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Transdermal Drug Delivery System: A Review of a New Drug Delivery System Approach

Manish singh Chouhan*[1],Dr. Hariom Sharma[1], Dr. Rishi Kumar[1]
Student*[1] ,Professor[1],Associate Professor[1]

School of Pharmacy ,Raffles University, Neemrana , Alwar, Rajasthan 301705

Corresponding author- Manish singh Chouhan , School of Pharmacy, Raffles University ,Neemrana Alwar Rajasthan

Mail Id- **manav3505@gmail.com**

Abstract

Transdermal patch is a transdermal delivery system that can overcome problems in conventional drug administration, such as oral drug administration. Patches can provide controlled drug release and have advantages over oral administration, such as avoiding first-pass metabolism, increasing drug bioavailability, avoiding adverse effects on the gastrointestinal (GI) tract, minimizing patient variability, maintaining a constant drug in plasma, and providing a stable therapeutic effect. The effectiveness of a patch is determined by the drug's ability to release from the patch matrix and penetrate the stratum corneum. The methods used to make the patches are divided into single layer, multi-layer, reservoir system, and matrix system patches. The basic components of a patch are polymer matrix, membrane, drug, permeation enhancer, pressure-sensitive adhesives, backing film, release liner, and plasticizer. Methods of review: This review refers to several previously published data regarding physical characteristics and transdermal drug release. This review also explains the patch as a transdermal drug delivery system. Conclusion: This review focuses on patch analysis methods after the manufacturing process, such as physical characteristics test, in vitro drug release test, in vitro skin permeation test, skin irritation test, and stability test, as well as some explanations related to transdermal drug delivery system.

Keywords

Patch, transdermal, characteristics, in vitro release, in vitro skin permeation.

1. Introduction

A transdermal drug delivery system (TDDS) is a method of topical drug delivery that can provide a controlled systemic effect(1) . TDDS has advantages over oral drug administration, such as increasing patient compliance, avoiding first-pass metabolism, sustaining drug delivery, minimizing patient variability, maintaining constant and prolonged drug administration in plasma and easily discontinuing drug administration if an allergic reaction or poisoning occurs(2) . This route can also avoid drugrelated side effects such as gastric irritation. In transdermal delivery, the drug must have a small molecular size, adequate solubility in the carrier, short half-life, low dose, and suitable lipophilicity(3) . One of the dosage forms in the transdermal drug delivery system is a patch(4) . However, the stratum corneum on the skin becomes a barrier to the transdermal patch; thus, only drugs with small molecules can easily penetrate the stratum corneum, but this can also be overcome by adding enhancers(5) . Therefore, patch effectiveness is determined by the ability of drugs to be released from the patch matrix and penetrate the stratum corneum. The drug particles must first be dissolved to form molecules that can diffuse through the matrix, and then the drug will penetrate through the skin(6) . The advantages of having a Transdermal Drug Delivery System (TDDS) include that, unlike the limited controlled release of the oral and intravenous routes, TDDS provides a stable infusion of the drug over a long period of time, suitable for drugs with short biological half-lives that require frequent dosing, leading to on improving patient compliance. In addition, therapeutic failure or side effects frequently associated with intermittent dosing for chronic disease can be avoided using this route(7) .

2. Patch

The transdermal patch is a transdermal carrier system that allows medications to be delivered directly into the bloodstream via the skin, allowing a specific amount of treatment to be delivered. Because the patch may manage the release of the medication, it can lessen systemic adverse effects and maximize the therapeutic efficacy of a treatment. This is one advantage of this route over other methods of drug administration, such as oral, intravenous, and intramuscular. The primary goal of the transdermal drug delivery system is to distribute the medicine into the systemic circulation via the skin at a predefined pace, with minimum variation across patients(8) .

2.1 Common materials used for making patches:

1. Polymer matrix/drug reservoir

The polymer in TDDS serves to control drug release from the patch. Therefore, the polymers used in TDDS must have good biocompatibility and chemical compatibility with drugs and other system components, such as penetration enhancers and PSA. Besides that, polymers must provide consistent and effective drug delivery(9) . Based on the source, polymers are divided into two, namely natural and synthetic polymers. The examples of polymers that are often used in transdermal preparations can be seen in the following table.

2. Membrane

The membrane controls drug release from the reservoir in a multilayer patch. The diffusion properties of the membrane are used to control the availability of drugs and/or excipients in the skin. For instance, ethylene vinyl acetate, silicone rubber, and polyurethane. These are used as a membrane to regulate drug release(9) .

3. Drugs

The success of TDDS development is also determined by the drug to be used. For example, transdermal patches offer many advantages for drugs that undergo extensive firstpass metabolism, drugs with a narrow therapeutic window or drugs with short half-lives, leading to no adherence due to frequent dosing(9) .

4. Permeation enhancer

Enhancers function to increase skin permeability to reach the desired therapeutic level. The ideal properties of enhancers are non-toxic, non-allergic, non-irritating, controlled and reversible enhancing action, pharmacological inertness, ability to act specifically for the predictable duration, chemical and physical compatibility with drugs and other pharmaceutical excipients, odourless and colourless (8) .

5. Pressure-sensitive adhesives (PSA)

PSA is a material that adheres to the substrate, in this case, is leather, with a light force application and leaves no residue when removed. PSA polymers widely used in TDDS are polyacrylate, polyacrylate, polyisobutylene, and silicon-based adhesives(8) .

6. Backing film

Backing films are selected for their appearance, flexibility, and the need for occlusion. Therefore, when designing a backing layer, it is of utmost importance to consider the material's chemical resistance. In addition, excipient compatibility should also be considered because prolonged contact between the backing layer and the excipient may cause the additives to detach from the backing layer or cause diffusion of the excipient, drug or enhancer penetration through the layer(8) . These materials include vinyl, polyethylene, polyester, aluminium, and polyolefin films(9) .

7. Other excipients such as plasticizers or solvents

(a) Solvents: chloroform, methanol, acetone, isopropanol, and dichloromethane are used to manufacture drug reservoirs(8) . (b) Plasticizers: dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol are also added to provide plasticity to the transdermal patch(8) .

3. Patch advantages and disadvantages

3.1 Advantages

1. It can avoid first-pass metabolism(13) .

2. The duration of action can be extended and predictable(13) .

3. In order to relieve the challenges of drug absorption in the gastrointestinal system, the use of TDDS is recommended(14) .

4. TDDS can replace oral medication if the route is unsuitable, such as in patients who experience vomiting and diarrhoea (14) .

5. Drug plasma concentration can be maintained(15) .

6. TDDS is non-invasive, so it can avoid parenteral therapy's inconvenience (14) .

7. It reduces the occurrence of fluctuations(14) .

8. It can be used for drugs with a short half-life and therapeutic range(14) .

9. Drug therapy can be easily stopped if poisoning occurs(14) . 10. It reduces the frequency of drug administration so as to improve patient compliance(14) .

3.2 Disadvantages

1. Only relatively potent drugs can be used for transdermal delivery systems because the drug entry limits are determined by skin impermeability(14) .

2. Hydrophilic drugs are less suitable than lipophilic drugs because of their low permeability(13)

3. A larger drug molecule size (above 1000) makes drug absorption difficult (13) .

4. It cannot be used on drugs in high doses(14) .

5. The drug molecule must be strong because the size of the patch limits the amount that can be administered(9) .

6. This system may produce allergic reactions at the drug application site, such as itching, rash, and local oedema (13).

4. Types and methods for creating patch

1. Single-layer Drug in Adhesive In this type of patch, the adhesive layer serves to adhere the various layers and the entire system to the skin and is responsible for drug release. The adhesive layer is surrounded by a temporary liner and backing(16) .

2. Multi-layer Drug in Adhesive This type of patch is similar to a single-layer patch in that both adhesive layers are also responsible for drug release. However, in this system, there is another layer to adhere to the drug, usually separated by a membrane (but not in all cases). This patch also has temporary and permanent liner layers(16) .

3. Reservoir In this system, a drug reservoir is deposited between the support layer and the rate-control membrane and the drug is released through the micropore rate-controlled membrane. The drug can be in the form of a solution, suspension, or gel or dispersed in a solid polymer matrix in the reservoir compartment(15) .

4. Matrix The main component of the matrix system is the adhesive and backing material, the backing layer as the outer layer of the formulation. First, drugs and other additives such as polymers and enhancers are formulated together into an adhesive solution, and then the solvent is evaporated to form a matrix film. Then the matrix film and adhesive are attached to the backing film. The matrix-type patch is the market's most commonly used transdermal patch. One advantage of this matrix system is that the patch will form a thin and elegant preparation; hence it is convenient to use, and the manufacturing process is easy, fast, and inexpensive(17) .

5. Parameters for the Characterization

1. Organoleptic observations Organoleptic patches can be observed visually, including colour, odour, flexibility and surface texture(19) .

2. Thickness test The thickness of the patch can be measured using a calliper by dividing the five areas to be measured. Then the thickness of each side of the section is measured, and the average is determined(20) .

3. Weight uniformity test This test is performed by weighing each patch on a digital scale and then determining the average value(20) .

4. Moisture content (%) For 24 hours in a desiccator filled with calcium chloride, fabric patches have been produced, weighed, and stored at room temperature. The patch was weighed again after 24 hours in order to calculate its moisture content % using the formula:(4) . %moisture content= [Initial weight – final weight / Final weight] × 100(4) .

5. Drug content The drug content of the patch preparation was measured by dissolving a predefined amount of patch preparation in phosphate buffer saline (pH 7.4 0.05). A filter was placed over the solution, and the drug content was measured using UV or HPLC spectroscopy, respectively(6) .

6. Test the uniformity of the active ingredient content This examination was conducted by cutting the patch preparation into three parts as much as 1 cm and dissolved in phosphate buffer saline pH 7.4 ± 0.05 as much as 25 ml. Then the results of the concentration values were observed using UV or HPLC spectrophotometry(9) .

7. Surface morphology test Surface morphology test on patch preparations using a scanning electron microscope (SEM) which aims to see more clearly the preparation surface with various magnifications(9) . The physical characteristics of various transdermal patches of different polymers can be seen in table 3.

8. Stability test Stability tests are performed to see and evaluate changes to the patch under any environmental conditions during storage and use. This test was carried out by following the guidelines of the International Conference on Harmonization (ICH). Patch samples were stored at 40±0.5°C and 75±5% RH for 6 months, and then samples were observed at 0, 30, 60, 90 and 180 days and analyzed for drug content(6)(20) .

9. In vitro release test The patch release test is important because it can determine the cumulative drug levels that can be released from the carrier matrix. This test is performed to determine whether a patch can maintain a consistent drug concentration in the skin's stratum corneum and maintain it substantially higher than the drug concentration in the body to achieve a constant level of drug permeation. A transdermal patch release test can be performed using the paddle over disc method from USP apparatus V brand Parmeq using 500 ml of phosphate saline buffer pH 7.4 ± 0.5 as the dissolution medium. First, samples are included in the disc. Then the disc was placed in 500 ml of dissolution medium, and the paddle was placed at a distance of 2.5 cm from the container and then rotated at a speed of 50 rpm while maintaining the temperature at 37±0.5 °C. There are 5 ml samples taken at several time intervals for 24 hours and analyzed by UV or HPLC spectrophotometer, then replicated 3 times, and the average value could be calculated(28)(29)(30) .

10. In vitro penetration test A patch penetration test can be conducted using the Franz diffusion cell method, which can be used to test drug permeation through mouse skin in vitro. First, the hair from the rat's stomach area had to be carefully removed and then the skin was thoroughly cleaned with distilled water to remove the adhering tissue or blood vessels, which would later become the membrane in the Franz diffusion cell method. This device consists of a receptor compartment, a donor compartment, and a water jacket. The water jacket maintains a constant temperature while the Franz diffusion cell operates. In the donor compartment and the receptor compartment, rat skin is placed with the epidermis facing upwards. The cell temperature was maintained at 37±0.5 °C using a thermostatically controlled heater, and the medium used was phosphate saline buffer pH 7.4 ±0.5. At a certain minute, the volume is taken from the receptor compartment periodically and replaced with new media with the same volume. Then the sample was filtered through a filtering medium and analyzed by spectrophotometry or HPLC(31)(32) .

11. Skin irritation test Skin irritation and sensitisation tests can be performed on healthy rats, rabbits, and mice. Patches can be put on the backs of mice and rabbits. The patch mixture can then be applied to the skin of mice and rabbits after they have been thoroughly cleaned and dehaired. Before using the patch, mice and rabbits' backs must be well cleaned. After 24 hours after patch application, mice and rabbits' skin is checked for signs of oedema and/or erythema (redness and swelling). To classify a symptom into four severity levels (none, mild, moderate, and severe), this severity is compared to the standard 0.8% formalin irritation(29)(36)(37) .

6. Conclusions

A transdermal patch has many advantages over conventional drug administration, such as increasing bioavailability, not undergoing first-pass metabolism, avoiding adverse gastrointestinal effects, maintaining drug in plasma, and increasing patient compliance. The characteristics of the patch formed from various polymers and in vitro release and penetration tests are the determining factors for the suitability of a patch for transdermal delivery.

7. Conflict of Interest

None

8. References

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