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THE EVOLUTION AND RECENT TRENDS OF TRANSDERMAL DRUG DELIVERY SYSTEM - A REVIEW

Chaitanya Gajanan Narwade[1]*, Shivani Subhash Pangarekar[2] and Tejeswini Vikramsingh Deshmukh[3]

[1,2]PG Student, SVPM's College of Pharmacy Malegaon Bk. Baramati Pune, Maharashtra India.

[3]Professor, SVPM's College of Pharmacy Malegaon Bk. Baramati Pune, Maharashtra India.

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***Corresponding Author**
Chaitanya Gajanan Narwade
PG Student, SVPM's College of Pharmacy Malegaon Bk. Baramati Pune, Maharashtra India.

ABSTRACT

To get around the challenges of oral medicine delivery, the transdermal drug delivery method was developed. A transdermal patch is an adhesive pharmaceutical patch applied to the skin that allows a prescribed dosage to enter the bloodstream through the skin. This frequently aids in the recovery of a damaged bodily part. The patch offers a controlled release of the medication into the patient, typically through a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. This is an advantage of a transdermal drug delivery route over other medication delivery methods like oral, topical, intravenous, intramuscular, etc. Some possible benefits of transdermal medication delivery include controlled absorption, more consistent plasma levels, enhanced bioavailability, fewer adverse effects, painless and easy application, and the ability to stop drug administration by simply removing the patch from the skin. Transdermal drug delivery (TDDS) is a promising technology that can reduce the need for needles for drug administration. However, the high cost of TDDS makes it a hidden part of therapy in developing nations such as India, where the population is the second highest.

KEYWORD: Transdermal, topical drug delivery, physicochemical evaluation, in vitro and in vivo drug release studies, Stability.

1) INTRODUCTION

A group of physicochemical technologies that may regulate the transport and release of pharmacologically active chemicals into cells, tissues, and organs such that these active substances can have the best possible effects are collectively referred to as drug delivery systems (DDS).[1,2] To put it another way, DDS addresses the drug formulations and modes of administration that effectively deliver the medication to optimize therapeutic efficacy and minimize adverse effects.[3–4] There are numerous administration methods, including intravenous injection, lung inhalation, mucosal administration, transdermal administration, and oral administration, depending on the delivery method. The transdermal drug delivery system (TDDS) is one of the more appealing of these.

TDDS has a major impact on the delivery of a number of therapeutic drugs, particularly in the areas of hormone therapy, pain management, and the treatment of disorders affecting the central nervous system and cardiovascular system.[5–6] Drugs can be administered without interference from pH, enzymes, or intestinal microbes since TDDS does not require transit via the gastrointestinal system, negating loss from first-pass metabolism. Its great persistence can also be attributed to the fact that TDDS can be utilized to regulate medication release in accordance with usage constraints. Most significantly, children and the elderly can get medications safely and conveniently thanks to TDDS, a noninvasive administration technique that causes little discomfort or strain on the patient.[7–8]

Numerous innovative TDDS procedures have been thoroughly designed to address this issue and have become appealing management strategies. Furthermore, in terms of the delivered dose, cost-effectiveness, and therapeutic efficacy, such development may offer a competitive edge over alternative drug delivery techniques.[9–10]

In 1979, the FDA authorized Transderm SCOP, the first transdermal device, to reduce travel-related nausea and vomiting. After being applied to the skin, the majority of transdermal patches are made to release the active component at a zero order rate for a few hours to days. This is particularly beneficial for preventative treatment of long-term illnesses.[11] Measurable drug levels in the blood, detectable drug and metabolite excretion in the urine, and the patient's clinical reaction to the prescribed medication therapy can all be used as indicators of percutaneous drug absorption.[12]

One of the methods that fall under the category of controlled drug delivery is the transdermal drug delivery system (TDDS), whose goal is to distribute the medication through the skin at a precise and regulated rate. TDDS are defined-surface area adhesive drug-containing devices that apply a fixed dosage of medication to undamaged skin at a pre-programmed rate in order to enter the bloodstream.[13,14]

The transdermal route has been compared to oral treatment as the most successful innovative research area in drug delivery. This is because oral treatment involves introducing a fixed dose at regular intervals to achieve and maintain the drug concentration in the body within a therapeutically effective range. As a result, the drug concentration in the body follows a peak and trough profile, increasing the risk of side effects or therapeutic failure; a significant amount of drug is lost in the vicinity of the target organ, and close monitoring of therapy is necessary to prevent overdosing. The drawbacks of the oral route can be addressed, and intravenous medication infusion offers advantages such as avoiding the hepatic "first pass" hepatic elimination (HEPE) to keep levels steady.[15–16]

Transdermal Membrane

The outermost layer of the skin is called the stratum corneum, which is basically a multilamellar lipid milieu punctuated by protein-filled corneocytes that greatly increase membrane tortuosity and enhance membrane integrity. With the exception of highly lipophilic species that may experience issues at the interface between the stratum corneum and viable epidermis, where they must partition into a primarily aqueous environment, the stratum corneum’s lipophilic nature and inherent tortuosity guarantee that it almost always serves as the primary barrier to the entry of drug molecules into the organism.

Drugs can be applied as solutions or suspensions, and their formulations can be as simple as gels or ointments or as complicated as multilayer transdermal patches. In this review, we outline the theoretical underpinnings of transdermal release and demonstrate how drug release kinetics into this intricate biological membrane can be explained by comparatively straightforward membrane transport models based on the proper solution to Fick’s second law of diffusion.

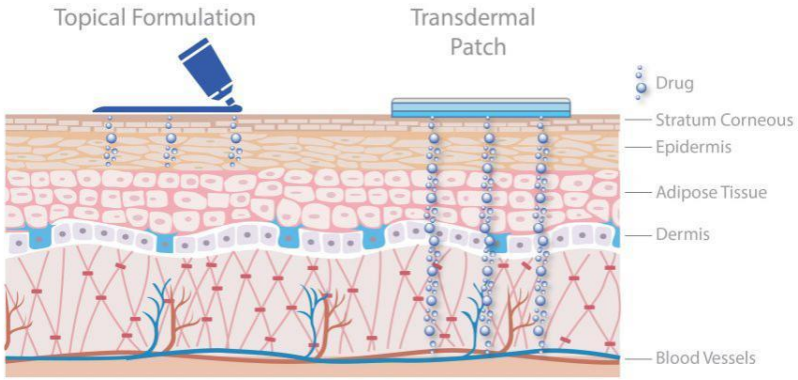

Fig. 1.

As a result, the perfect therapeutic candidate would be both hydrophilic enough to facilitate the second partitioning step into the viable epidermis and ultimately the systemic circulation, as well as lipophilic enough to partition into the SC. Transit across the SC is the rate-determining step for drug transport across the skin for the majority of medicines, with the exception of those with severe lipophilicity (log Ko/w>5). To achieve consistent input rates and lessen inter-individual variability, it is much preferable from the perspective of medication administration that rate control is housed within the delivery device. When a medicine is administered transdermally, a formulation or device (such a transdermal patch) keeps the drug's blood concentration within the therapeutic window, guaranteeing that it neither drops below nor rises over the minimum effective concentration.[17]

Anatomy of Skin

There are four primary layers that make up the anatomy of human skin : The epidermis, the viable epidermis, the stratum corneum, a non-viable epidermis, and the dermis that lies on top of it The hypodermis, the deepest layer of subcutaneous fat.[18]

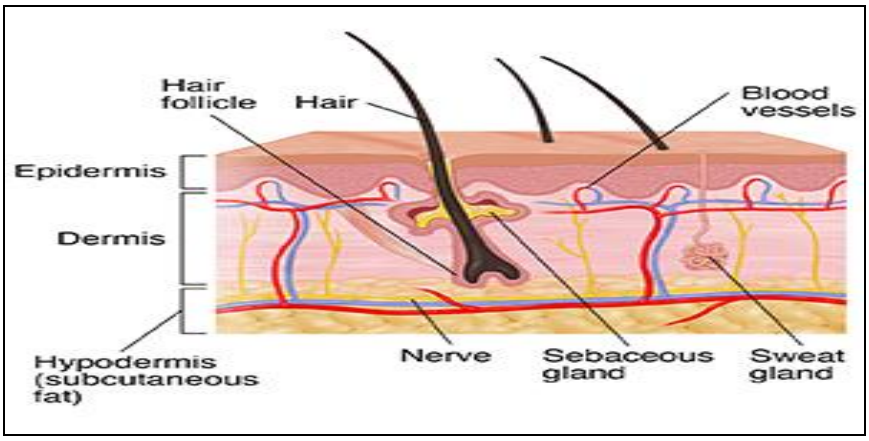

Fig. 2.

The epidermis

It is a continuously self-renewing, stratified squamous epithelium that covers the body's entire exterior. It is mainly made up of two components: the dead cells of the stratum corneum, also known as the horny layer, and the living or viable cells of the Malpighian layer, also known as the viable epidermis.[19] The viable epidermis is moreover classified into four distinct layers as shown in following Figure.[20]

- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum basale.

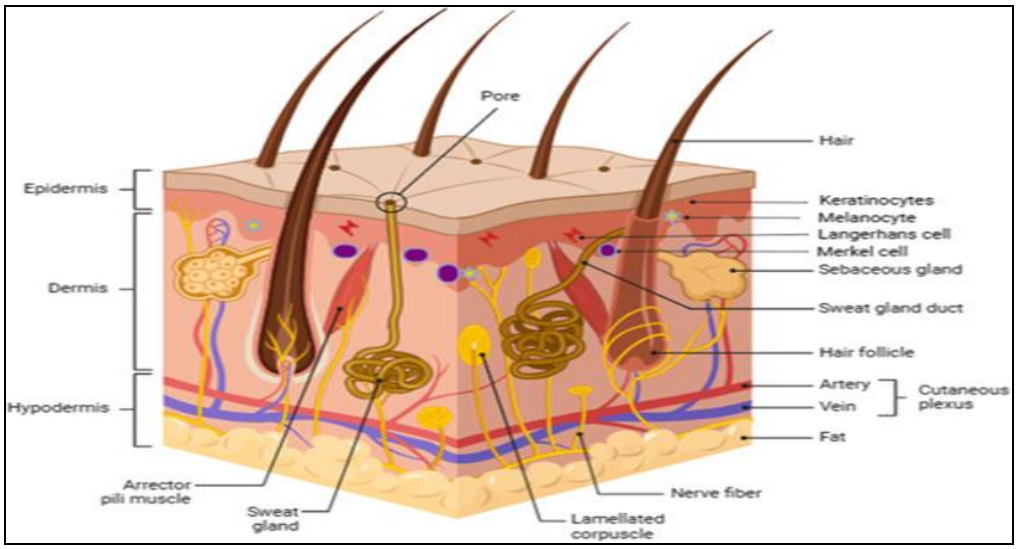

Fig. 3.

Stratum corneum

It is outermost layer of skin, often known as the horny layer, is called the stratum corneum. It is the rate-limiting barrier that prevents chemicals from moving both inward and outside. The components of the horny layer—75–80% proteins, 5–15% lipids, and 5–10% ondansetron material on a dry weight basis—are crucial to its barrier properties. When completely hydrated, the stratum corneum swells several times its dry thickness of about 10 mm. Despite its flexibility, it is not very porous. Protein bricks and lipid mortar can be used to model the horny layer's (figure 3) design as a wall-like structure. It is made up of corneocytes, or horny skin cells, which are joined by desmosomes, which are protein-rich cell membrane extensions.[21]

Viable epidermis

The stratum corneum is covered by the viable epidermis, which ranges in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. It is made up of several layers that run inward, including the stratum lucidum, stratum granulosum, stratum spinosum, and the stratum basale. The epidermis is continuously renewed at the basal layer by cell mitosis, which also makes up for the loss of dead horny cells from the skin's surface. The cells generated by the basale layer undergo morphological and histochemical changes as they proliferate, passing through keratinization to create the stratum corneum's outermost layer.[22]

Dermis

The layer of skin immediately beneath the epidermis is called the dermis. It is 3 to 5 mm thick and is made up of a matrix of connective tissues that includes nerves, lymph vessels, and blood vessels. One vital role of the cutaneous blood supply is to regulate body temperature. Along with eliminating waste and impurities, it also gives the skin oxygen and nourishment. The majority of molecules that penetrate the skin barrier find sink conditions in capillaries, which extend to within 0.2 mm of the skin’s surface. Thus, the blood supply maintains a very low dermal concentration of permeate, and the crucial driving factor for transdermal permeation is the concentration differential that results across the epidermis.[23]

Hypodermis

The dermis and epidermis are supported by the hypodermis, or subcutaneous fat tissue. It acts as a place to store fat. This layer offers mechanical support, nutritional support, temperature regulation, and defense. It may include sensory pressure organs and transports the skin’s main blood vessels and nerves. The medicine must pass through all three layers and enter the systemic circulation in order to be delivered transdermally.[24]

Transdermal significance

The success rate is frequently determined by three key constraint characteristics: low therapeutic dose, high lipophilicity, and low molecular weight (500 Daltons). Another method of drug delivery that can greatly deliver larger molecules in powerful quantities is transdermal administration. This method helps to overcome the drawbacks of oral administration, such as poor bioavailability caused by first-pass metabolism and occasionally high blood levels. Transdermal administration of medications may improve both their safety and potency. The creation of transdermal patch delivery devices is one example of such progress.

To get over the challenges of the oral route, experts in transdermal drug technology are still looking for novel ways to deliver bigger molecules in therapeutic quantities in an efficient and painless manner. A transdermal drug delivery system is one in which the active elements of the medication are delivered by means of the skin.

Advantages of Transdermal Drug Delivery[25,26,27,28,29,30]

1. TDDS is a drug delivery method that circumvents extra restrictions imposed by other dosage forms by applying a device, typically referred to as a patch, to the skin's surface. This allows the medication to enter the systemic circulation through the skin at a predetermined concentration for therapeutic benefits.
2. It provides consistent medication penetration through the skin, achieving the therapeutic objective of a stable serum drug level. 3. For patients who have trouble taking medications orally, it can be utilized as a substitute for oral drug delivery systems.
3. For individuals who have trouble taking medications orally, it can be utilized as a substitute for oral drug delivery systems.
4. For patients who are nauseous or unconscious, it can be used as a substitute.
5. Drugs can be administered to patients with gastrointestinal issues via TDDS since there won't be any direct contact between drug and stomach.
6. It provides a consistent plasma level, just as intravenous infusion.
7. It is very convenient as application of drug is very easy.
8. It has a long-lasting effect.
9. Self-management is possible.
10. The first pass metabolism is eliminated.
11. It lessens drug interactions throughout the body.

Disadvantages of Transdermal Drug Delivery System[26,28,30]

1. A lot of hydrophilic medications either don't penetrate the skin at all or do so extremely slowly. This will impact the medication's therapeutic effectiveness.

2. Patches can cause a variety of issues, including erythema, edema, and itching.

3. The skin's barrier function might vary from person to person, as well as with age or between various parts of the same individual.

4. The area where the medication is administered may experience some degree of irritation.

5. An unprofitable drug delivery system.

6. It is only used for chronic diseases; it is not used for acute ones.

7. Ionic medications are incompatible with TDDS.
8. Dosage dumping could happen.
9. Both lipophilic and hydrophilic phase-affinity drugs are employed.
10. A high blood drug level cannot be

A shortlist of transdermal patch Polymers[31.32.33.34]

Natural Polymers

1. Chitosan
2. Sodium alginate
3. Pectin
4. Gelatin
5. Gum Arabic

Synthetic Polymers

1. Ethylene vinyl acetate (EVA)
2. Polyvinyl alcohol (PVA)
3. Polyvinylpyrrolidone (PVP)
4. Polyurethane
5. Silicone elastomers

Semi-Synthetic Polymers

1. Hydroxypropyl methylcellulose (HPMC)
2. Carboxymethyl cellulose (CMC)
3. Ethylcellulose (EC)
4. Cellulose acetate phthalate (CAP).

Elastomeric Polymers

1. Silicone rubber
2. Acrylic adhesives
3. Polyisobutylene (PIB)
4. Styrene-butadiene rubber (SBR).

TYPES OF TRANSDERMAL PATCHES[35,36,37]

Transdermal patches are classified into different types. They are of Single layer of transdermal patch

Adhesive single-layer medication In this form, the medicine is present in the sticky layer. The adhesive layer is in charge of delivering the medication onto the skin in addition to holding the several layers together. A backing and a temporary liner encircle the adhesive layer.

1. Multi -layer drug in adhesive
2. Vapour patch
3. Reservoir system
4. Matrix system

i. Drug-in-adhesive system

ii. Matrix-dispersion system

5. Microreservoir system.

VARIOUS METHODS FOR PREPARATION TDDS

a. Asymmetric TPX membrane method[38]

A heat-sealable polyester sheet (type 1009, 3m) with a concave of 1 cm in diameter can be utilized as the backing membrane to create a prototype patch. A TPX asymmetric membrane is placed over the drug sample after it has been distributed into the concave membrane and sealed with an adhesive.

b. Circular teflon mould method[39]

In an organic solvent, solutions with different ratios of polymers are employed. Half the amount of the same organic solvent is used to dissolve the calculated amount of medication. The remaining half of the organic solvent is used to dissolve enhancers at varying concentrations, which are then added. A plasticizer called di-N-butylphthalate is added to drug polymer solutions. After 12 hours of stirring, the entire mixture should be placed into a circular teflon mold. To regulate solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s, the molds must be set up on a level surface and covered with an inverted funnel. A 24-hour period is given for the solvent to evaporate.A 24-hour period is given for the solvent to evaporate. To remove aging effects, the dried films must be kept in a desiccator with silica gel for an additional 24 hours at 25±0.5°C prior to examination. Within a week of their preparation, the type films must be assessed.

c. Method of mercury substrate[40]

This approach involves dissolving the medication and plasticizer in a polymer solution. After agitating the aforementioned solution for ten to fifteen minutes to create a uniform dispersion,

it should be poured onto a flat mercury surface and covered with an inverted funnel to regulate solvent evaporation.

d. By using IPM membranes" method[41]

Using a magnetic stirrer, the medication is dissolved in a solution of water and propylene glycol that contains the carbomer 940 polymer and swirled for 12 hours. Triethanolamine is added to the dispersion to neutralize it and make it viscous. If the drug's solubility in aqueous solution is extremely low, solution gel can be generated using buffer pH 7.4. The IPM membrane will incorporate the gel that has been created.

e. By using EVAC membranes" method[42]

Polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes, and 1% carbopol reservoir gel can all be utilized as rate control membranes to produce the intended transdermal therapeutic system. Gel is made with propylene glycol if the medication is insoluble in water. Propylene glycol is used to dissolve the drug; carbopol resin is then added to the mixture and neutralized using a 5% w/w sodium hydroxide solution. The medication (in gel form) is applied to the designated region on a backing layer sheet. To create a leak-proof device, a rate-controlling membrane will be positioned over the gel and the edges will be heated to seal.

f. Aluminium backed adhesive film method[43]

If the loading dose for a transdermal drug delivery system is more than 10 mg, unstable matrices may result. The sticky film approach with an aluminum backing is appropriate. Since most medications and adhesives dissolve in chloroform, it is the solvent of choice for making the same. Adhesive substance is added to the drug solution and dissolved once the drug has been dissolved in chloroform. Aluminum foil is used to line a custom-made aluminum former, and closely fitted cork blocks are used to blank off the ends.

g. Preparation of TDDS by using Proliposomes[43,44]

The film deposition technique is used in the carrier approach to create the proliposomes. Lecithin and the previously mentioned reference medicine in a ratio of 0.1:2.0 can be utilized as an optimized one. In order to create the proliposomes, 5 mg of mannitol powder is placed in a 100 ml round-bottom flask that is maintained at 60 to 70°C. The flask is then rotated at 80 to 90 rpm, and the mannitol is vacuum-dried for 30 minutes. The water bath's temperature is regulated to 20 to 30°C after drying. A 0.5 ml aliquot of the organic solution is added to the

round-bottomed flask at 37°C after the drug and lecithin have been dissolved in an appropriate organic solvent mixture. Another 0.5 ml aliquot of the solution is to be added once the flask has completely dried. The flask containing the proliposomes is attached to a lyophilizer following the final loading, and the drug-loaded mannitol powders (proliposomes) are then left in a desiccator overnight before being sieved through 100 mesh. Before being characterized, the gathered powder is placed in a glass bottle and kept at the freeze temperature.

h. By using free film method[45]

Casting on the surface of mercury creates a free film of cellulose acetate. Chloroform should be used to create a 2% w/w polymer solution. A 40% w/w concentration of polymer weight is required for the incorporation of plasticizers. A glass ring set over the mercury surface in a glass petri dish was filled with five milliliters of the polymer solution. An inverted funnel is placed over the Petri dish to regulate the solvent's rate of evaporation. After the solvent has completely evaporated, the mercury surface is examined to observe the film creation. Before being used, the dried film will be separated and kept in a desiccator between the wax paper sheets.

EVALUATION OF TRANSDERMAL PATCH5

Transdermal patches, which provide a lesser dose of medication at a predefined rate, have been created to increase patient compliance and improve the drug's clinical efficacy. To guarantee their intended performance and reproducibility under the given environmental conditions, evaluation studies become even more crucial as a result. These studies can be divided into the following categories and are predictive of transdermal dosage forms:

- Physicochemical evaluation
- in vitro evaluation
- In vivo evaluation

1. Physicochemical evaluation

Thickness: The thickness of transdermal film is determined by traveling Microscope, dial gauge, screw gauge or micrometer at different Points of the film**.**[46]

Uniformity of weight: Weighing randomly chosen patches one at a time and figuring out the average weight allows us to study weight fluctuation. The average weight and the individual weight shouldn't differ all that much.[47.48]

Drug content determination: A precisely weighed piece of film, approximately mg_7, is dissolved in mL of an appropriate solvent in which the medication is soluble, and the solution is then continuously agitated for h in a shaker incubator. The entire solution is then subjected to sonication. The amount of medication in solution is determined spectrophotometrically by suitable dilution following sonication and subsequent filtration.[49.50]

Content uniformity test

Ten patches are chosen, and each patch's content is decided. Transdermal patches pass the content uniformity test if nine of ten have content that is between 85% and 115% of the prescribed value, and one has content that is at least 75% to 125% of the given value. However, 20 more patches are examined for drug content if three of them contain content between 75% and 125%. The transdermal patches pass the test if the range of these 20 patches is between 85% and 115%.[51]

Moisture content

Each produced film is weighed separately and stored for 24 h at room temperature in a desiccator filled with calcium chloride. After a predetermined amount of time, the films are weighed once more until their weight remains constant. The following formula is used to compute the percentage moisture content.[52]

Flatness

The surface of a transdermal patch should be smooth and should not tighten over time. This can be shown through the study of flatness. One strip is cut from the center to determine the flatness as well as two from each patch side. Each strip's length is measured, and the percentage of constriction is used to calculate the variance in length Percent. flatness is equal to 100 percent constriction.

% constriction = 100

12= Final length of each strip

11= initial length of each strip.[51]

Folding Endurance

Determining the folding capability of the films exposed to frequent, an intense folding condition is the first step in evaluating folding endurance. Folding the film repeatedly at the

same spot until it breaks is how folding endurance is measured. Folding endurance value is the number of times the films could be folded in the same spot without breaking.[53.54]

Tensile Strength

Corked linear iron plates are used to sandwich polymeric films independently in order to measure tensile strength. An iron screen keeps one end of the films stationary, while a freely moveable thread is attached to the other end via a pulley. The weights are gradually added to the pan that is fastened to the thread's hanging end. The elongation of the film is measured with a pointer on the thread. The weight is just enough to cause the film to shatter. The following formula can be used to determine the tensile strength. Tensile strength is equal to F/a.b (1+L/1) F is the force needed to break the film, an is its width, b is its thickness, L is its length, and l is its elongation at break.[47]

Thumb tack test

The force needed to separate the thumb from the adhesive is a tack measurement. ental factors such as temperature, humidity and light. Formulations are selected for stability on the basis of the *In-vitro* drug release profile. The optimized formulations will be subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) Q1A guidelines.[55]

Rolling ball test: In this test, the distance a stainless steel ball travels along an upward-facing adhesive is measured. The ball will move farther if the adhesive is less sticky.[53]

Stability

Physical Stability: stability of the patch during long-term storage in a variety of environmental settings (such as temperature and humidity) to prevent deterioration or performance loss.

Chemical stability: Maintaining the active ingredient's chemical stability over the product's shelf life is known as chemical stability.

Microbial Contamination: Assessing the patch's microbial growth to guarantee safety, especially for patches that need to be protected from microbial contamination or may have a longer shelf life.[53]

Environmental Factors

Moisture Content: Assessing the patch's water content is important since it might affect the stability of the patch and the release of the medication.

API Solubility in Patch Matrix: This refers to how easily the active ingredient dissolves in the matrix of the patch, guaranteeing steady release.[56]

Permeation and Penetration of the Skin

Permeation studies are used to assess the amount of medication absorbed via the skin. These investigations are typically conducted ex vivo using human or animal skin or in vitro with skin models.

Skin Irritation or Sensitization: Using clinical or laboratory testing (such as patch tests on human volunteers) to check for skin irritation or allergic responses.

In vivo studies The accurate representation of the drug's performance is provided by in vivo tests. In vivo investigations allow for a thorough exploration of the variables that are not possible to consider in vitro. The following methods can be used to evaluate TDDS in vivo

- **Animal models**
- **human volunteers**

Animal models: The most popular animal species used to test transdermal drug delivery systems are guinea pigs, mice, rats, dogs, rabbits, and hairless rhesus monkeys.

Human volunteers: After the patch is applied to human volunteers, pharmacokinetic and pharmacodynamic data are gathered as the last step in the development of a transdermal device. Clinical trials have been carried out to evaluate the effectiveness, associated risks, adverse effects, patient compliance, etc.[55.53.54]

Recent trends in TDDS

Transdermal patches are primarily used to market fentanyl and nitroglycerine, as shown in the pie diagram below.[57.58]

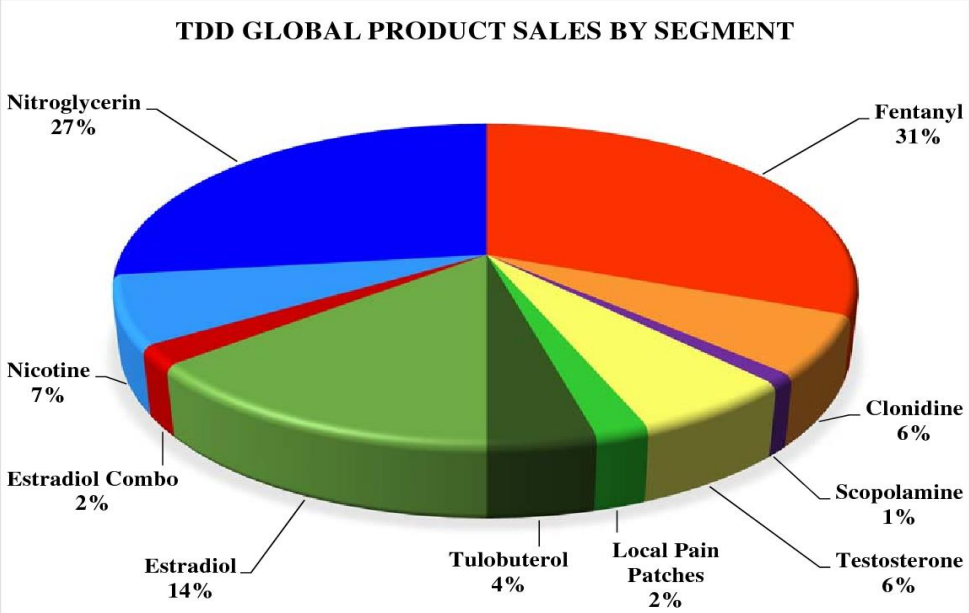

Fig. 4.

Adhesive technology is the main method for transdermal drug administration. Formulation research focuses on adhesives and excipients. Adhesive research aims to enhance skin adhesion, improve medicine stability and solubility, reduce lag time, and accelerate delivery. Customizing adhesive chemistry allows transdermal formulators to optimize patch performance, as a one-size-fits-all adhesive cannot support all drug and formulation chemistries.

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