Panacea Journal of Pharmacy and Pharmaceutical Sciences 2023:12(2), 54-68
International Journal

Panacea Journal of Pharmacy and Pharmaceutical Sciences
ISSN: 2349 7025

PJPPS
Panacea Research Library
http://internationaljournal.org.in/journal/index.php/pjpps

Review Article **Volume 12 Issue 2** **April-June 2023**

CURRENT REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM

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Abstract

Transdermal drug delivery systems (TDDS) have gained significant attention as a non-invasive method for administering pharmaceuticals through the skin, offering advantages over traditional oral and injectable routes. This review provides a comprehensive overview of current advancements in TDDS, focusing on the technology, formulations, and applications. TDDS facilitate controlled and sustained release of drugs, enhance patient compliance, and improve therapeutic efficacy by bypassing the gastrointestinal tract and first-pass metabolism. Key technologies discussed include adhesive patches, microneedle systems, and iontophoresis. The review also addresses challenges such as skin permeability, drug selection, and formulation stability. Emerging innovations in TDDS, such as smart patches and nano-based carriers, are explored for their potential to further enhance drug delivery efficiency and patient outcomes. Overall, TDDS represents a promising approach for modern drug delivery, with ongoing research aimed at overcoming existing limitations and expanding its clinical applications.

Keywords: Transdermal drug delivery systems, adhesive patches, microneedles, iontophoresis, drug permeability, smart patches, nano-based carriers.

Introduction

Drugs administered in the conventional dosage forms usually produce large range in fluctuations in plasma drug concentrations leading to undesirable toxicity or poor effectiveness. These factors as well as other factors such as repetitive dosing and unpredictable absorption, led to the concept of the controlled drug delivery system or therapeutic system. A dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ is a controlled drug delivery system. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent

dosing. Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation[1, 2].

The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene[3].

1. Anatomy and Physiology of Skin

Human skin consists of three distinct layers

- Epidermis
- Dermis
- Hypodermis

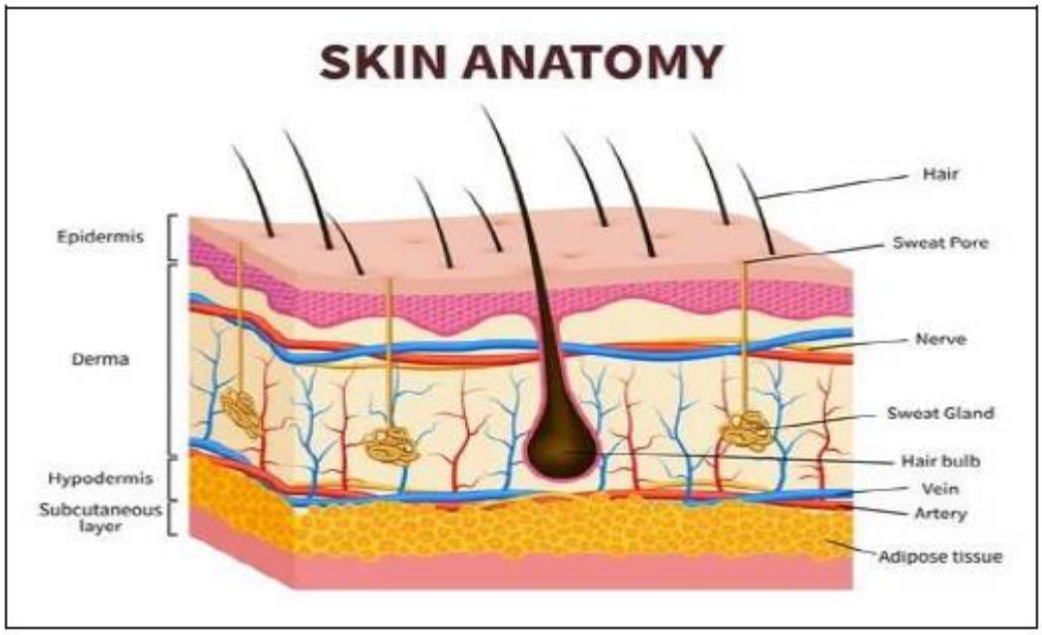

Figure 1: Skin Anatomy and Physiology.

The human body's outer layer of skin spans an estimated area of around 2 square meters. It plays a vital role in our overall health as it receives approximately one-third of the total circulating blood in the body. In simpler terms, our skin serves as a large canvas that interacts with a significant portion of our blood supply, facilitating important functions and maintaining the well-being of our body as a whole.[4]

1.1. Epidermis

It is the peripheral hard and thin surface of the skin, as shown in Figure No.1. Mainly, the cells present in the epidermis are Keratinocytes; these cells form cells in the inner layer of skin, known as basal layer. It is a barrier like– structure, and they are composed of dead cells, which are the outermost part of the epidermis. This layer acts as obstacle;

many drugs are not able to penetrated through the stratum corneumbut lipotropic drugs can easily penetrate as compared to hydrophilic drugs.[5]

1.2. Dermis

Dermis is 3 - 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerve tissue. The cutaneous blood supply plays a vital role in the regulation of body temperature. Additionally, it also provides nutrients and oxygen to the skin, eliminating toxins and waste products. The capillaries reach up to0.2mm of skin surface and provide sink conditions for most of the molecules penetrating through the skin barrier. The blood providation thus keeps the dermal concentration of a permeant very low, and the resulting concentration difference across the epidermis provides the essential concentration gradient for transdermal permeation. [6]

1.3. Hypodermis

The hypodermisor subcutaneous fat tissue holds up the dermis and epidermis. It is described as a fat storage area. This layer helps to regulate temperature, provides nutritional support, and spontaneous protection. It carries the principal blood vessels and nerves to the skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrateall the three layers and arriving in systemic circulation.[6]

2. Drug Permeation Pathway through the Skin [7]

Transdermal absorption involves the passive diffusion of drug material through the skin. Amoleculemay use two distinct diffusionalroutesto successfully penetrate normal, intact skin.

2.1. Appendagial route

2.2. Epidermal route –a) Trans-cellular b) Para-cellular

2.1. Appendagial route: The appendagial route comprises transport via sweat glands and hair follicles with their associated sebaceous glands. These routes found a way to penetrate through the stratum corneum and are thus known as “shunt” routes. This route is considered tobe of minor significance because of its fairly small area, roughly0.1 of the total skin area.

2.2. Epidermal route

a) Trans-cellular: Pathway means transport of drug molecules across the epithelial cellularmembrane. These include unresisting transport of small molecules, active transport of ionic and polarcompounds, and endocytosis and trans-cytosis of macromolecules.

b) Para-cellular: The para-cellular pathway means the transport of molecules around or between the cells. Tight junctions or analogous situations live between the cells. The top pathway taken by a permeant is determined substantially by the

partitioncoefficient. Hydrophilic drugs tend to primarily enter the intracellular regions, while lipophilic drugs cross the stratum corneum via the intercellular pathway.

3. Advantages of TDDS

1. To prevent first-pass metabolism, transdermal delivery ensures a sustained and continuous permeation of a substance over an extended period. [8]

2. Increase Patient compliance.

3. It does not interfere the liquid of the stomach and intestines. [9]

4. Sustains stable and constant blood levels, providing control over an extended period.[10, 11]

5. Reduced plasma concentration levels of drugs.

6. Reduce fluctuations of drug in plasma levels, Utilize drug candidates with short half-life and Low therapeutic index. [12]

7. In case of toxicity drug delivery is easy eliminated.

8. Reduce of dosing frequency an enhance Patients compliance. [13]

9.Transdermal delivery enhances the effectiveness of numerous drugs by circumventing certain issues related to the medication, such as poor absorption and gastrointestinal irritation.

10. The streamlined medication schedule results in decreased differences in drug response both within and among patients.

4. Disadvantages of TDDS

1. The drug must possess favorable physicochemical properties to permeate through the stratum corneum.

2. For daily dosages, the drug quantity should not exceed 5mg/day; if it surpasses 10-25 mg/day, transdermal drug delivery becomes challenging.

3. The patch constituents, including the drug, adhesive, and other additives, can potentially cause local irritation.

4. There should be a clear clinical requirement established for utilizing the transdermal delivery system.

5. High drug levels in Blood/ plasma could not be achieved. [14]

6. Large molecular size of drugs cannot be formulated.

7. Possibility of inflammation on the site of application. [15]

8. Not comfortable to wear.

9. May not be economical.

10. The skin barrier varies among individuals and can even change within the same person over time. [16]

5. Types of transdermal patches: [17, 18]

a) Single layer drug in adhesive:

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi -layer drug in adhesive: This type is also similar to the single layer but it contains a immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

c) Vapour patch: In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) Reservoir system: In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

e) Matrix system:

i. Drug-in-adhesive system: In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. Matrix-dispersion system: In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

f) Microreservoir system: In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

6. Various methods for preparation TDDS:

a. Asymmetric TPX membrane method: [19]

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive.

[(Asymmetric TPX membrane preparation): These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°c to form a polymer solution.

The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs].

b. Circular teflon mould method: [20]

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butylphthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

c. Mercury substrate method: [21]

In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10- 15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

d. By using "IPM membranes" method:[22]

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

e. By using "EVAC membranes" method: [23]

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes.

If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

f. Aluminium backed adhesive film method: [24]

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one.

For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

g. Preparation of TDDS by using Proliposomes: [25, 26]

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

h. By using free film method: [27]

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored

between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

7. Limitations of TDDS

- Limited skin permeability
- Restricted to potent drugs
- Not suitable for large molecules i.e., above 500 Daltons
- Adhesion of the patch to the skin
- Drug may undergo degradation in the skin
- Drugs that are highly melting cannot be given by this route due to their low solubility both in water and fat
- This system cannot deliver ionic drugs.

8. Evaluation:

8.1 Drug excipients interaction:

- Differential scanning calorimetry&Fourier-transform infrared spectroscopy were used for studying drug excipient compatibility. [28]

- **Thickness:**

The thickness uniformity was measured at different site by using Vernier calliper and the average values and standard deviation were determined. [29]

- **Folding endurance:**

The folding endurance was performed manually on the strip of patch (4 x 2 cm) reputedly folding at same place until it breaks. Folding endurance is defined as number of times of the film folding at same place until it breaks or cracks. [30]

- **Weight variation:**

Films are weighed individually and also the average weight is measured. The difference between individual and average weight gives weight variation. [31]

- **Drug content:**

Patch (1 X 1 cm^2) from different formulations were cut and dissolved in solvent and allowed for continuous stirring up to 24 h using magnetic stirrer. The solution was filtered and diluted further with solvent and percent drug content was measured. [32]

- **Percentage moisture absorption:**

The films are weighed before keeping into desiccator. Then the weighed films should be subjected to desiccator at room temperature (24 h) containing saturated solution of potassium chloride to maintain 84 % RH. After 24 h films are reweighed and percent moisture uptake is determined by following formula. [33]

$$\% \text{ Moisture Uptake} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{initial weight}} \times 100$$

- **Percentage moisture content/loss:**

The films are weighed individually and subjected to desiccator with fused Calcium chloride or activated silica at room temperature for 24 h. After 24 h films are reweighed and determine percentage moisture content/loss by following formula.[34]

$$\% \text{ Moisture Loss} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Final weight}} \times 100$$

- **Swelling index:**

Pre-weighed films are totally deep in 50 ml beaker having 25 ml phosphate buffer pH 7.4 maintain 25° using water bath. Then at specified interval of time the swollen films are reweighed after removal of excess water by light blotting with filter paper. The swelling index is calculated by following formula. [35]

$$\text{Swelling index} = \frac{(\text{Weight after time intervals} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

- **Flatness:**

Longitudinal strips are cut out from right, left and middle of the prepared patch and length of each strip was measured and variation in length due to flatness also measured, by determining percent constriction. Zero percent constriction consider as hundred percent flatness. [36]

- **Tensile strength:**

Three strips are cut off from prepared patch (2 X 1 cm^2). Pulley system is used for the measurement. Weights in pan were gradually added until patch was broken. The distance travelled by pointer before brake of patch was noted with the help of magnifying glass on the graph paper. Tensile strength was measured in Kg/cm^2. [37]

- **In vitro permeation study:**

In vitro permeation study can be carried out by using Franz diffusion cell with the help of diffusion membrane e.g. artificial diffusion membrane, egg shell membrane, skin of dorsal region of Swiss albino mice, pork ear skin etc. in phosphate buffer solution pH 7.4 with continuous shaken using magnetic stirrer. The phosphate buffer used was isotonic solution and resembles pH 7.4 as same body fluid. [29, 38]

- **In vivo study:**

In vivo evaluation of formulation is carried out in animal model e.g. Sprague-Dawley rat, human cadaver skin etc. The abdominal hairs of animals were removed with the help of electric clipper or hair removing cream and skin is observed for any damage. The patch

was applied over shaved skin and fixes using adhesives tapes. Then blood samples were collected at predetermined time interval and subjected to UV or HPLC analysis. [39]

- **Irritancy test:**

The skin irritancy test was performed on animals like rats. The aqueous solution of formalin was used as standard irritant. After 24 h patch was removed and examine for development of edema or erythema (Table 1). [39]

Table 1: Standard Irritancy Values

(A) Erythema and Eschar formation	Standard score	(B)Edema formation	Standard score
Very slight erythema	1	Very slight edema	1
Well defined erythema	2	Slight edema	2
Moderate to severe erythema	3	Moderate edema	3
Severe erythema	4	Severe edema	4

Stability test:

The stability of prepared patch is studied according to ICH guideline for 6 months. The conditions are maintained 40 ± 2° temp and 75 ±5% RH using stability chamber.[40]

9. Applications of TDDS:

- The highest selling transdermal patch in the United States of America is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007.

- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form, fentanyl CII (marketed as Duragesic) and buprenorphine CIII (marketed as BuTrans).

- Hormonal patches:
    - Oestrogen patches are sometimes prescribed to treat menopausal symptoms (as well as postmenopausal osteoporosis) and to transgender women as a type of hormone replacement therapy.
    - Contraceptive patches (marketed as Ortho Evra or Evra)
    - Testosterone CIII patches for both men (Androderm) and women (Intrinsa).

- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.

- Transdermal scopolamine is commonly used as a treatment for motion sickness.
- The anti-hypertensive drug clonidine is available in transdermal patch form.
- Emsam, a transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant approved for use in the U.S. in March 2006.
- Daytrana, the first methylphenidate transdermal delivery system for the treatment of attention deficit hyperactivity disorder (ADHD), was approved by the FDA in April 2006.[41]
- Secuado, a transdermal form of the atypical antipsychotic asenapine, was approved by the FDA in October 2019.[42]
- Vitamin B12 may also be administered through a transdermal patch. Cyanocobalamin, a highly stable form of vitamin B12, is compatible with transdermal patching. [43]
- 5-Hydroxytryptophan (5-HTP) can also be administered through a transdermal patch, which was launched in the United Kingdom in early 2014. [44]
- Rivastigmine, an Alzheimer's treatment medication, was released in patch form in 2007 under the brand name Exelon.[45]
- In December 2019, Robert S. Langer and his team developed and patented a technique whereby transdermal patches could be used to label people with invisible ink in order to store medical information subcutaneously. This was presented as a boon to "developing nations" where lack of infrastructure means an absence of medical records. The technology uses a "quantum dot dye that is delivered along with a vaccine". [46]
- Caffeine patches, designed to deliver caffeine to the body through the skin. [47]

10. Future of transdermal drug delivery system:

Liposomes, niosomes, and micro emulsion are a few of the innovative formulation techniques and approaches of the future. The purpose of this method is to enhance the delivery of drugs with limited intrinsic solubility in the majority of excipients used in traditional formulations. Steroids, antifungal, antibacterial, interferon, methotrexate, and local anaesthetics are only a few examples of the many potential medications that could be delivered. Transdermal device sales are expected to grow in the future and have lately grown at a pace of 25% annually.Future technological advancements and an expanding list of transdermal drugs will result in an increase in this number.[48] As there are more advancements in design, transdermal distribution of analgesics is probably going to gain prominence. Research is being done to improve effectiveness and safety. To enable more precise medication distribution with an extended duration of action, as well as to improve practical aspects like the patch wearer's experience.[49] Improved transdermal technology that uses precise medication delivery and has a longer duration of action is another possible improvement. Improved transdermal technology, which either modifies the skin barrier or boosts the energy of the drug molecules, can increase drug flux across the skin by using mechanical energy. Following the development of

iontophoresis-based patches, multiple 'active' transdermal technology modes are being researched for various medications.These include sonophoresis (which uses low-frequency ultrasonic energy to disrupt the stratum corneum), thermal energy (which uses heat to make the skin more permeable), and electroporation (which uses brief, high-voltage electrical pulses to temporarily create aqueous pores in the skin). The use of magnetic energy, or magnetophoresis, to boost medication flux over the skin has been studied. An underutilised method for managing both acute and chronic pain may be the transdermal patch. We anticipate that this method of drug delivery will become more widespread and applicable with enhanced delivery and a wider selection of analgesics. With about 40% of the drug delivery candidate products currently in clinical trials related to transdermal or dermal system, transdermal route of drug delivery system is currently the most successful innovative research area in new drug delivery system when compared to oral treatment.[50]

Conclusion

Transdermal drug delivery systems (TDDS) offer significant advantages, including controlled release, improved patient compliance, and avoidance of gastrointestinal issues. Recent advancements, such as microneedles and smart patches, enhance drug delivery efficiency and expand therapeutic options. However, challenges like skin permeability and formulation stability persist. Ongoing research aims to address these issues and further improve TDDS, making it a promising approach for future drug administration.

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