Designing an LSD Micro-Dose Transdermal Patch for Mental Illness Drug Therapy

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Abstract *— There is a very high incidence of mental health problems throughout the world, Depression, Post Traumatic Stress Disorder (PTSD), traumas, Schizophrenia, etc. Psychedelics have been in history for a long time now, used by indigenous people for rituals, recreationally by the hippies because of the war ranging on and now, by scientific researchers for the investigation of psychedelic therapy for mental illness. Lysergic Acid Diethylamide (LSD) is a semi-synthetic compound first developed in 1938 by Dr. Albert Hofmann at the Sandoz pharmaceutical company. LSD quickly became recognized for its possible therapeutic effects. Using the therapeutic effects advantage then there have been various anecdotal reports suggesting that repeated use of very low doses of LSD, known as micro-dosing, improves mood and cognitive function.*

Transdermal patches are designed to deliver active drugs across the skin into the systemic circulation in a sustained or controlled manner. Using this mechanism, a transdermal patch was designed that uses LSD as an active ingredient for drug therapy as treatment for mental illness with a controlled delivery of micro-doses.

Key Terms *— lysergic acid diethylamide, mental illness, psychiatry, transdermal patches*

INTRODUCTION

There is a very high incidence of mental health problems throughout the world, Depression, Post Traumatic Stress Disorder (PTSD), traumas, Schizophrenia, etc. [1]. Psychedelics have been in history for a long time now, used by indigenous people for rituals, recreationally by the hippies because of the war ranging on and now, by scientific researchers for the investigation of psychedelic therapy for mental illness. The Multidisciplinary Association for Psychedelic Studies or MAPS is a non-profit research and educational organization that develops medical, legal, and cultural contexts for people to benefit from the careful uses of psychedelics and marijuana. One of those major psychedelics being researched is commonly known as LSD or Lysergic Acid Diethylamide [2]. LSD is a semi-synthetic compound first developed in 1938 by Dr. Albert Hofmann at the Sandoz pharmaceutical company in Basel, Switzerland. After Dr. Hofmann first discovered its effects in 1943, LSD quickly became recognized for its possible therapeutic effects. LSD also played a significant role in the discovery of the serotonin neurotransmitter system [3], [4].

Transdermal patches are designed to deliver active drugs across the skin into the systemic circulation in a sustained or controlled manner. “Apart from improved patient convenience and compliance, the transdermal route offers other advantages of bypassing first-pass metabolism and avoidance of gastric/enzymatic drug degradation [5].” Using this mechanism, we want to design a transdermal patch that uses LSD as an active ingredient for mental illness drug therapy with a controlled delivery of micro-doses.

MAIN OBJECTIVE

The main goal of this research is to design a transdermal patch using LSD micro-doses as active drug as mental illness therapy.

BACKGROUND REVIEW

Lysergic Acid Diethylamide (LSD)

Lysergic Acid Diethylamide or LSD is a synthetic amide of lysergic acid found in a fungus on grains called ergot. LSD has powerful mind-altering effects, usually called hallucinogenic or psychedelic, which is what makes it illegal and a

Schedule I controlled substance in the United States and other countries.

LSD was synthesized in 1938 by Albert Hoffman, as part of a research program seeking new medicines of Sandoz Laboratories in Basel, Switzerland, LSD did not seem to offer such promise. Nevertheless, in 1943 Hoffman accidentally ingested a dose when a drop just touched his skin, and experienced its psychoactive effects, and described these effects as being surprisingly transformational.

Then in 1949, LSD was introduced into the United States as a psychiatric therapeutic wonder drug used to treat a variety of psychological problems like schizophrenia, depression, various kinds of sexual deviance, alcoholism, and criminality. In the late 1940's and 1950's, even the U.S. military and intelligence communities (including the U.S. Army, Navy, Office of Strategic Services, and Central Intelligence Agency) experimented with LSD as a possible truth serum, incapacitant, or "unconventional warfare" agent but at the end found its properties too unpredictable for their purposes.

Before its criminalization, more than forty thousand patients were treated with LSD psychotherapy with notable results in alcoholics, felons, and the terminally ill, persons who normally are resistant to successful therapeutic outcomes.

The normal threshold dose is 25 micrograms (mcg), and 100 to 250 mcg is typical; beyond 400 mcg no further change seems to occur [1].

LSD in Psychiatry

The experiential effects of LSD include positive aesthetic, psychological, and spiritual transformations. Aesthetically, the effects center on perceptual changes, especially to the visual field, which is intensely enhanced with greater mobility, colorfulness, transiency, luminosity, energy, swelling, vividness, and synesthesia. Psychologically, the effects of LSD include mood changes, particularly feelings of well-being and euphoria; a new and greater awareness of the world and of self; a deeper understanding of human relationships; a transcendence of time and space; and a sense of ineffability. Spiritually, the effects of LSD include a sense of rebirth; a sense of encounters with divinity; a sense of the world as sacred; and a sense of communion, unity, and non-duality [2], [3], [6].

LSD Microdoses in Psychiatry

Using the therapeutic effects advantage then there have been various anecdotal reports suggesting that repeated use of very low doses of lysergic acid diethylamide (LSD), known as micro-dosing, improves mood and cognitive function.

In the study Acute subjective and behavioral effects of micro-doses of LSD in healthy human volunteers the effects of single very low doses of LSD (0-26 μg) on mood and behavior in healthy volunteers under double-blind conditions are examined. single microdoses of LSD produced orderly dose-related subjective effects in healthy volunteers, indicating that a threshold dose of 13 μg of LSD might be used safely in an investigation of repeated administrations [7], [8].

Transdermal Therapy and Patches

Controlled drug delivery systems offer numerous advantages over conventional dosage forms, including improved therapeutic effects, reduced toxicity, and increased patient compliance and convenience, it is a method of drug administration to the needs of a condition at hand so that the optimal amount of drug is used to cure or control the condition in a minimum time [9]. A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. It has several components like liners, adherents, drug reservoirs, drug release membrane etc., which play a vital role in the release of the drug via skin [7].

There are four types of transdermal drug delivery system (figure 1):

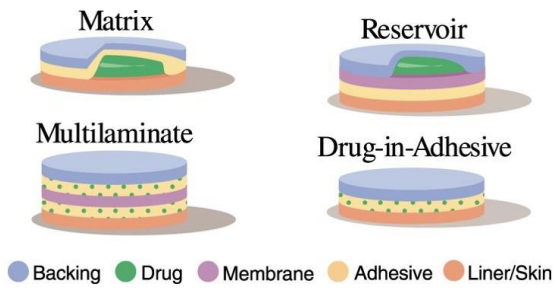

Figure 1
The four types of transdermal delivery systems

- **Membrane permeation-controlled systems:** In this type, the drug can be totally or partially encapsulated within the drug reservoir, its drug release surface is covered by a rate controlling polymeric membrane. The drug molecules are permitted to release only through the rate-controlling membrane having a specific permeability. In the drug reservoir compartment, the drug solids are either dispersed in a solid-polymer matrix or suspended in a viscous liquid medium to form a paste like suspension. A thin layer of adhesive polymer is applied to the external surface of the rate-controlling membrane to achieve an intimate contact of the transdermal system and the skin surface [9].
- **Matrix diffusion-controlled system**: The most popular drug delivery system has been the matrix diffusion-controlled system, in which it contains the drug such as tablets and granules, uniformly dissolved or dispersed throughout the polymer matrix, because of its low cost and ease of fabrication. The resulting polymer matrix with the drug is then sculpted into a disc with a defined surface area and controlled thickness. The reservoir containing the polymer disc is then attached on to an occlusive base plate fabricated from a drug impermeable plastic backing then the adhesive is extended to form a strip of adhesive border around the disc [9].
- **Adhesive dispersion type system**: This type transdermal delivery, which is kind of a mutated form of the membrane permeation system, the drug reserve is formed by directly dispersing the adhesive polymer. This adhesive is done by formulating a drug reservoir by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive, by solvent casting or hot melt onto on to a flat sheet of metallic plastic laminate, by which is impermeable to the drug. On the top of the drug reservoir layer, thin layers of non- medicated, rate controlling adhesive polymer of a specific permeability are applied to produce an adhesive diffusion - controlled delivery system [9].
- **Micro-reservoir type or micro-sealed dissolution-controlled systems**: This type of transdermal delivery system is more of a combination of reservoir and matrix dispersion type. The drug reservoir is done by suspending the solid drug particles in an aqueous solution of a water-soluble polymer, so the drug suspension formed is homogenously dispersed in a lipophilic polymer by high shear mechanical force to form a large number of micro-reservoirs. A transdermal therapeutic system is produced by positioning the medicated disc at the center and surrounding it with an adhesive border, then it is spread on to the occlusive base plate with an adhesive foam pad [9].

Basic Components of a Transdermal Patch

The basic components of transdermal patches are the polymer matrix or matrices, the drug, Permeation enhancers and other excipients.

- **Polymer matrix or matrices**: The polymer should be stable, non-reactive with the drug, easily manufactured into the desired product and inexpensive. The Polymer controls the release of the drug from the device. Possible useful polymers for transdermal devices are Natural Polymers, like for example, Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch. As for possible Synthetic Elastomers, there is Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile,

Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc and Synthetic Polymers, like Ethylene Vinyl Acetate, Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Epoxy etc. [9].

- **The drug:** The transdermal patch design is dictated by the properties of the drug (table 1). The main characteristics to evaluate and consider are the drug's Molecular weight, in other words, the size of the drug molecule, only small molecules can penetrate the skin, so it is typically less than 500 g/mol or Daltons; lipophilicity of the drug which determines how readily the drug is absorbed into the body's oils. When it comes to Dosage form of the drug what it means is in what form will the drug be administered? Solid, Semi-solid, Liquid or Gas forms [11].

Table 1
Ideal properties of drugs for transdermal patch

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
Liophilicity	10 < Ko/w < 1000
Oral bioavailability	Low
Therapeutic index	Low
Melting point	<200°C
pH	Between 5.0 and –9.0

- **Permeation enhancers:** Permeation enhancers are the chemical compounds that increase permeability of the stratum corneum or outer layer of the skin (epidermis), so as to open the transdermal route for a wider range of drugs, since the majority of drugs will not permeate into skin for therapeutic use.
- **Other excipients**: The "tape" used for all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive. Another type of excipient used for transdermal devices is the backing membrane. The backing membrane should be flexible and provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing [9], [11].

PROJECT METHODOLOGY

For this project's methodology, the DMADV Methodology from Lean Six Sigma is used for designing a new product of LSD Transdermal Patch (figure 2).

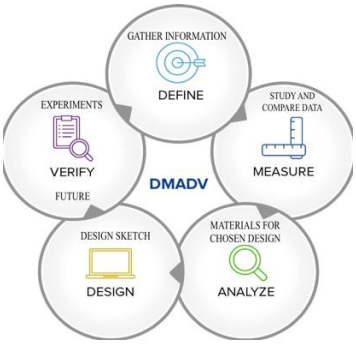

Figure 2
DMADV project methodology used

RESULTS AND DISCUSSION

Define

As studies show, there are high incidences on mental health disorders and there are many psychedelic-assisted therapies for mental disorders attributed to the lasting change from experiential avoidance to acceptance that these treatments appear to facilitate. This includes, studies that show the therapeutic properties and incredible advances of LSD in treating alcoholism, understanding schizophrenia and other psychoses, and achieving empathy with their patients [1]. LSD micro-dosing has, also therapeutical benefits without necessarily causing hallucinations and other side effects. Transdermal Patches are an easier and efficient method to administer these micro-doses by absorbing it through the skin [7].

Measure

The basic materials that make up a transdermal patch are [9]:

- **Backing:** The outermost layer of the patch, which protects the formulation during the wear period.

- **Drug:** The drug contained within the membrane or in the adhesive.
- **Membrane:** The film that controls the rate of drug diffusion out of the patch, to the skin.
- **Adhesive:** The skin contacting layer that adheres the patch to the skin.
- **Overlaminate tape:** The external protective covering or functional layer which can be directly integrated into the patch design.
- **Release liner:** Protects the skin-contacting adhesive during storage and is removed prior to application of the patch.

The transdermal patch design is dictated by the properties of the drug. If you're working with an active ingredient, you've likely already characterized it. The following are typically the main areas considered (table 2).

Table 2
Ideal Drug Properties vs. LSD Drug Properties

Property	Ideal Drug Properties	LSD Drug Properties
Molecular Weight	< 500 Daltons	323.4 g/mol(Daltons)
Lipophilic (Log P)	Log P $\geq$ 0	Log P = 3
Hydrophilic	pKa $\leq$7	pKa = 7.8
Half-life	Short	2.5 hours
Melting point	Low melting point	82.5 °C.
Dosage Form	Liquid, Solid, Semi-solid or gas	Liquid
Dose	Low doses	13 – 25 µg

The size of the drug molecule is considered since only small molecules can penetrate the skin, so typically less than 500 Daltons, in which 1 Dalton = 1g/mol. LSD has a Molecular weight of 323.4 g/mol or 323.4 Daltons, which in turn is less than 500 Daltons.

The drug should have affinity for both – lipophilic and hydrophilic phases. The most commonly used measure of lipophilicity is LogP, this is the partition coefficient of a molecule between aqueous and lipophilic phases, usually octanol and water. A positive value for logP denotes a higher concentration in the lipid phase. LogP = 1 means there is a 10:1 partitioning in Organic : Aqueous phases. Therefore, Log P should equal or more than 0, in this case LSD has a Log P = 3.

Another property for the ideal drug would be water solubility, we can use the value of its pKa. Drugs with a pKa under 7 (i.e. weak acids) will usually be water-soluble. LSD does not have a pKa under 7, it is 7.8 but it is still on that threshold of 7 not 8 yet, so it is fairly neutral. Also, one of its properties is that is very rapidly absorbed and has a water solubility of 0.27 mg/mL.

The Dosage form, in this case, it should be in liquid form, since that is the normal state of LSD.

Findings indicate that a threshold dose of 13 µg to 25 µg of LSD might be used safely in an investigation of repeated administrations.

As for the Melting point of the ideal drug, it should be a low melting point so that it has good solubility properties. So, the ideal drug in a transdermal patch it can't be at a level where it prohibits the actual manufacture of the patch itself. LSD has a 176 to 185 °F or 82.5 °C.

Permeation enhancers are mostly used when the drug will no permeate through but in this case with LSD, there is no problem with permeating skin, it is absorbed pretty fast through the skin.

Now that we've chosen the ideal drug, we need to choose the transdermal patch design For the LSD Transdermal patch, the Membrane permeation Controlled system would be the ideal design. The DIA cannot be because we need the LSD drug to be secured inside the patch, out of contact from light to minimize degradation of the molecule, so it can't just be in an adhesive. The matrix diffusion-controlled system, also does not work because we want LSD release to be at once not a slow release, because of the same reason of degradation, after a time it the drug won't have the same effect, same for micro-reservoirs. Therefore, the membrane permeation-controlled system is the one chosen.

Now that we have our design, the next step would be choosing the right materials. This includes the liner, backing, membrane, over laminate tapes.

Ethylene vinyl acetate copolymer is an important part of the Transdermal Drug Delivery growth. This polymer can be used as a rate-controlling membrane in transdermal patches, which is the most used in reservoir for transdermal patch designs.

Analyze

A possible product for this design in the future could be 3M™ CoTran™ Ethylene Vinyl Acetate Membrane Film, for the rate controlling membrane. It has properties of being Translucent, has a Matte finish on both sides, Corona treated,18.5% Vinyl Acetate, Non-porous, rate-controlling EVA membrane, 4 mils thick, 18.5%VA [12].

While designing a backing layer, the consideration of chemical resistance of the material is most important. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate. For this, we have chosen, 3M™ Scotchpak™ Polyester Backing Film Laminate with properties of being Tan in color, Occlusive, Conformable, with Controlled caliper

In this case, 3M™ CoTran™ Polyethylene Tape was chosen because of its properties of being Tan in color, Breathable, Conformable, has Pressure sensitive acrylate adhesive. This tape consists of a tan polyethylene backing coated with an acrylate adhesive.

3M™ Scotchpak™ Release Liner Fluorosilicone Coated Polyester Film, was chosen because of its Excellent chemical stability and resistance to amines and its occlusive to secure the LSD drug from getting in contact with light [12].

Design

A sketch of a preliminary design of the LSD transdermal patch was done using the membrane permeation-controlled system as the transdermal mechanism chosen (figure 3). The diagrammatic representation of membrane permeation-controlled system in which the drug reservoir in the rate-controlling membrane is stacked between layers the drug's impermeable plastic laminate or backing liner and the adhesive which faces the skin surface.

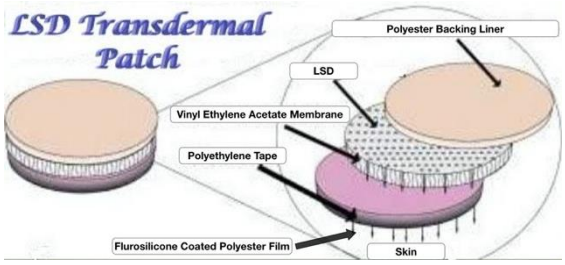

Figure 3
LSD micro-dose transdermal patch design

Verify

For the last phase, it would be ideal to be able to assess the effectiveness of this transdermal patch based on dose, area, vehicle and device, as well as, quantify the rate of the time of absorption of Lysergic Acid Diethylamide micro-dose from the transdermal patch designed.

CONCLUSIONS

Repeated use of very low doses of lysergic acid diethylamide (LSD), known as micro-dosing, improves mood and cognitive function. These therapeutic effects are consistent both with the known actions of LSD on serotonin receptors

Since LSD is so easily absorbed through the skin, a transdermal patch or skin patch was chosen. A transdermal patch or skin patch, which is a medicated adhesive patch that delivers a specific dose of medication through the skin and into the bloodstream, to cure or control a condition in a minimum time overcoming various side effects.

After evaluating LSD's drug properties to match for a transdermal patch, Membrane Permeation Controlled system was chosen as the mechanism for a transdermal patch. In this type, the drug can be totally or partially encapsulated within the drug reservoir, its drug release surface is only done through a rate controlling polymeric membrane.

Once the type of mechanism was chosen, the specific materials for each component of the transdermal patch was chosen. These components

were liners, adhesives, drug reservoirs, drug release membrane etc., which play a vital role in the release of the drug via skin. The materials were chosen from real products from 3M manufacturer, leader in making transdermal patches.

After choosing material a first design was made and then after further evaluation a second one was made.

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