citrome, L. Asenapine: An Atypical Antipsychotic with Atypical Formulations. *Ther. Adv. Psychopharmacol.* **2021**, *11*, 20451253211035268.
10. Investigators, A.P.I.S. (APIS) One Year Efficacy and Tolerability of Clonidine Administered by the Transdermal Route in Patients with Mild to Moderate Essential Hypertension—a Multicentre Open Label Study: The Antihypertensive Patch Italian Study (APIS) Investigators. *Clin. Auton. Res.* **1993**, *3*, 379–383.
11. Kang, H.; Zhang, Y.-F.; Jiao, F.-Y.; Guo, X.-Y.; Gao, X.-M. Efficacy of Clonidine Transdermal Patch for Treatment of Tourette's Syndrome in Children. *Zhongguo Dang dai er ke za zhi= Chinese J. Contemp. Pediatr.* **2009**, *11*, 537–539.
12. Ke, G.-M.; Wang, L.; Xue, H.-Y.; Lu, W.-L.; Zhang, X.; Zhang, Q.; Guo, H.-Y. In Vitro and in Vivo Characterization of a Newly Developed Clonidine Transdermal Patch for Treatment of Attention Deficit Hyperactivity Disorder in Children. *Biol. Pharm. Bull.* **2005**, *28*, 305–310.
13. Song, P.-P.; Jiang, L.; Li, X.; Hong, S.-Q.; Li, S.-Z.; Hu, Y. The Efficacy and Tolerability of the Clonidine Transdermal Patch in the Treatment for Children with Tic Disorders: A Prospective, Open, Single-Group, Self-Controlled Study. *Front. Neurol.* **2017**, *8*, 32.
14. Cutler, A.J.; Suzuki, K.; Starling, B.; Balakrishnan, K.; Komaroff, M.; Castelli, M.; Meeves, S.; Childress, A.C. Efficacy and Safety of Dextroamphetamine Transdermal System for the Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents: Results from a Pivotal Phase 2 Study. *J. Child Adolesc. Psychopharmacol.* **2022**, *32*, 89–97.
15. Yamashita, T.; Ikeda, T.; Akita, Y. Comparison of Heart Rate Reduction Effect and Safety between Bisoprolol Transdermal Patch and Bisoprolol Fumarate Oral Formulation in Japanese Patients with Persistent/Permanent Atrial Fibrillation (BISONO-AF Study). *J. Cardiol.* **2019**, *73*, 386–393.
16. Smyth, M.; Haupt, T.S.; Gregoire, M.-C. Retrospective Review of the Use of Transdermal Buprenorphine Patches (Butrans) in a Pediatric Population. *J. Palliat. Med.* **2020**, *23*, 1094–1097.
17. Davis, M.P.; Pasternak, G.; Behm, B. Treating Chronic Pain: An Overview of Clinical Studies Centered on the Buprenorphine Option. *Drugs* **2018**, *78*, 1211–1228.
18. James, I.G. V; O'Brien, C.M.; McDonald, C.J. A Randomized, Double-Blind, Double-Dummy Comparison of the Efficacy and Tolerability of Low-Dose Transdermal Buprenorphine (BuTrans® Seven-Day Patches) with Buprenorphine Sublingual Tablets (Temgesic®) in Patients with Osteoarthritis Pain. *J. Pain Symptom Manage.* **2010**, *40*, 266–278.
19. Wokovich, A.M.; Shen, M.; Doub, W.H.; Machado, S.G.; Buhse, L.F. Evaluating Elevated Release Liner Adhesion of a Transdermal Drug Delivery System (TDDS): A Study of Daytrana™ Methylphenidate Transdermal System. *Drug Dev. Ind. Pharm.* **2011**, *37*, 1217–1224.

20. Perng, R.P.; Hsieh, W.C.; Chen, Y.M.; Lu, C.C.; Chiang, S.J. Randomized, Double-Blind, Placebo-Controlled Study of Transdermal Nicotine Patch for Smoking Cessation. *J. Formos. Med. Assoc. Taiwan yi zhi* **1998**, *97*, 547–551.
21. Chen, H.-K.; Lan, T.-H.; Wu, B.-J. A Double-Blind Randomized Clinical Trial of Different Doses of Transdermal Nicotine Patch for Smoking Reduction and Cessation in Long-Term Hospitalized Schizophrenic Patients. *Eur. Arch. Psychiatry Clin. Neurosci.* **2013**, *263*, 75–82.
22. Yoon, S.K.; Bae, K.-S.; Hong, D.H.; Kim, S.S.; Choi, Y.K.; Lim, H.-S. Pharmacokinetic Evaluation by Modeling and Simulation Analysis of a Donepezil Patch Formulation in Healthy Male Volunteers. *Drug Des. Devel. Ther.* **2020**, 1729–1737.
23. Kim, Y.H.; Choi, H.Y.; Lim, H.-S.; Lee, S.H.; Jeon, H.S.; Hong, D.; Kim, S.S.; Choi, Y.K.; Bae, K.-S. Single Dose Pharmacokinetics of the Novel Transdermal Donepezil Patch in Healthy Volunteers. *Drug Des. Devel. Ther.* **2015**, 1419–1426.
24. Clemente, C.; Caruso, M.G.; Berloco, P.; Buonsante, A.; Giannandrea, B.; Di Leo, A. α-Tocopherol and β-Carotene Serum Levels in Post-Menopausal Women Treated with Transdermal Estradiol and Oral Medroxyprogesterone Acetate. *Horm. Metab. Res.* **1996**, *28*, 558–561.
25. Aguirre, W.; Chedraui, P.; Mendoza, J.; Ruilova, I. Gabapentin vs. Low-Dose Transdermal Estradiol for Treating Post-Menopausal Women with Moderate to Very Severe Hot Flushes. *Gynecol. Endocrinol.* **2010**, *26*, 333–337.
26. Zieman, M. The Introduction of a Transdermal Hormonal Contraceptive (Ortho Evra™/Evra™). *Fertil. Steril.* **2002**, *77*, 1–2.
27. Zieman, M.; Guillebaud, J.; Weisberg, E.; Shangold, G.A.; Fisher, A.C.; Creasy, G.W. Contraceptive Efficacy and Cycle Control with the Ortho Evra™/Evra™ Transdermal System: The Analysis of Pooled Data. *Fertil. Steril.* **2002**, *77*, 13–18.
28. Baumrucker, S.J. Duragesic®(Transdermal Fentanyl) in Hospice Care. *Am. J. Hosp. Palliat. Med.* **1996**, *13*, 13–15.
29. Le, T.N.; Adler, M.T.; Ouillette, H.; Berens, P.; Smith, J.A. Observational Case Series Evaluation of the Granisetron Transdermal Patch System (Sancuso) for the Management of Nausea/Vomiting of Pregnancy. *Am. J. Perinatol.* **2017**, *34*, 851–855.
30. Howell, J.; Smeets, J.; Drenth, H.-J.; Gill, D. Pharmacokinetics of a Granisetron Transdermal System for the Treatment of Chemotherapy-Induced Nausea and Vomiting. *J. Oncol. Pharm. Pract.* **2009**, *15*, 223–231.
31. Abramowicz, M.; Zuccotti, G.; Pflomm, J.M.; Daron, S.M.; Houst, B.M.; Zanone, C.E.; Dalton, V.K.; Epstein, E.J.; Hirsch, J.; Juurlink, D.N. A Granisetron Patch (Sancuso). *Med. Lett. Drugs Ther.* **2008**, *50*, 103–104.
32. Bădoi, D.; Crauciuc, E.; Rusu, L.; Luca, V. Therapy with Climara in Surgical Menopause. *Rev. Med. Chir. Soc. Med. Nat. Iasi* **2012**, *116*, 828–833.
33. Taggart, W.; Dandekar, K.; Ellman, H.; Notelovitz, M. The Effect of Site of Application on the Transcutaneous Absorption of 17-β Estradiol from a Transdermal Delivery System (Climara). *Menopause* **2000**, *7*, 364–369.
34. Karmarkar, A.; Lieberman, I. Management of Complex Regional Pain Syndrome Type II Using Lidoderm 5% Patches. *Br. J. Anaesth.* **2007**, *98*, 261–262.
35. Desai, M.J.; Siriki, R.; Wang, D.

Treatment of Pain in Dercum's Disease with Lidoderm®(Lidocaine 5% Patch): A Case Report. *Pain Med.* **2008**, *9*, 1224–1226.

36. Savonitto, S.; Motolese, M.; Agabiti-Rosei, E. Antianginal Effect of Transdermal Nitroglycerin and Oral Nitrates given for 24 Hours a Day in 2,456 Patients with Stable Angina Pectoris. The Italian Multicenter Study. *Int. J. Clin. Pharmacol. Ther.* **1995**, *33*, 194–203.
37. Dahlstrøm, C.G.; Rasmussen, K.; Bagger, J.P.; Henningsen, P.; Haghfelt, T. Transdermal Nitroglycerin (Transiderm-Nitro) in the Treatment of Unstable Angina Pectoris. *Dan. Med. Bull.* **1986**, *33*, 265–267.
38. Mammen, M. V; Tripathi, M.; Chandola, H.C.; Tyagi, A.; Bais, P.S.; Sanjeev, O.P. Comparison of Enhancement of Analgesic Effect of Intrathecal Neostigmine by Intrathecal Clonidine and Transdermal Nitroglycerin Patch on Bupivacaine Spinal Anesthesia. *Anesth. Essays Res.* **2017**, *11*, 993–997.
39. Greco, R.; D'Alterio, D.; Schiattarella, M.; Boccia, A.; Greco, L.; Marsico, F. Efficacy of a New Transdermal Nitroglycerin Patch (Deponit 10) for Stable Angina Pectoris. *Am. J. Cardiol.* **1988**, *61*, 44–51.
40. Archer, D.F.; Furst, K.; Tipping, D.; Dain, M.-P.; Vandepol, C.; Group, C.S. A Randomized Comparison of Continuous Combined Transdermal Delivery of Estradiol-Norethindrone Acetate and Estradiol Alone for Menopause. *Obstet. Gynecol.* **1999**, *94*, 498–503.
41. Ho, C. Transdermally-Delivered Oxybutynin (Oxytrol (R) for Overactive Bladder. *Issues Emerg. Health Technol.* **2001**, 1–4.
42. Dull, P. Transdermal Oxybutynin (Oxytrol) for Urinary Incontinence. *Am. Fam. Physician* **2004**, *70*.
43. Lefevre, G.; Pommier, F.; Sedek, G.; Allison, M.; Huang, H.-L.A.; Kiese, B.; Ho, Y.-Y.; Appel-Dingemanse, S. Pharmacokinetics and Bioavailability of the Novel Rivastigmine Transdermal Patch versus Rivastigmine Oral Solution in Healthy Elderly Subjects. *J. Clin. Pharmacol.* **2008**, *48*, 246–253.
44. Kurz, A.; Farlow, M.; Lefevre, G. Pharmacokinetics of a Novel Transdermal Rivastigmine Patch for the Treatment of Alzheimer's Disease: A Review. *Int. J. Clin. Pract.* **2009**, *63*, 799–805.
45. Chatsis, V. Rotigotine Transdermal Patches (Neupro) for the Treatment of Parkinson's Disease. *Issues Emerg. Health Technol.* **2008**, 1–6.
46. Swaminathan, S.K.; Strasinger, C.; Kelchen, M.; Carr, J.; Ye, W.; Wokovich, A.; Ghosh, P.; Rajagopal, S.; Ueda, K.; Fisher, J. Determination of Rate and Extent of Scopolamine Release from Transderm Scōp® Transdermal Drug Delivery Systems in Healthy Human Adults. *AAPS PharmSciTech* **2020**, *21*, 1–10.
47. Johnson, P.; Hansen, D.; Matarazzo, D.; Petterson, L.; Swisher, C.; Trappolini, A. Transderm Scop for Prevention of Motion Sickness. *N. Engl. J. Med.* **1984**, *311*, 468–469.
48. De Sanctis, V.; Vullo, C.; Urso, L.; Rigolin, F.; Cavallini, A.; Caramelli, K.; Daugherty, C.; Mazer, N. Clinical Experience Using the Androderm Testosterone Transdermal System in Hypogonadal Adolescents and Young Men with Beta-Thalassemia Major. *J. Pediatr. Endocrinol. Metab. JPEM* **1998**, *11*, 891–900.
49. Bhasin, S.; Storer, T.W.; Asbel-Sethi, N.; Kilbourne, A.; Hays, R.; Sinha-Hikim, I.; Shen, R.; Arver, S.; Beall, G. Effects of Testosterone Replacement with a Nongenital, Transdermal System,

Androderm, in Human Immunodeficiency Virus-Infected Men with Low Testosterone Levels. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 3155–3162.
50. Youngkin, E.Q. Estrogen Replacement Therapy and the Estraderm Transdermal System. *Nurse Pract.* **1990**, *15*, 19–31.
51. Rozenbaum, H.; Birkhäuser, M.; De Nooyer, C.; Lambotte, R.; Pornel, B.; Schneider, H.; Studd, J. Comparison of Two Estradiol Transdermal Systems (Oesclim® 50 and Estraderm TTS® 50). I. Tolerability, Adhesion and Efficacy. *Maturitas* **1996**, *25*, 161–173.
52. Buch, A.; Shen, L.; Kelly, S.; Sahota, R.; Brezovic, C.; Bixler, C.; Powell, J. Steady-State Bioavailability of Estradiol from Two Matrix Transdermal Delivery Systems, Alora and Climara. *Menopause* 1998, *5*, 107–112.
53. Wokovich, A.M.; Prodduturi, S.; Doub, W.H.; Hussain, A.S.; Buhse, L.F. Transdermal Drug Delivery System (TDDS) Adhesion as a Critical Safety, Efficacy and Quality Attribute. *Eur. J. Pharm. Biopharm.* **2006**, *64*, 1–8.
54. Permana, A.D.; Tekko, I.A.; McCrudden, M.T.C.; Anjani, Q.K.; Ramadon, D.; McCarthy, H.O.; Donnelly, R.F. Solid Lipid Nanoparticle-Based Dissolving Microneedles: A Promising Intradermal Lymph Targeting Drug Delivery System with Potential for Enhanced Treatment of Lymphatic Filariasis. *J. Control. release* **2019**, *316*, 34–52.
55. Wei-Ze, L.; Mei-Rong, H.; Jian-Ping, Z.; Yong-Qiang, Z.; Bao-Hua, H.; Ting, L.; Yong, Z. Super-Short Solid Silicon Microneedles for Transdermal Drug Delivery Applications. *Int. J. Pharm.* **2010**, *389*, 122–129.
56. Kim, Y.-C.; Park, J.-H.; Prausnitz, M.R. Microneedles for Drug and Vaccine Delivery. *Adv. Drug Deliv. Rev.* **2012**, *64*, 1547–1568.
57. Lee, J.W.; Park, J.-H.; Prausnitz, M.R. Dissolving Microneedles for Transdermal Drug Delivery. *Biomaterials* **2008**, *29*, 2113–2124.
58. Ita, K. Dissolving Microneedles for Transdermal Drug Delivery: Advances and Challenges. *Biomed. Pharmacother.* **2017**, *93*, 1116–1127.
59. Dillon, C.; Hughes, H.; O'Reilly, N.J.; McLoughlin, P. Formulation and Characterisation of Dissolving Microneedles for the Transdermal Delivery of Therapeutic Peptides. *Int. J. Pharm.* **2017**, *526*, 125–136.
60. Dalvi, M.; Kharat, P.; Thakor, P.; Bhavana, V.; Singh, S.B.; Mehra, N.K. Panorama of Dissolving Microneedles for Transdermal Drug Delivery. *Life Sci.* **2021**, *284*, 119877.
61. Gill, H.S.; Prausnitz, M.R. Coated Microneedles for Transdermal Delivery. *J. Control. release* **2007**, *117*, 227–237.
62. Chen, Y.; Chen, B.Z.; Wang, Q.L.; Jin, X.; Guo, X.D. Fabrication of Coated Polymer Microneedles for Transdermal Drug Delivery. *J. Control. Release* **2017**, *265*, 14–21.
63. Chen, B.Z.; He, M.C.; Zhang, X.P.; Fei, W.M.; Cui, Y.; Guo, X.D. A Novel Method for Fabrication of Coated Microneedles with Homogeneous and Controllable Drug Dosage for Transdermal Drug Delivery. *Drug Deliv. Transl. Res.* **2022**, *12*, 2730–2739.
64. Ma, Y.; Gill, H.S. Coating Solid Dispersions on Microneedles via a Molten Dip-Coating Method: Development and In Vitro Evaluation for Transdermal Delivery of a Water-Insoluble Drug. *J. Pharm. Sci.* **2014**, *103*, 3621–3630.
65. O'Mahony, C.; Sebastian, R.; Tjulkins, F.; Whelan, D.; Bocchino, A.; Hu, Y.; O'Brien, J.; Scully, J.; Hegarty, M.;

Blake, A. Hollow Silicon Microneedles, Fabricated Using Combined Wet and Dry Etching Techniques, for Transdermal Delivery and Diagnostics. *Int. J. Pharm.* **2023**, *637*, 122888.
66. Cheung, K.; Das, D.B. Microneedles for Drug Delivery: Trends and Progress. *Drug Deliv.* **2016**, *23*, 2338–2354.
67. Ita, K. Transdermal Delivery of Drugs with Microneedles—Potential and Challenges. *Pharmaceutics* **2015**, *7*, 90–105.
68. Ashraf, M.W.; Tayyaba, S.; Nisar, A.; Afzulpurkar, N.; Bodhale, D.W.; Lomas, T.; Poyai, A.; Tuantranont, A. Design, Fabrication and Analysis of Silicon Hollow Microneedles for Transdermal Drug Delivery System for Treatment of Hemodynamic Dysfunctions. *Cardiovasc. Eng.* **2010**, *10*, 91–108.
69. Invernale, M.A.; Tang, B.C.; York, R.L.; Le, L.; Hou, D.Y.; Anderson, D.G. Microneedle Electrodes toward an Amperometric Glucose-Sensing Smart Patch. **2014**.
70. Yu, J.; Zhang, Y.; Ye, Y.; DiSanto, R.; Sun, W.; Ranson, D.; Ligler, F.S.; Buse, J.B.; Gu, Z. Microneedle-Array Patches Loaded with Hypoxia-Sensitive Vesicles Provide Fast Glucose-Responsive Insulin Delivery. *Proc. Natl. Acad. Sci.* **2015**, *112*, 8260–8265.
71. Veiseh, O.; Langer, R. A Smart Insulin Patch. *Nature* **2015**, *524*, 39–40.
72. Iversen, M.; Monisha, M.; Agarwala, S. Flexible, Wearable and Fully-Printed Smart Patch for PH and Hydration Sensing in Wounds. *Int. J. Bioprinting* **2022**, *8*.
73. Gilpin, V.; Surandhiran, D.; Scott, C.; Devine, A.; Cundell, J.H.; Gill, C.I.R.; Pourshahidi, L.K.; Davis, J. Lasered Graphene Microheaters Modified with Phase-Change Composites: New Approach to Smart Patch Drug Delivery. *Micromachines* **2022**, *13*, 1132.
74. Economidou, S.N.; Pissinato Pere, C.P.; Okereke, M.; Douroumis, D. Optimisation of Design and Manufacturing Parameters of 3D Printed Solid Microneedles for Improved Strength, Sharpness, and Drug Delivery. *Micromachines* **2021**, *12*, 117.
75. Jang, M.J.; Bae, S.K.; Jung, Y.S.; Kim, J.C.; Kim, J.S.; Park, S.K.; Suh, J.S.; Yi, S.J.; Ahn, S.H.; Lim, J.O. Enhanced Wound Healing Using a 3D Printed VEGF-Mimicking Peptide Incorporated Hydrogel Patch in a Pig Model. *Biomed. Mater.* **2021**, *16*, 45013.
76. Maurizii, G.; Moroni, S.; Khorshid, S.; Aluigi, A.; Tiboni, M.; Casettari, L. 3D-Printed EVA-Based Patches Manufactured by Direct Powder Extrusion for Personalized Transdermal Therapies. *Int. J. Pharm.* **2023**, *635*, 122720.
77. Lim, S.H.; Kathuria, H.; Amir, M.H. Bin; Zhang, X.; Duong, H.T.T.; Ho, P.C.-L.; Kang, L. High Resolution Photopolymer for 3D Printing of Personalised Microneedle for Transdermal Delivery of Anti-Wrinkle Small Peptide. *J. Control. release* **2021**, *329*, 907–918.
78. Rodgers, A.M.; McCrudden, M.T.C.; Courtenay, A.J.; Kearney, M.-C.; Edwards, K.L.; Ingram, R.J.; Bengoechea, J.; Donnelly, R.F. Control of Klebsiella Pneumoniae Infection in Mice by Using Dissolving Microarray Patches Containing Gentamicin. *Antimicrob. Agents Chemother.* **2019**, *63*, 10–1128.
79. Lee, I.; Lin, W.; Shu, J.; Tsai, S.; Chen, C.; Tsai, M. Formulation of Two-layer Dissolving Polymeric Microneedle Patches for Insulin Transdermal Delivery in Diabetic Mice. *J. Biomed. Mater. Res. Part A* **2017**, *105*, 84–93.
80. Kim, H.; Seong, K.-Y.; Lee, J.H.; Park, W.; Yang, S.Y.; Hahn, S.K.

Biodegradable Microneedle Patch Delivering Antigenic Peptide–Hyaluronate Conjugate for Cancer Immunotherapy. *ACS Biomater. Sci. Eng.* **2019**, *5*, 5150–5158.

81. Li, Y.; Liu, F.; Su, C.; Yu, B.; Liu, D.; Chen, H.-J.; Lin, D.; Yang, C.; Zhou, L.; Wu, Q. Biodegradable Therapeutic Microneedle Patch for Rapid Antihypertensive Treatment. *ACS Appl. Mater. Interfaces* **2019**, *11*, 30575–30584.
82. Adli, S.A.; Ali, F.; Azmi, A.S.; Anuar, H.; Nasir, N.A.M.; Hasham, R.; Idris, M.K.H. Development of Biodegradable Cosmetic Patch Using a Polylactic Acid/Phycocyanin–Alginate Composite. *Polymers (Basel).* **2020**, *12*, 1669.
83. Zhang, S.; Liu, C.; Song, Y.; Ruan, J.; Quan, P.; Fang, L. High Drug-Loading and Controlled-Release Hydroxyphenyl-Polyacrylate Adhesive for Transdermal Patch. *J. Control. Release* **2023**, *353*, 475–489.
84. Yang, D.; Liu, C.; Piao, H.; Quan, P.; Fang, L. Enhanced Drug Loading in the Drug-in-Adhesive Transdermal Patch Utilizing a Drug–Ionic Liquid Strategy: Insight into the Role of Ionic Hydrogen Bonding. *Mol. Pharm.* **2021**, *18*, 1157–1166.
85. Yang, D.; Liu, C.; Quan, P.; Fang, L. Molecular Mechanism of High Capacity-High Release Transdermal Drug Delivery Patch with Carboxyl Acrylate Polymer: Roles of Ion-Ion Repulsion and Hydrogen Bond. *Int. J. Pharm.* **2020**, *585*, 119376.
86. Ogawa, R.; Stachnik, J.M.; Echizen, H. Clinical Pharmacokinetics of Drugs in Patients with Heart Failure: An Update (Part 1, Drugs Administered Intravenously). *Clin. Pharmacokinet.* **2013**, *52*, 169–185.
87. Lainscak, M.; Vitale, C.; Seferovic, P.; Spoletini, I.; Trobec, K.C.; Rosano, G.M.C. Pharmacokinetics and Pharmacodynamics of Cardiovascular Drugs in Chronic Heart Failure. *Int. J. Cardiol.* **2016**, *224*, 191–198.
88. Mangoni, A.A.; Jarmuzewska, E.A. The Influence of Heart Failure on the Pharmacokinetics of Cardiovascular and Non-cardiovascular Drugs: A Critical Appraisal of the Evidence. *Br. J. Clin. Pharmacol.* **2019**, *85*, 20–36.
89. Ahad, A.; Aqil, M.; Kohli, K.; Sultana, Y.; Mujeeb, M.; Ali, A. Interactions between Novel Terpenes and Main Components of Rat and Human Skin: Mechanistic View for Transdermal Delivery of Propranolol Hydrochloride. *Curr. Drug Deliv.* **2011**, *8*, 213–224.
90. Corbo, M.; Liu, J.-C.; Chien, Y.W. Bioavailability of Propranolol Following Oral and Transdermal Administration in Rabbits. *J. Pharm. Sci.* **1990**, *79*, 584–587.
91. Matsuoka, H.; Kuwajima, I.; Shimada, K.; Mitamura, H.; Saruta, T. Comparison of Efficacy and Safety between Bisoprolol Transdermal Patch (TY-0201) and Bisoprolol Fumarate Oral Formulation in Japanese Patients with Grade I or II Essential Hypertension: Randomized, Double-blind, Placebo-controlled Study. *J. Clin. Hypertens.* **2013**, *15*, 806–814.
92. Yasui, T.; Oka, T.; Shioyama, W.; Oboshi, M.; Fujita, M. Bisoprolol Transdermal Patch Treatment for Patients with Atrial Fibrillation after Noncardiac Surgery: A Single-Center Retrospective Study of 61 Patients. *SAGE open Med.* **2020**, *8*, 2050312120907817.
93. Kiuchi, S.; Hisatake, S.; Kabuki, T.; Oka, T.; Dobashi, S.; Fujii, T.; Sano, T.; Ikeda, T. Bisoprolol Transdermal Patch Improves Orthostatic Hypotension in Patients with Chronic Heart Failure and Hypertension. *Clin. Exp. Hypertens.* **2020**, *42*, 539–544.
94. Shinohara, M.; Fujino, T.; Koike, H.;

Kitahara, K.; Kinoshita, T.; Yuzawa, H.; Suzuki, T.; Fukunaga, S.; Kobayashi, K.; Aoki, J. Assessment of a Novel Transdermal Selective B1-Blocker, the Bisoprolol Patch, for Treating Frequent Premature Ventricular Contractions in Patients without Structural Heart Disease. *J. Cardiol.* **2017**, *70*, 212–219.

95. Hara, T.; Yagi, S.; Akaike, M.; Sata, M. Transdermal Patch of Bisoprolol for the Treatment of Hypertension Complicated with Aortic Dissection. *Int. J. Cardiol.* **2015**, *198*, 220–221.
96. Takahashi, Y.; Sonoo, T.; Nakano, H.; Naraba, H.; Hashimoto, H.; Nakamura, K. The Influence of Edema on the Bisoprolol Blood Concentration after Bisoprolol Dermal Patch Application: A Case-Control Study. *Medicine (Baltimore).* **2021**, *100*, e27354.
97. Onesti, G.; Bock, K.D.; Heimsoth, V.; Kim, K.E.; Merguet, P. Clonidine: A New Antihypertensive Agent. *Am. J. Cardiol.* **1971**, *28*, 74–83.
98. Groom, M.J.; Cortese, S. Current Pharmacological Treatments for ADHD. *New Discov. Behav. Neurosci. Attention-Deficit Hyperact. Disord.* **2022**, 19–50.
99. Elliott, W.J.; Prisant, L.M. Drug Delivery Systems for Antihypertensive Agents. *Blood Press. Monit.* **1997**, *2*, 53–60.
100. Fujimura, A.; Ebihara, A.; Ohashi, K.; Shiga, T.; Kumagai, Y.; Nakashima, H.; Kotegawa, T. Comparison of the Pharmacokinetics, Pharmacodynamics, and Safety of Oral (Catapres) and Transdermal (M-5041T) Clonidine in Healthy Subjects. *J. Clin. Pharmacol.* **1994**, *34*, 260–265.
101. Thakur, R.; Anwer, M.K.; Shams, M.S.; Ali, A.; Khar, R.K.; Shakeel, F.; Taha, E.I. Proniosomal Transdermal Therapeutic System of Losartan Potassium: Development and Pharmacokinetic Evaluation. *J. Drug Target.* **2009**, *17*, 442–449.
102. Marsh, N.; Marsh, A. A Short History of Nitroglycerine and Nitric Oxide in Pharmacology and Physiology. *Clin. Exp. Pharmacol. Physiol.* **2000**, *27*, 313–319.
103. Nicholls, M. Nitric Oxide Discovery Nobel Prize Winners: Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad Shared the Noble Prize in 1998 for Their Discoveries Concerning Nitric Oxide as a Signalling Molecule in the Cardiovascular System. *Eur. Heart J.* **2019**, *40*, 1747–1749.
104. Noonan, P.K.; Gonzalez, M.A.; Ruggirello, D.; Tomlinson, J.; Babcock-Atkinson, E.; Ray, M.; Golub, A.; Cohen, A. Relative Bioavailability of a New Transdermal Nitroglycerin Delivery System. *J. Pharm. Sci.* **1986**, *75*, 688–691.
105. Choi, I.-J.; Cha, H.-R.; Hwang, S.J.; Baek, S.-K.; Lee, J.M.; Choi, S.-O. Live Vaccinia Virus-Coated Microneedle Array Patches for Smallpox Vaccination and Stockpiling. *Pharmaceutics* **2021**, *13*, 209.
106. Sullivan, S.P.; Koutsonanos, D.G.; del Pilar Martin, M.; Lee, J.W.; Zarnitsyn, V.; Choi, S.-O.; Murthy, N.; Compans, R.W.; Skountzou, I.; Prausnitz, M.R. Dissolving Polymer Microneedle Patches for Influenza Vaccination. *Nat. Med.* **2010**, *16*, 915–920.
107. Nasrollahzadeh, M.; Ganji, F.; Taghizadeh, S.M.; Vasheghani-Farahani, E.; Mohiti-Asli, M. Drug in Adhesive Transdermal Patch Containing Antibiotic-Loaded Solid Lipid Nanoparticles. *J. Biosci. Bioeng.* **2022**, *134*, 471–476.
108. Zhao, L.; Vora, L.K.; Kelly, S.A.; Li, L.; Larraneta, E.; McCarthy, H.O.; Donnelly, R.F. Hydrogel-Forming Microarray Patch Mediated Transdermal Delivery of Tetracycline Hydrochloride. *J. Control. Release*

2023, *356*, 196–204.
109. Singh, P.; Muhammad, I.; Nelson, N.E.; Tran, K.T.M.; Vinikoor, T.; Chorsi, M.T.; D'Orio, E.; Nguyen, T.D. Transdermal Delivery for Gene Therapy. *Drug Deliv. Transl. Res.* **2022**, *12*, 2613–2633.
110. Xu, Q.; Li, X.; Zhang, P.; Wang, Y. Rapidly Dissolving Microneedle Patch for Synergistic Gene and Photothermal Therapy of Subcutaneous Tumor. *J. Mater. Chem. B* **2020**, *8*, 4331–4339.
111. Islam, M.R.; Uddin, S.; Chowdhury, M.R.; Wakabayashi, R.; Moniruzzaman, M.; Goto, M. Insulin Transdermal Delivery System for Diabetes Treatment Using a Biocompatible Ionic Liquid-Based Microemulsion. *ACS Appl. Mater. Interfaces* **2021**, *13*, 42461–42472.
112. Jorge, L.R.; Harada, L.K.; Silva, E.C.; Campos, W.F.; Moreli, F.C.; Shimamoto, G.; Pereira, J.F.B.; Oliveira Jr, J.M.; Tubino, M.; Vila, M.M.D.C. Non-Invasive Transdermal Delivery of Human Insulin Using Ionic Liquids: In Vitro Studies. *Front. Pharmacol.* **2020**, *11*, 243.
113. Sugumar, V.; Ang, K.P.; Alshanon, A.F.; Sethi, G.; Yong, P.V.C.; Looi, C.Y.; Wong, W.F. A Comprehensive Review of the Evolution of Insulin Development and Its Delivery Method. *Pharmaceutics* **2022**, *14*, 1406.
114. Seong, K.-Y.; Seo, M.-S.; Hwang, D.Y.; O'Cearbhaill, E.D.; Sreenan, S.; Karp, J.M.; Yang, S.Y. A Self-Adherent, Bullet-Shaped Microneedle Patch for Controlled Transdermal Delivery of Insulin. *J. Control. Release* **2017**, *265*, 48–56.
115. Le Roux, Y.; Borg, M.L.; Sibille, M.; Thebault, J.; Renoux, A.; Douin, M.J.; Djebbar, F.; Dain, M.P. Bioavailability Study of Menorest®, a New Estrogen Transdermal Delivery System, Compared with a Transdermal Reservoir System. *Clin. Drug Investig.* **1995**, *10*, 172–178.
116. Marty, J.-P. Menorest®: Technical Development and Pharmacokinetic Profile. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **1996**, *64*, S29–S33.
117. Müller, P.; Botta, L.; Ezzet, F. Bioavailability of Estradiol from a New Matrix and a Conventional Reservoir-Type Transdermal Therapeutic System. *Eur. J. Clin. Pharmacol.* **1996**, *51*, 327–330.
118. Reginster, J.-Y.; Albert, A.; Deroisy, R.; Colette, J.; Vrijens, B.; Blacker, C.; Brion, N.; Caulin, F.; Mayolle, C.; Regnard, A. Plasma Estradiol Concentrations and Pharmacokinetics Following Transdermal Application of Menorest® 50 or Systen®(Evorel®) 50. *Maturitas* **1997**, *27*, 179–186.
119. Andersson, T.L.G.; Stehle, B.; Davidsson, B.; Höglund, P. Bioavailability of Estradiol from Two Matrix Transdermal Delivery Systems: Menorest® and Climara®. *Maturitas* **2000**, *34*, 57–64.
120. Zhang, H.; Cui, D.; Wang, B.; Han, Y.-H.; Balimane, P.; Yang, Z.; Sinz, M.; Rodrigues, A.D. Pharmacokinetic Drug Interactions Involving 17α-Ethinylestradiol: A New Look at an Old Drug. *Clin. Pharmacokinet.* **2007**, *46*, 133–157.
121. Abrams, L.S.; Skee, D.M.; Natarajan, J.; Wong, F.A.; Anderson, G.D. Pharmacokinetics of a Contraceptive Patch (Evra^{TM}/Ortho Evra^{TM}) Containing Norelgestromin and Ethinyloestradiol at Four Application Sites. *Br. J. Clin. Pharmacol.* **2002**, *53*, 141–146.
122. Dittrich, R.; Parker, L.; Rosen, J.B.; Shangold, G.; Creasy, G.W.; Fisher, A.C.; Group, O.E. 001 S. Transdermal Contraception: Evaluation of Three Transdermal Norelgestromin/Ethinyl Estradiol Doses in a Randomized,

Multicenter, Dose-Response Study. *Am. J. Obstet. Gynecol.* **2002**, *186*, 15–20.
123. Bhasin, S.; Brito, J.P.; Cunningham, G.R.; Hayes, F.J.; Hodis, H.N.; Matsumoto, A.M.; Snyder, P.J.; Swerdloff, R.S.; Wu, F.C.; Yialamas, M.A. Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline. *J. Clin. Endocrinol. Metab.* **2018**, *103*, 1715–1744.
124. Dobs, A.S.; Meikle, A.W.; Arver, S.; Sanders, S.W.; Caramelli, K.E.; Mazer, N.A. Pharmacokinetics, Efficacy, and Safety of a Permeation-Enhanced Testosterone Transdermal System in Comparison with Bi-Weekly Injections of Testosterone Enanthate for the Treatment of Hypogonadal Men. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 3469–3478.
125. Raynaud, J.-P.; Aumonier, C.; Gualano, V.; Betea, D.; Beckers, A. Pharmacokinetic Study of a New Testosterone-in-Adhesive Matrix Patch Applied Every 2 Days to Hypogonadal Men. *J. Steroid Biochem. Mol. Biol.* **2008**, *109*, 177–184.
126. Priano, L.; Gasco, M.R.; Mauro, A. Transdermal Treatment Options for Neurological Disorders: Impact on the Elderly. *Drugs Aging* **2006**, *23*, 357–375.
127. Klein, S.R.; Blum, K.; Gold, M.S.; Thanos, P.K. Chronic Methylphenidate Effects on Brain Gene Expression: An Exploratory Review. *Psychol. Res. Behav. Manag.* **2024**, 577–592.
128. Pierce, D.; Dixon, C.M.; Wigal, S.B.; McGough, J.J. Pharmacokinetics of Methylphenidate Transdermal System (MTS): Results from a Laboratory Classroom Study. *J. Child Adolesc. Psychopharmacol.* **2008**, *18*, 355–364.
129. Frampton, J.E. Rotigotine Transdermal Patch: A Review in Parkinson's Disease. *CNS Drugs* **2019**, *33*, 707–718.
130. Elshoff, J.-P.; Braun, M.; Andreas, J.-O.; Middle, M.; Cawello, W. Steady-State Plasma Concentration Profile of Transdermal Rotigotine: An Integrated Analysis of Three, Open-Label, Randomized, Phase I Multiple Dose Studies. *Clin. Ther.* **2012**, *34*, 966–978.
131. Elshoff, J.-P.; Cawello, W.; Andreas, J.-O.; Mathy, F.-X.; Braun, M. An Update on Pharmacological, Pharmacokinetic Properties and Drug–Drug Interactions of Rotigotine Transdermal System in Parkinson's Disease and Restless Legs Syndrome. *Drugs* **2015**, *75*, 487–501.
132. Chrisp, P.; Mammen, G.J.; Sorkin, E.M. Selegiline: A Review of Its Pharmacology, Symptomatic Benefits and Protective Potential in Parkinson's Disease. *Drugs Aging* **1991**, *1*, 228–248.
133. Mahmood, I. Clinical Pharmacokinetics and Pharmacodynamics of Selegiline: An Update. *Clin. Pharmacokinet.* **1997**, *33*, 91–102.
134. Barrett, J.S.; Hochadel, T.J.; Morales, R.J.; Rohatagi, S.; DeWitt, K.E.; Watson, S.K.; DiSanto, A.R. Pharmacokinetics and Safety of a Selegiline Transdermal System Relative to Single-Dose Oral Administration in the Elderly. *Am. J. Ther.* **1996**, *3*, 688–698.
135. Frampton, J.E.; Plosker, G.L. Selegiline Transdermal System in the Treatment of Major Depressive Disorder. *Drugs* **2007**, *67*, 257–265.
136. Moreta, M.P.-G.; Burgos-Alonso, N.; Torrecilla, M.; Marco-Contelles, J.; Bruzos-Cidón, C. Efficacy of Acetylcholinesterase Inhibitors on Cognitive Function in Alzheimer's Disease. Review of Reviews. *Biomedicines* **2021**, *9*, 1689.
137. Marucci, G.; Buccioni, M.; Dal Ben, D.; Lambertucci, C.; Volpini, R.; Amenta, F. Efficacy of Acetylcholinesterase Inhibitors in Alzheimer's Disease. *Neuropharmacology* **2021**, *190*, 108352.

138. Rogers; Friedhoff Pharmacokinetic and Pharmacodynamic Profile of Donepezil HCl Following Single Oral Doses. *Br. J. Clin. Pharmacol.* **1998**, *46*, 1–6.
139. Bickel, U.; Thomsen, T.; Weber, W.; Fischer, J.P.; Bachus, R.; Nitz, M.; Kewitz, H. Pharmacokinetics of Galanthamine in Humans and Corresponding Cholinesterase Inhibition. *Clin. Pharmacol. Ther.* **1991**, *50*, 420–428.
140. Farlow, M.R. Clinical Pharmacokinetics of Galantamine. *Clin. Pharmacokinet.* **2003**, *42*, 1383–1392.
141. Ameen, D.; Michniak-Kohn, B. Development and in Vitro Evaluation of Pressure Sensitive Adhesive Patch for the Transdermal Delivery of Galantamine: Effect of Penetration Enhancers and Crystallization Inhibition. *Eur. J. Pharm. Biopharm.* **2019**, *139*, 262–271.
142. Ramadon, D.; Permana, A.D.; Courtenay, A.J.; McCrudden, M.T.C.; Tekko, I.A.; McAlister, E.; Anjani, Q.K.; Utomo, E.; McCarthy, H.O.; Donnelly, R.F. Development, Evaluation, and Pharmacokinetic Assessment of Polymeric Microarray Patches for Transdermal Delivery of Vancomycin Hydrochloride. *Mol. Pharm.* **2020**, *17*, 3353–3368.

التطورات في أنظمة توصيل الأدوية عبر الجلد: الابتكارات والتطبيقات والاتجاهات المستقبلية

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الخلاصة:

تقدم أنظمة توصيل الدواء عبر الجلد تقنية مريحة وغير جراحية لتوصيل الدواء من خلال الجلد مباشرة إلى الدورة الدموية. كما توفر هذه الأنظمة عدة مزايا مثل تجاوز الأيض الأولي، وتجنب الجهاز الهضمي، والسماح بالجرعات المستمرة على مدى فترات طويلة. تأتي الرقع الجلدية في أنواع متعددة، بما في ذلك الرقع المصفوفية، والرقع الخزانية، والرقع المحتوية على الدواء، وأنظمة ميكروالخزان، ولكل نوع آليات مميزة للتحكم في إطلاق الدواء. وتشمل التطورات الحديثة الرقع الذكية التي تحتوي على أجهزة استشعار لمراقبة وضبط توصيل الدواء، والرقع الذائبة التي تحل مشكلة التخلص منها، والرقع ثلاثية الأبعاد المطبوعة للطب الشخصي، والرقع عالية الحمولة لزيادة فعالية الدواء. وتمتد التطبيقات المحتملة لتشمل توصيل اللقاحات، وعلاج الجينات، ونقل الأنسولين لإدارة مرض السكري، وعلاج أمراض القلب. مع تقدم البحث، تستمر الرقع الجلدية في التطور، مما يقدم حلاً واعدًا لمجموعة من الاحتياجات العلاجية. يغطي هذا المقال إنشاء واستخدام الرقع الطبية لنقل الدواء عبر الجلد، مع التركيز على التطورات التكنولوجية والإبداعية الحديثة التي أدت إلى إنشاء الرقع الذكية، القابلة للتحلل، عالية الحمولة، وثلاثية الأبعاد.