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Review Article

A REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM: A NOVEL TOOL FOR IMPROVING BIOAVAILABILITY

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ABSTRACT

Among all the dosages, oral is the best route of administration for its advantages but due to flow of its demerits like poor bioavailability due to first pass metabolism and unpredictable nature of gastrointestinal absorption. Moreover, oral route is cost prohibitive and inconvenient. Transdermal patches are medicated adhesive patches when it was placed on the skin layer it will deliver the drug into the blood stream through skin layer. To overcome the side effects caused by the oral route, drugs given through transdermal are preferred as transdermal patch. By employing sustained release polymers, transdermal patches can be prepared using solvent casting method. Drug excipients compatibility studies are very important to determine whether the excipients are suitable for that drug or not. These compatibility studies are very important to maintain the stability of dosage form. Evaluation studies are very important to determine the accuracy of dosage form at the same time therapeutic action also. Some of the parameters such as weight variation, physical appearance, drug content, moisture uptake, folding, endurance, swelling study and physical appearance, *in vitro* dissolution studies, *ex vivo* studies, and *in vivo* studies were evaluated.

Keywords: Transdermal, Reservoir, Epidermis, Bioavailability, Skin Permeation.

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INTRODUCTION

Transdermal drug delivery system (TDDS) also known as "patches" (non-invasive delivery) is dosage form designed to deliver a medication across a patient skin [1,2]. Skin is the largest and most accessible organ of human body with the help of skin layers drug reaches into the blood stream given as sustained release, controlled release, or extended-release formulation and shown in Fig. 1 [1].

Transdermal delivery systems are specifically designed to obtain systemic blood levels and have been used in the US since the 1950s. The first transdermal system, transdermal SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Most transdermal patches are designed to release the active ingredient from several hours to days following application to the skin. This is especially advantageous for prophylactic therapy in chronic conditions. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug, and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy [3].

Transdermal permeation or percutaneous absorption can be defined as the passage of a substance, such as a drug, from the outside of the skin through its various layers into the blood stream [2].

Certainly, each dosage form has its unique place in medicine, but some attributes of the transdermal delivery system provide distinct advantages over traditional methods. In the development of the transdermal delivery system [4], a series of interrelated elements must be taken into consideration. These elements can be classified into five basic areas:

1. Bioactivity of the drug.
2. Skin characteristics.
3. Formulation.
4. Adhesion.
5. System design.

The transport of drugs through the skin is complex since many factors influence their permeation to simplify the situation somewhat, one should consider the following [4]:

- Skin structure and its properties.
- The penetrating molecule.
- Physical-chemical relationship to the skin.
- The delivery platform.
- The platform or delivery system carrying the penetrant.
- The combination of skin.
- Penetrant.

Advantages

- Avoidance of first-pass metabolism.
- Avoidance of gastrointestinal compatibility.
- Minimizing undesirable side effects.
- Avoiding the fluctuation in drug levels.
- Maintain plasma concentration of potent drugs [5-9].

Limitations

- Transdermal patches cannot deliver ionic drugs.
- Transdermal patches cannot achieve high drug levels in blood/plasma.
- Transdermal patches cannot deliver drugs in a pulsatile fashion.
- It cannot develop for drugs of large molecular size [6-10].

The process of drug absorption through the percutaneous route is shown in Fig. 2 and different types of transdermal patches are shown [14,15] in Fig. 3.

COMPONENTS OF TRANSDERMAL PATCHES

Some of the components used for transdermal patch are [16-21]:

- Liner: It is removed before using it gives protection to patch during storage. For example, polyester film.
- Drug: It is directly in contact with release layer. For example, nicotine, methotrexate, and estrogen

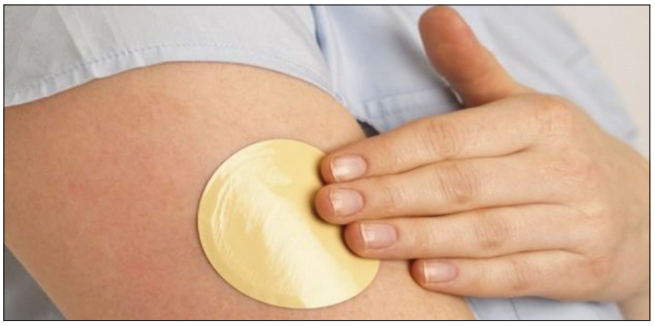

Fig. 1: Transdermal patch application on the skin

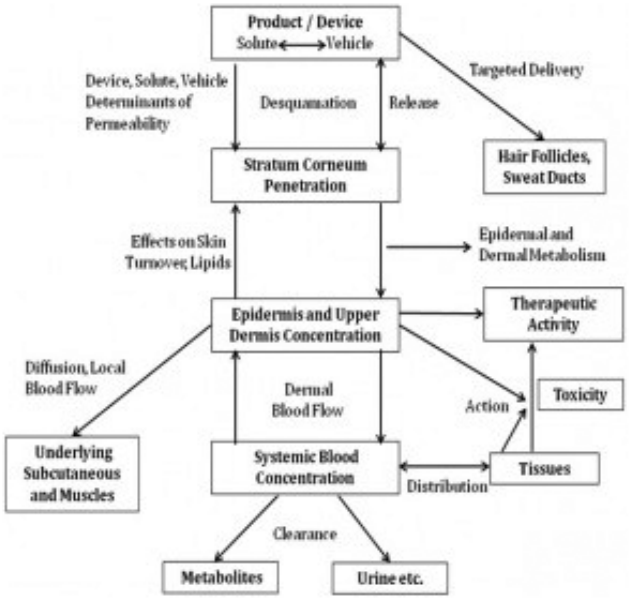

Fig. 2: Schematic representation of percutaneous absorption

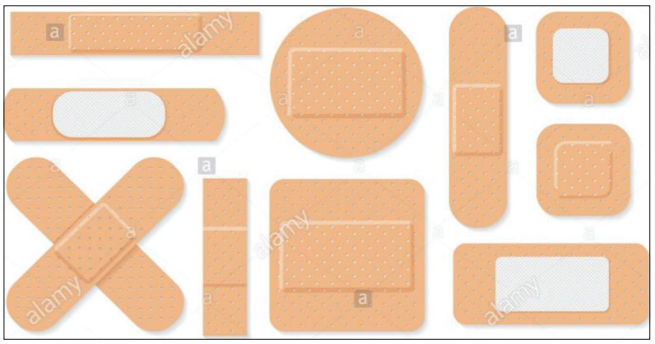

Fig. 3: Different types of transdermal patches

- Adhesive: It helps in adhering the components of patch with each other and helps in adhering the patch to skin patch. For example, acrylates, polyisobutylene, silicones, etc.
- Membrane: It helps in release of drug from reservoir and multilayer patches.
- Backing: It gives protection to the patch from the atmosphere. For example, cellulose derivatives and polyvinyl alcohol.

TYPES OF TRANSDERMAL PATCH

Transdermal patches were categorized into four main types [22-25]:

1. Matrix type.
2. Reservoir type.
3. Membrane matrix hybrid.
4. Microreservoir type.
5. Drug in adhesive.
    - Single layer drug in adhesive.
    - Multilayer drug in adhesive.
6. Miscellaneous: Hybrid matrix type, vapor patch, etc.

Matrix type

Matrix type of transdermal patch was designed in the year 1990s. Here, the patch is very slim and less visible when sticked on the skin. In this type, the film controls release of medication from the patch. In this method, the drug and polymer dissolved in solvent (soluble) or insoluble drug homogeneously dispersed in hydrophilic or lipophilic polymer. To the above, add required quantity of plasticizer and permeation enhancer. Medicated polymer formed is then molded into the ring with defined surface area and controlled thickness over the mercury on horizontal surface followed by solvent evaporation at an elevated temperature. Thus, film formed is separated from the ring and mounted onto the occlusive base plate in a compartment fabricated from a drug impermeable backing. Then, an adhesive polymer is then spread along the circumference of the film. The adhesive layer and backing are integrated into one layer, are shown in Fig. 4 [17]. A few examples of matrix type transdermal patches are Nitro-glycerin transdermal patch-Nitro Dur®.

Advantages

1. Avoidance of first-pass effect.
2. Avoid gastrointestinal track difficulties which are caused by enzymes and food interactions.
3. Stable and controlled blood level.
4. Ease of termination of drug action if necessary.
5. Poor oral bioavailability.
6. Narrow therapeutic window.
7. No interference with gastric and intestinal fluids.
8. Less chances for overdose.

Disadvantages

1. The transdermal delivery is unsuitable when the dose is high.
2. Drug is skin sensitizing, skin irritating and it gets metabolized in skin.
3. Drug undergoes protein binding in skin.
4. Drug is highly lipophilic or hydrophilic.

Reservoir type

It is different from single layer drug in adhesive and multilayer drug in adhesive systems. It is having separate drug layer. In this, the drug reservoir layer is a liquid compartment which is consisting of drug solution or the suspension where the drug particle is suspended in silicon fluid gives paste such as suspension/gel/clear solution in ethanol, which is separated by the adhesive layer. The rate controlling membrane is prepared by solvent evaporation or compression method. This patch is also consisting of backing layer, as shown in Fig. 5 [17]. Advantage of this type is it follows true zero order release to achieve a constant serum drug level, for example: Duragesic®, Estraderm®, and Androderm®.

Membrane matrix hybrid

It is the modified form of reservoir matrix in which the liquid form of drug reservoir is replaced with solid matrix polymer (polyisobutylene), example for this type is Catapress®.

Micro reservoir type

In this type, the drug is suspended in an aqueous solution of water miscible drug solubilizer poly ethylene glycol (PEG) or drug suspension is homogenously dispersed by a high shear mechanical force in lipophilic polymer, forming 1000s of unleachable microscopic drug particles. The dispersion is quickly stabilized by immediately cross-linking the polymer chain, *in situ* produces a medicated polymeric disc of specific area a thickness, is shown in Fig. 6 [17], the example for this type is Nitrodisc®.

Drug in adhesive

In this, drug and excipient are incorporated in organic solvent-based pressure sensitive adhesives solutions and mixed. Then, cast as a thin film and dried to evaporate the solvent, then the dried adhesive matrix film is sandwiched between release liner and backing layer. Some of the examples are Climara®, Nicotrol®, and Deponit®.

Single-layer drug-in-adhesive

The adhesive layer consisting of drug. In this type of patch, adhesive layer not only serves to adhere to various layers of patch together and with entire patch to the skin but it is also responsible for drug release from the patch. The adhesive layer is surrounded by temporary layer and backing is shown in Fig. 7.

Multilayer drug-in-adhesive

It is similar as that of single-layer drug-in-adhesive. Here, both the adhesive layers are responsible for releasing the drug. However, the multilayer patch is somewhat different that it adds another layer of drug-in-adhesive and it was separated by a membrane in some cases. This patch is having temporary liner layer and a permanent backing, is shown in Fig. 8.

BASIC COMPONENTS OF TRANSDERMAL PATCHES

1. Active pharmaceutical ingredient (API).
2. Polymer matrix/drug reservoir.
3. Permeation enhancers.
4. Pressure sensitive adhesive.
5. Backing laminates.
6. Release liner.
7. Other excipients such as plasticizers and solvents.

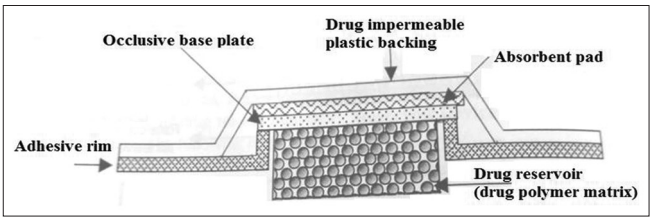

Fig. 4: Matrix type drug in adhesive

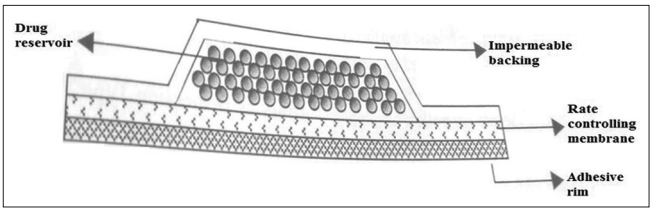

Fig. 5: Reservoir type drug in adhesive

API

API selection for the preparation of transdermal patches should meet the following conditions [26-29]:

- Must no induce cutaneous irritant and allergic response and should not cause adverse effects to non-target tissues.

Polymer matrix

Polymer selection criteria for the preparation of transdermal patches are as follows [30-33]:

- Provide consistent and effective delivery of drug.
- Should not deteriorate throughout the shelf life of the drug.
- Stable, easily manufactured and fabricated into the desired product.
- If degraded must be non-toxic and non-antagonistic to host.
- Biocompatible and chemical compatibility with drug and others.

Polymers are classified based on the nature:

- Natural polymer: Cellulose derivatives, gelatin, shellac, waxes, gums, etc.,
- Synthetic elastomers: Polybutadiene, hydrin rubber, butyl rubber, etc.,
- Synthetic polymer: Poly vinyl acetate (PVA), poly vinyl cellulose (PVC), poly ethylene (PE) polypropylene, etc.

Few examples of mostly used polymers for transdermal patches are for matrix former (PEG, Eudragit, Ethylene cellulose (EC), poly vinyl pyrrolidine (PVP), and hydroxy propyl methyl cellulose (HPMC)) and rate controlling membrane (Ethylene vinyl acetate (EVA), silicon rubber, and polymethane).

Pressure sensitive adhesive

These selections are based on patch design and drug formulation (helps in maintaining an intimate contact between transdermal patch and the skin surface) [34,35].

- Matrix system: Peripheral adhesives-incidental contact between adhesives and the drug and penetration enhancers.
- Reservoir system: Face adhesive diffusing drug must not affect the adhesive.
- Drug in adhesive matrix system: Rate at which the drug and permeation enhancers will diffuse through the adhesive.

Pressure sensitive adhesive should be selected based on the following criteria:

- Adhere with Not more than (NMT) applied finger pressure.
- Permanently tachy and exert a strong holding face.
- Be removable from the smooth surface without leaving a residue.
- Physicochemical and biologically compatible and should not alter drug release.

Mostly used pressure sensitive adhesives are polysiloxane, polyacrylate, polyisobutylene, and silicon.

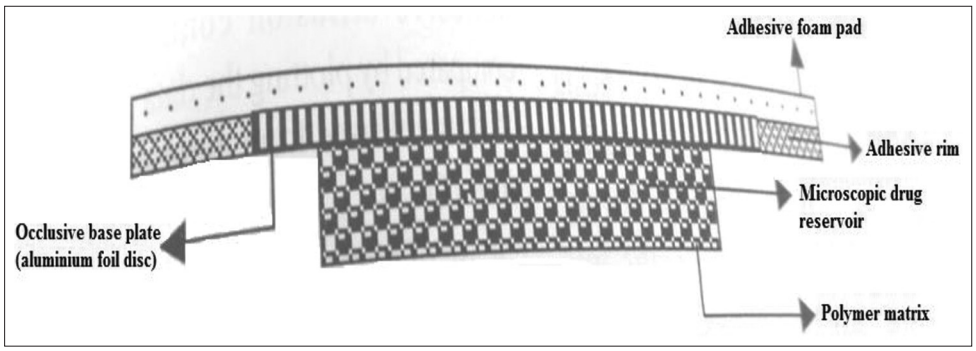

Fig. 6: Micro reservoir type drug in adhesive

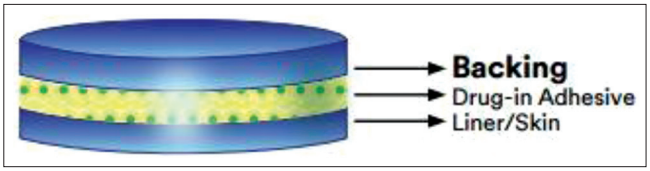

Fig. 7: Single-layer drug in adhesive

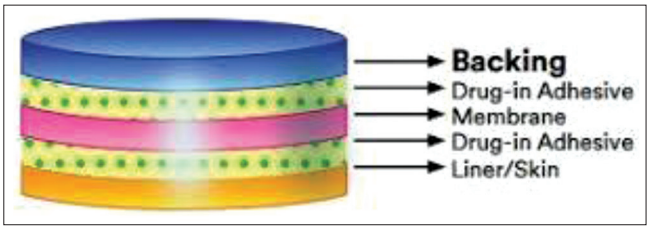

Fig. 8: Multilayer drug in adhesive

Permeation enhancers

These play a major role in preparation of transdermal patches, thereby enhancing the permeation of drug through the skin can be by the following functions:

- Increase permeability of stratum corneum to attain higher therapeutic levels of the drug.
- These interact with structural components of stratum corneum, that is, protein/lipids.
- They alter the protein and lipid packaging of stratum corneum, thus chemically modify the barrier functions leading to increased permeability.
- Solvates: Increase permeations by swelling the polar pathway and/or fluidizing lipids. For example: Water, ethanol, methanol, propylene glycol, pyrrolidone, isopropyl myristate, and azone
- Surfactants: Enhance the polar pathway transport for hydrophilic drugs. For example, SLS, dimethyl sulfoxide, sodium deoxycholate, etc. [36-38].

Backing laminates

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the other side of the transdermal patch, and accept printing. It is impermeable. Substance that protects the product during use on the skin, for example, metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate, adhesive foam pad with occlusive base plate, etc. [39-41].

Release liner

- Primary packing material for delivering drug.
- Protective liner that is remover and discharges immediately before the applying the patch to skin.
- As the liner is in intimate contact with the delivery system, it should be chemically inert, permeation to the drug, and penetration enhancers and water.
- It is composed of a base layer which may be non-occlusive (paper fabric) or occlusive (polyethylene and PVC) and release coating layer made up of silicon or Teflon.
- For example: Polyester foils and metalized laminates [42].

Other excipients such as plasticizers and solvents

- Various solvents: Chloroform, methanol, acetone, isopropanol, and dichloromethane are used to prepare drug reservoir.
- Plasticizers: Dibutyl phthalate, triethyl citrate, PEG, and Propylene glycol added to provide plasticity to TD patches [43].

EVALUATION OF TRANSDERMAL PATCHES

Transdermal patches were developed to improve the efficacy of the drug and to enhance the patient comfort by delivering the small amount of the drug only at predetermined rate. Evaluation tests should be done to know the performance, stability, shelf life, and reproducibility of the drug, under environmental conditions. The following are the some of the classes of evaluation studies carried out for evaluating the transdermal patches:

1. Physicochemical evaluation
2. *In vitro* evaluation
3. *In vivo* evaluation

Physicochemical evaluation

Physicochemical evaluation is done by considering the following parameters [44-46]:

- Thickness
- Uniformity of weight
- Drug content determination
- Drug content uniformity test
- Moisture content
- Moisture uptake
- Flatness
- Folding endurance
- Swelling index

Thickness

The thickness of the transdermal patches was measured by the microscope, screw gauge, and dial gauge at different points of the film.

Uniformity of weight

It is also called weight variation. It can be studied individually by weighing 10 randomly selected patches. Then, the average weight of the patches was taken. The individual weight should not deviate from the average weight.

Drug content determination

Accurately weigh the film and dissolve it in the 100 mL of suitable solvent in which the drug is soluble. Then, this solution is shaken continuously for 24 h in the shaker incubator. Then, this solution can solicit. After the fornication and filtration, the drug in the solution is estimated by the spectroscopy by making appropriate dilutions.

Drug content uniformity test

Ten patches were selected randomly, and the content is determined for patches individually. The results should be like this, out of these 10 patches, 9 should be in the range between 85% and 115% of the specified value and remaining 1 patch should be in the range of 75–125%, then, it is considered as the patches have passed the test. If three patches have the content in the range of 75–125%, then other 20 patches should be taken and those should be present in the range of 85–125% to pass the test.

Moisture content

Prepared films were taken and then weigh them individually and then keep them in the desiccator which is containing calcium chloride. After completion of 24 h at the room temperature, all the films should again weigh. Using the formula given in Eq. 1, the percentage moisture content is determined.

$$\% \text{ Moisture content} = \left[\frac{\text{Initial weight-Final weight}}{\text{Final weight}}\right] \times 100 \quad (1)$$

Moisture uptake

Weigh the films first and then these films were kept in the desiccator at the room temperature for 24 h. The relative humidity of 84% is exposed to those patches using the saturated solution of potassium chloride in the desiccator until the constant weight is achieved. The moisture uptake is determined by the formula given in Eq. 2.

$$\% \text{ Moisture uptake} = \left[\frac{\text{Final weight-Initial weight}}{\text{Initial weight}}\right] \times 100 \quad (2)$$

Flatness

The transdermal patch should be smooth and should not be constricted with the time. Hence, this study was performed. For the determination of the flatness, one patch is cut down from the center and the two from each side of the patch. The length can be determined by the percent constriction given in Eq. 3. About 0% constriction is equivalent to 1005 flatness.

$$\% \text{ Constriction} = \left[\frac{I1\text{-}I2}{I2}\right] \times 100 \quad (3)$$

Where: I1 = Initial length of the strip and I2 = Final length of the strip.

Folding endurance

Evaluation of folding endurance involves determining folding capacity of films after that subject them to the extreme conditions of folding. Folding endurance can be determined by repeatedly folding the film at the same place without breaking. That is the folding endurance value of that patch.

***In vitro* release studies**

The amount of drug available for the absorption into the blood is depends on the release of the drug from the polymeric transdermal film. The drug that reaches the surface of the skin is passed to usual permeation studies, which were performed by attaching the transdermal patch to the rat skin or to the synthetic membrane which is present in between the receptor and donor in vertical diffusion cells. The transdermal system is applied to hydrophilic side of the membrane and the lipophilic side is in contact with the receptor fluid. The receiver compartment is maintained at specific temperature usually 32°C and stirred continuously. The samples were withdrawn at equal time intervals and an equal amount of buffer is replaced at each time. The samples were diluted, and the absorbance is determined using UV spectrophotometer. The amount of the drug permeated per square centimeter at each interval is calculated. Drug release is depending on design of the system, patch size, surface area of the skin, thickness of the skin and temperature, etc. [47,48].

***In vivo* studies**

In these evaluation studies, the drug performance can be depicted truly. In this study, the TDDS can be carried out using.

- Animal models.
- Human volunteers or human models.

Table 1: Marketed products of transdermal patches

S. No.	Product	Active drug	Type of patch	Purpose
1.	Estraderm	Estradiol	Membrane	Postmenstrual syndrome
2.	Alora [12]	Estradiol	Membrane	Postmenstrual syndrome
3.	Duragesic [11]	Fentanyl	Reservoir	Pain relief patch
4.	Matrifen [12]	Fentanyl	Reservoir	Pain relief patch
5.	Transderm Scop [11]	Scopolamine	Matrix	Motion sickness
6.	Deponit [11]	Nitroglycerine	Drug in adhesive	Angina pectoris
7.	Lidoderm [11]	Lidocaine	Drug in adhesive	Anesthetic
8.	Testoderm TTS [11]	Testosterone	Reservoir	Hypogonadism in males
9.	Fematrix [11]	Estrogen	Matrix	Postmenstrual syndrome
10.	Nitro-Dur [11]	Nitroglycerine	Matrix	Angina pectoris
11.	Nitrodisc [12]	Nitroglycerine	Matrix	Angina pectoris
12.	Minitran [13]	Nitroglycerine	Matrix	Angina pectoris
13.	Nitro-Dur [13]	Nitroglycerine	Matrix	Angina pectoris

Animal models

Animal studies can be preferred mainly by the time and the resources which were required to carry out the human studies. Most common animal species used for the evaluating the transdermal patches on mouse. Hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig, etc., various experiments conducted on these animals lead us to the conclusion that the conclusions the hair less animals were preferred over the hairy animals in both *in vivo* and *in vitro* experiments. The most reliable model for performing this experiment is rhesus monkey.

Table 2: Examples of marketed transdermal drug delivery system

S. No.	Therapeutic ingredient	TDDS	Design [65]
1.	Clonidine	Catapres-TTS (Boehringer Ingelheim)	Four-layer patch
2.	Estradiol	Estraderm (Novartis)	Four-layer patch
3.	Estradiol	Vivelle (Novartis)	Three-layer system
4.	Estradiol	Climara (Novartis)	Three-layer system
5.	Fentanyl	Duragesic (Janssen)	Four-layer patch
6.	Nicotine	Prosstep (Lederie)	Multilayer round patch
7.	Testosterone	Testoderm (Alza)	Three-layer system
8.	Nicotine	Habitrol (Novartis Consumer)	Multilayer round patch
9.	Nicotine	Nicoderm CQ (Smithkline Beecham Consumer)	Multilayer rectangular patch
10.	Nicotine	Nicotrol (McNeil Consumer)	Multilayer rectangular patch

Table 3: Research works on transdermal drug delivery systems

S. No.	Name of the drug	Method	Uses
1.	Topiramate [51]	Solvent casting technique	Epilepsy, Migraine
2.	Simvastatin [52]	Solvent casting technique	Hypercholesterolemia
3.	Repaglinide [53]	Solvent casting technique	Diabetes mellitus
4.	Isosorbide dinitrate [54]	Solvent casting technique	Angina pectoris
5.	Metoprolol succinate [55]	Solvent casting technique	Heart failure
6.	Glipizide [56]	Solvent evaporation technique	Diabetes mellitus
7.	Carvedilol [57]	Solvent evaporation technique	Hypertension
8.	Propranolol [58]	Solvent evaporation technique	Hypertension
9.	Ketoprofen [59]	Solvent evaporation technique	Osteoarthritis
10.	Celecoxib [60]	Solvent evaporation technique	Rheumatoid arthritis
11.	Carvedilol Phosphate [61]	Solvent casting method	Antihypertensive
12.	Ibuprofen [62]	Gel preparation	NSAID
13.	Glipizide [63]	Membrane moderated TDS	Antidiabetic
14	Diclofenac Diethylamine [38]	Solvent evaporation method	Anti-inflammatory
15.	Doxophylline [64]	Solvent evaporation method	Antiasthmatic

Human models

It is the final stage for the development of the transdermal device involving the collection of the pharmacokinetic and pharmacodynamic data from the human volunteers by the application of the patch. The clinical trials were conducted by various parameters such as efficacy, risk involved, side effects, and patient compliance. Phase 1 clinical trials are conducted to determine the safety of the volunteers and the Phase 2 clinical trials were mainly to determine the short-term safety and the effectiveness in the patient. Phase 3 trails indicate the safety and effectiveness in the large number of patients. Phase 4 trials at the post marketing surveillance are done for the marketed patches to detect the adverse drug reactions. These are the best to assess the performance of the drug [49,50].

Few of the marketed products of transdermal patch in different forms with purposes and designs were given in Tables 1 and 2. The recent research works carried out on transdermal patches were given in Table 3.

Few examples for improved drug delivery over other routes such as insulin delivery [66], improve penetration [67,68], improve bioavailability when compared with oral route of administration [69].

CONCLUSION

Improvement in the TDDS is a successful story of the pharmaceutical endeavor. Several transdermal patches are present in the market, which were a valid proof that the transdermal systems were feasible, safe, and effective with maximum patient compliance. Transdermal drug delivery of tacrine was developed mainly to overcome first-pass metabolism and to reduce the frequency when compared to oral route of administration. Oral route of administration is having many disadvantages like less bioavailability, high dose is needed or frequent dosing, which may be cost prohibitive and also not convenient to some patients. Using Eudragit polymer, transdermal patches can be prepared by solvent casting method. In general, matrix type of transdermal patches was manufactured using polymers. All these transdermal patches were evaluated for various parameters such as physical appearance, thickness, weight variation, drug content, moisture uptake, moisture content, and swelling studies.

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