Transdermal patches: Design and current approaches to painless drug delivery

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ABSTRACT

Transdermal patches can be used to avoid a variety of problems with oral medication distribution, including first-pass hepatic metabolism, enzymatic digestion assault, drug hydrolysis and degradation in acidic environments, drug fluctuations, and gastrointestinal irritation. This page discusses the numerous transdermal patch types, structural elements, polymer roles, and necessary assessment methods that are currently on the market. Even though transdermal patches have medical uses for angina pectoris, motion sickness, pain treatment, osteoporosis, contraception, smoking cessation, and cardiac problems, formulation research is still ongoing to make transdermal patches capable of de-livering more difficult medications. The physicochemical characteristics of the active and inactive ingredients, as well as their suitability for long-term usage, can be taken into account while designing and developing transdermal patches. As a result, many chemical strategies and physical methods for developing transdermal patches are being researched.

Keywords:*Polymer matrix, adhesives, transdermal patch, transdermal medication administration, and skin formulation*

1. Introduction

The goal of every pharmaceutical researcher and firm is to create a safe and effective drug delivery system (1). Local and systemic therapeutic effects can be obtained by using the transdermal method of drug delivery (2). Transdermal drug delivery is a desirable alternative to oral medication administration since it avoids first pass metabolism and gastrointestinal side effects. Additionally, it can improve patient compliance problems linked to other drug delivery methods (3-6). In order to generate a local or systemic effect, transdermal medication delivery is self-administered and enables the drug to pass through undamaged skin over a predetermined period of time (2). Drugs that are in dissolved lipid-based form can be given by transdermal patches to achieve the needed efficacy (7, 8). The US Food and Drug Administration (FDA) approved the first transdermal system containing scopolamine in 1979, and nicotine patches were allowed in 1984 (9). Transdermal patches for hormone replacement therapy, contraception, and pain management were FDA-approved and marketed a decade later (10), and advancements in this area are still being made today. Table I shows some transdermal patch products currently on the US market (2, 9, 11–13). Transdermal drug delivery systems evade a variety of issues associated with other routes of drug administration, such as first-pass hepatic metabolism, enzymatic digestion, drug hydrolysis in acidic environments, gastrointestinal irritation, drug fluctuations, adverse effects and therapeutic failure, and disease transmission risk. Further advantages include patient compliance, low cost, and controlled drug release (14). Limitations to

transdermal drug delivery include the possibility of skin irritation, macromolecular agents and that ionic drugs cannot be delivered, and it is not suitable for patients in shock or with low peripheral blood flow (14, 15). On the basis of drug molecule size and the presence of penetration enhancer materials, transdermal drug delivery systems have been divided into three generations (11, 16). Small medication molecules from the first generation might be delivered topically without the use of substances that increase transdermal penetration. The penetration of topically applied tiny drug molecules was improved in the second generation by the addition of transdermal boosting agents. In the third generation, medication used topically was capable of macromolecule penetration. Transdermal patch development should take into account factors including physicochemical qualities, chemical nature, strength, molecular weight, ionisation degree, drug partition coefficients, and the hydrophile-lipophile balance (HLB) of polymers (17–22). Numerous permeation enhancer materials can be used to modify transdermal drug delivery systems, allowing for predictable control of the drug absorption profile. Different transdermal drug delivery systems, such as vapour patches, membrane-moderated, microreservoir transdermal systems, matrix systems containing drug-in-adhesive, or matrix-dispersion systems, use different mechanisms to control the drug release rate. A brief description of the various transdermal patch types currently on the market with FDA approval, as well as information on their structural elements, ingredient physicochemical properties, designs, method of preparation, polymeric matrix components, and various evaluation techniques needed for assessments, are provided in the current review. The following is a description of FDA-approved transdermal patches that are currently on the market.

2. CATEGORIES OF TRANSDERMAL PATCHES

single-layer adhesive patches for drugs As shown in Fig. 1, a single layer of an adhesive polymer serves as a reservoir for the medication dispersion. Underneath the single layer lies an impervious backing laminate. The medication is released from the backing laminate layer that supports the drug reservoir after being deposited in and adhering to the single polymer layer (23). A single layer drug-in-adhesive transdermal patch containing methylphenidate is the transdermal product Daytrana®.

2.1 Adhesive patches with many layers of drugs

Drug release is controlled over time in multilayer transdermal patches, which have an adhesive layer and a drug reservoir layer (24–25). Multilayer systems consist of a permanent backing laminate as well as a temporary protective layer. Drug administration can be sustained for up to seven days with multilayer patches, which are used to administer hormone therapy, quit-smoking aids, and painkillers.

2.2 Transdermal vapour patches

The single layer of adhesive polymer that makes up vapour transdermal patches has the ability to release vapour (24–25). There are numerous vapour dermal patches on the market that are utilised for various uses. For instance, nicoderm CQ® are nicotine vapour transdermal patches that, when released, can assist in quitting smoking. In 2007, this product was released on the European market. Another type of vapour patch with essential oil content that can be used for decongestion is Al- tacura®. There are more vapour patch varieties on the market that contain sedatives or antidepressants (Table I).

patches with membrane-moderated transdermal reservoirs A transdermal patch with a drug reservoir, an impermeable metallic plastic laminate backing layer, and a porous polymeric membrane that regulates drug release over time is shown in Fig. 1. Various polymeric materials, include hypoallergenic

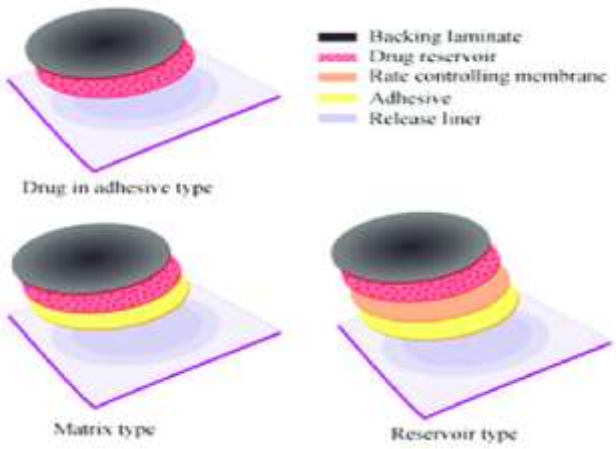

Fig. 1. Schematic diagram of various types of transdermal patches.

Ethylene vinyl acetate copolymer, a genic sticky polymer). Drug molecular dispersion in a polymer matrix, a component of the preparation, regulates drug in the transdermal patch (26, 27). Commercial transdermal patches with modified drug release include Catapres®, which contains clonidine for seven-day use, Transderm-Scop®, which contains scopolamine for three-day use, and Transderm-Nitro®, which contains nitroglycerin for one-day use.

2.3 Transdermal microreservoir patches

Matrix dispersion and a drug reservoir are combined in microreservoir transdermal patches. The drug is first suspended in an aqueous solution of a hydrophilic polymer before being uniformly dispersed on a lipophilic polymer to create the reservoir. A large shear mechanical force is used during dispersion, which causes thousands of minute, unleachable spheres to form. The drug release profile maintains a constant drug level in the plasma by following a zero order rate of kinetic drug release. Since the medication dispersion must be thermodynamically stable, crosslinking polymeric agents are typically included (25, 28).

Table I. FDA approved other transdermal delivery systems

Drug	Product name	Transdermal delivery system
Flurandrenolide	Cordran®	Transdermal tape Testosterone
AndroGel®	Transdermal gel	EstradiolEvamist®
Transdermal spray Fentanyl HCl		IONSYS®
Iontophoretic patch Insulin	Vyteris insulin patch®	Iontophoretical patch
Hydrocortisone	Tegaderm patch	Electrophotophoresis

2.4 System matrix: drug-in-adhesive

The drug reservoir is created to distribute the drug on an adhesive polymer using single layer or multilayer transdermal patches, as shown in Fig. 1. By melting the sticky polymeric components or casting the drug-polymer matrix in solvent onto an impermeable backing layer (29). There are many commercial transdermal patches of this type on the market; for instance, the Climara® patch contains 100 micrograms of estradiol for a one-day application and the NicoDerm® CQ patch contains nicotine to support quitting smoking for up to 10 weeks (Table I).

2.5 Systems with matrices: matrix-dispersion

A hydrophilic or lipophilic polymer matrix serves as the reservoir in a matrix transdermal patch, and the drug is homogeneously disseminated in the matrix by putting the drug-polymer matrix over a plate with an impermeable laminate backing (30). A continuous medication flow through undamaged skin is provided by commercial matrix dispersion patches like Nitro-Dur®, which comprises nitroglycerin and minitran (Table I)**.**

2.6 Transdermal patches of several kinds

As illustrated in Table II, other transdermal matrix delivery methods that have received FDA approval include transdermal patches with adhesive tapes, transdermal gel, transdermal spray, iontophoretic delivery, and phonophoresis delivery.

3 TRANSDERMAL PATCHES' STRUCTURAL ELEMENTS

3.1 Drug Choice

Designing transdermal patches requires taking into account the physicochemical characteristics of medications. Drug selection must take into account hydrophobicity and ionisation status because they affect skin penetration (14), which in turn affects drug solubility and diffusivity across the stratum corneum layer of the skin (31). The melting point (MP), partition coefficient (log P), aqueous solubility, molecular size and molecular weight (MW), dose concentration and saturation, permeability, absorbability, and diffusivity across the stratum corneum of human skin are additional physicochemical characteristics of the drug that directly affect skin penetration (32–33). The majority of transdermal patches include lipophilic medications in them, which are those that are above the lower Berner-Cooper boundary, which is defined as MW = 500, 1000 Daltons, a log P range of 1 to 5, and MP 250 °C. For instance, fentanyl has a low MP (83 °C), a moderate to high lipophilicity (log P = 3.9), and a moderate to high molecular weight (337 Da) (9). When administered via transdermal patches, medications with low dosage strengths, brief half-lives, easy hydrolysis in acidic environments, and those sensitive to hepatic metabolism can avoid the aforementioned problems (24, 32, 33).

3.2 Properties of polymer matrices

Polymers regulate the pace at which drugs are released from the transdermal patch's drug reservoir, enabling the body to receive drugs safely, consistently, and effectively (34). Businesses that sell transdermal patches frequently concentrate on the creation of a particular polymeric system. Microporous Polypropylene and Ethylene Vinyl Acetate (EVA) Copolymers are the area of expertise for Alza Corporation. Silicone rubber is highlighted by Searle Pharmacia (35, 36). Using ethylcellulose, Sigma creates isosorbide dinitrate matrixes. Hydroxypropyl methylcellulose (HPMC) is used by Colorcon in the UK to prepare the matrix for the transdermal administration of propranolol (37).

3.3 Transdermal patch matrix creation using polymers

Transdermal patches are made with polymers, which serve a variety of purposes including matrix construction, drug delivery rate control, pressure-sensitive adhesives, backing laminates, and protective drug release liners. They should produce a consistent and effective supply of the medicine for the duration of the manufacturer's promised delivery period, and they should be biocompatible with the skin (38). formulas for transdermal patches that employ polymers.

The choice of polymer is important for creating a polymer matrix because it influences the drug's release characteristics, the adhesion/cohesion balance, the stability of the product, and its compatibility with other product

elements and the recipient's skin (57). Below is a description of many polymers utilised in transdermal patch matrix production.

ethylene glycol polymer. Due to its great biocompatibility, polyethylene glycol (PEG) has a wide range of uses in the biomedical field. With the aid of the aurethane-allophanate bond, the polymeric network created by crosslinking PEG with tris(6-isocyanatohexyl)isocyanurate can expand and gel in phosphate buffered ethanol or saline. This system operates in a biphasic mode for solute release (58).

matrices made of acrylic acid. Plasticizers and acrylic acid matrices are frequently utilised in the production of medicament polymer matrix for transdermal patches. Eudragit S100, Eudragit E100, Eudragit RS PM, and Eudragit RL PM are a few examples of these polymers (59). Transdermal patches use the non-adhesive copolymer of ethyl acrylate and methyl methacrylate known as eudragit NE 40 D to produce the matrix (60).

derivatives of cellulose. - In order to create diltiazem HCl and indomethacin patch systems, ethyl cellulose and polyvinylpyrrolidone (PVP) with dibutyl phthalate (30%) as a plasticizer matrix were used. In order to increase the rate of drug release, water-insoluble films are combined with a water-soluble polymer, such as PVP, to create polymers like ethyl cellulose. Leaching of water-soluble components, which causes pore formation, is the cause of the high drug release rate (61).

HPMC, or hydroxypropyl methylcellulose. A polymer called HPMC that is water soluble expands when it absorbs water. In oral controlled release medication delivery systems, it is frequently utilised. It has undergone testing as a matrix-forming ingredient for transdermal preparations of propranolol. Since the medication is extremely soluble in the polymer, HPMC produces transparent films. Due to the burst effect observed during dissolution tests, HPMC matrices exhibit rapid drug release. This is explained by the polymer's simple hydration and swelling in the matrices (39).

PSAs, or pressure-sensitive adhesives. Transdermal devices depend heavily on the adhesive properties of transdermal patch preparations. For effective drug delivery, the patch and skin surface should make total and close contact. Interatomic and intramolecular attractive interactions that PSAs establish with the skin are thought to be the cause of this contact (60). Chemicals called PSAs are viscoelastic and stick to the skin when applied with little pressure (62). To achieve the necessary level of contact, PSAs must deform when under pressure (63).

PSAs may be removed from a smooth surface without leaving a trace and cling to the skin with just the application of finger pressure. They are aggressively and permanently sticky. Polyisobutylene, acrylic, and silicone-based adhesives are the most frequently utilised types in transdermal patches (63). When pressure is applied, an adhesive material that flows like liquid moistens the skin's surface, enabling adhesion. When elastic energy is stored throughout the bond-breaking process, adhesion occurs. As a result, viscoelastic materials exhibit pressure-sensitive adhesion, and the material's applicability depends on how well elastic energy and viscous flow are balanced (35).

Transdermal patch designs typically use silicone-based adhesives, acrylics, thermoplastic elastomers, polyisobutylene, and natural rubber (64). It is important to choose an adhesive that is compatible with the skin and other patch components as well as the drug formulation (35). Alkyl acrylate ester polymerization produces polyacrylics, which are water soluble, biodegradable, polyester-based polymers. In the pharmaceutical sector, polyacrylics are frequently employed, particularly as adhesives when making transdermal patches. At pH 5, they produce liquids, and at pH 7, gels (65).

As their molecular weight rises, so do their mechanical properties (63). A vinyl polymer called polyisobutylene (PIB) is created when an isobutylene monomer undergoes cationic polymerization. A semisolid, colourless, elastic material with extremely little moisture and air permeability called PIB. It has strong oxidative and thermal stability (66). As the molecular weight of anything increases, so do its physical properties. Compared to high MW polymers, low MW polymers are less viscous (35). Because they don't utilise solvents, are safe for the environment, and are

simple to make, pressure sensitive adhesives are becoming more and more important. They are created using tackifying resins from EscorezTM, plasticizers, and thermoplastic components. They have a high drug loading capacity and good cohesion, making them appropriate for the construction of matrix patches (67).

rate-regulating membrane. The active ingredient diffuses across an inert membrane at a limited and controlled rate in a transdermal patch. By changing the inert membrane's composition and thickness, the dose rate per patch area can be adjusted (35).

Ethylene vinyl acetate (EVA). - EVA is frequently used to make rate-regulating membranes for transdermal patches. By altering the amount of vinyl acetate in the polymer, the membrane's permeability can be changed (35).

Silicone rubber. – Silicone rubber is an elastomer (rubber-like material) composed of silicone, itself a polymer, along with carbon, hydrogen, and oxygen. It is often used in rate controlled devices because it is biocompatible, easily obtained, and permeable to many drugs, especially steroids. The high permeability of steroids is due to free rotation around the silicone rubber backbone which is responsible for the low microscopic viscosity in the polymer (35). Polyurethane. – Polyurethanes (PU) are polymers formed by the condensation of polyols (organic compounds containing multiple hydroxyl groups) and urethane. Polyurethanes made from polyester and polyols are called polyester urethanes whereas polyurethanes made from polyether and polyols are called polyether urethanes.

The majority of urethanes utilised in transdermal patches are polyether urethanes because of their resistance to hydrolysis (35). The fact that polyester urethanes degrade naturally, however, has drawn attention (35). Rubbery and permeable urethane polymers are available. By changing the hydrophilic and hydrophobic ratios of the added polymers, their permeability can be improved (68). Hydrophilic chemicals have minimal permeability in hydrophobic silicone or EVA membranes, making polyurethane membranes appropriate for passing them (69).

Open the lining. Before being placed to the skin, the protective layer covering a transdermal patch is instantly peeled off. The primary package contains this layer (38). Because the liner will be in close contact with the dosage form, it must also meet all criteria for inertness to delivery system components and penetration qualities (41). A release liner is frequently made of fluorpolymers, fluoroolefin-based polymers, and linear fluoroacrylates, for example, BIO PSA HighTack 7-4301, BIO PSA MediumTack 7-4201, Scotch Pak 1022, and Scotch Pak 1006 (70, 71).

supporting laminate. The backing layer's material should be resistant to chemicals and inert to other delivery system components. It should also prevent the leaching of chemicals. Flexibility and ease of oxygen and moisture transmission are characteristics of an effective backing layer. EVA, polyisobutylene, silicone oil, and 3M Scotchpak Backing 1006 are some examples (72).

Enhancers of Penetration: The skin's primary barrier function is provided by the stratum corneum (73). Chemicals known as penetration (or permeation) enhancers effectively and temporarily impair the stratum corneum barrier qualities, allowing medicines to pass through to deeper epidermal layers and enter the bloodstream (74). In effort to find inert permeation enhancers that are more effective and safe to use in transdermal patches, many chemical substances have been explored. The capacity of about 360 chemical substances to improve permeation is known (75), and there are numerous processes by which skin permeability is increased. Many substances increase the fluidity of intercellular lipids in the stratum corneum by interacting with the skin and solubilizing lipids within the stratum corneum. Other compounds hydrate the stratum corneum.

Skin permeability rises as the stratum corneum becomes more fluid (76). Terpenes, sulphoxides, pyrrolidones, laurocapram, fatty acids, alcohols, fatty alcohols, surfactants, glycols, urea, and bile salts are among the substances that promote permeation (77–79).

Additional excipients. Among the solvents used in transdermal patch preparation include acetone, dichloromethane, methanol, and ethanol. Within the drug reservoir, solvents are employed. Transdermal patches are made more plastic

by adding plasticizers such triethylcitrate and dibutylpthalate, which are utilised in quantities ranging from 5 to 20 percent (80, 81). The polymeric films in transdermal patches are also plastified using phosphate esters and glycol derivatives (polyethylene glycol and propylene glycol) (81).

4. Tools for characterization and evaluation in the preparation of transdermal patches

Transdermal patches should be described and evaluated using a variety of assessment and evolution procedures, including as dissolving, in vitro drug release, in vitro skin permeability, sticky characteristics, and excipient control. In accordance with the European Medicines Agency Guidelines on the quality of transdermal patches developed by the Committee for Medicinal Products for Human Use (82) these tests are included below. Additionally, additional physical, chemical, and biological tests, evaluations, and assessments like those for material interactions, patch thickness, weight uniformity, folding endurance, moisture content, weight gain due to moisture absorption, water vapour permeability, drug content, flatness, stability, swellability, and skin irritation tests should be carried out.

5. Drug-polymer interactions research

Several thermal and physico-analytical methods, including differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), X-ray powder diffractometry (XRPD), nuclear magnetic resonance (NMR) spectroscopy, and infrared (IR) radiation, can be used to analyse the interactions between drugs and polymers in a lipid matrix (82–84). Each chemical in a mixture of eutectic drugs and polymers has a distinctive peak in the DSC, IR, and NMR spectra, making component identification possible. A florescence agent is bonded to the polymer, the complex is incubated with cells, and the polymer-cell complex is visualised under a confocal microscope to detect interactions between the cell surface and polymer. The impact of the polymer on the fluidization/stabilization of lipid membranes can be better understood via NMR.

5.1 Patch thickness

Using a digital micrometre screw gauge, measurements are taken three to five different locations on the patch to determine its thickness. To ensure that the patch thickness is suitable, the mean thickness and standard deviation of such numerous readings are calculated (85, 86).

5.2 Weight uniformity

The average weight and standard deviation of 10 randomly chosen patches are calculated to establish the weight uniformity. The weight of each patch must not deviate significantly from the mean (87).

5.3 Folding endurance

Folding endurance is the quantity of times a film can be folded without breaking after being uniformly cut across a patch and folded repeatedly at the same spot until it breaks (85).

5.4 Moisture content

A transdermal patch is precisely weighed, put in a desiccator with fused calcium chloride for 24 hours, and then reweighed to determine its moisture content (87). Equation (1) is used to compute the percentage of moisture in the patch:

Initial mass minus final mass equals moisture content (%). first/first mass multiplied by 100 (1)

5.5 Moisture uptake or mass gain (88)

A transdermal patch's mass growth typically denotes moisture absorption. The patch is weighed, put in a desiccator with a saturated KCl solution, and incubated for up to 24 hours with RH kept at about 84% to assess moisture uptake. The patch is then reweighed, and equation (2) is used to determine moisture uptake.

Moisture absorption (%) _= Total mass initial mass/100 times the initial mass (2)

The permeability of water vapour is evaluated.

WVP = W/A (3) where W = amount of water vapour (g per 24 h) permeated in the patch, A = surface area (m2) exposed on the patch sample, and W = amount of water vapour (g per 24 h) permeated in the patch are used to calculate the water vapour permeability (WVP) in a patch in a natural air circulation oven (89).

5.6 Drug content

To measure the drug content of a transdermal patch, a specific area of the patch is dissolved in a specific volume of a selected solvent. The solution is shaken continuously for up to 24 h, ultrasonicated for a specific period of time and then filtered. Drug content in the filtrate is determined using an appropriate analytical method (87).

5.7 Flatness test

Three longitudinal strips are cut from the right side, the left side, and the centre of a transdermal patch. Each strip is counted out at (90). For determining flatness, apply the following equation:

Constriction (%) = (I1 - I2) 100 (4), where I1 is the length of the starting strip and I2 is the length of the finished strip.

5.8 Studies on stability

Transdermal patches are kept at a temperature of 40 0.5 ℃ and a relative humidity of 75 5% for six months. The samples are removed from storage after a six-month period and analysed to identify the drug concentration at intervals of 0, 30, 60, 90, and 180 days (91).

5.9 Determination of adhesive properties

Several tests, including peel force tests, adhesive strength tests, and tack tests, can be used to describe the characteristics of an adhesive. To describe the drug's sticky qualities in a transdermal formulation, in vitro and in vivo assays can be employed (82).

5.10 Tack properties

Tack refers to a specific polymer's capacity to adhere to a substrate under light pressure. The composition and molecular weight of the polymer affect tact.

5.11 Probe tack test

The amount of tack is determined by the force used to pull a probe a fixed distance away from a sticky polymer. To measure the amount of force necessary to break the bond of the surface of a pressure-sensitive adhesive in a transdermal patch, the probing tack test can be employed in place of the thumb test (92). Plotting force vs time shows how much force is needed to break the bond over a given period of time.

5.12 Peel tack test/quick stick test

In this test, an adhesive tape is pulled over the transdermal patch at a pace of 12 inches per minute and an angle of 90 degrees. The peeling power required to sever the bond between the substrate and adhesive is known as the tack value (93).

5.13 Peel adhesion test

The amount of power required to peel off an adhesive polymer coating from a particular substrate is known as peel adhesion. A piece of tape is attached to a plate of stainless steel backing membrane and pushed 180 degrees away from the test substance to gauge peel adherence. Next, the amount of force needed to pull the tape is calculated. The test is carried out to ensure that there are no residues left on the skin and that the adhesive does not harm the skin (94).

5.14 Tensile strength

A tensiometer is used to gauge tensile strength. A patch is attached to the tensiometer assembly, the weight needed to break the patch is calculated, and the patch's subsequent elongation is measured (using the instrument's pointer). The patch's tensile strength is calculated as the average of three patch values (92). The patch's tensile strength is:

Tensile strength = break force / a ′ b (1 + ΔL/L) (5)

where, a = patch width, b = patch thickness, L = patch length, ΔL = patch elongation at breakage point, and break force = weight (kg) required for patch breakage.

5.15 Swellability

A transdermal patch's swellability is evaluated by applying the sample on a cover slip that has been preweighed in a Petri dish containing 50 mL of pH 7.4 phosphate buffer. Time t is the period during which the sample absorbs, which is typically 30 minutes (95). The cover slip is taken out of the Petri dish, cleaned, and weighed after time t has passed. The amount of water absorbed by the patch is represented by the change in mass.

The following equation (95) yields the percentage swelling (S).

S (%)=Wt-Wo/Wo*100 (6)

where S = % swelling, W0 = original mass of the patch at time zero, Wt = patch mass at time t after swelling

6. In vitro drug release

The rate and breadth of medication release from a transdermal patch can be accurately determined using an in vitro drug release evaluation experiment. The drug release from a transdermal formulation with a suitable, non-rate-limiting membrane can be assessed using a variety of techniques. Alternative techniques, however, with greater discriminatory power than compendial techniques, may be used (82). A transdermal formulation can be evaluated for drug release using a variety of techniques (96), which include: In contrast to the USP paddle dissolution apparatus, the paddle over disc (USP apparatus 5/PhEur 2.9.4.1) immerses a disc or cell containing the formulation at the bottom of the vessel and adjusts the temperature to skin temperature (32 5 °C). the USP apparatus 6 / PhEur 2.9.4.3 method, which is similar to the USP basket type dissolution apparatus method but uses a hollow cylinder immersed in medium and maintained at 32 5 °C; ii) the reciprocating disc (USP apparatus 7) method, in which the formulation is placed into holders and oscillated in small volumes of buffer medium; iii) the paddle over extrac method; and iv) the paddle over extrac method. The Franz-diffusion cell and its variant, the Keshary-Chien cell, are further diffusion cells that are frequently used to assess drug release from a transdermal formulation.

Higuchi, first order, zero order, Peppas and Korsenmeyer models are some examples of mathematical models that describe the kinetics of drug release from a transdermal patch. The model that best fits the data is utilised to ascertain the mechanism of kinetic drug release after data have been gathered and put into these models (97). At least three sample time points are advised, per the European Medicines Agency Guidelines on Quality of Transdermal Patches released by the Committee for Medicinal Products for Human Use (82).

7.Ex vivo skin permeation studies

Ex vivo skin permeation studies, which represent the thermodynamic activity of the product's active ingredient, may be regarded as a useful indicator of product quality even though they may not be reflective of the in vivo release assessment. Ex vivo skin permeation tests are to be repeated continuously for the duration of the transdermal preparation's shelf life (82). A vertical diffusion cell, also known as the Franz diffusion cell, is used for the ex vivo permeation research. Ex vivo permeation testing was done with two compartments for diffusion, an inner compartment with a volume of up to 10 mL and an upper compartment with a diffusion area of 1.54 cm2 (98). For the permeation investigation, an animal biological membrane, such as pig ear skin or rat skin, can be used and positioned between the two compartments. As an acceptor medium, a phosphate buffer solution with a pH of 7.5 is typically employed. The receptor solution in the diffusion cell's receptor compartment is continuously stirred using magnetic rods to maintain a temperature of 32 0.5 °C (99). The patch is positioned so that the drug-releasing surface faces the receptor side and is attached between the upper and inner compartments. Continuous constant-speed stirring is applied to the inner compartment buffer medium. Typically, samples of roughly 500 L are collected at predetermined intervals. A comparable volume of buffer is added when a sample is taken. The samples are further diluted, then analysed with the appropriate analytical HPLC technique. At regular intervals, drug penetration is monitored, and volume vs. time graphs are created.Skin irritancy research Different transdermal patches' ability to irritate skin can be assessed visually by looking for erythema and edoema using the PII test, or it can be studied microscopically by a light microscope for any histological abnormalities. Transdermal patches can be tested for skin sensitivity using albino rats with average weights of up to 230 g. After the rat's back has been washed with rectified spirit and shaved 24 hours before the experiment, patches are placed over an area of 8.1 cm2 (100). After 24 hours, the patch is removed, and the region is cleansed with a disinfectant swab. Visual inspection is done at the application areas to check for any potential erythema and edoema alterations to the skin. Erythema and edoema alterations can be graded on the Draize scale between 0 and 4 (101). Based on how severe the skin reactions were (101), this is rated. According to the following equation, PII is determined: PII is equal to (102)/(Sum of Erythema Grade on Many Days + Sum of Edoema Grade on Many Days).

8. Conclusion

Based on the results of the review, this article offers insightful literature on transdermal patches, as well as the structural elements, characterization, and assessment methods needed for the creation, advancement, and clinical effectiveness of the many types of patches.

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