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A Comprehensive Review on the Development of Transdermal Patches for Sustained Release of Medication in Migraine Therapy

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ABSTRACT

This extensive review study focuses on the developments and difficulties in the creation of transdermal patches for the treatment of migraines. Migraine is a common neurological condition marked by crippling headaches and frequently need early and effective treatment. A potential method for sustaining medication administration, transdermal patches provide regular dose and boost patient compliance. The composition of transdermal patches, the method of drug release, benefits, drawbacks, and potential applications in the treatment of migraines are all covered in this article.

KEYWORDS: Transdermal Patches, Migraine Disorders, Drug Delivery Systems, Sumatriptan,

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INTRODUCTION

Millions of people worldwide suffer from migraine, a complicated neurological illness marked by intense headaches frequently accompanied by nausea, vomiting, and increased sensitivity to light and sound.[1] It has a significant negative impact on the afflicted people's quality of life and adds significantly to the expense of both healthcare and the economy. Acute headache management and preventative measures to lessen the frequency and severity of subsequent attacks are frequently used in the treatment of migraines.[1,2] Affecting around 1 in 7 people worldwide, migraine is one of the most common and incapacitating illnesses. When compared to males, women experience the syndrome at a ratio of about 3:1 more frequently.[3] The development of migraines often happens in adolescence or early adulthood, and individual differences in frequency and severity of attacks can range from a few occurrences per year to many incapacitating attacks per month.[4,5]The causes of migraine are multifaceted and include intricate interactions between environmental, genetic, and neurovascular variables. Having a strong familial propensity, genetic predisposition plays a crucial impact in migraine instances. The pathogenesis of migraine has been linked to a number of genetic abnormalities and changes in neurotransmitter pathways.[1,4] Additionally, in those who are vulnerable, environmental variables including stress, hormonal changes, food triggers, irregular sleep patterns, and specific stimuli like bright lights or potent odours can cause or worsen migraines.[4,5] Globally, migraine was the second largest contributor to the disability-adjusted life-years (DALYs) lost due to neurological disorders in 2016, accounting for 16.3% of the attributable DALYs.[6] The global age-standardized prevalence of migraine increased by 1.7% (0.7–2.8) from 1990 to 2019, and in 2019 there were 1.1 billion (0.98–1.3) prevalent cases and 525.5 (78.8–1,194) years lived with disability (YLDs) per 100,000 population[7]. In the United States, the economic burden of migraine was significantly higher in patients with migraine, than among those without migraine.[1,]

Table 1: Migraine Prevalence

Continent	Migraine Prevalence (%)
North America	15.2
Europe	15.0
Asia	9.3
Africa	8.7
Latin America	10.2

Continent	Migraine Prevalence (%)
Oceania	15.2

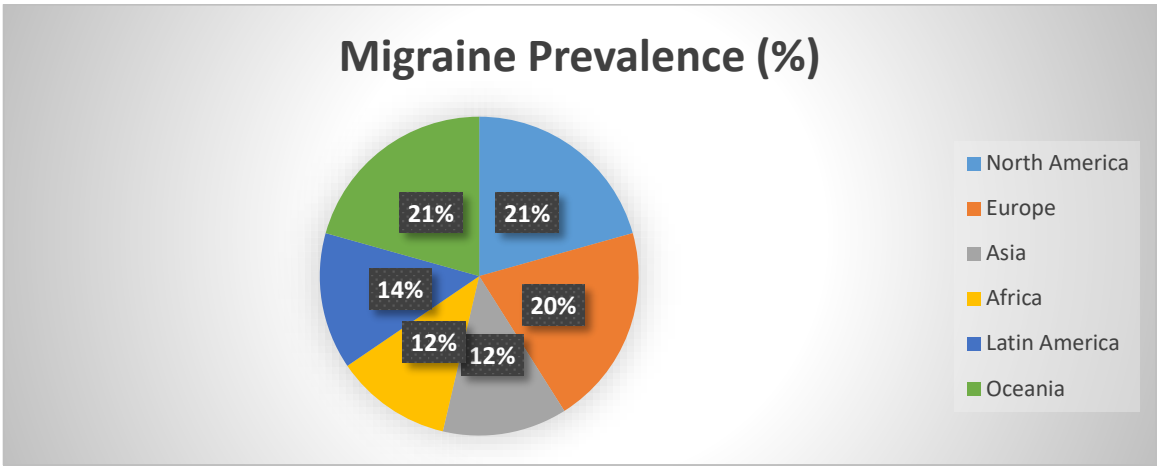

Figure 1: Migraine Prevalence

Traditional oral drugs have long been a cornerstone in the treatment of migraines, but they frequently have drawbacks including inconsistent absorption, systemic adverse effects, and problems with patient compliance. As a result, there is a growing demand for novel drug delivery systems that may provide pharmaceuticals with a prolonged and regulated release, assuring the best possible therapeutic results.[9,10]

In the realm of medication administration, transdermal drug delivery has become a promising method, notably for the treatment of migraines. In this method, the gastrointestinal tract is avoided by administering medication through the skin and directly into the systemic circulation. Transdermal patches, a crucial part of this delivery method, have drawn a lot of interest because of their ability to administer drugs in a regulated, sustained release, increasing the overall efficacy and compliance of migraine therapy.[11,12]

The goal of this in-depth research is to examine the history, workings, benefits, drawbacks, and potential of transdermal patches for the prolonged release of drugs in migraine treatment. This study aims to shed light on the potential of transdermal patches as a novel drug delivery strategy for successfully treating migraine headaches by examining their formulation elements, drug release processes, benefits, and drawbacks. Transdermal patches have the potential to revolutionise migraine medication and dramatically enhance the lives of those who suffer from this crippling neurological disorder. This review will also cover new trends and future possibilities.

FORMULATION OF TRANSDERMAL PATCHES

In order to transfer medications over the skin and into the circulation for systemic effects, transdermal patches are a critical part of transdermal drug delivery systems. To guarantee efficient medication distribution and therapeutic effectiveness, numerous components are carefully considered while creating transdermal patches. The medication, sticky matrix, backing membrane, permeation enhancers, and other excipients are important components.

- **Drug Selection:** The medication has to possess the right qualities for transdermal distribution, such as a molecular weight that is generally less than 500 Daltons, sufficient lipophilicity, and solubility in the patch's components. Because of their suitable physicochemical qualities for skin penetration, medications like fentanyl and nicotine, for instance, have been effectively integrated into transdermal patches.[12,13]
- **Polymer Matrix:** In drug delivery science and technology, polymers play a crucial role as carriers and matrices for drug formulations. Natural polymers, such as cellulose derivatives, zein, gelatin, and various gums, offer biocompatibility and sustainable sourcing. Additionally, substances like waxes and proteins fall under this category. On the other hand, synthetic elastomers like polybutadiene, silicone rubber, and nitrile are utilized for their resilience and flexibility, making them suitable for drug delivery applications. Synthetic polymers, including polyvinyl alcohol, polyethylene, and polypropylene, provide a wide range of properties and can be tailored to specific drug delivery requirements, encompassing diverse functionalities within the field. Overall, a diverse array of natural and synthetic polymers contribute significantly to advancing drug delivery techniques and formulations. Acrylic polymers including polyacrylates, silicones, polyvinylpyrrolidone, and ethyl cellulose are examples of frequently used polymers. The patch's flexibility, adhesive qualities, and medication release rates are all impacted by the polymer content. For instance, slower medication release from the patch may result from raising the polymer concentration. [14,15,16]
- **Backing Membrane:** Usually constructed of impermeable substances like polyester, polyethylene, or

metal foils. It gives the patch structural stability, preventing the medicine from escaping through the patch's back.[14,17,18]

- **Enhancers for Permeation:** Fatty acids, alcohols (such as ethanol), and surfactants are permeation enhancers that improve drug penetration across the stratum corneum barrier. For example, ethanol is frequently utilised as an enhancer in patches to increase medication penetration. Depending on the medication and its permeability, thanol is frequently employed in concentrations ranging from 5% to 50% as a permeation enhancer.[14,18,19]
- **Excipients:** Flexibility and pliability of the patch are influenced by the concentration and kind of plasticizers, including glycerol and propylene glycol. Plasticizers typically make about 10 to 30 percent of the polymer matrix. To increase the patch's stability and shelf life, tiny quantities (e.g., 0.1–10%) of stabilisers such tocopherol and antioxidants like ascorbic acid are added. To stop microbiological development and protect patch integrity, preservatives such parabens are used at doses of roughly 0.1%.[14,19,20]
- **Other Elements:** Drug release rates might be regulated using rate-controlling membranes. For instance, the pace at which the medication is delivered from the patch can be modulated using a membrane with certain permeability characteristics. The drug formulation can be stored via reservoir systems inside the patch, which will manage the release kinetics over time. Direct drug incorporation into the adhesive layer is achieved via drug-in-adhesive systems, which guarantees reliable drug delivery.[20,21]

PROCESS OF FORMATION OF TRANSDERMAL PATCH

A continuous process for creating a transdermal patch entails the following steps: continuously feeding a strip of material with a layer of permeable membrane; continuously feeding a second strip of impermeable backing material into close proximity and face-to-face relationship with the first strip; passing the first and second strips through a filling and sealing station where the material containing an active substance is introduced between the two strips. A number of crucial stages are involved in the creation of transdermal patches for prolonged drug release in the treatment of migraines.[23,24] To assess a drug's appropriateness, drug selection and characterisation are first carried out. To encapsulate the medicine and control its release, a polymer matrix is created using carefully selected polymers. Drug penetration through the skin can be increased by the use of permeation enhancers. To increase the flexibility and stability of patches, excipients such plasticizers and stabilisers are included. The patch is subsequently created by sandwiching the drug-loaded matrix between backing and adhesive layers. To verify patch integrity, drug release kinetics, and safety, in vitro/in vivo research and quality control testing are carried out. The effectiveness and customisation of transdermal patches for the best migraine treatment are being further improved through the combination of nanotechnology and personalised medicine methods.[22,25]

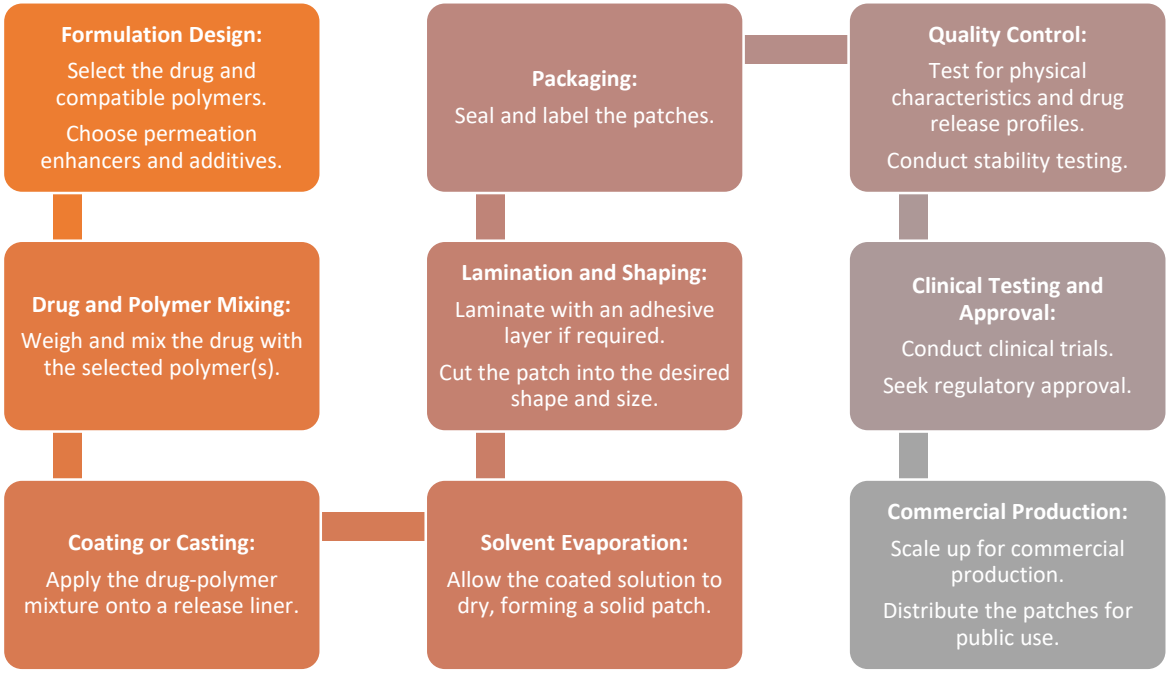

Figure 2: Process of Formation of Transdermal Patch

Various Drugs Used in Migraine Transdermal Patch

Sumatriptan has been investigated for transdermal administration and is a popular medication for the treatment of migraines. The composition of transdermal patches containing sumatriptan is discussed in research by Rams-Baron et al. (2015) with the goal of enhancing prolonged

medication release and maximising migraine therapy.[26] Another triptan known as zolmitriptan that is often used to treat migraines has been researched for transdermal application to enhance medication penetration and lessen gastrointestinal adverse effects. Transdermal patches, including those containing zolmitriptan, are thoroughly reviewed by Jain et al. (2011), who emphasise their potential for efficient drug delivery.[27] A nonsteroidal anti-inflammatory medicine (NSAID) called diclofenac has been contemplated for transdermal application in the treatment of migraines.[28] In their discussion of transdermal drug administration, Prausnitz and Langer (2008) highlight the potential of patches containing diclofenac and other medications for efficient pain treatment. An opioid analgesic called buprenorphine has been investigated for transdermal administration with the goal of providing migraine sufferers with long-lasting pain relief. In his discussion of transdermal buprenorphine in cancer pain, Mercadante (2012) offers information on how it may be used to treat severe migraine attacks.[29] Cannabinoids, such as cannabidiol (CBD), have drawn interest for their potential to treat migraines. In their 2010 study on transdermal cannabis administration and the function of permeability enhancers, Paudel et al. (2010) emphasise the possibility for tailored patch delivery.[30] Dihydroergotamine (DHE), one of the ergotamine derivatives, has been contemplated for transdermal application to give long-lasting migraine treatment. Ergotamine's usage is reviewed by Knezevic et al. (2018), who emphasise the drug's potential use in transdermal patches for effective migraine treatment. For the purpose of reducing migraine-related discomfort, transdermal administration of NSAIDs such ibuprofen and ketoprofen has been investigated.[31] The production and assessment of transdermal patches containing ketoprofen are discussed by Cilurzo et al. (2014), who also offer some information on the patches' potential effectiveness in treating migraines.[32] Transdermal administration of the antiemetic methoclopramide, which is frequently used to treat migraines, has been studied. Metoclopramide hydrochloride transdermal patches were developed and evaluated in a research by Bhagav et al. (2012) to examine the drug's potential for use in patch-based migraine treatments.[33]

Table 2: Various Drugs Used in Migraine Transdermal Patch.

Drug	Reference
Sumatriptan	Rams-Baron et al., 2015
Zolmitriptan	Jain et al., 2011
Diclofenac	Prausnitz & Langer, 2008
Buprenorphine	Mercadante, 2012
Cannabinoids	Paudel et al., 2010
Ergotamines	Knezevic et al., 2018
NSAIDs	Cilurzo et al., 2014
Metoclopramide	Bhagav et al., 2012

MECHANISM OF DRUG RELEASE

Several mechanisms that regulate the speed at which the medication is released from the patch and absorbed into the bloodstream through the skin make up the mechanism of drug release in transdermal patches.[34] To provide a continuous and regulated release of the medication, these processes are crucial. Here is further information:

- **Fickian Diffusion:** A crucial process for medication release from transdermal patches is called Fickian diffusion. It is based on the idea that drug molecules go from a region with a greater concentration (the patch itself) to a region with a lower concentration (the skin and bloodstream). A concentration gradient causes drug molecules to diffuse through the polymeric matrix or reservoir of the patch.[34,35]
- **Non-Fickian Diffusion, also known as Anomalous Diffusion:** Non-Fickian diffusion occurs when a drug release does not exactly adhere to Fick's diffusion law. Fickian diffusion and other processes, such as polymer relaxation, swelling, or matrix erosion, may occasionally combine during drug release to produce anomalous diffusion.[36,37]
- **Polymer Relaxation and Swelling:** When in touch with skin or bodily fluids, the patch's polymeric matrix may relax and swell. Drug distribution through the polymer and into the skin is facilitated by this relaxation and swelling, which also produce small holes.[37]
- **Case II Transport:** Case II transport, often referred to as non-Fickian transport, is frequently linked to drug release that is regulated by relaxation. Instead of simple diffusion, the rate-determining step for drug release in this process is polymer relaxation.[37,38]
- **Dissolution:** The medicine is frequently dissolved in a soluble polymer matrix in patches with a drug reservoir. When the matrix degrades in the presence of skin fluids, the medication is released, diffusing through the patch and into the skin.[39,40]
- **Partitioning:** Drug molecules from the patch may diffuse into the skin, dissolve in the lipids of the skin, and

then reach the circulation. The medication release rate is influenced by the partition coefficient between the polymer and skin.[34,37]

- **Osmotic Pressure:** Osmotic pumps inside the patch are used to achieve medication release based on osmotic pressure. A semipermeable membrane allows water to enter the patch, causing pressure that pushes the medication solution out of the patch.[41]
- **Zero-Order Release:** Using zero-order kinetics, certain transdermal patches release the medication at a consistent pace. This guarantees a constant drug concentration in the circulation since a constant amount of medication is delivered per unit of time.[34,36]
- **Mixed processes:** Depending on the composition and design of the patch, medication release through transdermal patches frequently includes a mix of the aforementioned processes.[34,35,36]

Transdermal patches must be designed with these processes in mind in order to obtain the optimal drug release kinetics and therapeutic impact.

Advantages of Transdermal Patches in Migraine Therapy:

Transdermal patches provide a number of benefits when used in migraine treatment, offering a distinctive and efficient means of administering medication to treat this crippling neurological condition.[42] A prolonged and regulated release of medicine is offered via transdermal patches. A more constant and lasting effect on migraine symptoms is made possible by this reliable medication administration, which helps maintain therapeutic drug levels in the body. The peak-to-trough variations associated with oral drugs are reduced with transdermal patches' regulated delivery of medication, which helps maintain constant drug levels in the circulation.[43,44] As a result of the decreased requirement for frequent dosage, this consistency frequently improves patient compliance. Transdermal patches might lessen or completely eliminate gastrointestinal adverse effects that are frequently related to oral migraine medicines since they avoid the gastrointestinal tract. This is especially advantageous for those who experience nausea or gastrointestinal irritability during migraine attacks.[42,45] Bypassing the liver and first-pass metabolism by transdermal administration, the medicine has a higher bioavailability and requires less medication to provide the intended therapeutic effect. This results in a more effective and efficient use of drugs.[46] Transdermal patches may be created with varying medication release rates, allowing for dosage titration according to the demands of the patient. This adaptability is essential for customising the course of therapy to the patient's particular migraine episode intensity. Transdermal patches are a benefit for migraines who require long-lasting pain relief since they constantly release medicine, prolonging pain relief and improving quality of life for migraine sufferers.[46,47] Transdermal patches can be made to persist for many days, allowing for less frequent administration compared to conventional oral drugs, depending on the composition. Those who lead hectic lives will value this convenience in particular. For some medications used in migraine treatment, transdermal administration can offer a more preferable pharmacokinetic profile, resulting in a later start of action and a longer duration of impact. This can help you properly manage migraine episodes[48,49]. Transdermal patches can increase the medication's safety and acceptability by reducing systemic adverse effects brought on by quick drug absorption and by improving patient comfort and compliance. Transdermal patches are a patient-friendly choice due to their non-invasive nature, which eliminates the need for injections and lessens discomfort brought on by other delivery techniques.[50,51]

A patient-friendly, effective, and efficient method of medication administration, transdermal patches provide considerable benefits in the treatment of migraines by improving adherence, lowering side effects, and improving therapeutic results for migraine sufferers.[52,53,54]

Challenges of Transdermal Patches in Migraine Therapy:

There are various difficulties in creating a transdermal patch that is useful for treating migraines. First of all, it is difficult to achieve the best medication loading within the patch while preserving its adhesive qualities and regulated release rate. Finding the ideal balance is difficult since different medications have different solubilities and affinities to patch components.[55,56] The second obstacle is the skin's natural barrier, in particular the stratum corneum. For therapeutic amounts to enter the circulation, drug molecules must successfully cross this barrier. Transdermal medication delivery has a significant problem in overcoming this resistance.[57,58] Last but not least, patch size and dosing restrictions are important factors. Transdermal patches may not be appropriate for medications needing greater dosages due to the patch's limited size and capacity.[56,58]

Limitations of Transdermal Patches in Migraine Therapy:

Transdermal patches have a number of drawbacks, one of which being the variability in medication absorption caused by individual differences in skin properties. It can be difficult to get consistent treatment results since variables including skin thickness, moisture levels, and local blood flow might induce irregular medication absorption rates.[54,58] Other typical restrictions include allergic reactions and skin discomfort. Transdermal patches' usage is restricted because certain of its components, such as their adhesives and permeation enhancers, might cause allergic reactions or skin rashes in vulnerable people. Transdermal patches may also be more expensive to produce and manufacture, and some patients may find them less affordable due to insurance coverage restrictions, which might limit their broad use for the treatment of migraines.[58,59] Last but not least, the range of

pharmaceuticals that may be properly supplied via transdermal patches is limited since not all migraine medications are suited for transdermal administration due to chemical qualities or dose requirements.[54]

An all-encompassing strategy that combines creative research, sophisticated formulation techniques, and ongoing improvements in patch technology is needed to address these problems and constraints. Transdermal patches' effective inclusion into migraine therapy regimens depends on finding ways to improve drug penetration, reduce side effects, and broaden their application to a wider spectrum of migraine drugs.

Future Perspectives:

Transdermal patches have a bright future in migraine therapy, with the potential to solve current drawbacks and substantially enhance therapeutic results. Transdermal patches are projected to revolutionise the market as a result of developments in materials science, nanotechnology, and personalised medicine.

Nanotechnology Integration: Transdermal patches with nanotechnology integration might represent a significant advance. Drugs can be enclosed in nanoparticles, improving their solubility and transdermal permeability. Additionally, these nanoparticles can help with focused medication distribution, enhancing therapeutic benefits and reducing adverse consequences. Precision and control in medication release patterns are made possible by nanotechnology, enabling specialised treatment plans for different migraine subtypes.[59,60]

Microneedle Technology: Transdermal medication administration using microneedles is a less invasive method. The stratum corneum of the skin can be penetrated by microneedles, removing the barrier function and enabling effective medication administration.[60,61] Microneedle patches are particularly well-suited for acute migraine therapies because they may have a quick beginning of effect and better medication absorption in the setting of headaches.[61,62]

Smart and Wearable Technology: Transdermal patches are an interesting potential application for smart and wearable technology. These patches can continuously track physiological variables like medication levels or skin temperature, giving doctors useful information for creating individualised treatment strategies. Additionally, based on these characteristics, smart patches may modify medicine release rates, ensuring that each patient receives the best possible care.[63]

3D Printing for Customization: Custom transdermal patches may be created using 3D printing to meet the demands of each patient individually. Drug absorption can be optimised and treatment effectiveness can be increased by creating patches with certain patient-specific skin properties. With an individualised approach to treatment, patient-centric customisation is a major trend that may be used to migraine treatments.[64]

Combination Therapies: To address the complex nature of migraines, future transdermal patches may include numerous medications. Combination treatments that focus on several migraine pathways may offer more effective relief. By increasing results and lowering the requirement for several drugs, the use of transdermal patches for synergistic drug delivery has the potential to revolutionise the treatment of migraines.[65,66]

Biofeedback and Neuromodulation: Transdermal patches, when combined with biosensors and neuromodulation technology, may provide a closed-loop therapeutic strategy for the treatment of migraines. These patches are a new age of responsive and focused migraine therapy since they can detect physiological changes related to migraines and start neuromodulation procedures to reduce pain and related symptoms.[67,68]

Transdermal patches have a bright future in migraine treatment thanks to developments in nanotechnology, wearable technology, personalised medication, and inventive manufacturing methods. These developments are anticipated to dramatically enhance patient compliance, medication delivery effectiveness, and treatment results, ultimately resulting in a more successful and patient-centered strategy to controlling migraines.

CONCLUSION

Transdermal patches provide a promising alternative to the drawbacks of traditional oral migraine treatments by providing prolonged drug delivery. Improved formulations and broader clinical use are anticipated to result from continued research and development in this area, which will eventually help those who suffer from migraines.

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