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Review Paper

A Review on Development of Transdermal Drug Delivery System

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ABSTRACT

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variations

INTRODUCTION

Transdermal drug delivery systems (TDDS), also knownas “patches,” are dosage forms designed to deliver atherapeutically effective amount of drug across a patient’s skin. In order to deliver therapeutic agents through thehuman skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oralroutes by increasing patient compliance and avoiding first pass metabolism respectively1. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic

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efficiency and maintenance of steady plasma level of the drug. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel, particularly by sea. Oral route is the popular route of drug delivery. Although it has some disadvantages including first pass metabolism, drug degradation in gastrointestinal tract due to enzymes PH etc.

Medicated adhesive patches or transdermal patches are of different sizes, having more than one ingredient. Once they apply on unbroken skin they deliver active ingredients into systemic circulation passing via skin barriers. A patch containing high dose of drug inside which is retained on the skin for prolonged period of time, which get enters into blood flow via diffusion process. Drug can penetrate through skin via three pathways-through hair follicles through sebaceous glands through sweat duct. Transdermal drug delivery systems are used in various skin disorders, also in the management of angina pectoris, pains, smoking cessation & neurological disorders such as Parkinson's disease.(3,4)

Advantages of transdermal drug delivery system

1. First pass metabolisms of drug get avoided.
2. Gastrointestinal incompatibilities get avoided.
3. Self-medication is possible.
4. Duration of action gets extended & predictable.
5. Unwanted side effects get minimized.
6. Drug plasma concentration gets maintained.
7. Number of doses get reduces which improve patient compliance. (5,6)

Disadvantages of Transdermal drug delivery System

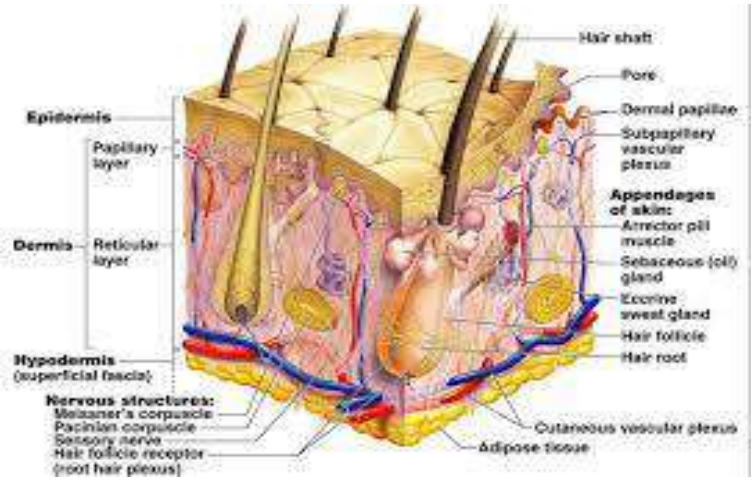
1. Chances of allergic reactions at the site of application like-itching,rashes,local edema etc.
2. Larger molecular size of drug (above 1000) creates difficulty in absorption.
3. Barrier function of skin varies from site to site on the same or different person. (7)

Anatomy and physiology of skin

Human skin comprises of three distinct but mutually dependent tissues: The stratified, vascular, cellular called as "epidermis" Underlying dermis of connective tissues, Hypodermis (Figure 1).

Epidermis

The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum. This is the outermost layer of skin also called as horny layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The architecture of horny layer may be modeled as a walllike structure. In this model, the keratinized cells function as protein "bricks" embedded in lipid "mortar." The lipids are arranged in multiple bilayers



There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form. Viable epidermis is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

Dermis

Dermis is 3 to 5 mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeate very low and the resulting concentration difference across the epidermis provides essential concentration gradient for transdermal permeation.

Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanically protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired. (8)

Components of transdermal pathches

Polymer Matrix

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in transdermal patches.

a) Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.

b) The polymer should be stable.

c) The polymer should be nontoxic

d) The polymer should be easily of manufactured

e) The polymer should be inexpensive

f) The polymer and its degration product must be nontoxic or non-antagonistic to the host.

g) Large amounts of the active agent are incorporated into it.

Types of polymer: -

a) Natural polymers: Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.

b) Synthetic Elastomers: Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.

c) Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode,polyurea, epoxy.

Drug: - Drug solution in direct contact with release liner

Physiochemical properties:

a) The drug should have a molecular weight less than 1000 Daltons.

b) The drug should have affinity for both lipophilic and hydrophilic phases.

c) The drug should have a low melting point.

Biological properties

a) The drug should be potent with a daily dose of the order of a few mg/day.

b) The half-life (t½) of the drug should be short.

c) The drug must not produce allergic response.

d) Tolerance to the drug must not develop under the near zero-order release profile of transdermal patches.

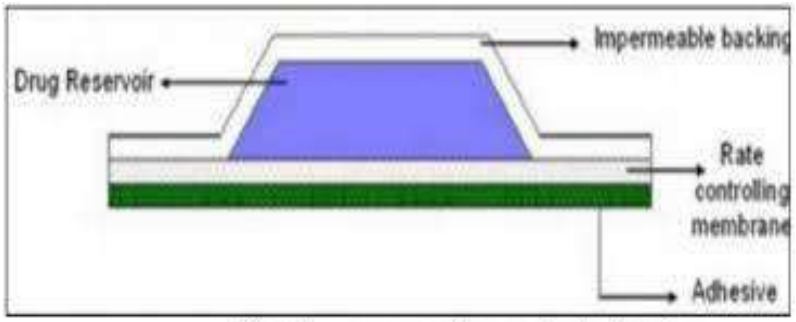
Technology for Developing Transdermal Drug Delivery System (9)

The technologies can be classified in four basic approaches

1. Polymer membrane partition controlled TDDS
2. Polymer matrix diffusion controlled TDDS
3. Drug reservoir gradient controlled TDDS
4. Micro reservoir dissolution controlled TDDS

Membrane Permeation – Controlled Systems

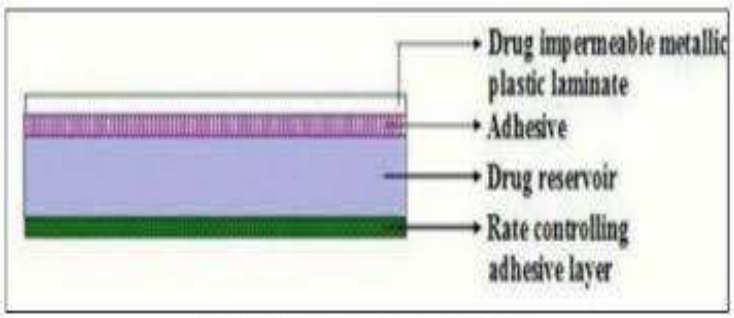
In this type of system, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro-porous or non-porous e.g., ethylene vinyl acetate (EVA) copolymer, with a defined drug permeability property. A cross-sectional view of this system. The drug molecules are permitted to release only through the rate-controlling membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium such as silicone fluid to form a paste like suspension. A thin layer of drug compatible, hypoallergenic adhesive polymer e.g. silicone or Polyacrylate adhesive may be applied to the external surface of the rate controlling membrane to achieve an intimate contact of the trans-dermal system and the skin surface the rate of drug release from this type of trans-dermal drug delivery system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane and adhesive. The constant release rate of the drug is the major advantage of membrane permeation controlled trans-dermal system. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or a rapid release of the entire drug content.



Membrane permeation controlled system.

Adhesive Dispersion Type Systems (9)

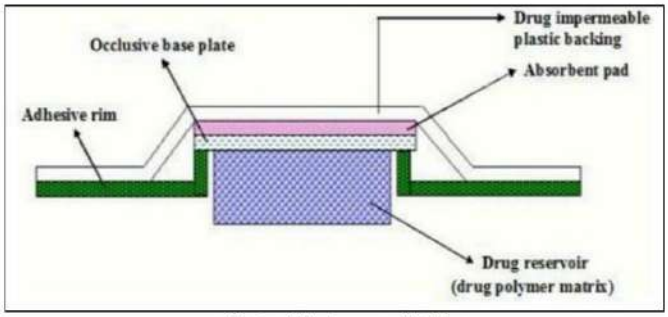
This is a simplified form of the membrane permeation-controlled system. As represented in the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer Eg. Poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to the flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On top of the drug reservoir layer, thin layers of non-medicated, rate controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion-controlled delivery system



Adhesive Dispersion – Type Systems

Matrix Diffusion Controlled Systems

In this approach, the drug reservoir is prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in the polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of the polymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temperature. The drug reservoir can also be formed by dissolving the drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or under vacuum. This drug reservoir containing polymer disc is then pasted on to an occlusive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc.

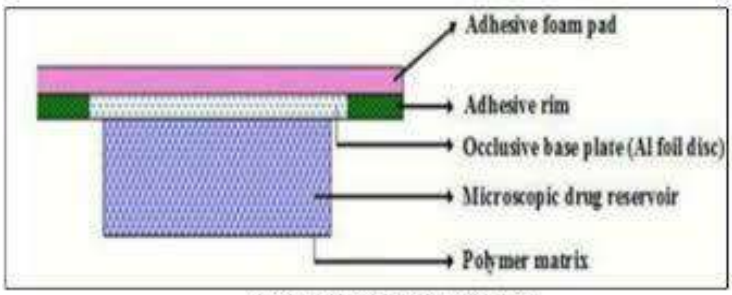


Matrix diffusion controlled Systems

Micro-Reservoir Type or Micro-Sealed Dissolution Controlled Systems

This can be considered a combination of the reservoir and matrix diffusion type drug delivery systems. Here the drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water soluble liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer viz. silicone elastomers by high energy dispersion technique to form several discrete, unleachable microscopic spheres of drug reservoirs. The quick stabilization of this

thermodynamically unstable dispersion is accomplished by immediately cross linking the polymer chains in situ which produces a medicated polymer disc with a constant surface area and a fixed thickness. Depending upon the physiochemical property of the drug and the desired rate of drug release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and rate of drug release. A trans-dermal therapeutic system is produced by positioning the medicated disc at the center and surrounding it with an adhesive rim.



Micro reservoir type Systems

Types of Transdermal Drug Delivery System (10)

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 an immediate drug-releaselayer 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:

The patch containing the adhesive layer not only serves to adhere the various surfaces together but also serves as to release the vapour. The vapour patches are new to the market, commonly used for releasing the essential oils in decongestion. Various other types of vapour 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:

This type of patch is formulated by mixing the drug with adhesive polymer to form drug reservoir. It then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by an unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-in-adhesive. The system is considered to be compatible with a wide variety of drugs. Moreover the system is competent to deliver more than one drug in a single patch. It offers advantages in reduced size and thickness and improved conformability to the application site, helping drive patient preference.

ii. Matrix-dispersion system:

The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with the definite shape and thickness. 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) Micro reservoir system:

The system consists of microscopic spheres of drug reservoirs which releases drug at a zero order rate for maintaining constant drug levels. Micro reservoir system is a combination of reservoir and matrix-dispersion system. The aqueous solution of water soluble polymer is mixed with drug to form a reservoir. It is then followed by dispersing the solution homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross linking agents are added to stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer.

Primary components involved in transdermal drug delivery systems:

1. **Drug Reservoir or Matrix**:
- This holds the drug in the system, either as a reservoir (liquid or gel compartment) or within a matrix (a solid polymer structure).
- The drug is released at a controlled rate, allowing for consistent delivery over time.

2. **Polymer Matrix or Carrier**:
- A polymer matrix or adhesive layer contains the drug and controls its release rate.
- Common polymers include silicone, polyisobutylene, and acrylics.

3. **Adhesive Layer**:
- This attaches the patch to the skin and allows for close contact with the skin surface for effective drug transfer.
- Adhesives are typically hypoallergenic and must maintain adhesion over the duration of wear.

4. **Rate-Control Membrane** (Optional):
- This membrane, present in reservoir-type systems, regulates the rate at which the drug is released from the reservoir to the skin.
- Materials include ethylene-vinyl acetate or polyurethane.

5. **Backing Layer**:
- This is the outermost layer of the patch that provides structural support, protects the drug from environmental factors, and prevents leakage.
- It is usually impermeable and made from materials like polyester or polypropylene.

6. **Release Liner**:
- A disposable layer that protects the adhesive and drug before application.
- Made from materials like silicone-coated paper, it is peeled off before applying the patch.

7. **Permeation Enhancers** (Optional):
- Permeation enhancers increase the skin's permeability to the drug by temporarily altering the skin's barrier.
- Common enhancers include alcohols, fatty acids, and terpenes.

Enhancement of transdermal delivery by equipment (active delivery)

External stimuli, such as electrical, mechanical, or physical stimuli, are known to enhance skin permeability of drugs and biomolecules, as compared to the delivery of drugs by topical application on the skin (11) TDDS supplemented by appropriate equipment is termed as active transdermal delivery, which is known to deliver drugs quickly and reliably into the skin. In addition, this mode of enhanced TDDS can accelerate the therapeutic efficacy of delivered drug (12-14)

1.Iontophoresis

Iontophoresis promotes the movement of ions across the membrane under the influence of a small externally applied potential difference (less than 0.5 mA/cm2), which has been proven to enhance skin penetration and increase release rate of several drugs with poor absorption/permeation profiles. This technique has been utilized in the in vivo transport of ionic or nonionic drugs by the application of an electrochemical potential gradient [15]. The efficacy of iontophoresis depends on the polarity, valency, and mobility of the drug molecule, the nature of the applied electrical cycle, and the formulation containing the drug. In particular, the dependence on current makes drug absorption through iontophoresis less dependent on biological parameters, unlike most other drug delivery systems (Fig. 2A, B) [16]. This modality could additionally include electronic means of reminding patients to change dosages, if desired, to increase patient compliance [17, 18].

2. Sonophoresis

The desired range of ultrasound frequencies generated by an ultrasound device can improve transdermal drug delivery [19,20]. Low-frequency ultrasound is more effective, because it facilitates drug movement by creating an aqueous path in the perturbed bilayer through cavitation (Fig. 2C) [21]. The drug under consideration is mixed with a specific coupler, such as a gel or a cream, which transmits ultrasonic waves to the skin and disturbs the skin layers, thereby creating an aqueous path through which the drug can be injected. Drugs typically pass through passages created by the application of ultrasonic waves with energy values between 20 kHz and 16 MHz. Ultrasound also increases the local temperature of the skin area and creates a thermal effect, which further promotes drug penetration.

3.Electroporation

This method uses the application of high voltage electric pulses ranging from 5 to 500 V for short exposure times (~ms) to the skin, which leads to the formation of small pores in the SC that improve permeability and aid drug diffusion [22, 23]. For safe and painless drug administration, electric pulses are introduced using closely positioned electrodes. This is a very safe and painless procedure involving permeabilization of the skin and has been used to demonstrate the successful delivery of not only low MW drugs, such as doxorubicin, mannitol but also high MW ones such as antiangiogenic peptides, oligonucleotides, and the negatively charged anticoagulant heparin. However, this method has the disadvantages of small delivery loads, massive cellular perturbation sometimes including cell death, heating induced drug damage, and denaturation of protein and other biomacromolecular therapeutics only low MW drugs, such as doxorubicin, mannitol but also high MW ones such as antiangiogenic peptides, oligonucleotides, and the negatively charged anticoagulant heparin. However, this method has the disadvantages of small delivery loads, massive cellular perturbation sometimes including cell death, heatinginduced drug damage, and denaturation of protein and other biomacromolecular therapeutics.

4. Photomechanical waves

Photodynamic waves transmitted to the skin can penetrate the SC, allowing the drug to pass through the transiently created channel [24-26]. The incident wave produces limited ablation, which is achieved by low radiation exposure of approximately 5–7 J/cm2 to increase the depth to 50–400 μm for successful transmission. This limited ablation showed a longer increase and duration as compared to that in other direct ablation techniques, which made it necessary to control properties of the photodynamic waves to ensure delivery of the product to the intended depth in the skin. The wave generated by a single laser pulse also showed increased skin permeability within minutes, allowing macromolecules to diffuse into the skin. Dextran

macromolecules of 40 kDa weight and 20 nm latex particles could be delivered by a single photodynamic laser pulse of a 23-ns duration.

1. Microneedle

The microneedle drug delivery system is a novel drug delivery system, in which drugs are delivered to the circulatory system through a needle [27]. This represents one of the most popular methods for transdermal drugdelivery and is an active area of current research. This involves a system in which micron-sized needles piercethe superficial layer of the skin, resulting in drug diffusion across the epidermal layer. Because these microneedlesare short and thin, these deliver drugs directly to the blood capillary area for active absorption, whichhelps in avoiding pain [28]. Scientists have attempted to use multiple techniques for appropriate optimizationand geometric measurements required for effective insertion of microneedles into human skin, which also represents the broad objective of research on microneedles. The fabrication of microneedle system has been widelyinvestigated with considering the objective, drug type and dose, and targets for use [29]. Up to now, the microneedle can be fabricated with laser-mediated techniques and photolithography. The laser-mediated fabricationtechniques are used for manufacturing metal or polymer microneedle. The 3D structure of a microneedle is generated through cutting or ablating on a flat metal/polymer surface using a laser [30,31]. Photolithography isknown as the method of elaborately fabricating microneedle and has the advantage of being able to manufactureneedles of various shapes using various materials. This method is mainly used to manufacture dissolving/hydrogel microneedles or silicon microneedles via making an inverse mold based on the microneedle structurethrough etching of photoresist [32]. In addition, 3D printing [33], Microstereolithography [34], and Twophotonpolymerization [35] are also investigated for preparing various microneedlesystem. The prepared microneedles could be of several types, such as solid microneedles that simply make a physical path through which drugs can be absorbed, drug-coated microneedles which facilitate delivery of drugs coated on the surfaces of the needles as the latter enter the skin, dissolving microneedles made of drug formulations that dissolve in the body, naturally delivered melting needles which involve drug storage in hollow needles followed by administration (such as a specific injection type), and microneedle patches combined with diverse patch types

[36-40].

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