IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
September 2022 Vol.:25, Issue:2

Dimethyltryptamine Transdermal Patches: A Paradigm Shift in the Management of Anxiety

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Payaam Vohra *[1], Shubham Sharma [2], Indira Parab [3]

Students of H.K college of Pharmacy (1,2), H.O.D Pharmaceutics of H.K college of Pharmacy (3). India.

Submitted: 25 August 2022
Accepted: 31 August 2022
Published: 30 September 2022

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Transdermal patches, Dimethyltryptamine, Psychoactive, Ayahuasca, Dose dumping

ABSTRACT

Adherence to prescribed psychiatric and nonpsychiatric medicine is a severe problem among people with mental illnesses, it led to negative health effects. Anxiety is how your brain responds to stress and warns you of impending danger. The most common treatments for anxiety are to avoid alcohol, reduce caffeine intake, do physical exercise, quit smoking, stress management etc. Anti-anxiety drugs mostly are alprazolam, clonazepam, chlordiazepoxide, diazepam and lorazepam. Ayahuasca is a plant-based psychedelic. Psychedelics affect all the senses, altering a person's thinking, sense of time and emotions. The active chemical in ayahuasca is DMT (dimethyltryptamine). DMT targets the serotonin receptors in the brain, working similarly to anti-anxiety. Human enzymes, particularly monoamine oxidase (MAO) and hepatic P450s break down DMT relatively quickly. The most crucial aspect of monoamine oxidase from a clinical perspective is that it is so active and quick that if someone takes DMT orally, which is the main method of administration, by the time it reaches the liver, monoamine oxidase will have eliminated all of it before it can have any biological effects. Therefore, to have a biological effect, one must either consume a large amount of DMT, which is not advisable or the alternate and best way is to bypass the liver. The transdermal drug delivery system (TDDS) offers a desirable alternative to oral drug administration, avoids the liver's first-pass metabolism. This review briefly describes the effect, advantages and disadvantages of ayahuasca which contains DMT in active form, by Transdermal route in the treatment of anxiety.

INTRODUCTION

A psychological component that manifests in behavior and affects a person's ability to develop their culture normally is the psychiatric disease. Every location, nation, and society has its share of people with mental and behavioral illnesses. It might be connected to how the nerve system or brain works. At least by adolescence or early adulthood, personality disorders start to manifest in children [1]. Contrarily, mental disorders influence a person's thinking, perception, and consciousness about themselves, other people, and the outside world through a variety of experiences and events of varying severity. Emotion, perception, thinking, and action are the four primary domains that are impacted by mental illnesses. The most common psychiatric diseases and a primary cause of impairment are anxiety disorders. While there continues to be expansive research on post-traumatic stress disorder (PTSD), depression and schizophrenia, there is a relative dearth of novel medications under investigation for anxiety disorders [2,3,4]. Anxiety sensitivity is linked to higher degrees of impairment and is a predictor of both anxiety and depressive disorders, conceptualized as the fear of somatic symptoms of anxious arousal (e.g., heart palpitations, sweating, shaking) and the belief that these symptoms will have negative consequences [5].

As per the data shown, the medication which is used to prefer for anxiety and for other mental illness are non-herbal drugs that may have the high chance of side effects. Benzodiazepines promote GABA inhibitory activity by binding to specific receptor sites on the GABA-A complex and acting on chloride ion channels. Even fewer people use azapirones and beta blockers. Because beta blockers can alleviate the peripheral physical symptoms of anxiety within 30–60 minutes but do not influence the cognitive and emotional symptoms of anxiety, they have been used as single-dose medications for performance-related anxiety. For those with anxiety disorders, certain antipsychotics have been administered as a monotherapy. A recent Cochrane analysis affirms quetiapine's exceptional efficacy in GAD monotherapy. However, due to its potentially dangerous adverse effect profile, quetiapine was recently rejected by the FDA for the treatment of GAD [6].5-MeODMT induces visual, auditory, and temporal perception abnormalities in humans.[7]. There are few treatments for psychiatric diseases that are supported by evidence. Currently, the most popular kind of treatment for mood disorders is pharmaceutical therapy. Drugs seem to play a significant role in cases of the most severe mental illness; however, there are numerous complaints that the drugs do not work for all individuals and cause a variety of side effects in addition to

tolerance. The use of herbs was recently discovered to be particularly common in people with psychiatric issues.

Harmine, tetrahydroharmine, and harmaline are reversible inhibitors of the monoamine oxidase (MAO) A-type isoenzyme, with tetrahydroharmine additionally acting as a selective serotonin reuptake inhibitor (SSRI). DMT, a hallucinogenic component found in plants, is also found in mammalian organisms; studies have shown it in human blood, brain, cerebrospinal fluid, and the pineal gland of rats While DMT is classed as an endogenous hallucinogen, its specific function, along with those of bufotenine and 5-methoxy-DMT, remains unknown [7,8]. Psychoactive substances affect the brain and cause people to experience changes in their mood, thinking, and behavior [9]. The primary ingredient of ayahuasca, which is taken as a tea, is wine. Ayahuasca, which means "soul vine" or "vine with a soul," is another name for the vine. This ayahuasca is called as a spirit molecule plant [10]. In addition to increased glutamate transmission and rapid electrophysiological changes, ubiquitination at this level has been shown to stimulate BDNF release and neurogenesis. These slow secondary events may also play a role in the beneficial effects of 5-HT2A agonists [11,12].

A DMT agonist at 5-HT2A receptor sites may indeed have antidepressant and anxiolytic effects. This possibility is supported by the success of recent clinical trials that have used several psychedelic drugs that have the common characteristic of stimulating this receptor [11]. Ayahuasca is used for medical and religious purposes, and it induces a psychedelic, visionary state of mind. Because of its powerful mental effects, researchers have hypothesized that ayahuasca could be used to treat substance abuse and other mental health issues. The naturally occurring psychedelic compound N, N-dimethyltryptamine (DMT) is frequently utilized for recreational and spiritual purposes.

Transdermal drug delivery system (TDDS) is topically administered medicaments in the form of patches as self-contained discrete dose forms that, when applied to undamaged skin, distribute medication into the systemic circulation at a predetermined time. It also allows for a continuous input of medications with short biological half-lives and prevents pulsed entry into the systemic circulation, which can result in unwanted side effects. As a result of limiting hepatic first-pass metabolism, a lower dose of drug can be achieved. Plasma level compared with oral formulations [13]. Reduced frequency of dosing. Constant drug serum level versus episodic peaks [14]. Avoidance of unpleasant and inconvenient parental administration.

Potentially reduces the risk of a drug overdose. Painless removal of the patch stops drug delivery [15].

Ayahuasca is a psychedelics-based plant. The major psychoactive ingredient in ayahuasca is N, N-Dimethyltryptamine (DMT). DMT, also known as yage, is a blend of two plants - the ayahuasca vine (*Banisteriopsis caapi*) and a shrub called chacruna (*Psychotria viridis*) and the -carboline derivative alkaloid harmine, harmaline, and tetrahydroharmine are the major constituents of ayahuasca from a pharmacological standpoint. [16], Studies on transdermal patches and mental disorders have included examples of schizophrenia, obesity, attention deficit disorder, and substance abuse. Most research focuses on disorders of anxiety, depression, and sleep. In numerous research, antipsychotic patches and add-ons have been used to treat the aforementioned problems (anxiety, depression, etc.) [16]. Recent years have seen extensive documentation on herbs used to treat depression, anxiety, or insomnia [17].

This review will briefly describe the effectiveness of DMT in anxiety treatment by formulating in a transdermal patch.

Mechanism of action of N, N-dimethyltryptamine (DMT)

Several serotonin receptors, including TAAR, sigma-1, ionotropic and metabotropic glutamate receptors, dopamine, and acetylcholine receptors are all affected by DMT. With affinities ranging from 39 nM to 2.1 μM, DMT binds the 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5A, 5-HT6, and 5-HT7 receptors [20]. Some reports of DMT use do correlate with the anxiolytic effects of 5-HT1 and 5-HT3 receptors. DMT has a greater affinity for the 5-HT1A receptor [21]. The reported psychological effects of DMT were greatly enhanced by a 5-HT1A antagonist [22]. DMT, like other tryptamine hallucinogens but not phenethylamines, prevents dorsal raphe cell firing. This mechanism is considered to be the underlying cause of psychedelic-like effects, and it may be mediated via 5HT1A somatodendritic receptor stimulation [23]. There are no signs of DMT acting as a dopamine receptor agonist [24]. Due to a direct release of acetylcholine, DMT considerably lowers the concentration of acetylcholine in the corpus striatum, which lowers the concentration of striatal acetylcholine. When its rate of release or turnover is accelerated, acetylcholine levels in the brain typically decrease [25]. In HEK293 cells transfected with rTAAR1, DMT binds to the rTAAR-1 with high affinity and functions as an agonist, activating adenylyl cyclase and resulting in cAMP formation [26]. It was once believed that the sigma-1 receptor was a

subtype of the opioid receptor. Numerous neurological disorders and conditions, including addiction, depression, amnesia, pain, stroke, and cancer, have been linked to it. It can be found throughout the body in a variety of locations, including the CNS, liver, heart, lungs, adrenal glands, spleen, and pancreas [27.28]. DMT appears to have agonist-like actions on sigma-1 receptors and binds to them at low micromolar doses. In HEK293 cells, COS-7 cells, and neonatal mouse cardiac myocytes, DMT blocks cardiac voltage-activated sodium ion channels at higher concentrations [29]. The sigma-1 receptor is critical for the hallucinogenic effects of DMT and may also be crucial for other physiological processes [30]. DMT can cause neural plasticity, a long-term healing process that goes beyond neuroprotection, and reduced inflammation apparently via the sigma-1 receptor [31, 32, 33]. The transcription factors c-fos, egr-1, and egr-2, which are linked to synaptic plasticity, are encoded by DMT through the influence of second messenger systems on the rate of genetic transcription [34.35].

After DMT administration, increased expression of the brain-derived neurotrophic factor (BDNF) is also seen [36].

Effects of DMT on Anxiety/ Aggression

It has been suggested that DMT acts at the trace amino acid receptor to produce endogenous anxiolytic effects [37]. In an early study, the effects of DMT were investigated in a rat model of anxiety and aggression that involved shocks administered to pairs of rats inside a test chamber. Anti-anxiety medications help to lessen the fighting that is brought on by shocks. Fighting was more prevalent when using LSD than when taking DMT [38]. Ayahuasca sessions yielded major moral insights and enabled the completion of a rehabilitation programmed in a case study of a homeless man with numerous convictions for manslaughter and a diagnosis of antisocial disorder [39]. In two larger investigations, ayahuasca lowered panic ratings in long-term users but not state- or trait anxiety. It also reduced anxiety ratings in depressive disorder patients [40]. Elevated levels of DMT and its analogues in body fluids are thought to be endogenous psychotoxin, and they may be linked to psychotic diseases including schizophrenia psychosis [41].

MATERIAL AND METHOD

Ayahuasca has DMT as active constituent which has a shorter half-life around 15 minutes. It has a rapid onset of action and its duration of action is around 30-45 minutes. TDDS has

significant advantages over other routes of administration, such as providing prolonged and steadier drug levels no dose dumping [42].

Current treatments for anxiety disorder

1. Serotonergic/Norepinephrinergic Antidepressants

One of the earliest classes of drugs used for anxiety disorders was tricyclic antidepressants (TCAs), which work as reuptake inhibitors of serotonin and norepinephrine transporters.

2. Buspirone, a partial agonist of 5-HT1A categorized among the azapirones, is FDA-approved for the treatment of anxiety and is typically used in conjunction with SSRIs or SNRIs.[44]

3. Benzodiazepines have long been used to treat anxiety and are still one of the most often prescribed psychiatric drugs in the world.[45]

4. Antihistamines

Hydroxyzine is the most extensively researched antihistamine for anxiety and the only antihistamine licensed by the FDA for this use.

5. Alpha- and Beta-Adrenergic Agents

Propranolol is a beta-adrenergic antagonist approved by the FDA for a variety of conditions, including hypertension, angina, atrial fibrillation and arrhythmias, migraine prevention, and essential tremor.

6. Antipsychotics

Only one antipsychotic, trifluoperazine, a first-generation antipsychotic (FGA), is now FDA-approved for anxiety treatment [46].

7. Neuropeptides

Neuropeptides are tiny proteins that act as neuronal signalling molecules and have a role in avariety of brain activities, including analgesia, reward systems, social behaviors, learning, and memory. Moreover, neuropeptides such oxytocin, substance P, neuropeptide Y (NPY),

arginine vasopressin (AVP), and cholecystokinin (CCK) play important roles in fear and anxiety modulation.[47]

8. Natural Remedies

Kava, a plant containing kavapyrones, is the most studied herbal substance. Kavapyrones are hypothesized to produce anxiolytic effects through activity on sodium and calcium channels, or most likely through action on GABA-A receptors.[48]

Method of transdermal patch preparation:

It can be prepared by Circular Teflon mould method.

Solutions containing polymers in various ratios maybe used in an organic solvent. The calculated amount of drug is dissolved in half the quantity of same organic solvent different concentrations are dissolved in the other half of the organic solvent and then added. Plasticizer (e.g., Di-N-butylphthalate) is added into the drug polymer solution. The total contents are to be stirred for aporimately12 hrs and then poured into a circular 604eflonmould. The moulds are to be placed on a levelled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are to be stored for another 24 h at 25±0.5°C in a desiccator containing silica gel before evaluation to eliminate aging effects. These types of films are to be evaluated within one week of their preparation. Films were cast from organic and aqueous solvents using various bioadhesive polymers namely: sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and Carbopol 934. The prepared films ca now be subjected to investigations for their physical and mechanical properties, swelling behavior, in-vitro bio adhesion, drug permeation via bovine buccal mucosa and in-vitro drug release. These properties were found to vary significantly depending on the preparation methods, the type of the polymers and the ratio of addition of both plasticizer (i.e., polyethylene glycol) and film forming agent (ethyl cellulose and polyvinylpyrrolidone). [43]

Formulation Table:

Table 1.1 Formulation Table

Ingredients	Content
Ayahuasca	Required quantity
Sodium alginate/HPMC	300 mg
Water	5ml
Chlorocresol	0.5ml
Calcium chloride solution	1%

Mechanism of Transdermal Patch

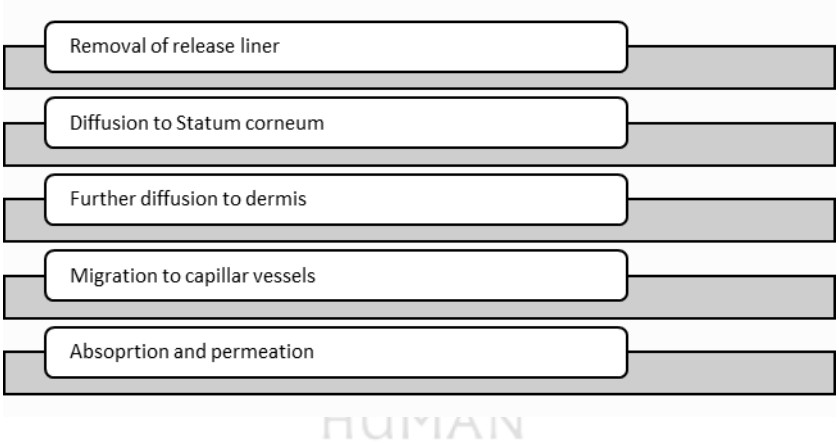

Figure 1.1 Mechanism of Transdermal Patch

Basic components of TDDS

- Polymer Matrix/ Drug reservoir
- Membrane
- Drug
- Penetration enhancers
- Adhesive layer
- Backing Laminate
- Release Liner
- Other excipients like plasticizers and solvents

1. Polymer matrix/ Drug reservoir

The foundation of TDDS is made up of polymers, which manage the drug's release from the reservoir. Drug dispersion in a synthetic polymer base in a liquid or solid form can be used to create a polymer matrix. The polymers utilized in TDDS should be chemically and biologically compatible with the medication as well as other system components like penetration enhancers and Pressure Sensitive Adhesives (PSA). They must also be secure and safe, and they must deliver a drug consistently and successfully for the duration of the product's stated shelf life [48-51].

Table no. 1.2 Polymer matrix/ Drug reservoir

Natural polymer	Synthetic elastomer	Synthetic Polymer
Gelatin	Neoprene	Polythene
Gum Arabic	Silicone	Polystyrene
Starch	Butyl rubber	PVC
Shellac	Chloroprene	PVP
Zein	Polysiloxane	Polyester

2. Membrane

A membrane may be utilized as a single layer in the patch construction or it may be adhered to the backing to create a pocket that will house the drug-containing matrix. The membrane's diffusion qualities are employed to regulate the drug and/or excipient access to the skin. As a rate-controlling membrane, ethylene vinyl acetate, silicone rubber, polyurethane, etc. are utilized as examples [51,52].

3. Drug

The medicine should be carefully selected to ensure the success of a TDDS. Drugs having a broad first-pass metabolism, a limited therapeutic window or a short half-life that require frequent doses and result in noncompliance can all benefit from transdermal patches [48,49].

Table no. 1.3 Ideal properties of drugs for TDDS

Parameters	**Properties**
Dose	Should be low (less than 20 mg/day)
Half-life	10 or less (h)
Molecular weight	<400 Da
Partition Coefficient	Log P (octanol-water) between 1.0 and 4.0
Skin permeability coefficient	>0.5* 10^{-3} cm/h
Lipophilicity	10 < Ko/w <1000
Oral bioavailability	Low
Therapeutic index	Low
Melting point	<200^{o}C
pH	Between 5.0 and -9.0

Table no. 1.4 Factors to be considered for transdermal dose calculation

Physiochemical	**Pharmacokinetic**	**Biological**
Solubility	Half-life	Skin toxicity
Crystallinity	Volume of distribution	Site of application
Molecular weight	Total body clearance	Allergic reaction
Polarity	Therapeutic plasma concentration	Skin metabolism
Melting point	Bioavailability factor	Skin permeability

4. Permeation Enhancers:

Penetration enhancers (also known as sorption promoters or accelerants), which raise the permeability of the SC to achieve higher therapeutic levels of the drug candidate, are one well-established method for enhancing TDD. Penetration enhancers interact with the SC's structural elements, altering how the barrier works and increasing permeability. For medication absorption through the skin, polar, nonpolar, and polar/nonpolar routes are all possible. Chemical and physical methods of augmentation are both used to affect the SC's barrier qualities to improve drug penetration (and absorption) through the skin.

Chemical enhancers

Accelerants, absorption promoters, or penetration enhancers are popular names for chemicals that facilitate the uptake of medications administered topically. Chemical stimulants function by:

- Improving (and advancing) the drug's thermodynamic performance when acting as a co-solvent
- Increasing the drug's partition coefficient to accelerate its release from the vehicle into the skin
- Preparing the subcutaneous (SC) to allow drug diffusion
- Promoting drug reservoir establishment and penetration in the SC.

The following are some of the most desirable characteristics for penetration enhancers operating on skin:

- They should not irritate the skin, be poisonous, or cause allergies.
- The duration of the effect must be foreseeable and repeatable.
- They should not bind to receptor sites or have any pharmacological effect on the body.
- The penetration enhancers should have a one-way action, allowing therapeutic materials to enter the body while preventing the loss of endogenous material.
- They should have adequate skin and acceptable facial features [51,52].

Sulfoxide (DMSO), fatty acids (oleic acid), alcohol (methanol), glycol (propylene glycol), surfactant (anionic surfactant), azone (lauracapran), and others are some of the permeation enhancers that have been the subject of the most research.

Physical enhancers

For improving the percutaneous penetration (and absorption) of various therapeutic drugs, physical means of improvement such as iontophoresis and ultrasound (also known as phonophoresis or sonophoresis) approaches have been used [48,53].

5. Backing Laminate:

Backings are chosen for their appearance, flexibility, and necessity for occlusion; as a result, the material's chemical resistance must be taken into account while creating a backing layer. Excipient compatibility should also be taken into account because extended contact between the backing layer and the excipients could result in additives leaching out of the layer or excipient, drug, or penetration enhancer diffusion. The backing with the lowest modulus or high flexibility, good oxygen transfer, and a high moisture vapor transmission rate will be the most comfortable. Vinyl, polyethylene, polyester films, metal, and polyolefin films are a few examples of backing materials [54,55].

6. Release Liner:

Before being applied to the skin, the protective liner that covers the patch while it is in storage is taken off and discarded. The liner should be chemically inert since it will be in close contact with the TDDS. A release liner typically consists of two layers: a silicon or Teflon release coating layer on top of a base layer that may be nonocclusive (for example, paper fabric) or occlusive (for example, polyethylene, polyvinyl chloride). Polyester foil and metalized laminates are other materials utilized to make TDDS-release liners [52,56,57].

7. Miscellaneous excipients like plasticizers and solvents

To produce the drug reservoir, a variety of solvents including chloroform, methanol, acetone, isopropanol, and dichloromethane are utilized. To give the transdermal patch some plasticity, additional plasticizers like dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol are added [56,57].

Adhesives - The fastening of the transdermal device is usually done by the adhesive. The adhesive should satisfy the following criteria.

- Do not irritate or sensitize the skin.
- Adhere to the skin during the dosing interval.
- It should be easily removed.
- It should not leave any nonwashable residue.

Evaluation/ Characterization

1. Drug–polymer interaction studies

2. Pre-formulation studies

a) IR Spectra:

To evaluate any possible interaction between Gm and polymeric materials, FTIR analysis can be performed.

b) Surface pH

Patches were kept in contact with 0.5 ml of double distilled water for 1 h in glass tubes and were allowed to swell. After a one-minute equilibration interval, pH readings were taken with a combination glass electrode placed near the patch's surface. [58]

c) Transmission of water vapour: The quantity of moisture conveyed through a unit area of film in unit time is known as the water vapour transmission rate (WVTR).

$$W.\ V.\ T. = WL/S$$

d) % Moisture content: This test is also carried out to check the integrity of films under dry conditions. Individual transdermal films (of a specific area) must be stored at room temperature in a desiccator containing fused anhydrous calcium chloride. The films were weighed at regular intervals of 24, 48, and 72 hours during this time.

3. Physical appearance

a) Color

b) Homogeneity

c) Patch Thickness: The thickness of the drug-loaded patches can be measured by using a screw gauge micrometer at three different points on the patches. For each drug-loaded patch, the average and standard deviation values of the three readings were calculated.

d) Folding endurance: This test can be carried out to check the efficiency of the plasticizer and the strength of the patch prepared using different polymers. The number of folds

necessary to break any polymeric patch is known as folding endurance. The folding endurance can be measured manually by repeatedly folding a small strip of the film (2 × 2 cm) at the same place until it broke. The value of folding endurance was determined by the number of times the patch could be folded in the same place without breaking or cracking. [59]

4. Drug content determination

UV–visible spectrophotometer was used for validation The percentage of DMT was determined using solution concentrations of 6.25, 12.5, 25.0, and 50.0 μg mL^{-1}. The measurements were performed at a wavelength of 275 nm [60].

5. Weight uniformity

The prepared patches are dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weighed in digital balance. The average weight and standard deviation values are to be calculated from the individual weights. [61]

6. Comparison of in vitro drug release of formulations

Franz diffusion cells can be employed for the in vitro characterization of transdermal formulations. This is a good way to predict medication movement over the skin from topical preparations. In vitro drug release tests can be performed using a synthetic cellophane membrane and 30.0 ml of phosphate-buffered saline (pH 7.4) in the receptor compartment of the diffusion cell.The prepared formulations can be dispersed evenly across the cellophane membrane in the donor compartment. The assembly must be constantly maintained at 37.0 ± 2.0 °C at 50 rpm.[62]

7. Stability study of transdermal patches at various temperatures and humidity.

8. R^2 values of all the prepared transdermal patches.

9. Skin Irritation test

The albino Wistar rats can be housed in cages, with free excess to standard laboratory diet and water. Before doing the trial, the rats' dorsal abdomen skin must be meticulously shaved to avoid peripheral injury. A non-sensitizing microporous tape can be used to cover a transdermal patch that was placed to the bare skin. A 0.8% *v/v* aqueous solution of formalin

must be applied as a standard skin irritant. Each day for up to 7 days, the animals must be given a new patch. After 7 days, the formulation can be removed, and the erythema score must be recorded and compared to a control group. The Draize scoring technique assigns a score of 0 to no erythema, 1 to very little erythema (light pink), 2 to well-defined erythema (dark pink), 3 to moderate to severe erythema (light red), and 4 to severe erythema (dark red).

10. Analytical Validation

Quantitation and impurities detection of optimized batch needs to be validated by a standardized method of validation.

Packaging of transdermal patches

The standard packaging method for a transdermal system entail enclosing it in a packing material that is sealed to produce a container, like a sealed pouch, from which the system may be removed and used after a considerable amount of time has passed. Such moisture may have been accidentally introduced into transdermal system components or exposed to the environment at the time the system was first packed. Different strategies have been used to stop or limit the quantity of moisture within such a sealed item which include raw material drying, additional transdermal system drying, pre-packing storage in a desiccating environment, vacuum packaging, or packaging in a dry space. Desiccants can be made from oxides of aluminum, calcium, titanium, zirconium, silicon, thorium, magnesium, and barium. They can also be made from alumina, alumina hydrates, natural and synthetic molecular sieves, silica gel, precipitated silica, clays, perchlorates, Zeolite, natural gums, magnesium or calcium sulfate, calcium, lithium, or cobalt chloride, and calcium. The moisture permeability of the packaging materials, however, also affects how well moisture is prevented or eliminated inside the sealed box, particularly during extended periods of storage. As a result, to provide an environmental barrier, packaging materials made of numerous layers—many of which include metal foils—are frequently needed. Even with the best tools, such containers may be somewhat moisture porous and may be challenging to open without the use of mechanical tools like scissors. Thermoplastic polymers that don't absorb, react with, or otherwise negatively impact the medicine or other excipients or components utilized in the transdermal system are the recommended packing material for use as the principal layer of the pouch. Copolymers of acrylonitrile and methyl acrylate modified with nitrile rubber are a particularly desired thermoplastic material. Metal foils, polyethylene, polyester, vinyl acetate

resins, ethylene/vinyl acetate copolymers, polyurethanes, polyvinyl chloride can all be found in a secondary layer sheet or laminate.[63].

CONCLUSION

Efforts can be made in the development of DMT transdermal patch, however long term pharmacokinetic and pharmacodynamic studies are needed to undertake establishment of the usefulness of these patches. The essential strategy for making patches entails extensive research and in-depth knowledge of the issue; this will ensure that the procedure will not fail and will last for a long time. Future advancements in anxiety treatment may include formulating a transdermal patch made up of DMT obtained from Ayahuasca. The present review concludes that DMT patches can have better compliance and are the most accurate.

ACKNOWLEDGMENT

This article would not have been possible without the exceptional support of Dr M.N Saraf and Mrs. Shifa Haju. Their enthusiasm, knowledge and exacting attention to detail have been an inspiration and kept our work on track.

REFERENCES

1. Celine TM, Antony J. A study on mental disorders: 5-year retrospective study. Journal of family medicine and primary care. 2014 Jan;3(1):12.
2. Malla A, Joober R, Garcia A. “Mental illness is like any other medical illness”: a critical examination of the statement and its impact on patient care and society. Journal of psychiatry & neuroscience: JPN. 2015 May;40(3):147.
3. Wilmer MT, Anderson K, Reynolds M. Correlates of Quality of Life in Anxiety Disorders: Review of Recent Research. Current Psychiatry Reports. 2021 Nov;23(11):1-9.
4. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Archives of general psychiatry. 2005 Jun 1;62(6):617-27.
5. Gaujac A, Ford JL, Dempster NM, de Andrade JB, Brandt SD. Investigations into the polymorphic properties of N, N-dimethyltryptamine by X-ray diffraction and differential scanning calorimetry. Microchemical Journal. 2013 Sep 1; 110:146-57.
6. Farach FJ, Pruitt LD, Jun JJ, Jerud AB, Zoellner LA, Roy-Byrne PP. Pharmacological treatment of anxiety disorders: Current treatments and future directions. Journal of anxiety disorders. 2012 Dec 1;26(8):833-43.
7. Shen HW, Jiang XL, C Winter J, Yu AM. Psychedelic 5-methoxy-N, N-dimethyltryptamine: metabolism, pharmacokinetics, drug interactions, and pharmacological actions. Current drug metabolism. 2010 Oct 1;11(8):659-66.
8. Frecska E, Bokor P, Winkelman M. The therapeutic potentials of ayahuasca: possible effects against various diseases of civilization. Frontiers in pharmacology. 2016 Mar 2; 7:35.
9. Domínguez-Clavé E, Soler J, Elices M, Pascual JC, Álvarez E, de la Fuente Revenga M, Friedlander P, Feilding A, Riba J. Ayahuasca: Pharmacology, neuroscience and therapeutic potential. Brain research bulletin. 2016 Sep 1; 126:89-101.

10. Dos Santos RG, Osório FL, Crippa JA, Hallak JE. Antidepressive and anxiolytic effects of ayahuasca: a systematic literature review of animal and human studies. Brazilian Journal of Psychiatry. 2016 Jan; 38:65-72.
11. Aronson JK. Plant poisons and traditional medicines. Manson's Tropical Infectious Diseases, 23rd ed.; Cereal grains Farrar, J., Hotez, PJ, Junghanss, T., Kang, G., Lalloo, D., White, NJ, Eds. 2014 Jan 1:1128-50.
12. Uthaug MV, Van Oorsouw K, Kuypers KP, Van Boxtel M, Broers NJ, Mason NL, Toennes SW, Riba J, Ramaekers JG. Sub-acute and long-term effects of ayahuasca on affect and cognitive thinking style and their association with ego dissolution. Psychopharmacology. 2018 Oct;235(10):2979-89.
13. Liechti M, Ley L. Effects of Dimethyltryptamine in Healthy Subjects (NCT04353024). ClinicalTrials. Gov.
14. Hamill J, Hallak J, Dursun SM, Baker G. Ayahuasca: psychological and physiologic effects, pharmacology and potential uses in addiction and mental illness. Current neuropharmacology. 2019 Feb 1;17(2):108-28.
15. Prajapati ST, Patel CG, Patel CN. Formulation and evaluation of transdermal patch of repaglinide. International Scholarly Research Notices. 2011;2011.
16. Bird D, Ravindra N. Transdermal drug delivery and patches—An overview. MEDICAL DEVICES & SENSORS. 2020;3(6).
17. Liu L, Liu C, Wang Y, Wang P, Li Y, Li B. Herbal medicine for anxiety, depression and insomnia. Current neuropharmacology. 2015 Jul 1;13(4):481-93.
18. Singh A, Bali A. Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride. Journal of Analytical Science and Technology. 2016 Dec;7(1):1-3.
19. Carbonaro TM, Gatch MB. Neuropharmacology of N, N-dimethyltryptamine. Brain research bulletin. 2016 Sep 1; 126:74-88.
20. Keiser MJ, Setola V, Irwin JJ, Laggner C, Abbas AI, Hufeisen SJ, Jensen NH, Kuijer MB, Matos RC, Tran TB, Whaley R. Predicting new molecular targets for known drugs. Nature. 2009 Nov;462(7270):175-81.
21. McKenna DJ, Repke DB, Lo L, Peroutka SJ. Differential interactions of indolealkylamines with 5-hydroxytryptamine receptor subtypes. Neuropharmacology. 1990 Mar 1;29(3):193-8.
22. Strassman RJ. Human psychopharmacology of N, N-dimethyltryptamine. Behavioural brain research. 1995 Dec 15;73(1-2):121-4.
23. Sprouse JS, Aghajanian GK. Responses of hippocampal pyramidal cells to putative serotonin 5-HT1A and 5-HT1B agonists: a comparative study with dorsal raphe neurons. Neuropharmacology. 1988 Jul 1;27(7):707-15.
24. Trulson ME, Ross CA, Jacobs BL. Lack of tolerance to the depression of raphe unit activity by lysergic acid diethylamide. Neuropharmacology. 1977 Nov 1;16(11):771-4.
25. Haubrich DR, Wang PF. N, N-dimethyltryptamine lowers rat brain acetylcholine and dopamine. Brain research. 1977 Aug 5;131(1):158-61.
26. Bunzow JR, Sonders MS, Arttamangkul S, Harrison LM, Zhang GE, Quigley DI, Darland T, Suchland KL, Pasumamula S, Kennedy JL, Olson SB. Amphetamine, 3, 4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. Molecular pharmacology. 2001 Dec 1;60(6):1181-8.
27. Weissman AD, Su TP, Hedreen JC, London ED. Sigma receptors in post-mortem human brains. Journal of Pharmacology and Experimental Therapeutics. 1988 Oct 1;247(1):29-33.
28. Hayashi T, Su TP. Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca2+ signaling and cell survival. Cell. 2007 Nov 2;131(3):596-610.
29. Fontanilla D, Johannessen M, Hajipour AR, Cozzi NV, Jackson MB, Ruoho AE. The hallucinogen N, N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. Science. 2009 Feb 13;323(5916):934-7.
30. Frecska E, Szabo A, Winkelman MJ, Luna LE, McKenna DJ. A possibly sigma-1 receptor mediated role of dimethyltryptamine in tissue protection, regeneration, and immunity. Journal of neural transmission. 2013 Sep;120(9):1295-303.
31. Ruscher K, Shamloo M, Rickhag M, Ladunga I, Soriano L, Gisselsson L, Toresson H, Ruslim-Litrus L, Oksenberg D, Urfer R, Johansson BB. The sigma-1 receptor enhances brain plasticity and functional recovery after experimental stroke. Brain. 2011 Mar 1;134(3):732-46.

32. Tsai SY, Hayashi T, Harvey BK, Wang Y, Wu WW, Shen RF, Zhang Y, Becker KG, Hoffer BJ, Su TP. Sigma-1 receptors regulate hippocampal dendritic spine formation via a free radical-sensitive mechanism involving Rac1· GTP pathway. Proceedings of the National Academy of Sciences. 2009 Dec 29;106(52):22468-73.
33. Kourrich S, Su TP, Fujimoto M, Bonci A. The sigma-1 receptor: roles in neuronal plasticity and disease. Trends in neurosciences. 2012 Dec 1;35(12):762-71.
34. O'Donovan KJ, Tourtellotte WG, Millbrandt J, Baraban JM. The EGR family of transcription-regulatory factors: progress at the interface of molecular and systems neuroscience. Trends in neurosciences. 1999 Apr 1;22(4):167-73.
35. González-Maeso J, Weisstaub NV, Zhou M, Chan P, Ivic L, Ang R, Lira A, Bradley-Moore M, Ge Y, Zhou Q, Sealfon SC. Hallucinogens recruit specific cortical 5-HT2A receptor-mediated signaling pathways to affect behavior. Neuron. 2007 Feb 1;53(3):439-52.
36. Gewirtz JC, Chen AC, Terwilliger R, Duman RC, Marek GJ. Modulation of DOI-induced increases in cortical BDNF expression by group II mGlu receptors. Pharmacology Biochemistry and Behavior. 2002 Sep 1;73(2):317-26.
37. Jacob MS, Presti DE. Endogenous psychoactive tryptamines reconsidered: an anxiolytic role for dimethyltryptamine. Medical hypotheses. 2005 Jan 1;64(5):930-7.
38. Walters JK, Sheard MH, Davis M. Effects of N, N-dimethyltryptamine (DMT) and 5-methoxy-N, N-dimethyltryptamine (5-MeODMT) on shock elicited fighting in rats. Pharmacology Biochemistry and Behavior. 1978 Jul 1;9(1):87-90.
39. Frecska E. Ayahuasca versus violence--a case report. Neuropsychopharmacologia Hungarica: a Magyar PszichofarmakologiaiEgyesuletlapja= official journal of the Hungarian Association of Psychopharmacology. 2008 May 1;10(2):103-6.
40. Osório FD, Sanches RF, Macedo LR, Dos Santos RG, Maia-de-Oliveira JP, Wichert-Ana L, De Araujo DB, Riba J, Crippa JA, Hallak JE. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. Brazilian Journal of Psychiatry. 2015 Jan; 37:13-20.
41. Benington F, Morin RD, Clark Jr LC. 5-methoxy-N, N-dimethyltryptamine, a possible endogenous psychotoxin. The Alabama journal of medical sciences. 1965 Oct;2(4):397-403.
42. Abdallah CG, Coplan JD, Jackowski A, Sato JR, Mao X, Shungu DC, Mathew SJ. A pilot study of hippocampal volume and N-acetylaspartate (NAA) as response biomarkers in riluzole-treated patients with GAD. European Neuropsychopharmacology. 2013 Apr 1;23(4):276-84.
43. Rao PR, Diwan PV. Permeability studies of cellulose acetate free films for transdermal use: Influence of plasticizers. Pharmaceutica Acta Helvetiae. 1997 Feb 1;72(1):47-51.
44. McKenna DJ, Repke DB, Lo L, Peroutka SJ. Differential interactions of indolealkylamines with 5-hydroxytryptamine receptor subtypes. Neuropharmacology. 1990 Mar 1;29(3):193-8.
45. Santos RD, Landeira-Fernandez J, Strassman RJ, Motta V, Cruz AP. Effects of ayahuasca on psychometric measures of anxiety, panic-like and hopelessness in Santo Daime members. Journal of ethnopharmacology. 2007 Jul 25;112(3):507-13
46. Smit HF, Cuijpers P, Oostenbrink J, Batelaan NM, de Graaf R, Beekman AJ. Costs of nine common mental disorders: implications for curative and preventive psychiatry. The journal of mental health policy and economics. 2006;9(4):193-200.
47. Stein DJ, Khoo JP, Ahokas A, Jarema M, Van Ameringen M, Vavrusova L, Höschl C, Bauer M, Bitter I, Mosolov SN, Olivier V. 12-week double-blind randomized multicenter study of efficacy and safety of agomelatine (25–50 mg/day) versus escitalopram (10–20 mg/day) in out-patients with severe generalized anxiety disorder. European Neuropsychopharmacology. 2018 Aug 1;28(8):970-9.
48. Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, Summergrad P, Nemeroff CB, American Psychiatric Association. A consensus statement on the use of ketamine in the treatment of mood disorders. JAMA psychiatry. 2017 Apr 1;74(4):399-405.
49. Arunachalam A, Karthikeyan M, Kumar DV, Prathap M, Sethuraman S, Ashutoshkumar S, Manidipa S. Transdermal drug delivery system: a review. Journal of Current Pharma Research. 2010 Oct 1;1(1):70.
50. Selvam RP, Singh AK, Sivakumar T. Transdermal drug delivery systems for antihypertensive drugs-A review. Int J Pharm Biomed Res. 2010 Feb;1(1):1-8.

51. Chien YW. Novel drug delivery systems (Drugs and the pharmaceutical sciences). Transdermal Drug Delivery and Delivery Systems. 1992.
52. Sugibayashi K, Morimoto Y. Polymers for transdermal drug delivery systems. Journal of Controlled Release. 1994 Feb 1;29(1-2):177-85.
53. Patel RP, Baria AH. Formulation and evaluation considerations of transdermal drug delivery system. International Journal of Pharmaceutical Research. 2011 Nov;3(1):1-9.
54. Soni M, Kumar S, Gupta GD. Transdermal drug delivery: A novel approach to skin permeation. J Pharm Res. 2009 Jan;2: 1184-90.
55. Pfister WR, Hsieh DS. Permeation enhancers compatible with transdermal drug delivery systems. Part I: selection and formulation considerations. Medical device technology. 1990 Sep 1;1(5):48-55.
56. Godbey KJ. Improving patient comfort with nonocclusive transdermal backings. American Association of Pharmaceutical Scientists. 1996:1-2.
57. Walters KA. Transdermal drug delivery system In: Swarbick K, Boylan JC, editors. Encyclopedia of Pharmaceutical Technology.
58. Foco A, Hadziabdić J, Becić F. Transdermal drug delivery systems. Medicinskiarhiv. 2004;58(4):230-4.
59. Sunitha C. Formulation and evaluation of nicotine transdermal patches by the using of hydrophilic and hydrophobic polymers. World journal of pharmaceutical Research. 2018 Jul 1;7(16):1101-15.
60. Rao PR, Diwan PV. Permeability studies of cellulose acetate free films for transdermal use: Influence of plasticizers. Pharmaceutica Acta Helvetiae. 1997 Feb 1;72(1):47-51.
61. Singh A, Bali A. Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride. Journal of Analytical Science and Technology. 2016 Dec;7(1):1-3.
62. Prajapati ST, Patel CG, Patel CN. Formulation and evaluation of transdermal patch of repaglinide. International Scholarly Research Notices. 2011;2011.
63. Kanios DP, Mantelle JA, Johnson P, Li C, inventors; Noven Pharmaceuticals Inc, assignee. Packaging system for transdermal drug delivery systems. United States patent US 8,186,506. 2012 May 29.

	Corresponding Author Name – Mr. Payaam Vohra Final year B pharmacy student-H.K college of Pharmacy HK Campus, Relief Road, Oshiwara, Jogeshwari West, Pratiksha nagar, Mumbai,
	Mr. Shubham Sharma Third Year B Pharmacy student HK Campus, Relief Road, Oshiwara, Jogeshwari West, Pratiksha nagar, Mumbai, Maharashtra 400102
	Dr Indira Parab H.O.D in Pharmaceutics-H.K college of Pharmacy HK Campus, Relief Road, Oshiwara, Jogeshwari West, Pratiksha nagar, Mumbai, Maharashtra 400102