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REVIEW ON HYDROGEL BASED TRANSDERMAL PATCHES: A NOVEL APPROACH FOR EFFECTIVE DRUG DELIVERY

Rinu Ramesh M.R., Swathy Krishna, Dr. Sr. Daisy P.A.*, Dr. Boby Johns and Praveen Raj R.

Department of Pharmaceutics, St. Joseph's College of Pharmacy, Dharmagiri Campus, Cherthala, Alappuzha.

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***Corresponding Author**
Dr. Sr. Daisy P.A.
Department of Pharmaceutics, St. Joseph's College of Pharmacy, Dharmagiri Campus, Cherthala, Alappuzha.

ABSTRACT

Transdermal drug delivery system is a novel approach of controlled drug delivery that aims to deliver drugs through the skin at a pre-determined and controlled rate. Hydrogels are three dimensional network of hydrophilic polymers which can retain significant volume of water without disrupting the structure. Hydrogel based transdermal patches provide a cooling effect for the skin over conventional patches which results in better patient compliance. Also, hydrogel based transdermal patches have excellent biocompactibility,High mechanical strength, reproducibility and biodegradability.

KEYWORDS: Transdermal patches, Hydrogels.

INTRODUCTION

Transdermal drug delivery system (TDDS) are defined as self-contained, discrete dosage form which when applied to the intact skin deliver the drugs, through the skin, at a controlled rate to the systemic circulation. Transdermal route is considered as a potential route of drug delivery through the skin for local and systemic effect. When compared to other routes of drug administration, TDDS has significant importance. It includes increased patient compliance, sustained drug delivery, avoidance of hepatic first pass metabolism and side effects associated with the drug, improved bioavailability, maintenance of fixed drug concentration in the blood, improved therapeutic efficacy and safety of drugs. TDDS is a novel approach of controlled drug delivery that aims to deliver drugs through the skin at a pre-determined and controlled rate. Transdermal patch consists of high dose of drug and are available in different sizes and also we can incorporate more than one ingredient. Working

mechanism of transdermal patch can be theoretically explained in a very simple way. When a medicated patch is applied on the skin, drug passes through various skin barriers and directly enters into the blood stream via diffusion process. Due to the higher concentration of drug on the patch and lower concentration of drug in the blood, drug will continues to diffuse into the systemic circulation and maintain constant drug concentration in the blood.

Hydrogels[2]

Hydrogels are three dimensional network of polymers which can retain significant volume of water without disrupting the structure. Hydrogels are considered as a novel carriers for the delivery of various drug molecules, immunological products and biological products.

History of hydrogels can be categorized into 3 different generations.

- First generation: Chemical alterations by crosslinking methods. Through these techniques, hydrogels achieve improved swelling and better mechanical properties.
- Second generation: Materials that are sensitive to specific stimuli were used to overcome the problems associated with mechanical strength of hydrogels.
- Third generation: In this generation, stereo complex materials were developed and cross linked hydrogels were made through physical interactions. These development leads to the formation of "smart hydrogels".

Hydrogels have the capacity to absorb water when placed in an aqueous environment. This ability makes the hydrogel as a potential material used for drug delivery and immobilisation of biological compounds. Hydrogel based transdermal patches provide,

- Cooling effect for the skin
- Better patient compliance
- Excellent biocompatibility
- High mechanical strength
- Biodegradability
- Reproducibility

Classification of Hydrogel products[11]

(1) Based on source: Hydrogels are categorised into two groups based on their natural and synthetic origins.

(2) Based on polymeric composition:

- Homopolymeric hydrogels: These are network of polymers produced from a single species of monomer. Depending on the nature of the monomer and polymerisation technique, homopolymers may have cross-linked skeletal structure.
- Copolymeric hydrogels: Consists of two or more different monomer species with atleast one hydrophilic component which is arranged in a block, random or alternating configuration.
- Multipolymer interpenetrating polymeric hydrogel (IPN): Composed of two independent cross-linked synthetic and/or natural polymers, contained in a network form.In case of semi-IPN hydrogel, one component is a cross-linked polymer and other component is a non-cross-linked polymer.

(3) Based on configuration:

- Amorphous (non-crystalline)
- Semi crystalline (complex mixture of crystalline and amorphous phases)
- Crystalline

(4) Based on type of crosslinking: According to the chemical or physical cross-linked junctions, hydrogels are classifieds into two groups.

- Chemically cross-linked network have permanent junctions
- Physically cross-linked networks have transient junctions which is arrised from either polymer chain entanglements or physical interactions like hydrogen bonds, hydrophobic interactions.

(5) Based on physical appearance: Depending on polymerisation techniques involved in the preparation process, hydrogels may appear as matrix,film or microscopic.

(6) According to network electrical charge: Based on the presence or absence of electrical charge on the cross-linked chains, hydrogels are divided into four groups,

- Non-ionic (neutral)
- Ionic (anionic or cationic)
- Amphoteric electrolyte (ampholytic) containing both acidic and basic groups
- Zwitter ionic containing both anionic and cationic groups in each structural repeating unit.

Features of an ideal hydrogel

- Non-toxic
- Inexpensive
- Colourless, Odourless
- Photostability
- Rewetting ability
- Neutral pH after swelling in water
- High stability and durability
- Greater absorption capacity
- High absorbency under load (AUL)
- High degradability and formation of non-toxic species on degradation

MERITS OF TDDS[3,4]

- Allows self-administration of drug.
- Frequent dosing gets minimised
- Avoids various side effects and enzymatic degradation of drug
- Plasma drug concentration gets maintained
- Painless delivery of drug improves patient compliance
- Drug administration can be terminated by removing the patch
- Ensure sustained release of drug
- Avoids hepatic first pass metabolism

DEMERITS OF TDDS[3,4]

- Not suitable for dugs having molecular weight above 1000 Daltons
- Allergic reactions at the application site
- Hydrophobic drugs are not a good candidate due to its low permeability
- The adhesion of patch may not be suitable for all skin types
- Causes detachment of patches from the skin during physical activities.

SKIN[4]

The skin is considered as the largest organ of the human body and it covers approximately 25sq.m of surface area.

- A barrier against chemical, physical and microbiological attacks
- Thermostat for maintaining body temperature

- Regulates blood pressure
- Prevent UV rays penetration.

Human skin layers are divided into three,

(1) The stratified, a vesicular, cellular epidermis

(2) Underlying dermis of connective tissues

(3) Hypodermis

Epidermis

Also called as stratum corneum.It is the outermost layer of skin having a thickness of approximately 10mm and it contains 10 to 25 layers of dead, keratinised cells called corneocytes. This part is devoid of any blood vessels and consists of stratified squamous epithelial cells. Epidermis can be further divided into 4 layers based on maturation of cells,

- Stratum germinativum
- Stratum spinosum
- Stratum granulosum
- Stratum corneum

Dermis

Dermis layer lies beneath the epidermis and above the subcutaneous layer having a thickness of 3 to 5mm. It comprised of a matrix of connective tissues which contains blood vessels, lymph vessels and nerves. Major functions of dermis are,

- Provide strength and flexibility to the skin
- Provide nutrients and oxygen
- Remove toxins and waste products
- Regulate body temperature

Dermis can be further categorised into 2 groups,

(1) The papillary dermis

(2) The Reticular dermis

Papillary dermis is a thin layer made up of loose coactive tissues such as capillaries, elastic fibers, reticular fibers and collagen.

Reticular dermis is the thickest layer of dermis and it consists of dense connective tissues such as blood vessels, elastic fibers, collagen fibers, fibroblast, mast cells, nerve endings and lymphatic's.

Hypodermis

Hypodermis is a fat storage area which is lying below the dermis. It is merged with blood vessels and nerves. The main function is to regulate temperature, provide nutrients and mechanical properties. Also provide structural support for the skin and insulation of the body from cold and aiding shock absorption.

For the transdermal delivery of drug, the drug must penetrate through these three layers of skin to enter into the systemic circulation.

TRANSDERMAL PERMEATION – BASIC PRINCIPLE

Passive diffusion is the main principle involves in transdermal permeation. The release and transport of drug from the patch into the blood stream is a multistep process.

- Drug diffusion to the rate controlling membrane
- Drug dissolution with in the patch and diffusion into the skin
- Sorption by stratum corneum
- Penetration through viable epidermis
- Uptake of drug by capillary network in the dermal papillary region
- Effect on target organ

BASIC COMPONENTS OF TDDS

(1) Polymer matrix
(2) Drug
(3) Permeation enhancers
(4) Adhesives
(5) Backings
(6) Release liners
(7) Other excipients

(1) Polymer matrix

Release rate of drug from the traditional patch can be altered by varying the concentration of polymer. The main function of polymer is to control the drug release from the transdermal

system. Hence, the selection of the polymer plays an important role in the formation of transdermal patches. Properties of polymer matrix includes,

- Stable
- Non-toxic
- Inexpensive
- Biocompatible with skin
- Easy to manufacture
- Shows specific drug diffusion

Classification of polymers

Table 1: List of polymers.

Natural polymers	Synthetic elastomers	Synthetic polymers
Cellulose derivatives	Hydrin rubber	Polyvinyl alcohol
Chitosan	Polybutadiene	Polyvinyl chloride
Zein	Polysiloxane	Polyethylene
Gelatin	Silicone rubber	Polyamide
Shellac	Acrylonitrile	Polyacrylate
Waxes	Neoprene	Polyvinyl pyrrolidone
Proteins	Nitrile	Polyurea
Gums and their derivatives	Butyl rubber rubber	Poly propylene

(3) Drug

Certain criteria's should be followed during drug selection. Mainly physico-chemical properties of drug and its biological properties.

Physico-chemical properties

- Molecular weight lessthan 1000 Daltons
- Affinity for both lipophilic and hydrophilic phases
- Low melting point (less than 200^0 C)
- Drug should be potent.

Biological properties

- Stable
- Short half life
- Non-allergic and non-irritating
- Oral bioavailability and therapeutic index of drug should be low.

Ideal properties of drug

Table 2: Ideal properties of drug.

Sl.No	Parameter	Properties
1.	Dose	Should be low in weight(less than 20mg/day)
2.	Half life	10 or less(hours)
3.	Molecular weight	Less than 1000 Daltons
4.	Melting point	Less than 200^0C
5.	Ph	Between 5.0 to -9.0
6.	Oral bioavailability	Low
7.	Therapeutic index	Low
8.	Skin reaction	Non-irritating Non-sensitising

(3) Permeation enhancer[6]

These are chemical compounds that improve the stratum corneum permeability to attain therapeutic level of drug. Theflux (J) of drug across the skin can be written as,

J = D dc/dx

J = Flux

D = Diffusion coefficient

C = Concentration of diffusing species

X = Spatial coordinate

Some examples are Dimethyl sulfoxide, Decylmethalsulfoxide, Propylene glycol, Ethanol etc. Penetration enhancement can be achieved through mainly three approaches,

Table 3: Approaches.

Chemical approach	• Lipophilic analogues synthesis • Stratum corneum delipidisation • Co-administration of skin permeation enhancers.
Bio-chemical approach	• Bio convertible pro-drug synthesis • Co-administration of skin metabolism inhibitors
Physical approach	• Sonophoresis using ultrasonic energy • Thermal energy • Iontophoresis • Stratum corneum hydration • Stratum corneum stripping

Ideal properties

- Non-toxic
- Non-irritant
- Non-allergic

- Odourless and colourless
- Should not show any pharmacological action
- Physically and chemically compactible with drug and other excipients
- Should be accepted cosmetically and provide better feeling to the skin.

(4) Adhesives

A pressure sensitive adhesives placed on the face or in the back of the device. This will increase the adherence of patch to the skin.Polyacrylates, Polyisobutylene and silicon based adhesives are commonly used in TDDS.Patch design and formulation of drug should be considered while selecting an adhesive. Ideal characteristics of adhesive materials are,

- Shows good adhesion to the skin
- Non-reactive towards drug
- Bio-compatible
- Should not affect drug permeation
- Should be easily removed from the skin

(5) Backing layer

It is an impermeable supportive material that holds the entire system together and protects the drug reservoir from atmospheric exposure. Backing layer should be impermeable to drug and permeation enhancers. Chemical resistance of the material and excipient compatibility should be considered during the designing of backing layer. It should have high affinity, good oxygen transmission and a high vapour transmission rate. Polyester aluminized polyethylene teraphthalate and siliconised polyethylene are commonly used backing materials.

(6) Release liners

Release liner is considered as primary packaging material that protects the patch during storage and application. It is composed of base layer which maybe Occlusive (Polyethylene, polyvinyl chloride) or Non-occlusive (paper fabric).Release liner allows the permeation of drug, penetration enhance and water.

(7) Other excipients

Plasticizers are used to provide plasticity to the patch. Examples are glycerol, glycol derivatives such as PEG 200, PEG 400, phthalate esters etc. Solvents like chloroform, acetone, isopropanol, dichloromethane are used for the preparation of drug reservoir.

TYPES OF TRANSDERMAL PATCHES[7]

(1) Single layer drug in adhesive

(2) Multilayer drug in adhesive

(3) Vapour patches

(4) Reservoir system

(5) Matric system

- Drug in adhesive system
- Matrix dispersion system

(6) Micro reservoir system

(1) Single layer drug in adhesive

In this system, drug is embedded in the adhesive layer which is surrounded by a temporary liner and a backing. Adhesive layer plays an important role in the releasing of drug into the skin and is responsible for the adhesion of various layers together along with the entire system to the skin.

(2) Multilayer drug in adhesive

Multilayer system consists of two drug-in-adhesive layer which is usually separated by a membrane. One of the layer is responsible for the immediate release of drug and other layer is for controlled release of drug. This patch also combines a temporary liner layer and a permanent backing.

(8) Vapour patches

In a vapour patch, the adhesive layer not only binds the different layers together but also helps to release the vapour. Vapour patches release essential oil for up to 5 to 6 hours and it is mainly used in the treatment of decongestion, smoking cessation and sleep aid.

(9) Reservoir type

The reservoir type has a separate drug layer which is a liquid compartment containing drug solution or suspension separated by the adhesive layer. The drug reservoir is encapsulated between impervious backing layer and rate controlling membrane. This reservoir patch mainly follows zero order kinetics.

(10) Matrix system

In this system, a drug solution or suspension is incorporated with in a semisolid matrix drug layer which is surrounded by adhesive layer.

- Drug in adhesive system: In this system, drug is dispersed in an adhesive polymer followed by spreading of medicated adhesive polymer by solvent casting or melting on an impervious backing layer. Unmedicated adhesive polymer layers are applied on the top of the reservoir for the purpose of protection.
- Matrix dispersion system: Drug is homogenously dispersed in a lipophilic or hydrophilic polymer matrix which is then fixed on to an occlusive base plate in a compartment. Adhesive layer should be spread along with the circumference to form a adhesive rim strip.

(f) Micro reservoir system

It is a combination of reservoir and matrix dispersion system. Drug is suspended in an aqueous solution of water soluble polymer followed by homogeneous dispersion in a lipophilic polymer results in the formation of thousands of unreachable, microscopic spheres of drug reservoir. This can be stabilised by crosslinking of polymers *insitu* by using crosslinking agents.

EVALUATION STUDIES[3]

- **Thickness:** By using digital micrometer, thickness of the patch is measured at different places. It determines the average thickness and standard deviation for the same to ensure the thickness of prepared patch.
- **Weight uniformity:** Prior to testing, prepared patches should be dried at 60^0 C for 4 hours and a specified area of the patch is to be cut in different parts and weighed in digital balance. Calculate average weight and standard deviation value from the individual weights.
- **Folding endurance:** A strip of the specified area of prepared patch is to be cut evenly and fold repeatedly 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 folding endurance.
- **Percentage moisture content:** Individually weigh the prepared patches and stored in a desiccator containing fused calcium chloride at room temperature for 24 hours. Reweigh the patches after 24 hours and calculate the percentage moisture content from the below mentioned formula,

Percentage moisture content = (Initial weight – Final weight / Final weight) ^{x} 100

- **Percentage moisture uptake:** The weighed patches are to be stored in a desiccator containing saturated solution of potassium chloride for 24 hours in order to maintain 84% RH. Reweigh the patches after 24 hours and calculate the percentage moisture uptake from the below mentioned formula,

  Percentage moisture uptake = (Final weight – Initial weight / Initial weight) x 100

- **Drug content:** In a particular volume of suitable solvent, a specified area of patch is dissolved and it is filtered through a filter medium. The drug content can be analysed using various methods such as HPLC, UVetc. Each value indicated average of three different samples.
- **Shear adhesion test:** Shear adhesion test is performed to measure the cohesive strength of an adhesive polymer. On a stainless steel plate, an adhesive coated tape is applied to affect it, pulling in a direction parallel to the plate, a specified weight is hung from the tape. This can be find out by measuring the time taken to pull the tape off the plate.
- **Peel adhesion test:** A single tape is applied to a stainless steel plate or a backing membrane of choice. The tape is pulled at an angle of 180^{0} C from the substrate. Measure the force required for the removal of tape.
- **Thumb tack test:** A qualitative test used for the determination of tack property of the adhesive. Here, the thumb is simply pressed on the adhesive and detect the relative tack property.
- **Quick stick (peel tack) test:** In this test, the tape is pulled away from the substrate at 90^{0} C at a speed of 12inches/min. Then measure the peel force required to break the bond between adhesive and substrate and recorded as tack value which is expressed in ounces or gram/inch width.

- ***Invitro* drug release studies**

(1) The paddle over disc (USP apparatus 5): The paddle over disc method can be used for the determination of drug release from the prepared patches. This apparatus having a sample holder or disc assembly for holding the product. The preparation is placed in a dissolution flask containing 500ml of dissolution medium which is maintained at a temperature of 32 ± 5^{0} C.Then the paddle is placed directly over the disc assembly and should be operated at a speed of 50rpm.Vessel should be covered to avoid evaporation

during test. Samples can be withdrawn at appropriate time intervals and analysed using UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the average value can be calculated.

(2) The cylindrical modified USP Basket (USP apparatus 6)

In this apparatus, the system is attached to the surface of hollow cylinder immersed in the dissolution medium maintained at a temperature of 32 ± 5^0 C.Except that, this method is similar to USP basket typeapparatus. The amount of drug availability for the systemic absorption mainly depends on drug release from the transdermal patch.

- **Skin irritation study**

Skin irritation study can be performed on healthy rabbit having an average weight about 1.2 to 1.5 kg. Remove the hair on the dorsal surface of rabbit by shaving and clean the surface by using rectified spirit. Apply the prepared patch over the skin and remove after 24 hours. Observe the skin and classified into 5 grades based on severity of skin injury.

CONCLUSION

Transdermal drug delivery system is a novel approach of drug delivery for Local and systemic effect in a controlled and predictable rate. It ensure the proper targeting of active pharmaceutical agent with minimal side effects. TDDS attracting the attention of researchers and scientists due to its various advantages over the other conventional methods of drug delivery. Transdermal route is becoming the most widely accepted route of administration due to the recent advances in technology and the incorporation of drug to the site of action without rupturing the skin membrane. TDDS ensures controlled release of drug in to the systemic circulation via skinover a period of several hours or days. For optimising the care, clinicians can offer more therapeutic options to their patients through TDDS which is a realistic practical application having a promising future as it overcomes the challenges associated with current popular drug delivery.

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