NOVEL TECHNIQUES IN TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT:

The skin offers an accessible and convenient site for the administration of medications. To this end, the field of transdermal drug delivery, aimed at developing safe and efficacious means of delivering medications across the skin, has in the past and continues to garner much time and investment with the continuous advancement of new and innovative approaches. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. This review article provides an overview of TDDS, its advantages over conventional dosage forms, drug delivery routes across human skin, penetration enhancers and various components of Transdermal patches, types of Transdermal patches, methods of preparation and its physicochemical methods of evaluation.

KEYWORDS : *Transdermal Drug Delivery System, Transdermal Patches.*

INTRODUCTION:

A recent approach to drug delivery into systemic circulation at predetermined rate using skin as a site of application. Transdermal Drug Delivery system is also known as "Patches" is a dosage form which designed to deliver a medications across the patient's skin.[1,2] Transdermal patches are medicated adhesive patches when it was put on the skin layer it'll deliver the medicament into the blood stream through skin layer. They has significantly influenced various therapeutic agent especially pain management and treatment of various disease. They does not involved passage through gastrointestinal tract; therefore, there is no loss due first pass metabolism, drug deliver without interference of pH, enzymes and intestinal bacteria.[3-6] This route of drug administration avoids hazards and discomfort associated with parental therapy and improve patient compliance, as it is easy to apply patch.

The bioavailability of the drug increased as variation in absorption when it is taken orally.[7] Transdermal route has competed with oral route as the most successful innovative research area in drug delivery. This is because treatment through oral route aims to attain and maintained drug concentration in the body within the therapeutic range. This is done by introducing a fixed dose at regular intervals, due to which the drug concentration in body follows a peak through profile and results in greater chance of adverse effect.

TDDS maintain the drug concentration within the therapeutic window for prolonged period of time to ensure that the drug levels neither fall below the minimum effective concentration nor exceeds maximum concentration. But also have some disadvantages such as one or more components of TDDS may cause dermatitis at the site of application in some patients, thus the treatment is discontinued and only potent drugs can be incorporated into transdermal

TYPES OF TRANSDERMAL PATCHES :

Transdermal patches were categorized into four main type[10-13]

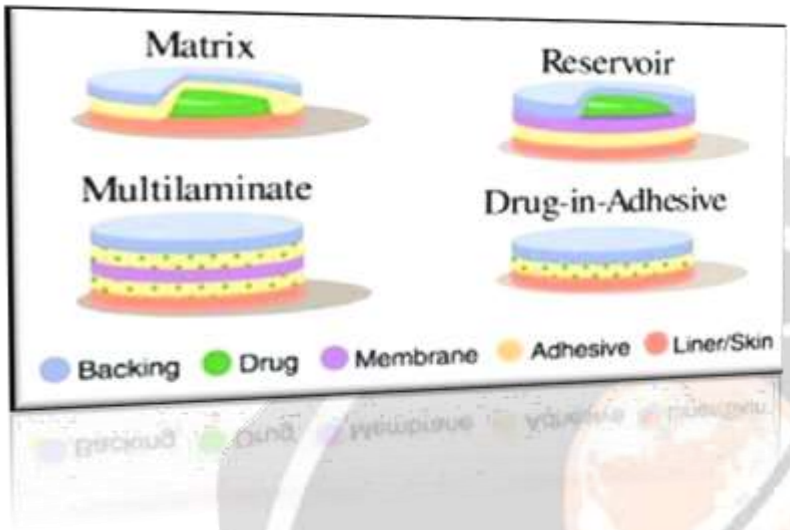


Fig. -1 Types of transdermal patches

1. Matrix type
2. Reservoir type
3. Membrane matrix hybrid
4. Micro reservoir type
5. Drug in adhesive
   - Single layer drug in adhesive
   - Multilayer drug in adhesive

1. Matrix Type:

This patch is very slim and less visible when sticked on the skin. In this type of system, the film control release of medication from the patch. In this type of drug reservoir homogeneously dispersed in hydrophilic or lipophilic polymer. Then molded in disk with defined surface area and thickness. Film formed is separated from the ring and mounted onto occlusive base pate in a compartment made up from drug impermeable backing. Then, an adhesive polymer is sprayed along the circumference of the film. The adhesive layer and backing layer integrated into one layer.[13]

2. Reservoir Type:

It is having separated drug layer. In this, the drug reservoir layer is a liquid compartment which is consisting of drug solution or suspension where the drug particle is suspended in silicon fluid. It is gives paste such as suspension/gel/clear solution, which 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.[13]

3. Membrane Matrix Type:

It is the modified form of reservoir matrix in which the liquid form of drug reservoir is replaced with solid matrix polymer

4. Micro Reservoir Type:

In this type, the drug is suspending 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 unleachable microscopic drug particle. The dispersion is quickly stabilized by immediately cross linking the polymer chain.[13]

5. Drug in Adhesive:

i. Single layer drug in adhesive:

In this type of patch, adhesive layer not only serve to affix the system to the skin, but it is also responsible for drug release from the patch. The adhesive layer is surrounded by backing layer.

ii. Multilayer drug in Adhesive:

The multilayer comprises either the addition of a membrane between two different drugs in adhesive or addition of multiple drug in

adhesive layer under in single backing film. This patch is having temporary liner layer and backing layer.

BASIC COMPONENTS OF TDDS:

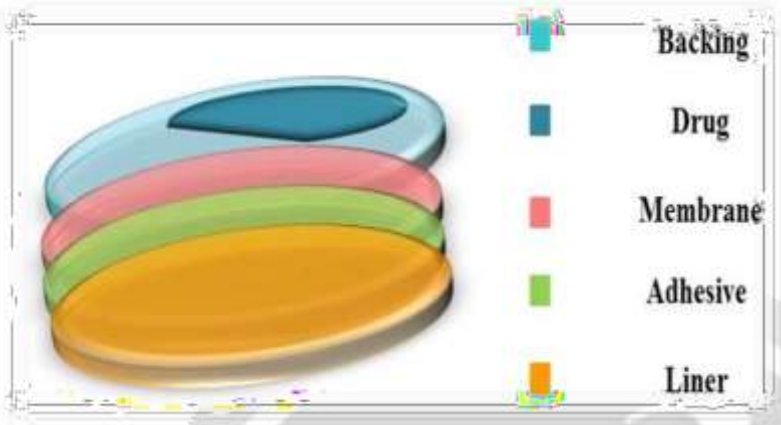


Fig.-2 Basic components of TDDS

1. Active Pharmaceutical Ingredient (API)
2. Polymer Matrix or Drug Reservoir
3. Permission enhancer
4. Pressure Sensitive Adhesive
5. Backing Laminated
6. Release liner
7. Other excipients such as plasticizer and solvents

1. Active Pharmaceutical Ingredient (API):

Selection of API should be based upon the following properties API should not induced cutaneous irritation and also should not affected to the non-target tissues. [15]

2. Polymer Matrix or Drug Reservoir:

Different classes of polymeric material is used to attained rate controlling membrane. Selection of polymer matrix or drug reservoir should be based upon following properties. The polymer should not interact physically or chemically with the drug. The polymer should be easily manufactured into the desired product and it should be inexpensive. The polymer must be stable, non-toxic and must not decomposed in the presence of drug and other excipients.

Natural Polymer: Gelatin, Gum Acacia, Methyl cellulose, Starch Protein etc.
Synthetic Polymer: Polyethylene, Polyester, Polyamide, Polyvinyl chloride etc.[15]

3. Permission enhancer:

These are substances added to the formulation to increase the permeability of the drug through skin. They can modify the structure of skin or enhance drug solubility.

4. Pressure Sensitive Adhesive:

The selection are based on patch design and drug formulation which helps to maintaining a closed contact with patch and skin surface. It is also based upon following criteria adhere with not more than applied finger pressure. It should be easily removal from smooth surface without leaving a residue.

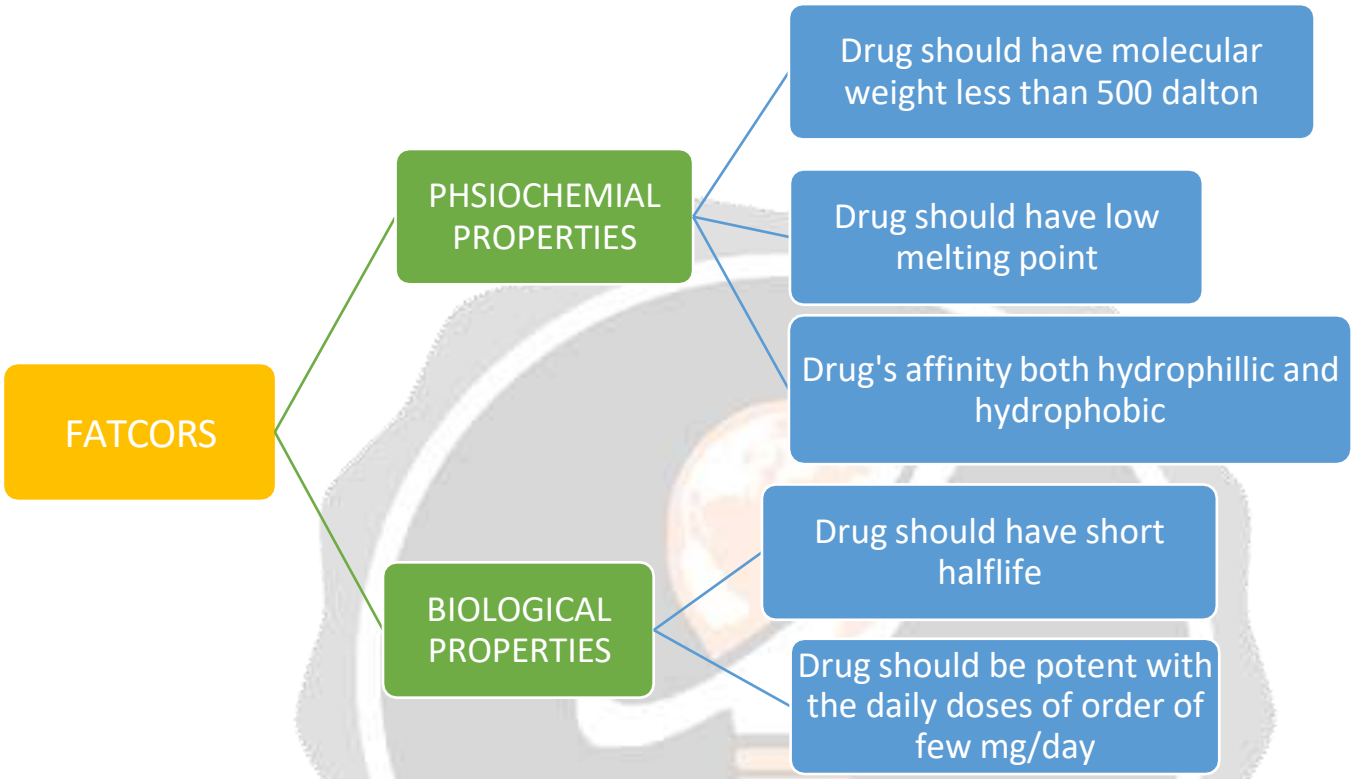
5. Backing Laminated:

Backing membrane are flexible. This layer provide the drug reservoir and provide mechanical support. It is also prevent loss of drug and protect the skin from any kind of irritation.

6. Release liner:

It is a protective layer that is removed before applying the transdermal system. It prevent the drug reservoir from drying and protect it from contamination. It is composed of abase layer which may be non-occlusive or occlusive and released coating layer made up of silicon or Teflon.

FACTORS AFFECTING TO PERMEATION :



APPROACHES OF TDDS:

There are several approaches to drug delivery system

Iontophoresis:

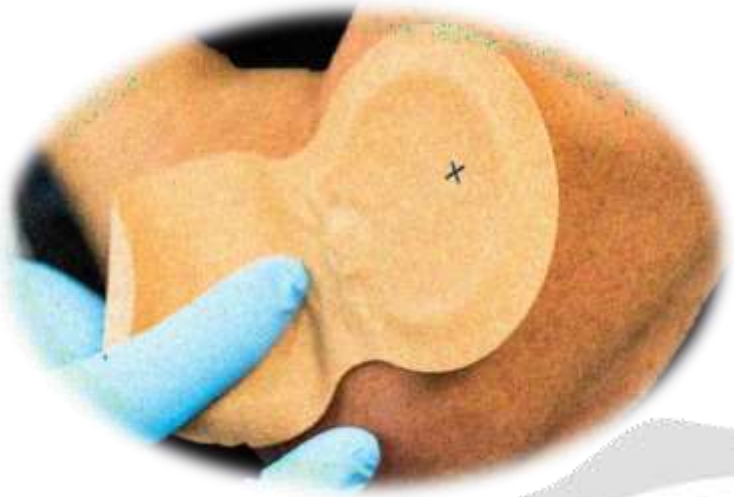


Fig. -3 Approaches of TDDS

Iontophoresis help to distribute drug over the barrier by passing a few milliamperes of current to a small area of skin through the electrode that is in contact with the formulation. [16] It has been demonstrated that iontophoresis improve skin penetration and speed up the release of number of medications with poor absorption or permeability profile. Using an electrochemical potential. [17] Iontophoresis effectives is influenced by the drug's polarity, valency and mobility as well as type of electrical cycle being used. [18]

Sonophoresis:

Transdermal drug delivery can be made more effective by using the ultrasound device's desired range of ultrasound frequencies. [19, 20] Low frequency of ultrasound is more effective because it promotes drug circulation by generating an aqu1ersed in an aqueous phase and stabilized by an interfacial membrane that is created by surfactant or co-surfactant molecules that are so small that they form very tiny droplets. Although an upper limit to the particle size has been proposed due to its Nano scale dimension, the particle size of routinely used Nanoemulsion range from 100 to 1000 nm. While they exhibit approximately the same droplet size range, content and appearance as micro emulsions, nanoemulsions. Are distinct from them in terms of structural characteristic and long term effect.

Needleless Injection:

A painless method of applying medications, to the skin is needleless injection. In this method the liquid or solid particles is fired supersonic particles through the stratum corneum. The high development costs for both the device and dosage form as well as the inability to program or control drug distribution to account for intersubject variability are drawbacks of this method. Permeability of skin mechanism for needleless injection a compressed gas, such as helium or nitrogen is forced through the nozzle as part of the mechanism and the resulting drug particles are entrained inside the jet flow and are said to move at a sufficient speed to penetrate the skin.

Abrasion:

To aid in the penetration of topically applied medications, the abrasion techniques directly removes or disrupts the top layers of the skin. Some of these devices are based on dermatologists techniques for superficial skin resurfacing (such as microdermabrasion), which are used to treat acne, scars, hyperpigmentation and other skin imperfection.

Laser Radiation:

This procedure includes applying a laser to the skin in a direct and regulated manner. This eliminates the stratum corneum while slightly affecting the epidermis beneath. It has been demonstrated that utilizing this technique to remove the stratum corneum improves

EVALUATION OF TRANSDERMAL PATHCES :

The prepared transdermal patches were estimated for colorful physiochemical parameters like physical examination, consistence, folding abidance, weight variation, tensile strength, humidity uptake, humidity loss and medicine content.

1. **Physically Examination** of Transdermal patches were visually checked for their
   •Colour
   •Clarity
   •Flexibility
   •Homogeneity
   • Smoothness

2. **Thickness :**

   The thickness of the medicine loaded patches is measured in different points by using digital micrometer and determine the average thickness and standard deviation to ensure thickness of prepared patch[28,29].

3. **Weight Uniformity :**

   The prepared patch are dried at 60 C for 4 hours before testing. A specific area of patch is to be cut in different zones of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from individual weights.[29].

4. **Folding endurance :**

   A strip of specific area is to be cut unevenly and constantly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the abidance.[30].

5. **Percentage Moisture Content :**

   The set of films are to be counted collectively and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hours. After 24 hours the films are to be revisited and determine the chance humidity content from the below mentioned formula.[29,30]

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

6. **Content Uniformity Test:**

   10 patches are selected and content is determined for individual patches. However, also transdermal patches pass the test of content uniformity. If 9 out of 10 patches have content between 85% to 115% of the specified value and bone has content not lower than 75% to 125% of the specified, also fresh 20 patches are tested for medicine content. However, also the transdermal patches pass the test. If these 20 patches have range from 85% to 115%.[28,29]

7. **Moisture Uptake :**

   Counted films are kept in desiccators at room temperature for 24 hours. These are also taken out and exposed to 84 relative moisture using impregnated result of potassium chloride in desiccators until a constant weight is achieved. Humidity uptake is calculated as given below[28,29]

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

8. **Drug Content :**

A specified zones of patch is to be dissolved in a suitable solvent in specific volume. also the result is to be filtered through a purifier medium and analyze the medicine contain with the suitable system.[28,30]

9. **Shear Adhesion Test :**

   This test is to be performed for the dimension of the cohesive strength of an adhesive polymer. It can be affected by the molecular weight, the degree of cross linking and the composition of polymer, type and the quantity of tackifier added. An adhesive coated tape is applied onto a pristine steel plate; a defined weight is suspended from the tape, to affect it dragging in a direction parallel to the plate. Shear adhesion strength is determined by scaling the time it takes to drag the tape off the plate. The longer the time take for discarding, lower is the shear strength.[31]

10. **Peel Adhesion Test :**

    In this test, the force needed to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and quantity of complements are the variables that dete rmined the peel adhesion properties. A single tape

is applied to a stainless steel plate or a backing membrane of choice and also tape is dragged from the substrate at a 180º angle, and the force needed for tape removed is measured.[31]

11. Water vapor transmission studies(WVT) :

For the determination of WVT, weigh one gram of calcium chloride and place it in preliminarily dried empty vials having equal diameter. The polymer films are sticked over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. also, the vials are directly counted and placed in moisture chamber maintained at 68 RH. the vials are again counted at the end of every 1st day, 2nd day, 3rd day over to 7 successive days and an increase in weight was considered as a quantitative measure of humidity transmitted through the patch. In other reported system, desiccators were used to place vials, in which 200 mL of impregnated sodium bromide and impregnated potassium chloride result were placed. The desiccators were tightly closed and moisture inside the desiccators was measured by using hygrometer. The counted vials were also placed in desiccators and procedure was repeated. W is the increase in weight in 24 hr, S is area of film exposed(cm2), T is the exposure time.[32]

12. Rolling Ball Tack Test :

This test measures the softness of a polymer that relates to speak. In this test, stainless steel ball of7/16 elevation in diameter is released on an inclined track so that it rolls down and comes into contact with vertical, upward facing adhesive. The distance the ball travels along the tenacious provides the dimension of technique, which is expressed in inch.[33]

13. Quick Stick (Peel-Method) :

In this test, the tape is dragged down from the substrate at 90ºC at a speed of 12 inches/ min. The peel force needed breaking the bond between adhesive and substrate is measured and recorded as method value, which is expressed in ounces or grams per inch range.[33]

14. Probe Tack Test :

In this test, the tip of a clean probe with a defined surface roughness is induced into contact with adhesive, and when a bond is formed between probe and adhesive. The posterior discarding of the probe mechanically breaks it. The force needed to drag the probe down from the adhesive at fixed rate is recorded as method and it's looked in grams.[33]

15. In Vitro Skin Saturation Studies :

An in vitro saturation study can be carried out by using diffusion cell. Full consistence abdominal skin of male Westar rats weighing 200 to 250g. Hair from the abdominal region is to be removed precisely by using a electric clipper; the dermal side of the skin is completely gutted with distilled water to remove any clinging apkins or blood vessels, equalized for an hour in dissolution medium or phosphate buffer pH7.4 before starting the trial and is placed on a glamorous stirrer with a small glamorous needle for invariant distribution of the diffusant. The temperature of the cell is maintained at 32 ±0.5 °C using a thermostatically controlled heater. The insulated rat skin piece is to be mounted between the chambers of the diffusion cell, with the epidermis facing overhead into the patron cube. Sample volume of definite volume is to be removed from the receptor cube at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be anatomized spectrophotometrically or HPLC. Flux can be determined directly as the pitch of the curve between the steady- state values of the amount of medicine permeated(mg cm- 2)vs. time in hours and permeability portions were derived by dividing the flux by the original medicine payload(mg cm- 2).[34,35]

16. Skin Irritation Study :

Skin irritation and sensitization testing can be performed on healthy rabbits(average weight1.2 to1.5 kg). The rearward surface(50cm2) of the rabbit is to be cleaned and remove the hair from the clean rearward surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hrs. and the skin is to be observed and classified into 5 grades on the base of the inflexibility of skin injury. [31]

17. Stability Studies :

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40 ±0.5 ° c and 75 ± 5 RH for 6 months. The samples are withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the medicine content.[34]

MARKETED PRODUCTS OF TRANSDERMAL PATCHES :

Sr.no.	Brand Name	Drug Name	Uses
1.	Tulomax 1.0	Tulobuterol	Preventing symptoms of asthma and chronic obstructive pulmonary disorder
2.	Powergesic 100mg	Diclofenac 100mg	to treat pain, swelling, stiffness and joint pain
3.	Nicotex	Nicotine	stopping the smoking habit
4.	Exelon Patch 15	Rivastigmin 27mg	treat mild to moderate dementia in Alzheimer's disease, Parkinson's disease
5.	Ilidotran	Lidocain 700mg	relief pain mild to moderate pain, relieve symptoms of musculoskeletal pain and inflammatio
6.	Riva-Spar	Rivastigmin 9mg	treat mild to moderate dementia in Alzheimer's disease, Parkinson's disease
7.	D-Touch	Diclofenac 100mg	to treat pain, swelling, stiffness and joint pain
8.	Nico-Touch	Nicotine	to help people quit smoking
9.	FenSpar	Fentanyl	Used in chronic pain
10.	Bue-Touch	Buprenorphine	Management of pain
11.	Evra	Norelgestromin/Ethinyestradol	Birth Control
12.	Xulane	Norelgestromin/Ethinyestradol	Birth Control
13.	Twirla	Levonorgestrol/ Ethinyestradol	Birth Control
14.	Nitroderm TTS	Glyceryl Trinitrate	Chest pain(angina pectoris)
15.	Nitroglycerin transdermal system	Nitroglycerin	Chest pain(angina pectoris)
16.	Nitro-Dur	Nitroglycerin	Chest pain(angina pectoris)
17.	BuTrans5	Buprenorphine	Management of pain
18.	Butec10	Buprenorphine	Management of pain
19.	Bupatch	Buprenorphine	Management of pain
20.	Themibuprine-P	Buprenorphine	Management of pain
21.	Buvalor 5	Buprenorphine	Management of pain
22.	Rupatch 5	Buprenorphine	Management of pain
23.	Zuprinor 10	Buprenorphine	Management of pain
24.	Deponit-NT 10	Nitroglycerin	Long term treatment of angina pectoris
25.	Nitrek	Nitroglycerin	Chest pain(angina pectoris)
26.	Emsam	Selegline	Antidepressant

CONCLUSION:

In recent years, the transdermal medication delivery technique has become more significant. An incredibly alluring delivery method for a medication with proper physical chemistry and pharmacology is transdermal. The transdermal drug delivery system may have the benefits of avoiding hepatic first pass metabolism maintain constant blood level for longer periods of times to improving bioavailability, reducing gastrointestinal irritation brought on by local contact with gastric mucosa and increased patient compliance. The advantages of intravenous medication infusion may now clearly be closely imitated it seems utilizing the skin as a part of medicine administration without its risks.

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