A Review on Topical Drug Delivery System Patches

Article · January 2022

DOI: 10.35629/7781-0701292302

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International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 292-302 www.ijprajournal.com ISSN: 2249-7781

A Review on Topical Drug Delivery System Patches

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Submitted: 02-01-2022 Accepted: 12-01-2022

ABSTRACT
Topicaldrug delivery systems have been shown to overcome difficulties in drug delivery, especially orally. A topical patch is a drug-containing adhesive patch that is attached to the skin, and a specific dose of drug can be delivered to the blood through the skin. It promotes the healing of an injured area of the body. Advantages of the drug delivery route through the skin compared to other routes such as oral, topical, intravenous, etc. is a patch that allows a controlled release of medication into the patient, usually through a porous membrane that covers a drug reservoir or by body heat melting thin layers of medication embedded in an adhesive.The main disadvantage of thetopical delivery system is that the skin is a very effective barrier, so only drugs with small molecules that can easily penetrate the skin can be delivered by this method. This review article describes introduction, physiology of skin, criteria for drug selection of topical patch, which conditions topical patches are used/not used, advantages, disadvantages, Factor affecting topical drug delivery system, Components of Topical Drug Delivery System, a general clinical considerations in the use of tdds, methods of preparation of tdds, evaluation parameter.

INTRODUCTION

Topical products are classified according to those that are applied to produce local and systemic effects. These systems are commonly used for localized skin infections when other routes of administration have failed. See in Figure 1[1,2].

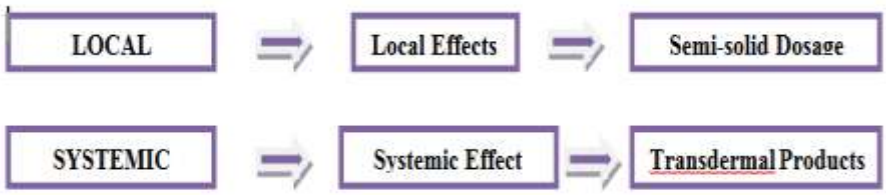

Fig. 1. :-Local and Systemic Actions

Effectively administered low-dose drug molecules are confined to a small area anywhere on the body. The stratum corneum is lipid in nature, made up of 40% fat,40% protein and only 20% water. The lipophilic properties of the drug make it most suitable for topical use, the delivery of which is facilitated by solubility in the intercellular lipids surrounding the cells of the stratum corneum. However, hydrophilic drugs are difficult to transport to the stratum corneum due to their low water content. These molecules are absorbed into the skin through "pores" or openings in hair follicles and sebaceous glands that limit the absorption of the drug. Percutaneous absorption is an ideal factor to be considered in a topical drug delivery system to achieve and maintain consistent systemic therapeutic levels throughout the duration of administration. Drugs that are administered passively through the skin must have appropriate lipophilicity and a molecular weight of less than 500 Da. The topical drug reaches the area at optimal concentrations reducing side effects and increasing bioavailability and patient compliance[3].

In topical drug use, the skin is one of the main and easily accessible organs of the human body. The stratum corneum forms a major barrier to penetration of drugs into and through the skin. However, this layer makes it selective for the

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distribution system. An important aspect of topical drug use is making the skin the target organ for diagnosis and treatment. This review is more concerned with all the details regarding conventional and current advances in topical drug delivery[4,5,6].

TOPICAL DRUG DELIVERY

A topical drug delivery system is a local drug delivery system for the delivery of topical drugs through the skin for the treatment of skin disorders. These systems are commonly used for local skin infections. Formulations are available in different forms, from solid to semi-solid to liquid. If the drug substance in solution has a favorable lipid/water partition and it is a non-electrolyte, the absorption of the drug is improved through the skin. Dermatological products come in a variety of formulations and their consistency, although the most common dermatological products are semi-solid dosage forms[7].

TOPICAL DRUG CLASSIFICATION SYSTEM (TCS)

Based on qualitative(Q1) & quantitative(Q2) composition, Semi solid products(Q3), TCS provides a framework for classifying topical drug products. Topical drug products are classified into 4 classes, as seen in Figure 2[8].

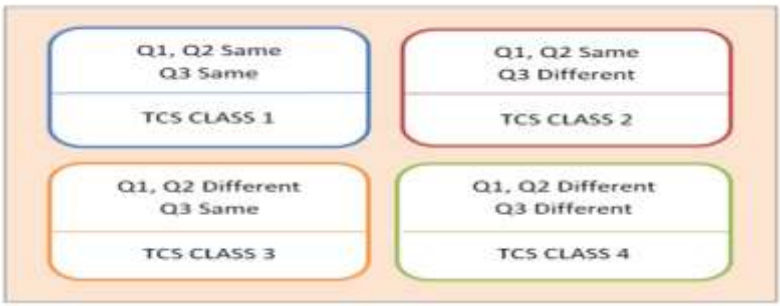

Fig. 2:-Classification of Topical Drug Products Based on Qualitative & Quantitative Composition

ANATOMY AND PHYSIOLOGY OF SKIN

The skin is most extensive part of the body. Human body covering an area in skin about 2 m^2. Human skin three distinct layer. Each layer has perform own function and own importance to maintain the integrity of skin.

❖ **Cellular epidermis**

The epidermis is a constantly renewing squamous epithelium that covers the entire outer surface of the body and is mainly made up of two parts: living cells or cells of the squamous layer (existing epidermis) and squamous cells. dead cells of the corneal layer.[5] called the stratum corneum. Viable epidermis further classified into four distinct layers, as shown in Fig.3[9].

- The stratum lucidum
- The stratum granulosum
- The stratum spinosum
- The stratum basale

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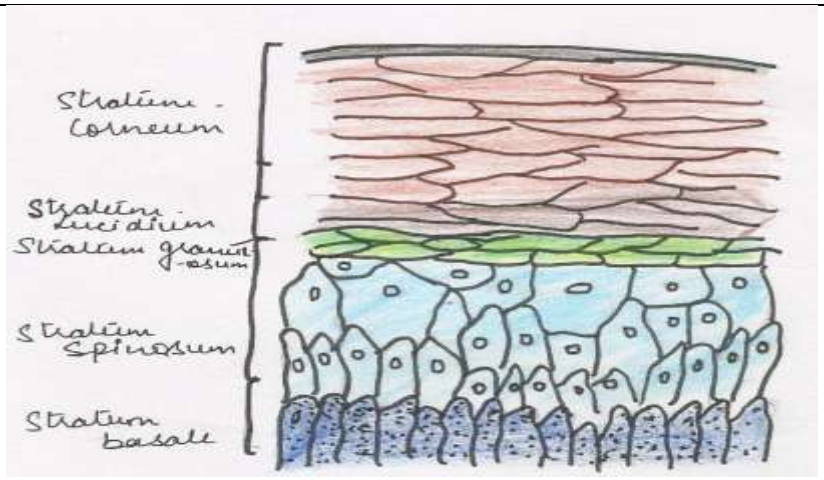

Fig. 3: Schematic Diagram Of Anatomy Of Cellular Epidermis

❖ **Stratum corneum:**

It is the outermost layer of the skin, also known as the stratum corneum. It is a flow restriction barrier that restricts the movement of chemicals in and out. The barrier nature of the stratum corneum is highly dependent on its constituents: 7580% protein, 515% lipid and 510% ondansetron on a dry weight basis.

The stratum corneum is about 10mm thick when dry, but will swell several times when fully hydrated. It is flexible but relatively waterproof. The architecture of the stratum corneum (Figure 4) can be modeled as a structure in the form of a wall of protein bricks and lipid mortar. It is made up of keratinocytes (corneal cells) bound together by desmomes (protein-rich appendages of cell membranes).The corneal cells are embedded in a lipid matrix that plays an important role in determining the permeability of this substance through the skin[10].

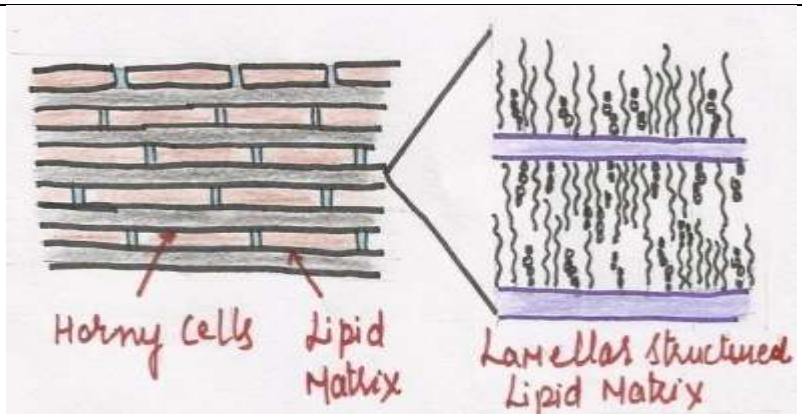

Fig. 4: Schematic Diagram Of Micro-Structure Of Stratum Corneum

❖ **Viable epidermis:**

It lies below the stratum corneum and varies in thickness from 0.06mm on the eyelids to 0.8mm on the palms. Going inside, it consists of various layers such as the lucidum layer, the seed layer, the organism layer and the substrate layer. In the basal layer, cell mitosis continuously renews the epidermis and this proliferation compensates

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for the loss of dead keratinocytes from the surface of the skin. As the cells produced by the basal layer migrate outward, they undergo morphological and histological changes on their own, undergoing keratinization to form the outermost layer of the stratum corneum[11]. shown in Fig. 5.

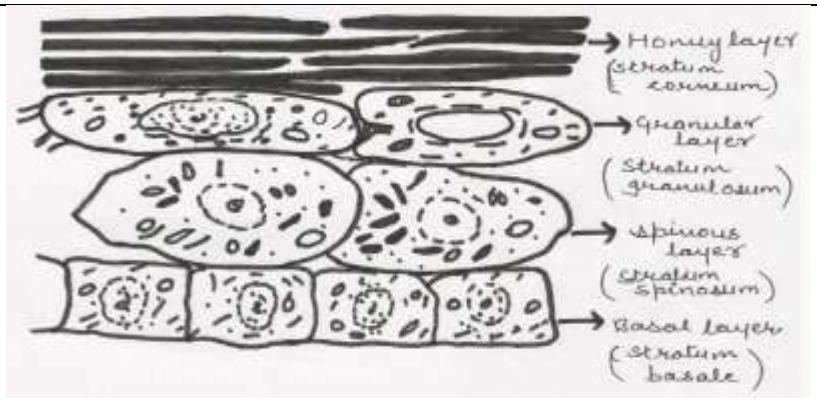

Fig. 5: Schematic Diagram Of Different Layers Of Viable Epidermis

❖ **Dermis:**

The dermis is the layer of skin just 3-5 mm below the epidermis and is made up of a matrix of connective tissue, containing blood vessels, lymph and nerves. The skin's blood supply has an essential function in regulating body temperature. It also delivers nutrients and oxygen to the skin, and removes toxins and waste. The capillaries reach within 0.2 mm of the skin surface and facilitate the escape of most of the molecules to penetrate the skin barrier. Thus, the blood supply maintains very low topical concentrations, and the difference in concentrations across the epidermis provides the essential driving force for topicalpenetration.for topical drug delivery system, this layer is generally considered to be mainly composed of water and thus providing a minimal barrier to the use of most polar drugs,, although the skin barrier may be important. important when using highly lipophilic molecules[12].

❖ **Hypodermis:**

The dermis or subcutaneous fatty tissue supports the dermis and epidermis. It serves as a fat storage area. This layer provides temperature regulation, nutritional support, and mechanical protection. It carries major blood vessels and nerves to the skin and may contain sensory pressure organs. In order for a drug to be delivered through the skin, it must penetrate all three layers and reach the circulatory system[11].

CRITERIA FOR DRUG SELECTION OF TOPICAL PATCH [13-15]

- Drugs should be selected for their short half-life.
- In topicalpatches, the dose should be chosen to be low.(<20mg/ml)
- Drugs should be chosen with lower molecular weight (<400 daltons)
- Drugs should be selected in the partition coefficient(logP) between 1.0-4.
- The drug should be chosen in an oral form with low bioavailability.
- Drugs should be selected with a low therapeutic index.
- The drug should be selected as non-irritating and non-sensitizing to the skin.
- Drugs must be selected in their affinity for the lipophilic and hydrophilic phases.

WHICH CONDITIONS TOPICAL PATCHES ARE USED:

Topicalpatches are used when:

- When a patient experiences side effects that are intolerable and cannot take oral medications (dysphagia) and an alternative medication approach is needed.
- Where pain control can be improved by reliable management. This can be helpful in patients with dementia or who for other reasons are unable to self-medicate with their pain medication.

WHICH CONDITIONS TOPICAL PATCHES ARE NOT USED:

The use of topicalpatches is not appropriate when:

(1)Treatmentof acute pain is necessary.

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(2) When rapid dose titration is required.
(3) When the required dose is equal to or less than 30 mg/24 hours[16,17].

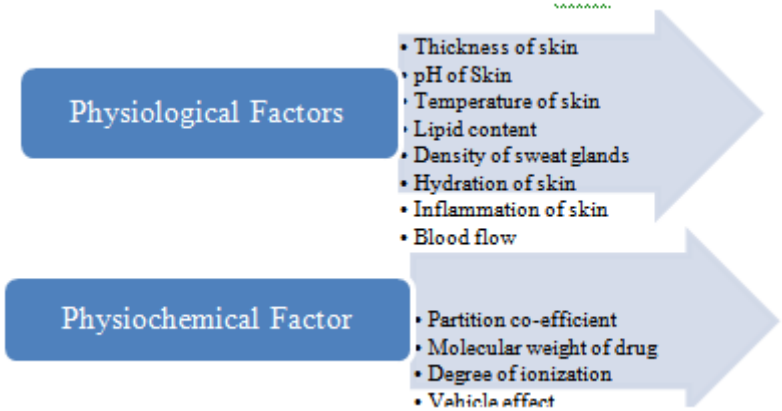
ADVANTAGES[18,19]

- Avoid first-pass metabolism.
- It is easy to use and easy to apply.
- Easy withdrawal of medicine.
- Drugs are selectively distributed to a specific location.
- Gastrointestinal incompatibility should be avoided.
- Provide the use of drugs with short biological half-lives and narrow therapeutic windows.
- Improve patient compliance.Self-medication.
- It gives effect at low dose and by continuous drug delivery.
- Avoid drug concentration fluctuations and risks.
- A wide field of application compared to other routes.
- Dispensing drugs to a specific location

DISADVANTAGES[18,19]

- Possibility of local skin irritation at the site of application.
- Drug-induced contact dermatitis may occur.
- Some drugs with low permeability are difficult to penetrate through the skin.
- Drugs with larger particles are difficult to penetrate.
- Possibility of an allergic reaction.
- Drugs with very low plasma concentrations may be used to action

FACTORS EFFECTING TOPICAL PERMEABILITY:[20,21]



COMPONENTS OF TOPICAL DRUG DELIVERY SYSTEM:[22-27]

- Polymer matrix/ Drug reservoir
- Drug
- Permeation enhancers.
- Pressure sensitive adhesive (PSA).
- Backing laminate.
- Release liner.
- Other excipients like plasticizers and solvents [5].

Polymer Matrix/ Drug Reservoir

Macromolecular control is the release of drugs from the device. The following criteria must e met for a polymer to e used in topical patches.

- The molecular weight and chemical function of the polymer should be such that the specific drug diffuses properly and is released through it.
- Polymers must be durable.
- Polymer must be non-toxic.
- Polymers must be easy to manufacture.
- Polymers must be cheap.
- The polymer and its degradation products must be non-toxic or non-antagonistic to the host.
- A large amount of active ingredients are incorporated in it.

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Types of polymer: -

Natural polymers:	Synthetic Elastomers:	Synthetic polymers:
Cellulose derivative, Waxes, Gelatin, Proteins, Gum, Shellac, starch, Natural rubber.	Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.	Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode, polyurea, epoxy.

- **Drug**

The drug solution in direct contact with the memrane releases

Physiochemical properties:

- The drug must have a molecular weight of less than 1000 Daltons.
- The drug must have affinity for both the lipophilic and hydrophilic phases.
- The drug must have a low melting point.

Biological properties

- The drug should have a strong effect at a daily dose of several mg/day.
- The half-life ($t_{1/2}$) of the drug should be short.The drug should not cause skin irritation or allergic reactions.
- Drugs that are degraded in the gastrointestinal tract, or inactivated by first-pass effects by the liver, are suitable candidates for topical administration.
- Tolerance is not developed below the level of release close to topical administration.
- Drugs that must be used for a long time or cause unwanted effects in non-target tissues may also be formulated for topical administration.

- **Permeation enhancer:-**

A penetration enhancer or promoter is an agent that has no inherent therapeutic properties but is able to transport drug absorption from the drug delivery system to the skin.11 The topical drug flow can be written as:J = D Xdc / dxwhere D is the diffusion coefficient and is a function of the size, shape and flexibility of the diffusing molecule as well as of the membrane resistance; C is the concentration of the diffuse species; x is the spatial coordinate.Although the solution for J for different boundary conditions and film heterogeneity can be very complex, the basic concepts of flux improvement can be found in the above equation. The concentration gradient is thermodynamically derived, and the diffusion coefficient is related to the size and shape of the entry and the energy required to create a hole for diffusion.

- **Pressure sensitive adhesive (PSA)**

PSA maintains close contact between the patch and the skin surface. It must adhere to maximum finger pressure, has a strong and long-lasting effect of tacho, and has a strong holding force. These include polyacrylate, polyisobutylene and silicone adhesives. The choice of an adhesive is based on many factors, including the design of the patch and the formulation of the drug. PSA must be physicochemically and biologically compatible and must not interfere with drug release. The PSA can be located on the face of the device (as in a reservoir system) or on the rear of the device and extend to the periphery (as in the case of the matrix system).

- **Backing laminate.**

The main function of the support plate is to provide support. The buffer layer must be chemically resistant and compatible with the excipients, as prolonged contact between the buffer layer and the excipients can cause leaching of the additives or may lead to diffusion of the excipients and drugs. or diaper enhancer. They must have a low steam transmission rate. They must have optimum elasticity, flexibility and tensile strength. Examples of some supporting materials are aluminum vapor coating, plastic film (polyethylene, polyester) and thermal backing.

- **Release liner**

During storage, the release liner prevents loss of drug that has migrated into the binder and contamination. It is therefore considered part of the primary packaging material rather than part of the dosage form for medicinal use. The release liner is composed of a backing that can be non-stick (tissue paper) or non-stick (polyethylene and polyvinyl chloride) and a non-stick coating consisting of silicon or teflon. Other materials used for TDDS release liners include a polyester foil and a metal lamination.

METHODS OF PREPARATION OF TDDS[28,29]

- Asymmetric TPX membrane method.
- Circular Teflon mould method.
- Mercury substrate method.
- By using “IPM membranes” method.
- By using “EVAC membranes” method.

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- Preparation of TDDS by using Proliposomes.
- By using free film method.

- **Asymmetric TPX Membrane Method:**This method was discovered by Berner and John in 1994 . By this method, a prototype patch can be prepared using a heat-sealable polyester film (1009.3 m type) with a diameter of 1 cm concave as support membrane. The drug was dispersed on a concave film, covered by an asymmetrical TPX [poly (4-methyl-1-pentene)] film, and sealed with an adhesive.

Preparation:They are prepared using either a dry or wet reverse process. In this TPX is dissolved in a mixture of solvents (cyclohexane) and solvent-free additives at 60 °C to form a polymer solution. The polymer solution was maintained at 40 °C for 24 h and poured onto a glass dish. The molded film was then evaporated at 50 °C for 30 s, after which the glass plate should be immediately immersed in a coagulation bath (temperature kept at 25 °C). After soaking for 10 min, the film can be removed, air-dried in a recirculating oven at 50 °C for 12 h.

- **Circular Teflon Mould Method:**It was discovered by Baker and Heller in 1989. A polymer solution in various proportions is used as an organic solvent. Then this solution is divided into two parts. In one part, the calculated amount of drug is dissolved, and in the other part, activators of different concentrations are dissolved, after which the two parts are mixed. Then a plasticizer (eg, diNbutyl phthalate) is added to the drug polymer solution. The total solution should be stirred for 12 hours and then poured into a round Teflon mold. The mold should be placed on a level surface and covered with an inverted funnel to control solvent evaporation in a laminar flow fume hood model with an air velocity of 0.5 m/s.The solvent was allowed to evaporate for 24 h. A dry film was then formed that was kept for an additional 2 h at 25 ± 0.5 °C in a desiccator containing silica gel prior to evaluation to eliminate the effects of aging.

- **Mercury Substrate Method:** In this method, the drug and plasticizer are dissolved in a polymer solution. It is stirred for 10 to 15 min to produce a homogeneous dispersion, after which it is poured onto a flat mercury surface, covered with an inverted funnel to control solvent evaporation.

- **By Using "IPM Membranes" Method:**In a mixture of water and polymers (propylene glycol polymers containing Carbomer 940), the drug was dispersed and stirred for 12 h in a magnetic stirrer. The dispersion shall be neutralized and made viscous by the addition of triethanolamine. If the solubility of the drug in aqueous solution is very low, a solution gel is obtained using pH 7.4 buffer. The resulting gel will be incorporated into the IPM membrane.

- **By Using "EVAC Membranes" Method:**To prepare TDS, a membrane consisting of a gel containing 1% carbopol, polyethylene (PE) and ethylene vinyl acetate copolymer (EVAC) is required as the flow control membrane. If the drug is insoluble in water, use propylene glycol to prepare the gel. The drug was dissolved in propylene glycol, carbopol resin was added to the above solution and neutralized with 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of carrier layer that covers the indicated area. A flow control film will be placed on the gel and the edges will be heat sealed to achieve a watertight device.

- **Preparation of TDDS by Using Proliposomes:**By an assisted method using film deposition technique,proliposomeswere prepared. The drug/lecithin ratio should be 0.1:2.0 to be considered as the optimized ratio compared to previous references. To prepare proliosomes in a 100 ml round-bottom flask, take 5 mg of mannitol powder, then maintain at 60-70°C and rotate the flask at 80-90 rpm and mannitol is dried under vacuum for 30 min. . After drying, the temperature of the water bath was adjusted to 20-30 °C. The drug and lecithin were dissolved in a suitable mixture of organic solvents, an amount of 0.5 ml of the organic solution was added. round bottom flask at 37 °C, after complete drying, a second portion (0.5 ml) of solution should be added. After the final loading, the vial containing the proliposome was joined in a freeze dryer and then the loaded mannitol powder (proliposome) was placed in a desiccator overnight and then sieved through a 100 mesh. The resulting powder was

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transferred to the vial. glassware and stored at cryogenic temperature until properties can be determined.

- **By using Free Film Method:** In this process, a cellulose acetate-free film is first prepared by casting it onto a mercury surface. And 2% w/w polymer solution was prepared using chloroform. Plasticizers should be added at a concentration of 40% by weight/weight of polymer. Then, 5 ml of the polymer solution was poured into a glass ring placed over the mercury surface in a glass petri dish. The solvent evaporation rate can be controlled by placing an inverted funnel over the Petri dish. Film formation was observed by observing the surface of the mercury after the solvent had completely evaporated. The dry film will be separated and stored between wax paper sheets in a desiccator until use. By this process, we can prepare freestanding films of different thicknesses, which can be prepared by varying the volume of the polymer solution.

EVALUATION PARAMETER OF TOPICAL PATCH:[30-47]

❖ **A Drug Excipients Interaction Studies of patch**

Drugs and excipients must be compatible to make a stable product and it is imperative to detect any possible physical and chemical interactions. Interaction studies are usually performed using thermal analysis, FTIR studies, UV techniques and chromatography comparing their physicochemical characteristics such as assays, fusion fusion, characteristic wave numbers and absorption maxima, etc.

❖ **Drug Content of patch**

A specific area of the patch must be dissolved in the appropriate solvent for a specific volume. The solution should then be filtered through a filter media and analyzed for drug content by an appropriate method (UV or HPLC technique). Each value represents the mean of three samples.

❖ **Weight Uniformity of patch**

Prepared patches should be dried at 60°C for 4 hrs prior before testing. A specific area of the patch should be cut into different parts of the patch and weighed in a digital balance. The mean and standard deviation values should be calculated from the individual weights.

❖ **Thickness of patch**

The thickness of the loaded patch was measured for different points by use of digital micrometer and the mean thickness and standard deviation of the patch were determined to ensure the thickness of the prepared patch.

❖ **Flatness Test:**

Three longitudinal strips should be cut from each film into different sections such as one from the center, another from the left side and another from the right side. The length of each strips was measured and the change in length due to non uniform flatness was measured by determining the percent constriction, with 0% constriction equivalent to 100% flatness.

❖ **A Percentage Moisture Uptake:**

A Weighed films should be stored in a desiccator at room temperature for 24 h containing saturated solution of potassium chloride to maintain 84% RH. After 24 h, the films should be reweighed and the percentage of moisture uptake determined according to the formula below.

Percentage moisture uptake = [initial weight-final weight/ final weight] × 100.

❖ **A Moisture Loss:**

Prepared films should be weighed individually and stored in a desiccator containing calcium chloride at 40 °C. After 24 h, the films should be reweighed and the percentage moisture loss determined according to the formula below.

% Moisture Loss = [Initial wt – Final wt/ Final wt] × 100

❖ **Water Vapor Transmission Rate (WVTR) Studies of patch**

Glass vials of equal diameter are used as a transmission cells. These transmission cells were thoroughly washed and dried in an oven at 100 °C for a period of time. Approximately 1 g of anhydrous calcium chloride was placed into the cells and the corresponding polymeric films were attached to the edge. Cells were accurately weighed and stored in a sealed desiccator containing a saturated solution of potassium chloride to maintain a relative humidity of 84 %. Cells were removed and weighed after storage. The amount of

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water vapor passed by found using following formula.
Water Vapor Transmission Rate = Final Weight – Initial WeightTime X Area
It is expressed in grams of moisture gained/hrs/cm.sq.

❖ **Swellability of patch**

The 3.1 cm2 patch were weighed and placed in10 ml of double distilled water petri dish and allowed to imbibe. Patch weight increase were determined at preset time intervals, until observed constant weight.
Degree of swelling (S) = Wt– Wo/Wo× 100
Where S is the percentage of swelling,
W_t is the weight of the patch at time t, and W_o is the weight of the patch at time 0.

❖ **Folding Endurance of patch:**

A specific area strip should be cut evenly and repeatedly folded in the same place until it breaks. The number of times the film can be folded in the same position without breaking gives value to its folding endurance.

❖ **Polariscope Examination of patch**

This test should be done to check for drug crystals in the patch with a polariscope. A specific surface area of the patch should be kept on a slide and observed for drug crystals to distinguish whether the drug is crystalline or amorphous in the patch.

❖ **Tensile Strength:**

The tensile strength of the film was determined using a universal strength tester. The sensitivity of the device is 1 g. It includes two force sensing handles. The bottom is fixed and the top is movable. Film of the test size (4×1 cm^2) was fixed between these cell clamps and a gradually force was applied until the film broke. The tensile strength of the patch is taken directly from the dial readings in kg. The tensile strength is expressed by following.
Tensile strength of patch =Tensile load at break / Cross section area

❖ **Probe Tack test of patch**

In this test, the tip of a clean probe with a defined surface roughness is exposed to the adhesive and when a bond is formed between the probe and the adhesive. The draw would then mechanically break it. The force required to remove the probe from the adhesive at a fixed rate is recorded as adhesive and expressed in grams.

❖ **Skin Irritation Study of patch**

Skin sensitization and irritation tests can be performed on healthy rabbits (mean weight 1.2-1.5 kg). The dorsal surface (50 cm2) of the rabbit should be cleaned and hair removed from the clean dorsal surface by scraping and cleaning the surface using disinfected alcohol and representative formulations may be used for application. onto the skin. The patch should be removed after 24 hours and the skin should be observed and graded into 5 grades based on the severity of the skin damage.

❖ **In-vitro drug release studies of patch**

The paddle-over-disk method (USP V device) can be used to assess drug release from prepared patches. The dry film of known thickness shall be cut into a defined shape, weighed and fixed to the glass plate with an adhesive. Then place the glass dish in 500 ml of dissolution medium or phosphate buffer (pH 7.4) and the apparatus equilibrated at 32 ± 0,5 °C. The stirrer isset from the glass plate 2.5 cm and operates at 50 rpm. Samples (aliquots 5 ml) can be sampled over an appropriate period of up to 24 h and analyzed by UV spectrophotometer or high performance liquid chromatography (HPLC). The test shall be carried out in triplicate and an average value may be calculated.

❖ **Stability Studies of patch**

Stability studies should be performed according to ICH guidelines by storing TDDS samples at 40 ± 0.5 ℃ and 75 ± 5% RH for 6 months. Samples were taken at 0, 30, 60, 90 and 180 days and analyzed for suitable drug content.

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