International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 916-925 www.ijprajournal.com ISSN: 2456-4494

Transdermal Delivery System of Testosterone Using Solid Lipid Particles

Riya Kumari, Mrs Jaya Singh, Mrs Chanda Ray
Innovative College of Pharmacy, Plot no. 6, Knowledge Park 2 Greater Noida, Uttar Pradesh 201308

Submitted: 01-04-2022 Accepted: 09-04-2022

ABSTRACT:
Transdermal drug delivery system (TDDS) emerged as an important component of innovative drug delivery systems with the introduction of a new era of pharmaceutical dosage forms. Transdermal patches are polymeric formulations that transport a medication through the dermis at a preset pace to produce systemic effects when applied to the skin. Though more expensive than traditional formulations, transdermal dosage forms are gaining popularity due to their distinct benefits. Some of the possible benefits of transdermal drug delivery include controlled absorption, more consistent plasma levels, better bioavailability, fewer adverse effects, painless and easy application, and the flexibility of stopping drug administration by simply removing the patch from the skin. The development of a controlled release transdermal dosage form is a lengthy and difficult procedure. The techniques for preparing several kinds of transdermal patches, such as matrix patches, reservoir patches, membrane matrix hybrid patches, drug-in-adhesive patches, and micro reservoir patches, are described in this review article. In addition, the different techniques of transdermal dosage form assessment have been examined.

Key words: Transdermal drug delivery system, permeation enhancers, design of transdermal patches, evaluation of transdermal system

I. INTRODUCTION:

Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin- the largest and most accessible organ of human body- through its layers, to the circulatory system. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. "Another advantage is convenience, especially notable in patches that require only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy." Designing and development of transdermal patches can be described as state of the art. The development of TDDS is multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an ex vivo and in vivo model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical and stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important the economy.

Transdermal Permeation

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows:

- Diffusion of drug from drug reservoir to the rate controlling membrane.
- Diffusion of drug from rate limiting membrane to stratum corneum.
- Sorption by stratum corneum and penetration through viable epidermis.
- Uptake of drug by capillary network in the dermal papillary layer.
- Effect on target organ.

Basic Components Of TDDS

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 916-925 www.ijprajournal.com ISSN: 2456-4494

- Other excipients like plasticizers and solvents

Polymer matrix / Drug reservoir:

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status.

Companies involved in the field of transdermal delivery concentrate on a few selective polymeric systems. For example, Alza Corporation mainly concentrates on ethylene vinyl acetate (EVA) copolymers or microporous polypropylene and Searle Pharmacia concentrates on silicon rubber6. Similarly

Colorcon, UK uses HPMC for matrix preparation for propranolol transdermal delivery and Sigma uses ethylcellulose for isosorbide dinitrate matrix. The polymers utilized for TDDS can be classified as:

- Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.
- Synthetic Elastomers: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber etc.
- Synthetic Polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.

The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for TDDS.

Other polymers like EVA15, silicon rubber and polyurethane are used as rate controlling membrane.

Drug: The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosing. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (dose in mg per day). Table 1 enlists the currently available drugs for transdermal delivery. In addition drugs like rivastigmine for alzheimer's and parkinson dementia, rotigotine for parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

Permeation Enhancers: These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate. Penetration enhancers interact with structural components of stratum corneum i.e., proteins or lipids. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability. Over the last 20 years, a tremendous amount of work has been directed towards the search for specific chemicals, combination of chemicals, which can act as penetration enhancers..

Pressure sensitive adhesives: A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDSs. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. For matrix systems with a peripheral adhesive, an incidental contact between the adhesive and the drug and penetration enhancer should not cause instability of the drug, penetration enhancer or the adhesive. In case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. In case of drug-in-adhesive matrix systems, the selection will be based on the rate at which the drug and the penetration enhancer will diffuse through the

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 916-925 www.ijprajournal.com ISSN: 2456-4494

adhesive. Ideally, PSA should be physicochemically and biologically compatible and should not alter drug release.

Backing Laminate: While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusivity to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate. Examples of some backing materials are vinyl, polyethylene and polyester films.

Release Liner: During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non- occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates.

Other excipients: Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

Preparation Of Different Types Of Transdermal Patches:
Several system designs have been used in development and fabrication of TDDSs. The systems that have been introduced in market can be classified into following types:

Matrix type

Reservoir type

Membrane matrix hybrid

Micro reservoir type

Drug in adhesive type

Matrix Type Transdermal Patch(s):

Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogenously dispersed in hydrophilic or lipophillic polymer. The required quantity of plasticizer like dibutylpthalate, triethylcitrate, polyethylene glycol or propylene glycol and permeation enhancer is then added and mixed properly. The medicated polymer formed is then molded into rings with defined surface area and controlled thickness over the mercury on horizontal surface followed by solvent evaporation at an elevated temperature. The film formed is then separated from the rings, which is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. Adhesive polymer is then spread along the circumference of the film. Some examples of matrix patches prepared by solvent evaporation method
Commonly used polymers for matrix are cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose.
The dispersion of drug particles in the polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature. Advantages of matrix patches include absence of dose dumping, direct exposure of polymeric matrix to the skin and no interference of adhesive.

Reservoir Type Transdermal Patch(s):

The drug reservoir is made of a homogenous dispersion of drug particles suspended in an unleachable viscous liquid medium (e.g. silicon fluids) to form a paste like suspension or gel

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 916-925 www.ijprajournal.com ISSN: 2456-4494

or a clear solution of drug in a releasable solvent (e. g. ethanol). The drug reservoir formed is sandwiched between a rate controlling membrane and backing laminate

The rate controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid filled micropores in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of nonporous membrane, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the thickness of membrane. Hence, the choice of membrane material is dependent on the type of drug being used. By varying the composition and thickness of the membrane, the dosage rate per unit area of the device can be controlled. Mostly EVA, ethyl cellulose, silicon rubber and polyurethanes are used to prepare rate controlling membranes1,. EVA is used most frequently to prepare rate controlling membrane in transdermal delivery systems because it allows the membrane permeability to be altered by adjusting vinyl acetate content of polymer. Polyurethane membranes are suitable especially for hydrophobic polar compounds having low permeability through hydrophobic polymers such as silicon rubber or EVA membrane.

Liang et al., studied controlled release of scopolamine through EVA membrane in transdermal patch formulations and release rates were compared with uncontrolled reservoirs. It was found that an EVA membrane patch released scopolamine at a constant rate for more than 72 hours

Krishna and Pandit prepared three transdermal formulations containing propranolol hydrochloride in a hydrophilic polymer matrix, one without rate controlling membrane and other two with EVA rate controlling membranes of different thickness. It was found that increased thickness of EVA led to greater retention of the drug in device and zero order profile was observed with EVA

Rate controlling membrane may be prepared by solvent evaporation method or compression method. In case of solvent evaporation method, polymer is dissolved in solvent with or without plasticizer. Then the solution is poured on the horizontal surface and left for evaporation of solvent in order to obtain a thin film. Examples of preparation of rate controlling membrane by solvent evaporation method . In case of compression method, polymer is compressed with required force at high temperature for specific period of time. Drugs that require relatively high doses or greater permeation enhancement, such as testosterone, use liquid reservoir systems. But the application of enhancers and adhesive technologies has allowed many drugs that were initially administered in liquid reservoirs to be used as matrix type systems e.g. estradiol, nicotine, nitroglycerine. The main advantage of reservoir type patches is that this patch design can provide a true zero order release pattern to achieve a constant serum drug level.

This is the modification of reservoir type transdermal patch. The liquid formulation of the drug reservoir is replaced with a solid polymer matrix (e.g. polyisobutylene) which is sandwiched between rate controlling membrane and backing laminate. Examples of marketed preparations are Catapress and TransdermScop.

Micro reservoir type transdermal patch(s):

The drug reservoir is formed by suspending the drug solids in an aqueous solution of water miscible drug solubilizer e.g. polyethylene glycol. The drug suspension is homogenously dispersed by a high shear mechanical force in lipophillic polymer, forming thousands of unleachable microscopic drug reservoirs (micro reservoirs). The dispersion is quickly stabilized by immediately cross linking the polymer chains in-situ which produces a medicated polymer disc of a specific area and fixed thickness. Occlusive base plate mounted between the medicated disc and adhesive form backing prevents the loss of drug through the backing membrane. This system is exemplified by development of Nitrodisc.

Drug in adhesive type transdermal patch(s):

The drug and other selected excipients, if any, are directly incorporated into the organic solvent based pressure sensitive adhesive solution, mixed, cast as a thin film and dried to evaporate the solvents, leaving a dried adhesive matrix film containing the drug and excipients. This drug in adhesive matrix is sandwiched between release liner and backing layer. Drug -in -adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 916-925 www.ijprajournal.com ISSN: 2456-4494

Some examples of suitable pressure sensitive adhesives are polysiloxanes, polyacrylates and polyisobutylene. These pressure sensitive adhesives are hydrophobic in nature and are prepared as solutions of polymer dissolved in organic solvents. Hence, this type of system is preferred for hydrophobic drugs as it is to be incorporated into organic solvent basedhydrophobic adhesive. prepared drug in adhesive patches of green tea extract and it was observed that major catechins and caffeine extracted from green tea were successfully delivered transdermally from drug-in-adhesive patches.

Kannikkanan et al. prepared and evaluated monolithic drug in adhesive type transdermal patches of melatonin and used eudragit E100 as adhesive polymer65. Lake and Pinnock (2000) proved that once a week drug in adhesive patch of estrogen is more patient compliant as compared to twice a week reservoir patch. Characteristics of drug in adhesive patch may account for improved patient compliance due to ease of remembering once weekly patch application, improved cosmetic acceptance and better adhesion66. Examples of marketed preparations of drug-in- adhesives patches are Climara, Nicotrol and Deponit.

Evaluation Of Transdermal Patches

Development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:
Physicochemical evaluation

In vitro evaluation

In vivo evaluation

Upon the success of physicochemical and in vitro studies, in vivo evaluations may be conducted.

Physicochemical Evaluation:

Thickness: The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution48.
Content uniformity test: 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patchespass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test

Moisture content: The prepared films are weighed individually and kept in a desiccatorscontaining calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula68.

% Moisture content = Initial weight – Final weight X 100 Final weight

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below68.

% moisture uptake = Final weight – Initial weight X 100 Initial weight

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 916-925 www.ijprajournal.com ISSN: 2456-4494

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness

% constriction = I1 – I2 X 100 (1) I1

I2 = Final length of each strip I1 = Initial length of each strip

Folding Endurance: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

Tensile strength= F/a.b (1+L/l) (2)

F is the force required to break; a is width of film; b is thickness of film; L is length of film; l is elongation of film at break point In another study, Tensile strength of the film was determined with the help of texture analyzer. The force and elongation were measured when the films broke.

Water vapor transmission studies (WVT):

For the determination of WVT, Rao et al., weighed one gram of calcium chloride and placed it in previously dried empty vials having equal diameter. The polymer films were pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials were accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials were again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch.

In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccator was measured by using hygrometer. The weighed vials were then placed in desiccator and procedure was repeated.

WVT =W/ST (3)

W is the increase in weight in 24 h; S is area of film exposed (cm2); T is exposure time

Microscopic studies: Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope.

Adhesive studies:

The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors:

- Peel Adhesion properties: It is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° angle. The test is passed if there is no residue on the substrate. Minghetti et al., performed the test with a tensile testing machine Acquati model AG/MC 1 (Aquati, Arese, Italy).

- Tack properties: It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 916-925 www.ijprajournal.com ISSN: 2456-4494

weight and composition of polymer as well as on the use of tackifying resins in polymer.

Thumb tack test: The force required to remove thumb from adhesive is a measure of tack

Rolling ball test: This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel

Quick stick (Peel tack) test: The peel force required breaking the bond between an adhesive
and substrate is measured by pulling the tape away from the substrate at 90◦ at the speed of 12 inch/min.

Probe tack test: Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

Shear strength properties or creep resistance : Shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate. Minghetti et al., (2003) performed the test with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification.

In vitro release studies:

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their in vivo performance. A number of mathematical model have been developed to describe the drug dissolution kinetics from controlled release drug delivery system e.g., Higuchi, First order, Zero order and Peppas and Korsenmeyer model. The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug.

There are various methods available for determination of drug release rate of TDDS.

- The Paddle over Disc: (USP apparatus 5/ PhEur 2.9.4.1) This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C
- The Cylinder modified USP Basket: (USP apparatus 6 / PhEur 2.9.4.3) This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5°C.
- The reciprocating disc: (USP apparatus 7) In this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method (PhEur 2.9.4.2) may be used85.
- Diffusion Cells e.g. Franz Diffusion Cell and its modification Keshary- Chien Cell: In this method transdermal system is placed in between receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment in which receptor fluid i.e., buffer is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of drug is determined spectrophotometrically.

The pH of the dissolution medium ideally should be adjusted to pH 5 to 6, reflecting physiological skin conditions. For the same reason, the test temperature is typically set at 32°C (even though the temperature may be higher when skin is covered). PhEur considers 100 rpm a typical agitation rate and also allows for testing an aliquot patch section. The latter may be an appropriate means of attaining sink conditions, provided that cutting a piece of the patch is validated to have no impact on the release mechanism. The dissolution data obtained is fitted to mathematical models in order to ascertain the release mechanism.

In vitro permeation studies:

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 916-925 www.ijprajournal.com ISSN: 2456-4494

penetration through cells of epidermis, between the cells of epidermis through skin appendages.

Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5℃ for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and temperature etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux i.e., drug permeated per cm2 per second.

Preparation of skin for permeation studies: Hairless animal skin and human cadaver skin are used for permeation studies. Human cadaver skin may be a logical choice as the skin model because the final product will be used in humans. But it is not easily available. So, hairless animal skin is generally favored as it is easily obtained from animals of specific age group or sex.

Intact Full thickness skin: Hair on dorsal skin of animal are removed with animal hair clipper, subcutaneous tissue is surgically removed and dermis side is wiped with isopropyl alcohol to remove residual adhering fat. The skin is washed with distilled water. The skin so prepared is wrapped in aluminum foil and stored in a freezer at -20C till further use. The skin is defrosted at room temperature when required.

Separation of epidermis from full thickness skin: The prepared full thickness skin is treated with 2M sodium bromide solution in water for 6 h. The epidermis is separated by using a cotton swab moistened with distilled water. Then epidermis sheet is cleaned by washing with distilled water and dried under vacuum. Dried sheets are stored in desiccators until further use.

In vivo Studies

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using:

- Animal models
- Human volunteers
- Animal models

Considerable time and resources are required to carryout human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man.

Human models

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug.

Skin irritation studies: White albino rats, mice or white rabbits are used to study any hypersensitivity reaction on the skin. Mutalik and Udupa carried out skin irritation test using mice. The mice were divided into 5 groups, each group containing 6 animals. On the previous day of the experiment, the hair on the backside area of mice were removed. The animals of group I was served

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 916-925 www.ijprajournal.com ISSN: 2456-4494

as normal, without any treatment. One group of animals (group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8% v/v aqueous solution of formalin was applied as standard irritant (group V). The animals were applied with new patch/ formalin solution each day up to 7 days and finally the application sites were graded according to a visual scoring scale, always by the same investigator. The erythema was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for scar formation. The edema scale used was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for severe. After visual evaluation of skin irritation, the animals were sacrificed and skin samples were processed for histological examination. The results of this study showed that the prepared systems (both blank and drug loaded) and USP adhesive tape produced negligible erythema and edema. While standard irritant, formalin produced severe edema and erythema. The histopathologic examination of the skin also indicated that adhesive tape and prepared patches produced mild inflammation and edema.

Stability studies: The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The transdermal formulations are subjected to stability studies as per ICH guidelines.

Regulatory requirements: A transdermal patch is classified by U.S. Food and Drug Administration (FDA) as a combination product, consisting of a medical device combined with drug or biologic product that the device is designed to deliver. Prior to sale, any transdermal patch product must receive approval from FDA, demonstrating safety and efficacy for its intended use.

II. CONCLUSION:

Since 1981, transdermal drug delivery systems have been used as safe and effective drug delivery devices. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment. If a drug has right mix of physical chemistry and pharmacology, transdermal delivery is a remarkable effective route of administration. Due to large advantages of the TDDS, many new researches are going on in the present day to incorporate newer drugs via the system. A transdermal patch has several basic components like drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers and solvents, which play a vital role in the release of drug via skin. Transdermal patches can be divided into various types like matrix, reservoir, membrane matrix hybrid, micro reservoir type and drug in adhesive type transdermal patches and different methods are used to prepare these patches by using basic components of TDDS. After preparation of transdermal patches, they are evaluated for physicochemical studies, in vitro permeation studies, skin irritation studies, animal studies, human studies and stability studies. "But all prepared and evaluated transdermal patches must receive approval from FDA before sale." Future developments of TDDSs will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care.

REFERENCES

[1]. Guy RH. Current status and future prospects of transdermal drug delivery, Pharm Res1996, 13, 1765-1769.
[2]. Guy RH, Hadgraft J, Bucks DA. Transdermal drug delivery and cutaneous metabolism Xenobiotica 1987, 7, 325-343.
[3]. Keith AD. Polymer matrix considerations for transdermal devices, Drug Dev. Ind. Pharm 1983, 9, 605.
[4]. Baker RW, Heller J. Material selection for transdermal delivery systems; In: Hadgraft J, Guys RH, editors. Transdermal Drug Delivery: Development Issues and Research Initiatives. New York, Marcel Dekker Inc. 1989; 293-311.
[5]. Guyot M, Fawaz F. Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol, Int J Pharm 2000, 204, 171-182.
[6]. Gabiga H, Cal K, Janicki S. Effect of penetration enhancers on isosorbide dinitrate penetration through rat skin from a transdermal therapeutic system, Int J Pharm 2000, 199, 1-6.
[7]. Minghetti P, Cilurzo F, Casiragh A, Molla FA, Montanari L. Dermal patches for controlled release of miconazole: Influence of drug concentration on the technical characteristics, Drug Dev Ind Pharm 1999, 25, 679-684.

[8]. Tsai CJ, Hu LR, Fang JY, Lin HH. Chitosan hydrogel as a base for transdermal delivery of berberine and its evaluation in rat skin, Biol. Pharm. Bull 1999, 22, 397-401.
[9]. Bromberg L. Cross linked polyethylene glycol networks as reservoirs for protein delivery, J Apply Poly Sci 1996, 59, 459-466.
[10]. Ubaidulla U, Reddy MV, Ruckmani K, Ahmad FJ, Khar RK. Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on in vitro and in vivo characteristics, AAPS PharmSciTech 2007, 8(1), Article 2.
[11]. Gannu R, Vamshi Vishnu Y, Kishan V, Madhusudan Rao Y. Development of nitrendipine transdermal patches: In vitro and ex vivo characterization, Current Drug Delivery 2007, 4, 69-76.
[12]. Gale R, Spitze LA. Permeability of camphor in ethylene vinyl acetate copolymers. In proceedings: Eighth International Symposium on Controlled Release of Bioactive Materials. Minneapolis, MN, Controlled Release Society. 1981; 183.
[13]. Boretos JW, Detmer DE , Donachy JH. Segmented polyurethane: a polyether polymer II. Two year experience, J Biomed Mat Res 1971, 5, 373.
[14]. Chung SJ. Future drug delivery research in South Korea, J Controlled Release 1999, 62, 73-79.