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PREPARATION AND EVALUATION OF THE MEDICINAL TRANSDERMAL PATCH: A REVIEW

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ABSTRACT:

Pain is a word that refers to the damage or destruction of cells, bodies, and body functions. The proposed study aims to determine the potency of herbs used in spinach and marigolds for improving pain when formulated as a transdermal patch. In this study, various phytochemicals found in spinach and marigold improved wound healing. The current invention involves the treatment, improvement, and prevention of various skin allergies, and wound healing through transdermal patches. The main purpose of this study is to develop an herbal transdermal patch containing spinach extract in marigold extract, which will help in the treatment of skin diseases such as redness and wound healing. Due to low side effects, herbal preparations are still the basis of the treatment of approximately more than 80 % of the world's population in many countries. They are also more compatible than synthetic drugs. The herbal formula consists of medicinal plants, and root and heeds of their root and heeds that are rich in various phytochemicals that help the treatment of various injuries, diseases, or disorders. In this study, spinach and marigold have been shown effective. Many studies have shown that there are creams and ointments for the treatment of skin diseases, but this study shows that transdermal delivery has many cosmetic advantages. Because the future application of TDDS is very broad, it can be applied to bulk penetration methods, photomechanical waves, etc. It has many new methods.

Keywords: - Transdermal Patches, Herbal Medicine, Wound Healing, Marigold, Spinach.

INTRODUCTION:

Transdermal drug delivery systems are new drug delivery systems that focus on the control of drug targets and release, including many drugs. System version: delayed release, delayed release, target release, system update, extended-release, etc. Transdermal drug delivery systems are used in many applications to create treatments such as local anesthetics and anti-inflammatory drugs due to their many advantages and drug use methods. The potential for innovation in TDDS is enormous, as are advances in healthcare. TDDS tends to improve the bioavailability of the drug and bypass first-pass metabolism. TDDS helps administer the drug within a therapeutic window to prolong the effects of the drug. Transdermal treatment systems are designed to provide controlled and continuous delivery of the drug through the skin into the body. Additionally, it overcomes many side effects that occur in other types of drug delivery, such as pain in drug delivery and first-pass metabolism of drugs. The medication is usually delivered to the skin through a transdermal patch that adheres to the skin. [1]

TRANSDERMAL PATCH:

The transdermal patch is defined as an adhesive patch that is placed on the skin and provides a precise drug release rate first. It reaches the body by entering the bloodstream. Most transdermal systems on the market today are based on semi-permeable membranes called patches. Transdermal drug delivery systems (TDDS), also known as transdermal patches or skin patches, are bulk materials designed to deliver effective medications into the body; skin, and nerve inflammation. [2, 3, 4, 5]

Too frequently stimulated veins heal the body's wounds. The first commercially available prescription approved by the U.S. Food and Drug Administration in December 1979 contained scopolamine to treat this condition. The best-selling transdermal patch in the United States is the nicotine patch, which releases nicotine to help quit smoking. The first commercially available vapor patch to reduce smoking was approved in

Europe in 2007. There are also many other patches on the market, including fentanyl (a medication used to treat severe pain), nitro-glycerine used to treat angina, and lidocaine. Patch sold under the name Lidoderm (may reduce pain). For peripheral pain in herpes zoster (shingles), buprenorphine, brand name Bu Trans, is used to treat moderate to severe pain. It is now used mostly off-label to treat acute and chronic pain. Flector (Diclofenac epolamine) Patch is a topical NSAID used to treat severe pain caused by minor strains, sprains, and contusions. It is also used to treat pain in chronic conditions that benefit from non-steroidal anti-inflammatory drugs, including fibromyalgia and arthritis. Recent advances have expanded its use in providing anti-hormonal drugs, anti-anxiety drugs, and even antibiotics and stimulants for the treatment of deficits, and hyperactivity disorder (ADHD). In 2005, the FDA announced that it was investigating reports of drug overdose-related deaths and other adverse events in patients using Duragesic, a fentanyl transdermal patch used to control pain. Duragesic product information was updated to include safety information after June 2005. In 2009, the FDA issued a public health warning regarding the risk of burns during MRI examinations using metal-backed anti-inflammatory drugs. Patients should be instructed to remove anti-inflammatory medications before the MRI scan and replace them with new ones after the scan is completed. [6,7]

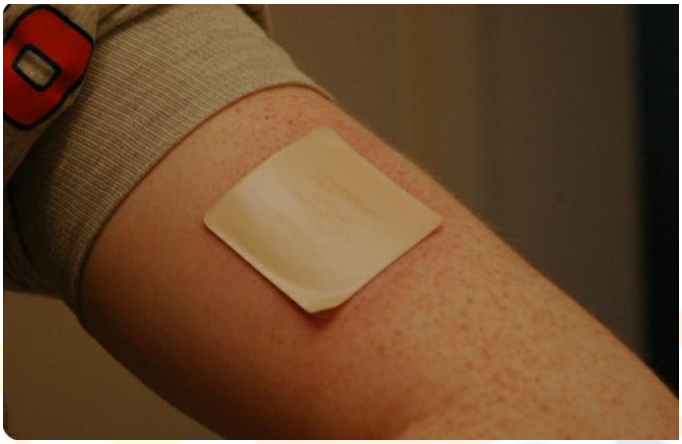

fig: -1 transdermal patch.

Skin structure:

The skin can be considered to consist of four different tissue layers: intact epidermis, active substance, usable skin, and subcutaneous tissue. The epidermis is the thin, tough outer layer of the skin. The stratum corneum is the outer layer of the epidermis and is waterproof; If not damaged, it prevents most bacteria, viruses, and other foreign substances from entering the body. The epidermis also protects internal organs, muscles, nerves, and blood vessels from injury. The keratin layer of the epidermis is much thicker. The thickness of the active epidermal layer of the skin is 50-100 µm. The cellular structure of the living epidermis is physico-chemically similar to other living tissues. Cells are held together by many fibrils. Humidity is approximately 90%. The next layer of the skin, the dermis, is a thick layer of fibrous and elastic tissue that gives the skin flexibility and strength. The dermis contains blood vessels, sweat glands, sebaceous glands, hair follicles, and blood vessels. It consists of loose white fibrous connective tissue containing blood and lymphatic vessels. [8]

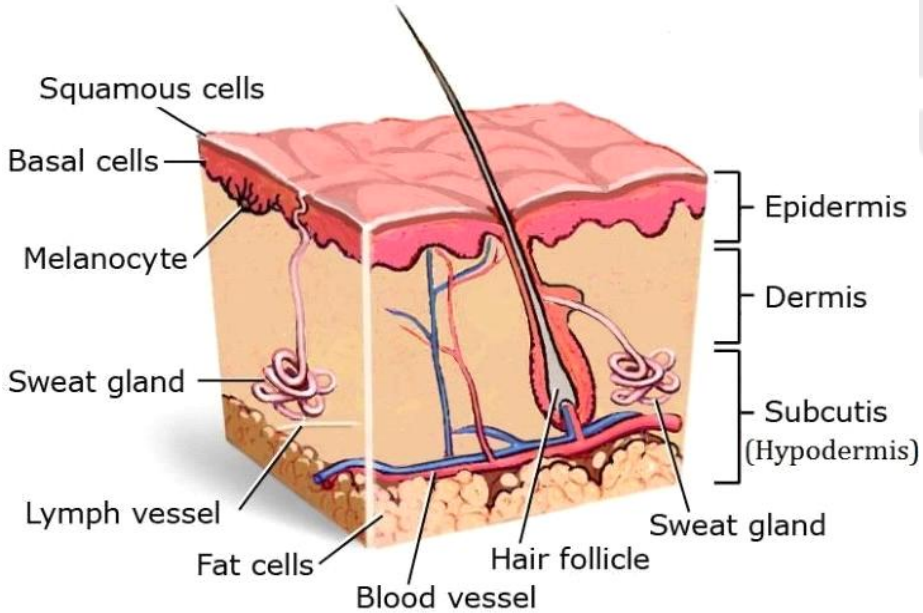

fig:- 2 Skin model.

Types of Transdermal Drug Delivery Systems:

- **Single-Layer Drug Adhesive System:** In this type of patch, the adhesive layer of the body contains the drug. The adhesive layer is not only responsible for individual processes for the skin and therefore for the entire system, but also the release of the drug. The adhesive layer is surrounded by a temporary liner and backing.

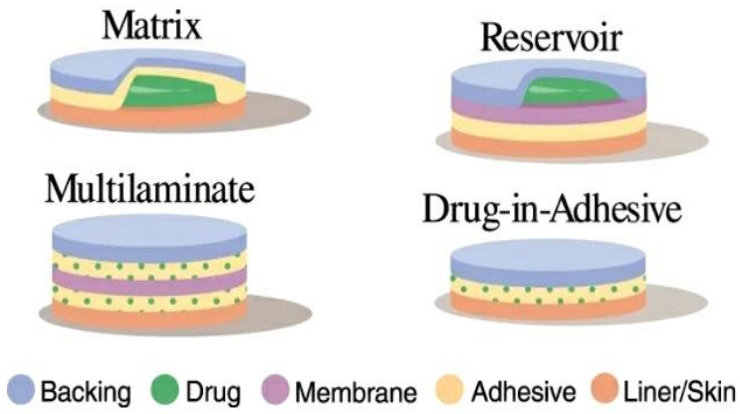

fig:- 3 Drug adhesive system

- **Reservoir System**: In this system, the chemical reservoir is kept in the membrane between the back layer and the rate control layer. The amount of drug entering the micropores controls membrane release. The drug may be in the form of a solution, suspension, or gel, or dispersed in a solid polymer matrix in the reservoir compartment.
- **Matrix Systems:**
  - **a) Drug Binding Systems:** melt from the solvent or adhesive (in the case of hot glue) to form a frost-free layer that will expose the polymer adhesive.
  - **b) Matrix dispersion system:** In this system, the drug is mixed into a hydrophilic or lipophilic polymer matrix. The polymer is immobilized with the drug on an occlusive substrate within a chamber made of a drug-impermeable back sheet. In this process, the adhesive is spread around the circle rather than being coated on the surface of the medication chamber, creating a sticky edge. [9]

❖ **Micro reservoir system:** This system is a combination of reservoir and matrix-dispersion systems. In which the drug is suspended in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. [10]

ADVANTAGES:

a) First-pass metabolisms of the drug get avoided.

b) Gastrointestinal incompatibilities are avoided.

c) Self-medication is possible.

d) Duration of action gets extended & predictable.

e) Unwanted side effects get minimized.

f) Drug plasma concentration is maintained.

g) The number of doses is reduced which improves patient compliance.

h) The therapeutic value of many drugs is increased by avoiding problems associated with drugs like lower absorption, GI irritation, and decomposition due to hepatic first-pass metabolism. [11,12]]

DISADVANTAGE:

1. Chances of allergic reactions at the site of application like- itching, rashes, local edema, etc.
2. A larger molecular size of the drug (above 1000) creates difficulty in absorption.
3. The barrier function of skin varies from site to site on the same or different person.
4. Drug with hydrophilic character is less suitable as compared to drug with lipophilic character because of their low permeability.[13]

LIMITATIONS FOR SELECTION OF TDDS:

- All types of drugs cannot be administered through this route; the drug must have some desirable Physicochemical properties.
- Not suitable for drugs that require high plasma levels.
- Not suitable for drugs that produce skin irritation and contact dermatitis.
- Not suitable for drugs with high molecular weight.
- Not suitable for drugs that undergo metabolism during the passage through the skin.
- The Transdermal route cannot be employed for a large
- Several drugs, as the skin is a very efficient barrier for penetration of drugs.
- Only a low dose can be administered.
- The barrier nature of the skin changes from one site to another in the same person, from person to person, and also with age. [13]

MATERIAL AND METHOD:

- **Material**:

The Marigold Extract, Spinach Extract, Quercetin, and Terpenes extract [Citrus Fruit] were prepared in the lab. The Starch powder was obtained from Potatoes on a laboratory scale in Vidya Niketan College of Pharmacy, Lakhewadi. Chloroform and methanol were purchased from Swaroop Enterprises, Aurangabad, Maharashtra.

- **Preparation method of the transdermal patch**:

a) Asymmetric TPX membrane method.
b) Circular Teflon Mold method.
c) Mercury substrate method.
d) Use the "IPM film" method.
e) Use the "EVAC membrane" technique.
f) Preparation of TDDS using preformed liposomes.
g) Use the free film method.
h) Solvent casting method.

❖ **Solvent casting method:**

A drug-loaded matrix-type marigold transdermal patch is prepared by solvent casting method. Use a Petri dish with a total area of 44.15 cm2. Carefully measure the polymer (starch), dissolve it in 10 mL of water and methanol (1:1) solution, and let it sit until a clear solution forms. Dissolve the medicine (spinach extract) in the above solution and stir until a clear solution is obtained. Quercetin (30% w/w of the total polymer) was used as the plasticizer and terpenes (15% w/w of the total polymer) as the penetrant. The resulting mixture is thrown into a Petri dish, lubricated with glycerol, and dried at room temperature for 24 hours. Place an inverted funnel over the Petri dish to prevent rapid evaporation of the solvent. After 24 hours, dried patches were removed and stored in a desiccator for further studies. [14]

EVALUATION OF TRANSDERMAL ROUTES:

1. **Physical and chemical measurements:**

- **Thickness:** The thickness of the transdermal membrane is measured from different points of the membrane using a kinetic meter, comparator, screw meter, or micrometer. [15,16,17]

- **Weight uniformity:** Examine the weight variation by weighting 10 randomly selected blocks individually and calculate the average weight. A person's weight should not differ from their average weight. [18]
- **Determination of the content of the drug:** It can be determined by filling a small area (1cm2) of the polymer film with a certain volume of appropriate solvent. Choose a freely soluble solvent. Measure the selected area before dissolving in a solvent. All contents were shaken continuously for 24 h in a shaking incubator and then sonicated and filtered. Analyse chemicals in solution using appropriate analytical techniques. [19]
- **Evaluation of Ingredients (content uniformity test):** This test is the gold standard and analyses the amount of active ingredients in a dose. The testing was done by measuring the chemical content of the polymer film on the patch. According to the USP, the process has two stages. The first phase consists of reviewing ten selected units. When the first stage fails, the second stage is executed on twenty additional units. Initially, ten patches are selected and the content of each patch is determined. The test was passed when the content of all 10 dose units was ≥ 85% and ≤ 115% (RSD < 6%). If the content of 9 out of 10 patches is between 85% and 115% of the set value and the content of 1 is not less than 75% to 125% of the listed price, the variable changes the content comparison. However, if 3 patches have drug content in the range of 75% to 125%, then try to add 20 patches to the drug content. If the RSD of all 30 units is <7.8%, no more than 1 value exceeds 85-115% if there is no test clan and no value exceeds 75-125% then the test.
- **Moisture content:** The prepared films were weighed one by one and stored in a desiccator containing calcium chloride at room temperature for 24 hours. The video gets heavier after a certain period until it finds a constant weight. Use the formula below to calculate moisture content. [20]

$$\% \text{ moisture content} = \frac{\text{(starting weight - final weight) x100}}{\text{Final weight Moisture}}$$

- **Absorption:** Keep the film weight on in a dryer at room temperature for 24 hours. It is then removed and exposed to 84% relative humidity in a desiccator using saturated potassium chloride solution until the weight becomes constant. The % moisture absorption is calculated as follows. [21]

$$\% \text{ Moisture Absorption Rate} = \frac{\text{Final Weight - Starting Weight x100}}{\text{Starting Weight}}$$

- **Flatness:** Transdermal patches should have a smooth surface and not fade or shrink over time. This can be seen by surveying the plains. Cut one strip down the middle of the patch and two strips on each side of the patch to determine flatness. The length of each strip is measured and the change in length is measured by determining the percent shrinkage. Zero percent shrinkage equals 100% flatness.

$$\% \text{ Flatness} = \frac{\text{(L1-L2) x100}}{\text{L1}}$$

Where,

L2 = Final length of each strip L1 = Initial length Length of each strip.

- **Folding Durability:** Evaluation of folding durability involves determining the ability of the film to resist folding under many folding conditions. Folding is determined by repeatedly folding the film in the same position until it breaks. The number of films that can be folded in the same position without breaking is the folding resistance value. [22]
- **Tensile strength:** To measure tensile strength, polymer films were mixed on cork linear metal plates. One end of the membrane is held tightly with the help of a metal sieve, and the other end is tied to the free string of the ruby. Slowly add weight to the plate attached to the hanging end of the rope. The pointer on the line is used to measure the elongation of the film. Gather enough weight to break the film. The tensile strength can be calculated using the following formula.

$$\text{Tensile strength} = F/a.b(1+L/l)$$

Where,

'F' is the force required to break;

'a' is the width of the film;

'b' is the thickness of the film;

'L' is the length of the movie;

"l" is the elongation of the film at the breaking point.

In another study, the tensile strength of the film was determined with the help of tissue testing. When the film breaks, force and elongation are measured. [23,24]

- **Water Vapor Test (WVT):** WVT is determined by taking 1 g of calcium chloride into a pre-dried empty bottle of the same crossed line. Apply the polymer film to the edges using a silicone-like adhesive and let it sit for 5 minutes. The vials were weighed appropriately and placed in a humidity chamber maintained at 68% relative humidity. The bottles are then weighed for seven consecutive days, and the increase in weight is considered a measure of the amount of water transferred from the site. In another report, a dryer was used to decant vials containing 200 mL of saturated sodium bromide and saturated potassium chloride solutions. The dryer is turned off and a hygrometer is used to measure the humidity inside the dryer. The bottles are then weighed before and after being placed in the desiccator, and the process is repeated.

$$WVT = \frac{W}{SxT}$$

"W" is weight gain in 24 hours;

"S" is the exposure area of the film (cm^2);

"T" is the correct tense.

- **Microscopic studies:** The distribution of drug and polymer in the film can be studied using a scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double-sided adhesive tape. The sections are then coated with gold-palladium alloy using a fine coat ion sputter to render them electrically conductive. Then the sections are examined under a scanning electron microscope. [25]
- **Adhesive studies:** The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. Adhesion of TDDS to the skin is achieved using PSA, which is defined as an adhesive that can bond to a surface using high-pressure light. The adhesive properties of TDDS can be characterized by considering the following factors. [26]
- **Peel Adhesion Performance:** The force required to remove the adhesive from the test substrate. The test is performed by measuring the force required to pull a strip of coated tape applied at a 180° angle to the substrate. If there is no residue on the substrate, the test is over. Minghetti et al., (2003) performed the test with a tensile testing machine Acquati model AG/MC 1 (Aquati, Arese, Italy).
- **Tack properties**: The polymer can adhere to the substrate with little contact pressure. Tack is dependent on the molecular weight and composition of the polymer as well as on the use of tackifying resins in the polymer [27] It includes a thumb tack test, rolling ball test, quick stick (Peel tack) test, and probe tack test. A thumb tack test is performed by touching the surface of a pressure-sensitive adhesive with the thumb and feeling the force required to break the bond. Thus, the force required to remove the thumb from the adhesive is a measure of tack. Measuring ball roll involves measuring the distance a stainless-steel ball travels with the rod pointing up. The less sticky the ball can travel further.
- **Rapid Adhesion (Peel Adhesion) Test:** The tape is pulled away from the substrate at a speed of 12 inches/minute at a 90° angle to measure the peel force required to break the adhesive and substrate. The probe rod is made by a probe that is pushed forward until it comes into contact with the adhesive and then retracted at a high speed. Measure the force required to break the bond after a short contact time. The test may be performed with the help of a Texture Analyser.
- **Shear strength properties or creep resistance:** Shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., the device should not slip on application determined by measuring the time it takes to pull an adhesive-coated tape off a stainless plate. Minghetti et al., (2003) performed the test with an apparatus that was fabricated according to PSTC-7 (pressure sensitive tape council) specification.[28]

2. In-vitro studies

❖ **In-vitro release studies:**

The amount of drug available for absorption into the systemic pool is greatly dependent on the drug released from the polymeric transdermal films.[29] Drug release mechanisms and kinetics are two characteristics of the dosage forms that play an important role in describing the drug dissolution profile from controlled release dosage forms and their in-vivo performance. Several mathematical models have been developed to describe the drug dissolution kinetics from controlled release drug delivery systems e.g., Higuchi, first order, zero order, and Peppas and Korsenmeyer models. The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug. Various methods are available for the determination of drug release from TDDS.[30,31,32,33,34,35]

In this method, a transdermal system is placed in between the receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment paddle over disc method (USP apparatus 5/PhEur 2.9.4.1) is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C. The paddle-over disk method in conjunction with a watch glass-patch-screen sandwich assembly is thought to be the preferable method. It is easier, more convenient, and exhibits experimentally almost the same release profile when compared with other more complicated methods. The Cylinder Modified USP Basket (USP Apparatus 6 / PhEur 2.9.4.3) method is similar to the USP Basket Dissolution Apparatus except that this system is attached to the surface of a hollow cylinder in an environment of 32 ± 5°C. The device 7) method involves mounting the patch on a holder and releasing a small amount into the medium, allowing the equipment to be used in systems providing low concentrations. The paddle over-extraction cell method can also be used (PhEur 2.9.4.2). Diffusion cells include the Franz diffusion cell and the modified Keshary-Chien into which receptor fluid (such as solution) is placed. stirring speed and temperature were stable. The whole assembly is kept on a magnetic stirrer and the solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of a drug is determined by a suitable analytical method. The pH of the dissolution medium ideally should be adjusted to pH 5 to 6, reflecting physiological skin conditions. For the same reason, the test temperature is typically set at 32°C (even though the temperature may be higher when skin is covered). PhEur considers 100 rpm a typical agitation rate and also allows for testing an aliquot patch section. The latter may be an appropriate means of attaining sink conditions, provided that cutting a piece of the patch is validated to have no impact on the release mechanism. The dissolution data obtained is fitted to mathematical models to ascertain the release mechanism.

❖ **In vitro penetration study:**

After being released from the polymer material, the drug penetrates the skin and then enters the dermal microcirculation through the penetration of epidermal cells and/or epidermal cells. Skin inserts. In general, permeation studies are performed by placing bandages of rat skin or synthetic material between the recipient and donor areas of the vertical beam (such as a Franz diffusion cell or a Keshary-Chien diffusion cell). The transdermal system is applied to the hydrophilic side of the membrane, which is then placed in a cell junction with the lipophilic side in contact with the receptor fluid. The receiving chamber is maintained at a low temperature (usually 32 ± 5°C for the skin) and stirred continuously at a constant speed. Samples were taken at different times and the balance of parameters was changed each time. The sample is diluted appropriately and analyzed by an appropriate analytical method. Calculate drug penetration per square centimeter each time. Many variables, such as design, patch size, skin area, skin thickness, and temperature, can affect the in vitro properties of drugs. Therefore, permeability research involves preparing the skin, placing skin permeability cells, setting conditions such as temperature, agitation, and tank conditions, removing the sample at different times, and observing and calculating the flow (such as chemical permeability per unit) (time. area) [36]

2. In vivo studies/research:

In vivo research is a true definition of performance. Changes that cannot be detected in in vitro studies can be detected in in vivo studies (Sun et al., 2012; Park et al., 2012). In vivo testing of TDDS can be performed using animal models and human volunteers or both.[37]

A. Animal Model:

Human studies require significant time and resources, so small animal studies are preferred. The animals most commonly used to test transdermal drug use are rats, hairless mice, hairless dogs, rhesus monkeys, rabbits, guinea pigs, etc. Based on the experiments conducted so far, it was concluded that hairless animals were better than hairy animals in both in vitro and in vivo experiments. [38] The rhesus monkey is one of the most reliable models to evaluate in vivo transdermal drug delivery. [39,40]

B. Human model:

The final phase of transdermal product development involves collecting pharmacokinetic and pharmacodynamic data after field administration to human volunteers. Clinical studies are being conducted to evaluate the transdermal system, including effectiveness, associated risks, side effects, and patient compliance. Phase I clinical trials are typically conducted to determine safety in volunteers, while Phase II clinical trials are typically conducted to determine safety and effectiveness in patients. Phase III trials demonstrate safety and effectiveness in a broad patient population, and Phase IV trials are conducted after clinical trials at commercial sites to determine whether the drug is suitable. Although human studies are resource-intensive, they are the best way to measure performance. [41]

RESULTS AND CONCLUSIONS:

Transdermal drug delivery is a painless, simple, and effective method to deliver high doses of various drugs. It can deliver a variety of drugs, improve the absorption of medicine, have fewer complications and side effects, and is low-cost and easy to use. A variety of drugs have been developed that can deliver agents such as steroids, antibiotics, antibiotics, interferons, and local anesthetics. Transdermal drug delivery is one of the fastest-growing areas of new drug delivery. The transdermal method has become a widely accepted method of drug delivery due to its cutting-edge technology and ability to deliver medication without damaging the skin. TDDS is designed to control the release of drugs from the skin to body organs while maintaining the same function. It allows the drug to be given in lower doses, prevents the recipient from harming the drug, and increases bioavailability. This can be done by bypassing the primary metabolism of the liver. TDDS is produced by almost every pharmaceutical company, large and small. Developmental capabilities in drug delivery include the use of adhesives and/or advanced technology; and using heat, electricity, ultrasound, or other efforts to pass molecules through the stratum corneum or microneedles across the stratum corneum in a controlled type A system with the occlusive properties of the layer.

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