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REVIEW ARTICLE
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TRANSDERMAL DRUG DELIVERY SYSTEM: TRANSDERMAL PATCH AN EFFECTIVE APPROACH TO TREAT MIGRAINE.

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Abstract
In January 2013, the US Food and Drug Administration approved an iontophoretic transdermal system (ITS) (skin patch) formulation of sumatriptan for the immediate treatment of migraine attacks. Migraine is one of the most common primary headache disorders, affecting around 12% of the general population in Western countries. Merriam Webster indicates that the term "transdermal" is very new to the field of medicine and pharmacology, dating it to 1944. Transdermal medications come in a discreet, self-contained dose form. Drug distribution via skin to have a systemic impact without causing variations in the drug's plasma concentration. The topical distribution of therapeutic agents presents numerous benefits in comparison to traditional oral and invasive drug delivery techniques.further offer a prolonged amount of time for the drug's controlled release. This review article discusses the benefits of transdermal drug delivery systems (TDDS) as ionopheretic transdermal system for treatment of acute migraine attacks, use of Sumatriptan as the most effective drug product to treatment of migraine, skin pathways for TDDS, different transdermal patch components, preparation methods, transdermal system evaluation, general clinical considerations when using TDDS, and limitations of TDDS.

Keywords:- Transdermal drug delivery systems (TDDS), Iontophoretic Transdermal system, Migraine, Migraine treatment, Transdermal patch, Sumatriptan

1. INTRODUCTION

Drug Delivery System

A group of physicochemical technologies that may regulate the release and transport of pharmacologically active chemicals into cells, tissues, and organs such that these active substances can have the greatest possible effects are collectively referred to as drug delivery systems (DDS).[1,2] Stated differently, drug delivery systems (DDS) encompass drug delivery routes and formulations that optimize therapeutic efficacy while minimizing side effects.[3-5] There are numerous forms of administration modalities, including oral, transdermal, lung inhalation, mucosal, and intravenous injection, depending on the delivery route.

Transdermal drug delivery system

The transdermal drug delivery system (TDDS) is one appealing strategy among them. Scopolamine was the medication used in the first transdermal drug delivery (TDD) system, Transderm-Scop, which was created in 1980 to treat motion sickness.

A membrane-moderated system powers the transdermal device.

In this technology, a micro porous polypropylene sheet serves as the membrane. The medicine is dissolved in a mixture of mineral oil and poly isobutylene to form the drug reservoir. This research release is sustained for duration of three days.

Advantages of Transdermal drug delivery

There are many advantages of transdermal drug delivery

- The medication's increased bioavailability results from their bypassing of hepatic and pre-systemic metabolism.
- IV therapy's risks and drawbacks are avoided.
- Decreased frequency of doses and a consistent, long-lasting duration of effect.
- Simple way to stop taking medication.
- Because there are no longer any numerous dose intervals, patient compliance is increased.
- Increased therapeutic efficacy by preventing the systemic drug level peaks and troughs linked to traditional delivery methods.
- It is feasible to self-administer.

Disadvantages of Transdermal drug delivery[8-10]

- Many drugs especially drugs with hydrophilic structures permeate the skin too slowly may not achieve therapeutic level.
- The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema.
- The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.

STRUCTURE OF THE SKIN[8,13,14]

The skin on an adult average has a surface area of around 2 m^2 and receives approximately 1/3 of the blood that circulates throughout the body. Skin's uppermost layer, the epidermis, is made up of highly cornified (dead) cells embedded in a continuous matrix of lipid membrane sheets. It comprises four morphologically distinct regions: the basal layer, spiny layer, stratum granulosum, and uppermost stratum corneum. Ceramides, cholesterol, and free fatty acids make up the distinct composition of these extracellular membranes. Every square centimeter of human skin is known to contain between 200 and 250 sweat ducts and 10 to 70 hair follicles on average. It is among the human body's easiest organs to reach.[11, 12]

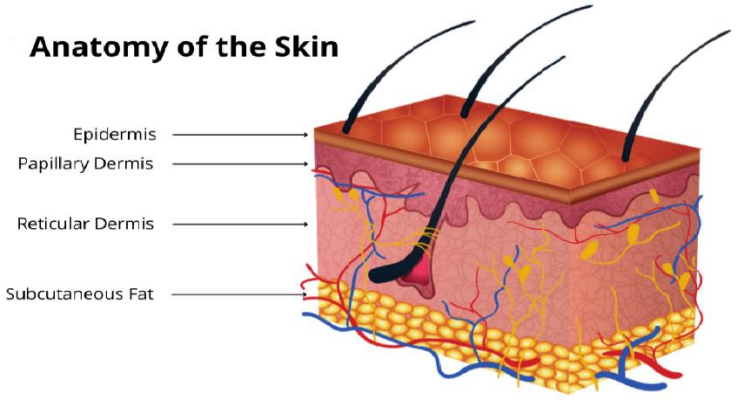

Figure 1: Anatomical and physiological Structure of skin

The Site of Percutaneous Absorption

An adult human's skin has a surface area of around 2 m^2, and it receives approximately one-third of the blood that flows through the body. The epidermis, dermis, and subcutaneous tissues are the three primary histological layers that make up skin under a microscope. The stratum corneum, or nonviable epidermis, and the viable epidermis are the two additional divisions of the epidermis. The stratum lucidium, stratum granulosum, stratum spinosum, and stratum germinativum are the four layers that make up the viable epidermis.

Stratum corneum & Epidermis

The SC is made up of several layers of keratinized, dried, compressed, and sticky dead cells. Over the majority of the body, the horny cells are arranged in densely interdigitated columns, with 15–25 cells per column. The density of it is 1.55g/cc. Compared to the 70% water content found in the physiologically active stratum germinativum, the SC contains just 20% water. Just beneath the SC is the stratum lucidium layer, which is where keratinization, sulphahydryl-rich matrix production, and nuclei disintegration occur. It eventually ascends to create the SC.

DERMIS

The dermis is where systemic absorption occurs. The dermis is composed of an amorphous colloidal ground substance imbedded in a fibrous protein matrix mostly composed of collagen, elastin, and reticulum. It has a thickness of 0.2–0.3 cm. It is separated into two distinct zones: the deeper coarse reticular layer (the primary structural layer of skin) and the superficial finely structured thin papillary layer next to the epidermis. Additionally, blood arteries, sensory nerves, sweat gland segments, and pilosebaceous units are located in the dermis. Blood is supplied to the hair by the blood vessels.

Subcutaneous fatty tissue:

This fat layer, which cushions the dermis and epidermis, is where fat is produced and stored. It serves as a shock absorber and a heat insulator. Since it is located below the circulatory system, it practically has no influence on the percutaneous absorption of medications.

Transdermal Permeation[15,16,17]

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration. Skin is the most intensive and really accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows.

TRANSDERMAL PATCH

A unique membrane in a skin patch regulates how quickly the liquid medication inside the reservoir of the patch can permeate the skin and enter the bloodstream. The drug(s) dissolved or distributed in a reservoir or inert polymer matrix, an exterior backing film made of paper, plastic, or foil, and a pressure-sensitive adhesive that secures the patch to the skin are the fundamental parts of any transdermal delivery system. The release liner, which covers the adhesive, must be peeled off prior to placing the patch to the skin.

Among the medications applied topically are scopolamine, nicotine, estrogen, nitroglycerine, and lidocaine.

Transdermal Patch Design

A number of variables, including skin permeability, the area and length of the application, and the skin's metabolic activity (i.e., first pass metabolism), influence how well a drug travels through the skin. Actually, each medication has distinct qualities that can influence transdermal delivery. The medication needs to be non-ionic and somewhat lipophilic in order to penetrate the epidermal

barrier and achieve sufficient absorption and penetration. It is more difficult for molecules bigger than 500 Daltons to get through the stratum corneum, and the drug's therapeutic dose should preferably be less than 10 mg daily.

Basic components of transdermal patch

Transdermal patches are usually made up of many layers with the purpose of delivering the medication into the bloodstream through the skin, shows the essential elements of a medication patch. Depending on the medication being administered and the intended rate of drug release, the patch's precise shape and composition may change.

Figure: 2 Basic component of transdermal patch

TYPES OF TRANSDERMAL PATCH[18]

Transdermal medical patches can be broadly classified into four categories: drug-in adhesive, reservoir, matrix, and micro-reservoir systems (Figure 3). The reservoir or matrix systems are the most common categories for patches that are sold commercially.

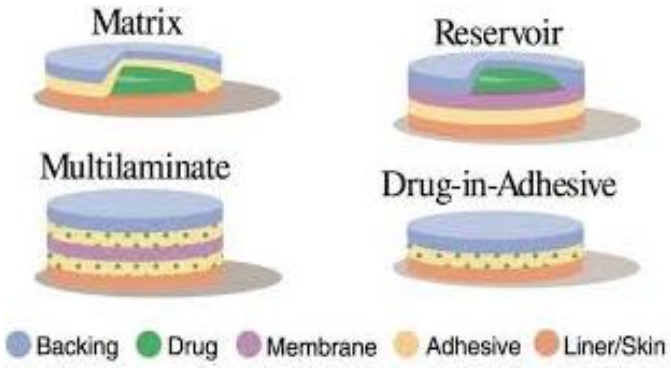

Figure: 3 Types of transdermal patch

Drug –in- adhesive patch

This is the simplest form of membrane permeation control system. The adhesive layer in this system contains drugs and serves to glue the different layers together. The drug mixture is sandwiched between the liner and backing.

Reservoir System

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

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

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

Micro needle based
Microneedles come in various varieties, each with special qualities and traits. In total, four primary categories of microneedle-based patches have been created: coated, hollow, solid, and dissolving microneedles. The user's needs and the particular application will determine which sort of microneedle is best.

EQUIPMENT-ASSISTED ENHANCEMENT OF TRANSDERMAL DELIVERY (ACTIVE DELIVERY)
When compared to topical drug treatment on the skin, external stimuli including electrical, mechanical, or physical stimulation are known to increase the permeability of medicines and biomolecules through the skin[19]. Active transdermal delivery, or TDDS enhanced by suitable equipment, is a fast and dependable method of delivering medications into the skin. Furthermore, this improved TDDS mode can hasten the therapeutic efficacy of medications that are administered.[20-21]

Iontophoretic Transdermal system
It has been demonstrated that iontophoresis increases the migration of ions across the membrane in response to a tiny external potential difference (less than 0.5 mA/cm2), hence improving skin penetration and speeding up the release of several medications with subpar absorption/permeation profiles. By applying an electrochemical potential gradient, this method has been used to transport ionic or nonionic medications in vivo[22]. The drug molecule's polarity, valency, and mobility, the type of electrical cycle that is delivered, and the drug formulation all affect how effective iontophoresis is. Specifically, unlike the majority of other drug delivery systems, the reliance on current reduces the sensitivity of drug absorption by iontophoresis to biological factors.[23]. To improve patient compliance, this approach could also include electronic reminders for patients to adjust their medications as needed.[24-25]

Sonophoresis
Transdermal medication administration can be enhanced by an ultrasound device's desired spectrum of ultrasound frequencies[26,27]. Because it creates an aqueous route through cavitation in the disturbed bilayer, low-frequency ultrasound is more effective at moving drugs.[28] In order to create an aqueous channel through which the drug can be injected, the drug under consideration is combined with a particular coupler, such as a gel or cream, which sends ultrasonic waves to the skin and disrupts the skin layers. Usually, drugs travel through channels made by applying ultrasonic waves with energies ranging from 20 kHz to 16 MHz.

Photomechanical waves
The medicine can enter the temporarily formed channel in the skin by means of photodynamic waves that are transferred to the skin and can permeate the SC[29,30]. The incident wave causes minimal ablation, which can be successfully transmitted by raising the depth to 50–400 μm with a low radiation dose of about 5-7 J/cm2. In comparison to previous direct ablation procedures, this

limited ablation demonstrated a longer rise and duration, necessitating the regulation of photodynamic wave characteristics to assure product delivery to the desired depth in the skin. Within minutes, the wave produced by a single laser pulse also demonstrated enhanced skin permeability, enabling macromolecules to permeate into the skin. Twenty nm latex particles and 40 kDa weight dextran polymers could be supplied by a solitary 23-ns photodynamic laser pulse.

Microneedle

A needle is used in the microneedle drug delivery system, a revolutionary drug delivery method, to administer medication to the circulatory system.[31] This is a popular approach of transdermal drug delivery and a topic of ongoing research at the moment. This approach includes puncturing the skin's superficial layer with needles the size of microns, which diffuses the medicine throughout the epidermal layer. These short, thin microneedles assist prevent pain by delivering medications directly to the blood capillary area for active absorption.[32] Researchers have endeavored to employ several methodologies to achieve the suitable optimization and geometric measurements necessary for the successful insertion of microneedles into human skin, which also signifies the overarching goal of microneedle research.

Numerous studies have been conducted on the creation of microneedle systems, taking into account the goal, drug kind and dosage, and intended application.[33] Thus far, photolithography and laser-mediated procedures have been used to produce microneedles. Metal or polymer microneedles are made via laser-mediated fabrication processes. A laser is used to cut or ablate a flat metal or polymer surface to create the three-dimensional structure of a microneedle .[34,35] The process of intricately creating microneedles is called photolithography, and it offers the benefit of allowing the production of needles in a variety of shapes and materials.

Thermal ablation

Through the creation of microchannels in the skin, thermal ablation, sometimes referred to as thermophoresis, is a potentially effective method for locally using heat to selectively disturb the stratum corneum structure, thereby improving drug administration.[36] In order to thermally ablate the stratum corneum, a temperature exceeding 100 °C is necessary, which causes keratin to heat up and evaporate. Furthermore, the degree of the stratum corneum structure alteration is directly related to the locally elevated temperature, suggesting that this technique is perfect for accurate drug delivery management. In order to produce a high enough temperature differential across the skin for the stratum corneum to be selectively ablationed without harming the viable epidermis, the thermal exposure should be brief—less than a few microseconds. The 50–100 μm diameter micron-scale flaws produced by thermal ablation are small enough to exclude the possibility of discomfort, bleeding, irritation, and infection. As a result, if the deeper tissues' cells are unharmed, the patient is well tolerated. Additionally, compared to alternative methods like mechanical abrasion, chemical treatment, or tape-stripping, thermal ablation offers greater control and reproducibility. Additionally, it provides efficient transport of both high molecular weight and tiny molecules.

Chemical enhancers are used in TDDS (passive delivery).

Drugs should have low molecular weight (less than 1 kDa), an affinity for lipophilic and hydrophilic phases, a short half-life, and little skin irritation in order to maximize transdermal distribution and therapeutic efficacy.[36] Numerous factors, including species variations, skin temperature, age and site, skin condition, area of application, length of exposure, skin moisture content, pretreatment techniques, and physical properties of the penetrant, influence how well a medicine penetrates the skin. Aspects of transdermal drug delivery technologies have been the subject of recent studies.[37,38] These include the creation of chemical enhancers that improve drug solubility or spread across the skin, as well as new and creative approaches that expand this idea to the creation of ultra-strong formulations, microemulsions, and vesicles. With demonstrated better skin penetration than that of individual chemicals, penetration enhancers can be employed either alone or in conjunction with chemical penetration enhancers.

MIGRAINE

Approximately 12% of people in Western countries suffer from migraine, one of the most prevalent main headache conditions. Its clinical signature is episodic bouts of mild to severe headaches. More than one-third of migraine sufferers experience up to three severe episodes every month, and six out of ten experience at least one severe attack each month. About 15% of patients experience photophobia, osmophobia, phonophobia, and aura in addition to their frequent pounding headache pain Headache Classification Subcommittee of the International Headache Society. The frequent and incapacitating gastrointestinal (GI) symptoms of nausea, vomiting, and gastroparesis make it difficult to effectively treat migraines. Nine out of ten patients report experiencing nausea, and half of migraineurs are thought to have it during half of their attacks Furthermore, it has been demonstrated that the presence of nausea and vomiting increases the burden of migraine symptoms and medication-related impairment in daily activities, as well as the intensity of the migraine headache The generally incapacitating nature of migraine is caused by a confluence of factors including repeated, intense headache attacks, autonomic and gastrointestinal symptoms, interictal anxiety, and coexisting conditions including anxiety and depression.[39,40]

Formulations for the treatment of migraine attack

For almost all migraine patients, acute treatment of migraine attacks is advised. For people without contraindications, selective serotonin receptor agonists, or triptans, are proven therapies for migraines.[41] In Western medicine, triptans constitute the cornerstone of treatment for acute migraine attacks. Sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, frovatriptan, and almotriptan are the seven triptans that are available globally, albeit some aren't in every nation. Triptans are more effective when taken soon after the start of a migraine attack, before central sensitization develops, according to clinical trials However, GI symptoms have frequently been demonstrated to reduce the use of oral medications in at least one-third of patients.[42]

TRIPTANS (SELECTIVE SEROTONIN RECEPTOR AGONISTS)

Triptans are the most effective and common evidence-based drugs for the treatment of migraine patients without any contraindications. Subcutaneous injections, nasal sprays, and suppositories are the parenteral triptan formulations that are currently on the market [three injectable formulations of sumatriptan; two nasal sprays (sumatriptan and zolmitriptan); no suppository in the USA]. The use of these parenteral formulations is limited since injections are viewed as intrusive, unpleasant, and associated with a higher risk of adverse events (AEs).

SUMATRIPTAN

Sumatriptan iontophoretic transdermal system (sumatriptan ITS) is a recently approved novel device that might help to avoid some of the limitations of other routes of administration of triptans.

INDICATION

Sumatriptan ITS (Zecuity, Teva Pharmaceuticals Industry Ltd, Tel Aviv, Israel) has been approved by the US Food and Drug Administration (FDA) for the immediate treatment of adult migraines with and without aura[44].

DOSAGES AND ROUTE OF ADMINSTRATION OF SUMATRITAN

Iontophoresis is a technique that transfers ionized medications through the skin, into the subcutaneous tissue beneath it, and then into the bloodstream. It does this by using a low electrical current. It is a non-invasive way to provide medication. The drug reservoir card for sumatriptan ITS has two nonwoven pads and two distinct gel formulations in wells: sodium salt and active sumatriptan succinate. The iontophoretic device is also included. Sumatriptan is driven through the skin and into the subcutaneous tissue by the produced current that is administered in the positive well (anode), where it is eventually passively absorbed from the blood vessels. The intended dosage for sumatriptan ITS is 6.5 mg over a 4-hour period.[45] Application of sumatriptan ITS is limited to

dry, intact, and non-irritated skin surfaces. The appropriate body parts to apply it on are the thigh and upper arm. Following the correct opening of the package, patch preparation, and skin application, the patient must press an activation button to cause a red light to illuminate, indicating that the device is operational. Following the 4-hour therapy, the medication delivery mechanism ceases, and the light signal automatically switches off.

CLINICAL PHARMACOLOGY OF SUMATRITAN

Pharmacodynamics and the action's mechanism

The selective agonist sumatriptan acts on the subtypes 1B and 1D of serotonin (5-hydroxytryptamine, or 5-HT) receptors. These receptors are located in the brain stem, presynaptic sites of sensory synapses, and blood arteries, in that order. Sumatriptan acts through two different mechanisms. The dilated meningeal blood arteries constrict when 5-HT1B receptors are activated. The release of vasoactive neuropeptides, such as substance P and calsitonin gene related protein, is inhibited by the simultaneous activation of 5-HT1D receptors on perivascular nerve terminals, obstructing the pro inflammatory cascade. At the level of the pons, where 5-HT1D receptors on the terminals of incoming trigeminal sensory fibers might disrupt the neurotransmission of pain, sumatriptan may also have a central mechanism of action.[46]

PHARMACOKINETICS

There has been research on the pharmacokinetics of sumatriptan ITS. In one investigation, the pharmacokinetic profile of four prototype sumatriptan patches was contrasted with that of an oral tablet (50 mg) and a subcutaneous injection (6 mg).[47] Eight healthy persons participated in the crossover design trial, which demonstrated a linear link between the amount of sumatriptan administered and the amount of electric potential used. The results validate iontophoresis as a successful technique for sumatriptan's regulated distribution. Other from that, application site reactions was documented as adverse events (AEs); no AEs due to triptans were.

CLINICAL PROOF OF TOLERANCE, SIDE EFFECTS, AND EFFICACY

530 persons were enrolled in a phase III trial (randomized, double-blind, placebo-controlled) investigating sumatriptan ITS for the immediate treatment of migraine.[48] The International Classification of Headache Disorders II criteria were used to make the diagnosis of migraine. One moderate-to-severe migraine attack was treated for each subject by applying either a placebo patch or sumatriptan ITS. In the sumatriptan ITS group, 18% of patients obtained complete relief from pain at 2 hours following patch activation, compared to 9% in the placebo group [number required to treat (NNT) =11.1; $p = 0.0092$]. Furthermore, a significantly higher number of patients who were administered the active substance were able to meet the secondary endpoints, which included not using rescue medication (60 percent versus 40%; NNT = 5; $p < 0.0001$), being free from phonophobia (55% versus 39%; NNT = 6.25; $p = 0.0002$), photophobia (51% versus 36%; NNT = 6.66; $p = 0.0028$), and nausea (84% versus 63%; NNT = 4.8; $p < 0.0001$), headache relief at 1 hour (29% versus 19%; NNT = 10; $p = 0.0135$), headache relief at 2 hours (53% versus 29%; NNT = 4.2; $p < 0.0001$), headache relief at 1 hour (29% versus 58%; NNT = 7.7; $p = 0.0251$), and headache relief that persisted for 2–24 hours following patch activation (34% versus 21%; NNT = 7.7; $p = 0.0015$). The NNTs for the reduction of headaches at one and two hours were in line with the NNTs reported in the literature for 20 mg intranasal sumatriptan (4.9 and 3.5, respectively)[49] and for 100 mg oral sumatriptan (6.8 and 3.5, respectively).[50]

PATIENT COMPLIANCE

A single-center, open-label trial has confirmed that the sumatriptan ITS is simple to assemble and apply for a single use during a migraine attack (Meadows and Pierce, 2014). A total of forty-eight participants, ranging in age from 20 to 64, were split into three equal groups: individuals with migraine who had received training on using sumatriptan ITS, individuals with migraine who had not received such training, and healthcare professionals who had not received such training.[51] Users

assessed usability on a range of 1 to 7, with 1 denoting difficulty and 7 denoting ease of use. Sumatriptan ITS is easy for patients to construct and apply during a migraine episode, as seen by the three groups' average ease of application scores of 6.8 and 6.1, respectively.

SPECIFIC NUMBER OF POPULATIONS

Pregnancy: - Because sumatriptan ITS is classified as a pregnancy category C drug, it should be taken carefully to weigh any potential advantages against any concerns to the developing fetus.

Lactation: - It is unknown if sumatriptan is eliminated through the skin after being administered transdermally. A choice between stopping the medicine or nursing should be made because sumatriptan exposure might cause serious adverse reactions in nursing infants. Notably, nursing mothers in the USA are permitted to take sumatriptan tablets; nevertheless, it is advised that infant exposure be minimized by refraining from breastfeeding for 12 hours following administration.

Children: - Safety and effectiveness in pediatric patients has not explained.

Elderly patient:-Since there haven't been enough senior individuals (over 65) participating in clinical trials, it's unknown whether they react to sumatriptanITS differently from younger ones.

Risk to the heart:-For elderly patients with established cardiovascular risk factors, a cardiovascular examination is advised.

CONCLUSION

Without triptan-related adverse events, sumatriptan ITS (Zecuity patch) provides an antimigraine effect that is comparatively fast, reliable, and well tolerated. ITS sumatriptan is well tolerated by patients with migraine and gastroparesis who experience a delayed, partial, or inconsistent response to oral formulations, according to the results and interpretations presented above, including data from a review Insufficient absorption in the GI tract, concerns about the possibility of vomiting after drinking water during a migraine attack, vomiting or severe nausea, which frequently results in delaying or avoiding oral therapy, and delays in using any type of medication for any reason are additional reasons to consider the patch, fear of administering sumatriptan injections because of adverse events (AEs) connected to triptans, discomfort, or equipment difficulties. We anticipate that the sumatriptan patch will be helpful for patients experiencing these problems.

CONFLICT OF INTREST

Authors declare none of conflicts

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