Innovative Horizons in Transdermal Drug Delivery: The Role of Transdermal Patches

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***Abstract*—The conventional oral route of drug administration is often challenged by issues like first pass metabolism, resulting in low drug bioavailability. The Transdermal Drug Delivery System(TDDS) was invented to upgrade drug characteristics and avoid these side effects, delivering medication via the skin for local and systemic effects. The transdermal patch is the preferred delivery method, offering advantages such as avoiding first-pass metabolism, providing sustained and controlled drug release, and allowing drug delivery to be stopped immediately if toxicity occurs by simply removing the patch. The first transdermal system was approved by the USFDA in 1979.The skin, the body's largest organ, acts as the primary barrier, composed of the epidermis, dermis, and hypodermis (subcutaneous fat).Drug penetration across the skin occurs via two pathways: the trans epidermal pathway (through the outermost stratum corneum layer via the intracellular or intercellular routes) and the transappendigeal pathway (through hair follicles and sweat glands).**

***Index Terms*—Anatomy and physiology of skin, drug absorption pathway, types, component's, evaluation parameters.**

I. INTRODUCTION

To overcome these issues and improve how drugs are delivered, scientists developed the Transdermal Drug Delivery System (TDDS). (Choudhary N etal,2021) TDDS involves delivering medication through the skin to treat both local skin issues and conditions affecting the whole body (systemic effects The most preferred and well-known way to do this is using a transdermal patch. transdermal patch is a small, self-contained adhesive patch that holds the medication. It's an easy, simple way to deliver drugs for various skin and body treatments (Valecha V,etal2011). The first transdermal system was approved by the U.S. Food and Drug Administration (FDA) in 1979. It contained the drug scopolamine. Nicotine patches were later approved in 1984. These patches are now commonly used for pain management, hormone replacement therapy, and delivering pain-relieving medication (analgesic activity).(Othman A.etal2019)

II. ADVANTAGES

- The transdermal patch is a substitute for the oral root.
- The transdermal drug delivery system avoids the first pass metabolism.
- By the transdermal root the medication should be given in a sustained and controlled manner.
- Drug delivery can be stopped in the case of toxicity by removing patches. (Tiwari c etal,2022)

Disadvantages

- This System only lipophilic drugs should be administered through skin.
- Those drugs which having high particle size should be not administered.
- Through this system Irritation and hypersensitivity reactions to the skin are possible. (ZhangL etal2016)
- Adhesive depends on patch type ran environmental factor.

III. ANATOMY AND PHYSIOLOGY OF SKIN

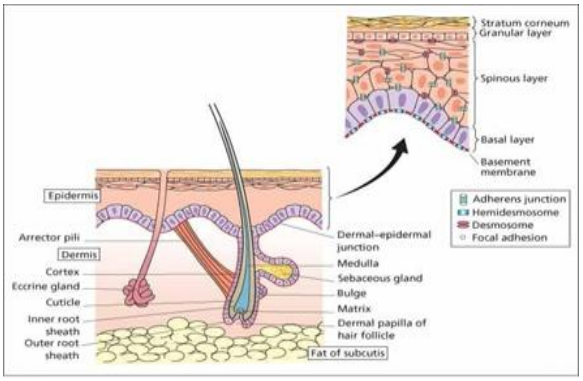

Fig .no 1 Anatomy of Skin

The skin is the largest organ in your body, covering an area of about 2 square meters. Your skin is made up of three main layers:

- Epidermis (the outer layer you see)
- Dermis (the middle layer)
- Hypodermis (subcutaneous fat)

3.1 Epidermis

The epidermis is a multi-layered layer whose thickness varies across your body: It's thickest on the palms of your hands and the soles of your feet (about 0.8 mm). It's thinnest on your eyelids (about 0.06 mm).Stratum Corneum: The Protective Shield The outermost part of the epidermis is called the stratum corneum, sometimes nicknamed the "horny layer." This is your body's main protective shield. It is made up of 10 to 25 layers of cells called corneocytes. These cells are dead, tough, and filled with keratin (a protein). The stratum corneum itself is composed of:40% Fat40% Protein20% Water Layers within the Epidermis The epidermis contains several sub-layers. (Tiwari c etal,2022)

3.2 Dermis (The Middle Layer)

The dermis is the thick layer of tissue just below the epidermis. Thickness: It ranges from 3 to 5 mm thick. What it contains: It's made up of connective tissue and is filled with nerves, lymph vessels, and blood vessels. A crucial function of the dermis is controlling your body temperature and ensuring a continuous blood supply to the skin. Dermis and Transdermal Patches This layer is very important for transdermal drug delivery: Tiny blood vessels called capillaries reach very close to the skin's surface (about 0.2 mm). These capillaries quickly carry away any drug molecules that successfully penetrate the top skin layer (the epidermis). By constantly removing the drug, the dermis keeps the drug concentration low. This low concentration on the bottom side and the high drug concentration on the top side (from the patch) creates a concentration gradient (a difference in concentration). (Nikhil Sharmaetal etal 2011)

3.3 Hypodermis (Subcutaneous Fat / Bottom Layer)

The hypodermis is the deepest layer of the skin, also known as subcutaneous fat. Support: It acts as a support system for the dermis and epidermis above it. It is the primary area for storing fat in your body. functions: This layer provides several protective functions: Temperature regulation (insulation)Nutritional support Mechanical protection (acting as a cushion)Vessels and Nerves: It contains the body's major blood vessels and nerves that connect to the rest of the skin layers, and it may contain organs that sense pressure.(Kumar D,etal2011)

IV. DRUG ABSORPTION PATHWAY THROUGH SKIN

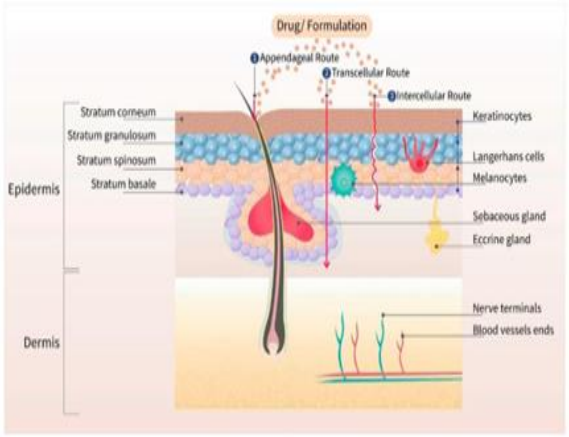

Fig .no 2 Drug Absorption Pathway Through Skin

When a drug is delivered through a patch, it has two main routes it can take to get across the skin:

- Transepidermal Pathway (The main route, through the skin's layers)
- Transappendageal Pathway (The side route, through natural openings like pores).(Shaikh N etal2024,)

1. Transepidermal Pathway (Through the Main Layers)

This is the primary way drugs penetrate. It involves the drug passing directly through the epidermis specifically, through the tough, outermost layer called the stratum corneum (the skin's main barrier). Drugs can take two paths within this layer:

- Intracellular Route (Through the Cells):
  Some drugs go through the specialized skin cells called corneocytes: Substances that dissolve well in water (called hydrophilic or polar solutes). (NgLC, etal2020)
- Intercellular Route (Between the Cells):
  Walking between the bricks in a wall, using the cement spaces. How it works: Drugs move through the fatty space that exists between the skin cells. They travel through the continuous layer of fat that holds the cells together. Substances that dissolve well in fat (called lipophilic or non-polar solutes). (NgLC, etal2020)

2. Transappendageal Pathway (Through Openings)

This pathway is like taking a shortcut, as it avoids going directly through the main barrier of the stratum corneum. Drugs pass through the skin's natural openings, such as hair follicles and sweat glands. You can think of hair follicles and sweat glands as tiny tunnels or openings in the skin that some substances can travel through to get to the layers underneath. (Schoellham mer CMetal2014 .ShahzadY,etal2015)

V. FACTOR AFFECTING TRANSDERMAL DRUG DELIVERY

5.1 Physiochemical properties affecting the penetration of molecule

5.1.1Molecular weight, size and structure the size and weight of a drug molecule are very important for how well it can penetrate the skin. Generally, drug molecules that are smaller in size and have a lower molecular weight can pass through the skin much more easily (they have higher "permission" or permeability). Molecules that are larger and heavier are less likely to penetrate the skin. The Drug molecules that weigh more than \text{500} Daltons (a unit for measuring molecular weight) usually have a hard time crossing the skin's barrier, which means less drug is absorbed into the body.(Ms. Pranjal N.etal2024.Mohammed Jahid Halderetal 20213.Jawale N. Retal2017)

5.1.2 Temperature and PH Higher Temperature, Better Absorption:

When your skin's temperature goes up (for example, if you are warm or exercising), the ability of the drug to pass through the skin (permeability) can increase significantly, sometimes up to ten times! If the temperature goes down, the diffusion coefficient (which is a fancy term for how fast the drug spreads and moves through the skin) also decreases, making absorption slower. The ph of the skin and the drug itself affects how much of the drug is in its unionized form (meaning it hasn't picked up an electrical charge). Drugs that are unionised are much better at dissolving in the fatty layers of the skin and are therefore the ones that penetrate most easily. Because the amount of unionized drug depends heavily on the \text{pH} and the drug's properties (pka value), the ph of the environment significantly affects how well the drug penetrates the skin. (Himanshi Tanwaretal 2016.Dimpy Jaiswal, etal 2023. Preetam ala, etal2014)

5.1.3 Drug concentration

The amount of drug passing from the patch, across the skin, and into the body (the flow rate) is directly related to the difference in drug concentration. This difference is created between the high concentration of the drug inside the patch and the low concentration of the drug inside your skin and bloodstream. If you have a higher concentration of the drug in the patch, the difference across the skin barrier will be greater. This larger difference acts like a stronger driving force, pushing the drug through the skin faster. (Himanshi Tanwaretal2016.Ms. Pranjal N.etal2024)

5.1.4.Solubility

Drug molecules are either: Fat-Loving (Lipophilic): They dissolve well in oils and fats. water-Loving(Hydrophilic): They dissolve well in water. the Skin's Dual Nature For a drug to get absorbed through the skin it Needs Fat Solubility: The skin's outer layer, the stratum corneum, is built like a fatty bilayer (a double layer of lipids). To get through this main protective wall, the drug must have some fat solubility. (Jawale N. Retal2017)

5.2 Physicochemical property of drug delivery system
5.2.1Release characteristics:
The best drugs for transdermal patches are those that have both fat and water solubility. The Regulator: This balance is measured by something called the partition coefficient, which shows how the drug divides its time between fatty (lipid) and watery (aqueous) environments. In summary: The drug must be fat-soluble enough to penetrate the skin's barrier, but water-soluble enough to then spread and diffuse through the inner layers to get to your bloodstream. (Mohammed Jah id Halderetal 2021Jawale N. Retal2017)

5.2.2. Composition of drug delivery system: This not only impacts the rate of drug release but also affects the skin's permeability through hydration and interaction with skin lipids. (Sadab, Sadab, etal 2022, Mohammed Jah id Halder etal 2021)

5.2.3. Permission enhancer: Various categories of permeation enhancers modify skin integrity temporarily, opening skin pores for absorption. These enhancers can be chemical substances that act chemically or physical agents that interact physically with the skin.(Sadab, Sadab, etal 2022, Mohammed Jah id Halder etal 2021)

5.3 Physiological and Pathological condition of skin:
5.3.1 Skin hydration: Hydration leads to the stratum corneum swelling, providing fluidity to the skin. This increased hydration enhances permeations solubility and partition in facilitating drug molecule permeation ((Sadab, Sadab, etal 2022, Mohammed Jah id Halder etal 2021)

5.3.2 Skin temperature: Warmer skin helps drugs absorb better from a patch because the heat does two things:It softens the fats (lipids) in the skin barrier, making it easier to penetrate. It increases blood flow by widening blood vessels, which quickly carries the drug away and pulls more drug out of the patch (Sadab, Sadab, etal 2022, Mohammed Jah id Halder etal 2021)

5.3.3 Skin age: The skin barrier is less effective in babies and older adults, allowing drugs to pass through more easily than in healthy middle-aged adults (Sadab, Sadab, etal 2022, Mohammed Jah id alder etal 2021)

5.3.4 Bloodflow
Increased blood flow near the skin helps transdermal drug absorption because:Faster blood flow removes the drug quickly, which boosts the patch's efficiency.(Neha Mishra,etal2022Sadab, Sadab, etal2022)

5.3.5 Regional site of skin:
Variations in anatomical feature such as stratum corneum thickness, hair follicles, and sweat gland density per unit area result in differing percutaneous absorption rates.(Neha Mishra,etal2022,Sadab, Sadab, etal2022)
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VI. TYPES OF TRANSDERMAL PATCH

6.1 Single layer drug in adhesive
This designing's a master class in simplicity and efficiency, exemplified by patches like Daytrana (containing the medication methylphenidate).At its heart is a single, sticky polymer layer. This layer isn't just an adhesive; it's a smart reservoir the sole component that performs three critical functions: - Drug Storage and Dispersion: it holds the medication within its matrix-Skin Adhesion: Itensures the patch stays firmly and comfortably in place.- Controlled Release: It actively aids in the steady, sustained release of the drug through the skin.(VirendraYa dav etal 20122, Othman Aetal2019 PatelD,etal20124 .MaliAD,etal2015)

6.2 Multi layer drug in adhesive

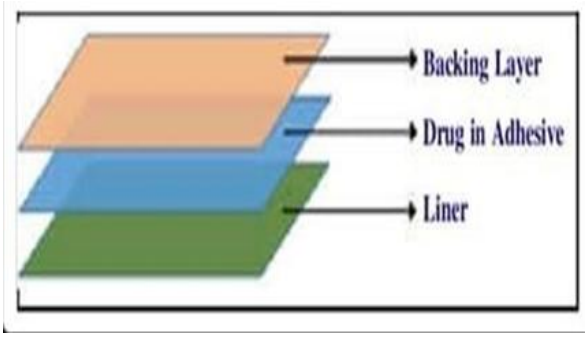

Fig.no3:Multi-layer drug in adhesive

The multi-layer drug-in-adhesive patch is an advanced version of the single-layer patch, built for powerful, sustained, and longer-lasting delivery sometimes for

up to a full seven days! This sophisticated system takes the basic idea of putting the drug in the sticky layer and improves it by stacking multiple layers to better control the medication release over a long time. A Backing Layer: This is a permanent, protective layer that faces outward (away from the skin).A Release Liner: This is a temporary, protective layer that you peel off just before applying the patch.(VirendraYa dav etal20122,Othman Aetal2019PatelD,etal20124 .MaliAD,etal2015)

6.3 Vapor transdermal patch.

The Vapor Transdermal Patch is a unique and interesting variation of patch technology. How it's Different: Unlike most patches that push medication into your bloodstream through the skin, these innovative, simple patches are designed to release beneficial vapors into the air. The Goal: You simply inhale the vapors. This makes the patch a discreet and effective way to deliver aromatherapy or other therapeutic treatments through your breath, not your skin. Market Success: This technology has proven successful. For example, patches like the Nicoderm CQ were first launched in the European market in 2007. (irendra Ya dav etal 20122, Othman A etal 2019 Patel D, etal 20124 .MaliAD, etal 2015)

6.4 Matrix system: Drug in adhesive

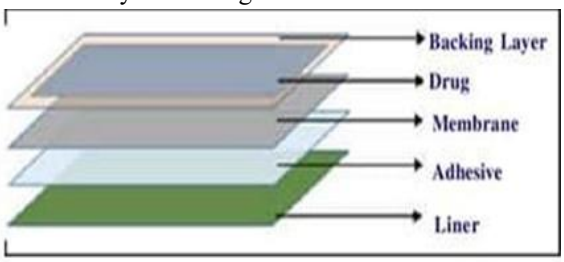

Fig.no.4:Matrix system drug in adhesive

The Matrix Transdermal System is a foundational patch design known for controlled and continuous drug delivery. Core: The drug is evenly mixed inside a special semi-solid polymer (the matrix). Function: This polymer matrix acts as the main reservoir and ensures the drug is released at a reliable, steady rate over time.(VirendraYa dav etal2012,Othman A etal 2019 Patel D, etal 2012 4 .Mali A D,etal 2015)

6.5 Reservoir transdermal patch.

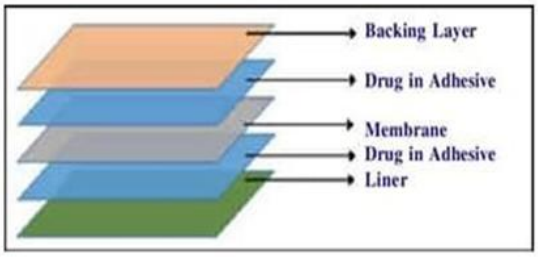

Fig.no.5:Reservoir transdermal patch

The Micro-Reservoir System is a sophisticated patch designed for precise drug delivery. How it works: It uses tiny, separate micro-reservoirs (pockets of drug) suspended in an adhesive layer. The Goal: It delivers the medication at a consistent, "zero-order" rate, meaning the drug enters the bloodstream steadily over time, avoiding drug level highs and lows.(VirendraYa dav etal 20122, Othman A etal 2019 Patel D, etal 20124 .Mali AD, etal 2015)

VII. COMPONANTS

7.1. Polymer Matrix/Drug reservoir

The Polymer Matrix is the most important part of a skin patch (Transdermal Drug Delivery System or TDDS). Think of it as the smart structure or framework inside the patch. It holds the drug: The medicine is spread out evenly within a solid or gel-like material called the polymer. It controls the release: It acts like an intelligent controller that makes sure the drug is released slowly and steadily, not all at once. This prevents too much medicine from coming out at one time. It ensures safety and effectiveness: By controlling the speed, the matrix makes the treatment safer, more effective, and provides a long-lasting therapeutic effect.(Heather AEetal2005Singh MC,etal2010 Aggarwal G.etal2009Aungst Bjetal1989)

7.2 Drug Requirements for the Drug in a Skin PatchPhysical and Chemical PropertiesPlacement: The drug liquid must touch the protective layer (called the release liner) that you peel off before applying the patch.Small Size: The drug's molecules must be very small (under 1000 Daltons) so they can easily pass through the skin.Versatile: The drug needs to be able to dissolve in both fatty/oily substances (lipophilic)

and water-based substances (hydrophilic) to navigate the different layers of the skin.Low Melting Point: The drug should melt easily, which often helps it move out of the patch and across the skin.Biological properties ;Short Half-Life: The drug should normally be cleared from the body relatively quickly (have a short half-life). This makes the slow, steady delivery from the patch especially beneficial, as it maintains a constant level without needing frequent pills.No Allergies: The medication must not cause a rash or an allergic reaction when applied to the skin. (Heather AE etal2005 Singh MC, etal2010 Aggarwal G. etal2009 Aungst Bj etal1989)

7.3 Pressure sensitive adhesive PSA)

The Pressure Sensitive Adhesive (PSA) is simply the sticky layer that keeps the patch firmly attached to your skin. What Makes a Good Adhesive? Strong Grip: It needs to stick well when you press it on with your finger, providing strong and long-lasting tack (initial stickiness). Holding Power: It must have a strong holding force to ensure the patch doesn't fall off, even with movement. Common Types: Examples of these sticky materials include polyacrylate, polyisobutylene, and silicone adhesives in a matrix system, the PSA can be part of the drug layer and might also extend around the edges of the patch. (Heather AE etal2005 Singh MC, etal2010 Aggarwal G. etal2009 Aungst Bj etal1989)

7.4 Backing laminate

The Backing Laminate (or Support Plate) is the foundation or the outer shell of the skin patch. It's the part you see on the outside, and it provides the main structural support. Key Roles Structural Anchor: It gives the patch its shape and essential physical support, making sure it holds together. Protection & Barrier Control: It acts as a shield to protect the drug and other ingredients from the outside world (like dirt or moisture). It also helps optimize the environment near the skin, which is important for drug absorption. (Heather AE etal2005 Singh MC, etal2010 Aggarwal G. etal2009 Aungst Bj etal1989)

7.5 Releaseliner:

The Release Liner is the protective cover that you peel off right before you apply the patch. Key Roles Protection During Storage: Its main job is to prevent the medicine from escaping into the adhesive layer and to keep the patch clean (preventing contamination) while it's in the package. Packaging, Not Medicine: Because it's removed before use, it's considered part of the packaging (the container), not an active part of the medicine or drug delivery system itself. The liner is typically made of two parts:A Base Material (Backing): This can be a flexible material like tissue paper or plastic films like polyethylene or polyvinyl chloride (PVC). A Non-Stick Coating: This is a layer, often made of silicone or Teflon, that allows the liner to be easily peeled away from the sticky part of the patch. (Heather AE etal2005 Singh MC, etal2010 Aggarwal G. etal2009 Aungst Bj etal1989)

VIII. MARKETED ORMULATIONS(JainNK.Etal1997)

Product	Drug	Types of patch	Purpose
Nitrodisc	nitroglycerine	Microreservoir	Anginapectoris
Captopresstts	Clonidine	Membraine	hypertension
Habitraol	nicotine	Druginadhesive	Cessation

Fig.no.6:Marketed formulations

IX. EVALUATION PARAMETERS

9.1Organolepticobservations

Fig.no 7 Organoleptic observations

Organoleptic observations are simply how the patches are checked using our senses, primarily sight and touch. This means checking the physical qualities of the patch that you can easily observe, including its: Colour (What color is it?) Odour (Does it have a smell?) Flexibility (How easily does it bend?) Surface Texture (How does it feel is it smooth, rough, etc.?)(48Schuetz YBetal2005)

9.1.1 Weight Uniformity:

Fig. no. 8 Weight Uniformity

Weight Uniformity testing makes sure that the amount of material (which contains the drug) is consistent across every part of the patch.The Process Drying: First, the finished patches are dried in an oven at 60 (140°F) for four hours to remove any leftover moisture. Cutting Samples: Small, precisely sized pieces are cut out from different sections of the patch. Weighing: Each small piece is then weighed using a very accurate digital scale Calculation: Scientists calculate the average weight of all the pieces and the standard deviation (which shows how much the individual weights differ from that average).(41,42KoteshwarK. B,etal20204 .Manvi F.V,etal2003)

9.1.2 Drug content

The Drug Content test makes sure that the patch actually holds the exact amount of medicine it's supposed to. The Process Dissolving the Patch: A specific, measured piece of the patch is dissolved in a liquid called phosphate buffer saline (which has a \text{pH} of 7.4 to mimic the body's fluid).Filtering: The resulting liquid is then filtered to remove any non-dissolved patch components. Measurement: The filtered solution is analyzed using special machines: UV Spectroscopy: This machine measures how the liquid absorbs ultraviolet light.(KumarJAetal2010)

9.1.3 Moisture content (%)

Fig. no. 9 Moisture content (%)

The Moisture Content (%) test measures how much water (moisture) is held within the patch material. Having too much or too little moisture can affect how the drug works. Initial Weighing: A newly made patch is weighed to get its initial weight. Drying: The patch is then placed inside a desiccator (a sealed box that removes moisture from the air) along with a drying agent, like calcium chloride, and stored for 24 hours at room temperature. This process removes any moisture from the patch. Calculation: The percentage of moisture is calculated using this simple formula: %moisture content=[Initial weight - final weight/Final weight] x100 (PrajapatiSTetal2011)

9.1.4 Flatness

Fig . no. 10 flatness test

The Flatness Test checks whether the transdermal patch stays perfectly flat and doesn't curl up or shrink after it's been made. This is important for the patch to stick correctly to the skin. The Process Cutting Strips: Small strips are cut from three different locations on the patch: The center, The right side, The left side Measuring Length: The original length of each strip is measured. Checking for Shrinkage: After the strips are exposed to conditions that might cause them to shrink or curl, the final length of each strip is measured again.Calculating Constriction: Any change in length (shrinkage) is calculated as a percentage constriction using this formula: %Constriction= (Initial Length-Final Length)/Initial Length x 100 .(Singh J,etal1993)

9.1.5 Thumbtack test

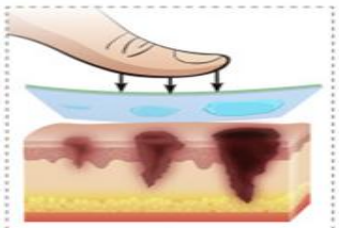

Fig. no.11 The Thumbtack

Test The Thumbtack Test is a simple way to measure the tackiness (initial stickiness) of the patch's adhesive layer. What It Measures Tackiness is determined by measuring the amount of force needed to pull an object (like a thumbtack or a finger) away from the sticky surface of the patch. (SakalleP etal2010)

9.1.6 Thickness test

Fig. no. 12 Thickness test

Measuring the Patch Thickness: To measure the patch's thickness, you need to: Divide the patch into five different areas where the measurement will be taken. Use a caliper (a tool for precise measurement) to measure the thickness of both sides of each of these five areas. Calculate the average of those side measurements to get the final thickness for that section. (PrabhuPetal2011)

9.1.7 Rolling balltack test.

Rolling Ball Tack Test Explained This test is used to measure how sticky or tacky an adhesive patch is. A steel ball (about half an inch wide) is used. The adhesive patch is placed horizontally (flat) with the sticky side facing up. The steel ball is rolled down an incline (a small ramp) and onto the sticky patch. The shorter the distance the ball travels across the patch before it stops, the stickier the patch is considered. (Neupane R, etal2012)

9.1.8 Folding Endurance

Fig.no.13FoldingEndurance

Folding Endurance Test Explained This test measures how tough and flexible a material (like a film or paper) is before it fails. A strip of the material is cut to a specific size. This strip is repeatedly folded back and forth at the exact same spot. The process continues until the strip finally breaks. (KoteshwarK. B,etal2020)

9.2 In-vitro drug release studies:

Fig. no. 14 In-vitro drug release studies

The paddleoverdisc method (USP apparatusV) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape,weighed and fixed overa glass plate with an adhesive. The glass plate was then placed in a 500-ml of the dissolution medium or phosphate buffer (pH 7.4) and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or high-performance liquid chromatography (HPLC). The experiment is to be performed in triplicate and the mean value can be calculated. (KoteshwarK. B,etal2020 .Manvi F.V,etal2003)

9.3 In Vivo studies

9.3.1Animalmodels:

Fig. no. 15 animal model

The most common animal species used for evaluating transdermal drug delivery systems are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc.(KoteshwarK. B,etal2020.Manvi F.V,etal2003)

9.3.2 Human models:

Fig. no. 16 human model

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, sideeffects, patient compliance etc.(KoteshwarK. B,etal2020.Manvi F.V,etal2003)

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