REVIEW ON TRANDERMAL DRUG DELIVERY SYSTEM

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Abstract

Transdermal medication delivery offers an innovative method for achieving systemic drug absorption consistently over time, with key advantages including reduced dosing frequency, avoidance of first-pass metabolism, suitability for elderly patients, and ease of self-administration with fewer side effects. This review explores various aspects, including how drugs are absorbed through the skin, the kinetics of absorption, factors affecting permeability, different types of patches, their components, and evaluation parameters. The effectiveness of these systems relies on the drug's ability to permeate the skin adequately to achieve the desired therapeutic effect. The article provides a comprehensive study covering the benefits, drawbacks, mechanisms, and types of transdermal systems, alongside the characterization of patches based on quality, size, adhesive properties, thickness, weight, moisture content, and uniformity.

Keywords: *Transdermal patch, Permeability, Polymer Matrix, Rate Controlling Membrane, Permeation Enhancers.*

1. Introduction

While oral drug delivery is the most widely used method, it has limitations that outweigh its convenience. These limitations include low bioavailability because the liver breaks down the drug before it reaches the bloodstream, and unstable levels in the blood, which require frequent or high doses. This can be expensive and inconvenient for patients. To overcome these challenges, there is a growing need for improved drug delivery systems that can place drugs precisely in the right location and at the right time, reducing the amount and frequency of doses.

These systems are especially important for new types of medicines, like genetically engineered drugs such as peptides and proteins, which need to be delivered directly to their target without triggering immune responses or losing their effectiveness.

Transdermal drug delivery systems (TDDS) are self-contained devices that deliver medication through the skin into the bloodstream at a steady and controlled rate. These systems have become an essential part of modern medicine. Along with problems like repeated dosing and inconsistent absorption, they have driven the development of controlled drug delivery systems. These systems release medication over a specific time period in a predictable way, either throughout the body or to a particular organ. The main objectives of controlled drug delivery are to improve the safety and effectiveness of drugs, as well as help patients follow their treatment plans by maintaining consistent drug levels in the blood and reducing the need for frequent dosing. The first TDDS, called Transderm-Scop, was introduced in 1980 and contained **scopolamine** for the treatment of motion sickness.

Advantages

- Hepatic first-pass metabolism, salivary metabolism, and intestinal metabolism are avoided thereby increasing bioavailability.
- This helps maintain steady levels of the drug in the body, avoiding fluctuation.
- They offer long-lasting treatment with a single dose, making it easier for patients to follow their medication plan compared to other forms that require frequent dosing.
- Transdermal drug delivery systems can be used instead of oral medications when the oral route is not suitable, such as in patients experiencing vomiting or diarrhea.
- In an emergency, removing the patch at any time during treatment can immediately stop the release of the drug.

Disadvantages

- Some patients may experience contact **dermatitis** at the site where the system components are applied, which may require stopping the treatment.
- Binding of the drug to the skin may result in dose dumping.
- This system is suitable only for long-term treatment of chronic conditions where ongoing drug therapy is needed, such as hypertension, angina, and diabetes.
- The system may cause allergic reactions at the application site, including itching, rash, and swelling.
- It does not allow for the delivery of drugs in a **pulsatile manner.**

- Drugs with very low or very high partition coefficients may not be able to enter the bloodstream effectively.

2. Basic components of T. D. D. S

2.1. Polymer Matrix

a) Natural Polymers: Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc

b) Synthetic Elastomers: Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

c) Synthetic Polymers: Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy etc.

2.2. Drug

For successfully developing a transdermal drug delivery system, the drug should be selected with great care.

Physicochemical properties

- It Should have a molecular weight less than approximately 1000 daltons.
- It Should have affinity for both the lipophilic and hydrophilic phases.
- It Should have low melting point. Along with these properties the drug should be potent, having short half life and non irritating.

2.3. Permeation Enhancers

Enhancers function to increase skin permeability to reach the desired therapeutic level. The ideal properties of enhancers are non-toxic, non-allergic, non-irritating, controlled and reversible enhancing action, pharmacological inertness, ability to act specifically for the predictable duration, chemical and physical compatibility with drugs and other pharmaceutical excipients, odourless and colourless.

2.4. Other excipients

a) Adhesives

The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be situated on the face of the device or in the back of the device and expanding peripherally. Both adhesive systems should fulfill the following criteria:

- Should adhere to the skin invasively, should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should not irritate or sensibilize the skin.
- Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
- The delivery of simple or blended permeation enhancers shouldn't affected.

b) Backing membrane

Flexible backing membranes securely adhere to the drug reservoir, preventing drug escape from the top of the dosage form and allowing for printing. These impermeable materials protect the product during skin application, examples include metallic plastic laminates, plastic backings with absorbent pads and aluminum foil occlusive base plates, or adhesive foam pads (made of flexible polyurethane) with aluminum foil disc occlusive base plates."

3. Methods for characterizing TDDS

The assessment of how effectively and efficiently a drug is delivered is a crucial process in transdermal drug delivery systems. Different methods are used for this evaluation, based on the type of drug and its intended purpose. However, three commonly used methods are diffusion cells, tape stripping, and microscopic and spectroscopic analysis. Each of these methods employs a unique way to analyze the drug delivery process. As the drug is absorbed through the skin surface, these techniques measure either the amount of drug present in different surface layers or use imaging materials to visually track how the drug is absorbed.

3.1 Diffusion cell method

Tests using diffusion cells are considered the standard approach for assessing transdermal drug delivery systems (TDDS), with Franz diffusion cells being the most widely used setup.This method helps establish key relationships between the skin, the active pharmaceutical ingredients, and the formulation's characteristics. A diffusion cell typically includes a compartment for applying the drug, a membrane through which the drug can pass, and a chamber containing the acceptor medium where samples are collected for analysis. Diffusion cells are generally divided into two types: static and flow-through cells. In static cells, such as

the commonly used Franz cell, the donor, membrane, and acceptor compartments can be arranged either vertically or horizontally. Some Franz cells have an opening at the top, allowing measurements to occur under normal atmospheric pressure. However, most cells are sealed at the top, which increases pressure and may lead to higher estimates of drug penetration. Recently, traditional "hand-sampler" Franz cells have been largely replaced by automated sampling systems. These automated systems make the research process more efficient and help minimize errors that can occur in manual sampling procedures.

3.2 Tape stripping

Tape stripping is a widely used minimally invasive technique to evaluate how topical formulations penetrate through the stratum corneum (SC). In this method, a layer of the SC is removed using an adhesive tape, and the collected skin layer is examined on the tape. The tape stripping process is carried out after a suitable period following the topical application of the test substance. The substance can be either removed or left on the skin, ensuring that the original amount of components is available for measurement. The adhesive tape is applied to the skin surface and is always removed from the same area. It is essential to apply the same force when flattening the tape as with a roller to prevent irregularities such as creases or uneven surfaces from influencing the results. The speed at which the tape is removed is also a key aspect; slower removal rates increase the adhesion of the SC to the tape, resulting in more skin being collected. The tape that is removed contains both the SC layer and the active ingredients of the formulation. Various methods can be employed to analyze the samples obtained with the adhesive tape. High-performance liquid chromatography (HPLC) provides quantitative results, while spectroscopic methods offer semi-quantitative insights. In HPLC, the material on the tape is extracted and analyzed using chromatographic separation. Atomic absorption spectroscopy can also be used to detect active ingredients. However, the most commonly used method for characterizing skin obtained via tape stripping is attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR). These spectroscopic techniques rely on the irradiation of the sample and the changes in atomic oscillations and bonding angles caused by the absorption or scattering of infrared light. The change in the radiation as it passes through the sample is measured by plotting the transmitted radiation against the wavelength or wavenumber. This process yields a spectrum that can be used for both qualitative and quantitative analysis. The depth of penetration is determined by the wavelength of the infrared light, the refractive index of the ATR crystal, and the measured material and angle of reflection. The combination of tape stripping with ATR-FTIR spectroscopy is effective for identifying

various exogenous substances in specific layers of the SC. However, a challenge with this method is that the characteristic peaks of the substance being detected often overlap with those of the skin itself. Microscopic and spectroscopic techniques also provide important insights into the spatial distribution of drugs within different skin layers or the mechanism of penetration. The most common types of microscopy used are confocal laser scanning microscopy (CLSM) and two-photon fluorescence microscopy (2 PFM). CLSM is a non-invasive method that has gained popularity for visualizing fluorescent model compounds in the skin. It allows the examination of skin structure without destroying the tissue and is commonly used to assess the impact of physical and chemical enhancers on skin permeability. CLSM is suitable for both in vivo and in vitro studies and is used in diagnosing skin disorders, identifying malignant lesions, and studying keratinization and pigmentation issues. It is also useful for understanding how nanoparticle formulations enhance transdermal transport. Fluorescent markers such as fluorescein, Nile red, and 5-bromodeoxyuridine can be included in these formulations. CLSM can be used to evaluate the therapeutic effectiveness of such formulations by assessing how these markers penetrate through skin tissue or skin appendages. Additionally, 2 PFM has become an important tool for imaging skin cells. This method typically uses a Ti-sapphire laser as the excitation source. In single-photon fluorescence, a high-energy photon excites the fluorophore, raising an electron to an excited state and producing a fluorescent photon. In two-photon excitation, the combined energy of two low-energy photons is sufficient to raise the same electron to a higher energy level. The setup of a two-photon microscope is similar to that of a CLSM, with two main differences. The 2 PFM setup uses an adjustable Ti-sapphire high-frequency pulsed laser, which emits red and near-infrared light in the wavelength range of 650–1100 nm. The other key difference is that there is no pinhole in front of the detector. One of the main advantages of 2 PFM is the significantly lower total energy delivered to the sample compared to other techniques. Additionally, two-photon excitation occurs in very small focal volumes, which reduces the chances of photobleaching and photodamage. Skin samples can be studied without cryofixation or sectioning. For imaging UV-absorbing fluorophores, using infrared excitation results in less scattering and absorption, allowing for deep tissue imaging. However, the limitations of 2 PFM include the need for relatively expensive lasers and complex cooling systems. It also has lower lateral resolution compared to some other technologies; but in practice, this difference is not as significant.

4. Various methods for preparation TDDS

4.1. Asymmetric TPX membrane method

A prototype patch can be made using a heat sealable polyester film (type 1009, 3M) with a concave area of 1 cm in diameter as the backing membrane.The drug sample is placed into the concave area of the membrane, then covered with an asymmetric TPX {poly(4-methyl-1-pentene)} membrane, and sealed using an adhesive.(Asymmetric TPX membrane preparation): These membranes are made using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to create a polymer solution. The polymer solution is kept at 40°C for 24 hours and then cast onto a glass plate to a predetermined thickness using a Gardner knife. After casting, the film is heated at 50°C for 30 seconds. The glass plate is then immediately immersed in a coagulation bath, which is maintained at 25°C. After 10 minutes of immersion, the membrane is removed and air-dried in a circulation oven at 50°C for 12 hours.

4.2. Circular Teflon mould method

Ten solutions containing polymers in various ratios are prepared in an organic solvent. A calculated amount of drug is dissolved in half the volume of the same organic solvent. Enhancers are dissolved in the other half of the solvent and then mixed in. Di-N-butylphthalate is added as a plasticizer to the drug and polymer solution. All the components are stirred together for 12 hours and then poured into a circular Teflon mold. The molds are placed on a level surface and covered with an inverted funnel to control the evaporation of the solvent within a laminar flow hood that has an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hours. The dried films are stored for an additional 24 hours at a temperature of 25±0.5°C in desiccators containing silica gel before evaluation to prevent any aging effects. The films are to be evaluated within one week of their preparation.

4.3. Mercury substrate method

The Mercury substrate method involves dissolving the drug in a polymer solution that also contains a plasticizer. The resulting mixture is stirred for between 10 to 15 minutes to achieve a uniform dispersion. This solution is then poured onto a flat surface made of mercury and covered with an inverted funnel to regulate the evaporation of the solvent.

4.4. By using the "IPM membranes" method

In this method, the drug is mixed into a solution containing water and propylene glycol along with carbomer 940 polymer. The mixture is then stirred for 12 hours using a magnetic stirrer. To neutralize the mixture and increase its viscosity, triethanolamine is added. If the drug has

poor solubility in water, a buffer with pH 7.4 can be used to form a solution gel. The resulting gel is then included in the IPM membrane.

4.5. By using “EVAC membranes” method

To prepare the transdermal therapeutic system, the "EVAC membranes" method can be used. This involves using 1% carbopol reservoir gel, polyethylene (PE), and ethylene vinyl acetate copolymer (EVAC) membranes as rate control membranes. If the drug is not water-soluble, propylene glycol is used to make the gel. The drug is dissolved in propylene glycol, and then carbopol resin is added to this solution. The mixture is neutralized using a 5% w/w sodium hydroxide solution. The drug in gel form is then placed on a backing layer that covers the required area. A rate controlling membrane is placed over the gel, and the edges are sealed with heat to create a leak-proof device.

4.6. Aluminium backed adhesive film method

The aluminium backed adhesive film method is a suitable approach for transdermal drug delivery systems. However, if the loading dose exceeds 10 mg, it may result in an unstable matrix.

5. Evaluation test of transdermal patch

5.1. Drug Excipients Interaction Studies

The drug and excipients should be compatible to produce a stable product, and it is mandatory to detect any possible physical and chemical interaction. Interaction studies are commonly carried out using thermal analysis, FT-IR studies, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, and absorption maxima etc.

5.2. Drug Content

A specific part of the patch should be dissolved in an appropriate solvent in a defined volume. The resulting solution is then filtered using a filter medium and the drug content should be analyzed using a suitable method, such as UV or HPLC technique. Each measurement value is the average of three samples.

5.3. Weight Uniformity

The prepared patches should be dried at a temperature of 60°C for a period of four hours prior to testing. From different sections of the patch, a specific area should be cut out and each sample should be weighed using a digital balance. The average weight and the standard deviation should be determined based on the individual weights obtained.

5.4. Thickness of the Patch

The thickness of the drug-loaded patch is assessed by measuring it at various points using a digital micrometer. This helps determine the average thickness and standard deviation, ensuring consistency in the prepared patch's thickness.

5.5. Flatness Test

For the flatness test, three longitudinal strips are cut from each film, taken from different areas— one from the center, one from the left side, and one from the right side.The length of each strip is measured, and the variation in length due to uneven flatness is calculated as a percentage constriction. A 0% constriction indicates 100% flatness.

5.6. Percentage Moisture Uptake

The weighed films should be placed in desiccators at room temperature for 24 hours. These desiccators must contain a saturated solution of potassium chloride to maintain a relative humidity of 84%. After 24 hours, the films should be reweighed, and the percentage moisture uptake should be calculated using the formula provided.

Percentage moisture uptake = [(Final weight – Initial weight) / Initial weight] × 100.

5.7. Moisture Loss

The prepared films should be weighed individually and placed in a desiccator containing calcium chloride at a temperature of 40°C. After 24 hours, the films should be reweighed, and the percentage of moisture loss should be calculated using the formula provided.

% Moisture Loss = [(Initial weight – Final weight) / Final weight] × 100.

5.8. Water Vapor Transmission Rate (WVTR) Studies

Glass vials with the same diameter were used as transmission cells. These cells were thoroughly cleaned and dried in an oven at 100°C for a certain period. Approximately 1 gram of anhydrous calcium chloride was placed inside each cell, and the respective polymer film was placed over the rim. The cell was then precisely weighed and placed in a closed desiccator containing a

saturated solution of potassium chloride to maintain a relative humidity of 84%. After the required storage time, the cells were removed and reweighed. The amount of water vapor that had passed through the film was calculated using the following formula.

Water Vapor Transmission Rate = (Final Weight – Initial Weight) / (Time × Area)

This value is expressed in grams of moisture gained per hour per square centimeter.

5.9. Swellability

Patches with an area of 3.14 cm^2 were weighed and placed in a petri dish containing 10 ml of double distilled water, allowing them to absorb the water.The increase in weight of the patch was measured at fixed time intervals until the weight remained constant.

The degree of swelling (S) was calculated using the formula:

S (%) = (Wt – Wo) / Wo × 100

Where S represents the percent swelling, Wt is the weight of the patch at time t, and Wo is the initial weight of the patch at time zero.

5.10. Folding Endurance

A specific area of the material is cut into a strip and folded repeatedly at the same spot until it breaks. The number of folds the material can withstand at that location before breaking determines its folding endurance.

5.11. Tensile Strength

The tensile strength of the film is measured using a universal testing machine.The machine has a sensitivity of 1 gram and includes two grips—one fixed and one movable. A test film of size 4 cm by 1 cm is placed between these grips. Force is applied gradually until the film breaks. The tensile strength is read directly from the dial in kilograms. Tensile strength is calculated using the formula:

Tensile strength = Tensile load at break / Cross-sectional area

5.12. Probe Tack Test

In this test, a clean probe with a defined surface roughness is pressed against the adhesive. When a bond forms between the probe and the adhesive, the probe is then removed, which

causes the adhesive to break. The force needed to pull the probe away from the adhesive at a fixed speed is recorded as tack and is expressed in grams.

5.13. In-vitro drug release studies

The paddle over disc method, which is USP apparatus V, can be used to evaluate the release of the drug from the prepared patches.Dry films of a known thickness are cut into a specific shape, weighed, and secured onto a glass plate using an adhesive. The glass plate is then placed in 500 ml of dissolution medium or phosphate buffer (pH 7.4). The apparatus is allowed to reach a temperature of 32 ± 0.5°C. The paddle is positioned 2.5 cm away from the glass plate and set to rotate at a speed of 50 rpm. At regular time intervals up to 24 hours, 5 ml samples are taken and analyzed using a UV spectrophotometer or high-performance liquid chromatography (HPLC). The experiment is conducted in triplicate, and the mean value is calculated.

5.14. In-vitro skin permeation studies

An in vitro permeation study can be performed using a diffusion cell.Full thickness abdominal skin from male Wistar rats weighing between 200 to 250 grams is used. Hair in the abdominal area is carefully removed using an electric clipper. The skin's dermal side is cleaned thoroughly with distilled water to eliminate any attached tissue or blood vessels. The skin is then equilibrated for one hour in the diffusion medium or phosphate buffer (pH 7.4) prior to the experiment. The diffusion cell is filled with the diffusion medium and placed on a magnetic stirrer with a small magnetic bead to ensure uniform mixing. The temperature of the cell is kept at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin is mounted between the compartments of the diffusion cell with the epidermis facing up into the donor compartment. At regular intervals, a definite volume of sample is removed from the receptor compartment and replaced with an equal volume of fresh medium. The samples are filtered through a suitable filter and analyzed using spectrophotometry or high-performance liquid chromatography (HPLC). The flux is calculated as the slope of the curve between the steady-state values of the drug amount permeated (mg/cm²) versus time in hours. The permeability coefficients are determined by dividing the flux by the initial drug load (mg/cm²).

5.15. In – Vivo studies

In-vivo evaluations accurately reflect how a drug performs in real-world conditions. Certain factors that cannot be fully assessed during in-vitro studies can be thoroughly examined

through in-vivo methods. The in-vivo evaluation of transdermal drug delivery systems (TDDS) can be conducted using the following approaches:

1) Animal models: Commonly used animals for testing TDDS include mice, hairless rats, hairless dogs, hairless rhesus monkeys, rabbits, and guinea pigs.

2) Human models: The final phase of developing a transdermal device involves gathering pharmacokinetic and pharmacodynamic data after applying the patch to human volunteers. Clinical trials are performed to evaluate the effectiveness, potential risks, side effects, and patient adherence to the treatment.

6. Conclusion

There are several methods, such as chemical techniques, electric fields, and ultrasound, that are used to enhance the transport of drugs through the skin. These technologies have made transdermal drug delivery a viable option for systemic drug administration. Over the past twenty years, there has been significant scientific interest in this area. Many studies have focused on safely overcoming the skin's barrier function to deliver an effective dose of medication. However, the practical application of these studies is limited because they have mainly used solution or suspension formulations. There is a need to develop transdermal systems that are both functional and practical. The most effective transdermal drug delivery systems would be those that incorporate electronic or mechanical methods, based on a thorough understanding of the drug's physicochemical properties, the skin's physiology, the mechanism of action of enhancers, and the interactions between formulation components. Additionally, through improved device design, a wider range of molecules can be effectively delivered using transdermal systems.

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