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TRANSDERMAL PATCHES

Thushara PV[1], Fathimath Afhida[2], Dr. Ajith Babu TK[3], Dr. L V Vigneshwaran[4]

[1]Asst. Professor, Dept. of Pharmaceutics, Malik Deenar College of Pharmacy
[2]Malik Deenar College of Pharmacy
[3]Principal, Malik Deenar College of Pharmacy seethangoli, Kasargod
[4]HOD, Dept. of pharmaceutics, Malik Deenar College of Pharmacy seethangoli, kasargod,

ABSTRACT

A Transdermal patch is used to deliver a specific dose of medication through intact of skin which reaches the systemic circulation. It is also used to produce a controlled release of drug and increase bioavailability by avoiding first pass metabolism. Transdermal drug delivery system overcomes the demerit of conventional dosage form. A Transdermal patch is otherwise known as transdermal drug delivery system is a novel drug delivery system. Transdermal patches comprises of 4 module. Module 1 deals with introduction and GMP and GLP requirements. Module 2 deals with preformulation and formulation studies. Module 3 deals with evaluation parameters and stability studies and finally Module 4 comprises of packaging and labeling.

Keywords:

INTRODUCTION

A transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream. Transdermal drug delivery systems, also known as ‘’patches’’, are dosage form designed to deliver a therapeutically effective amount of drug across a patient’s skin. It provides controlled, constant administration of drug, and allows continuous input of drugs with shorter biological half-life.

COMPONENTS OF TRANSDERMAL PATCHES

1. **Polymer Matrix:** Controls the release of the drug from the device. Eg: Polyethylene.
2. **Drug:** Molecular weight less than approximately 1000 Daltons, have affinity for both lipophilic and hydrophilic phases, should have low melting point.

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3. **Permeation Enhancers:** These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Eg: water, pyrolidines
4. **Backings Laminates:** Backings laminates are selected for appearance, flexibility and need for occlusion. Eg: polyester film, polyethylene film and polyolefin film.
5. **Release Liner:** During storage the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. Eg: paper fabric, polyethylene
6. **Other Excipients:** Various solvents such as chloroform, methanol, acetone, plasticizers.

ADVANTANGES

1. It is convenient method and requires only once weekly application.
2. Aid in patient adherence to drug therapy.
3. Used as an alternative route of administration to oral dosage forms.
4. It is of great advantage in patients who are nauseated or unconscious.
5. This method avoids direct effects on the stomach and intestine.
6. First pass metabolism can be avoided with transdermal administration.
7. Relative consistent plasma levels can be achieved.
8. The drug input can be terminated at any point of time by removing the patch.

DISADVANTAGES

1. Possibility of local irritation at the site of application.
2. Erythema, itching, and local edema can be caused by the drug, adhesives or excipients.
3. A molecular weight less than 500 Da is essential.
4. Sufficient aqueous and lipid solubility is required for permeate to transverse SC aqueous.
5. Drug must have desired physicochemical properties for penetration through stratum corneum.
6. Heat, cold and sweating prevent the patch from sticking to the surface of skin.
7. May not economical to some patients.
8. The adhesives used may not adhere well to all types of skin.

TYPES

Single layer Drug - in – Adhesive
Multi-layer Drug – in- Adhesive
Matrix type
Reservoir type membrane Matrix hybrid
Micro reservoir type
Drug in adhesive type

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Matrix Type

A matrix-style TDS product contains the active ingredient dissolved or suspended in a matrix containing adhesive, penetration enhancers, preservatives, and other excipients. Commonly used polymer is cross linked PEG, PVP. 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 seperated from rings, which is then mounted on to an occlusive base plate in a compartment fabricated from a drug impermeable backing.

Reservoir Type

A reservoir TDS product contains the drug in a heat-sealed area between the backing membrane and a semi-permeable membrane that contacts the skin. The drug reservoir is made of a homogeneous dispersion of drug particles suspended in an unleachable viscous liquid medium (silicon fluid) to form a paste like suspension or gel or a clear solution of drug in a releasable solvent (ethanol).

GMP REQUIREMENTS

Good Manufacturing Practices [GMP] is a regulation to govern the manufacturing of drugs of consistent quality, purity and efficacy, provided under schedule M of Drugs and Cosmetics rules 1945. It is divided into 2 parts:

PART 1: Deals with GMP relating to factory premises and materials.

PART 1 A

It includes general requirements such as location and surroundings, building and premises, water system, disposal of waste, raw material, warehouse area, production area ancilliary area.

GENERAL REQUIREMENTS

1.1 Location and Surroundings

Have measures as to avoid risk of contamination from external environment. Any factory, which produces obnoxious odors, fumes, dust, smoke, chemical or biological emissions.

1.2 Building and Premises

Permits manufacturing operations in hygienic conditions. Adequately provided with working space to avoid mixups. Designed to avoid entry of pests, birds, rodents etc. The production and dispensing area shall be well lightened, ventilated, and may have proper air handling system. The walls and floors of manufacturing area shall be free from cracks and open joints to permit easy and effective cleaning.

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1.3 Water System

There shall be validated system for treatment of water to render it potable. Potable water should be used to perform all the operations except cleaning and washing.

1.4 Disposal of Waste

Provision shall be made for proper storage of waste materials.

2. Warehousing Area

Adequate areas for proper warehousing of various categories of materials and products. Quarantine area shall be clearly restricted to authorized persons.

3. Production Area

Designed to allow the production preferably in uni-flow and with logical sequence of operations. Separate manufacturing facilities shall be provided for the manufacturing of contamination causing and potent products such as β-lactam, sex hormones and cyto-toxic substance.

4. Ancillary Areas

Rest and refreshment rooms shall be separate from other areas. Facility for changing, storing clothes and for washing and toilet purpose shall be easily accessible and adequate.

5. Quality Control Area

Quality control laboratories shall be independent of the production areas. Separate areas shall be provided each for physico-chemical, biological, microbiological or radio –isotope analysis. Adequate space shall be provided to avoid mix-ups and cross contamination.

6. Personnel

The manufacture and testing shall be conducted under direct supervision of qualified technical staff. Personnel for QA & QC shall be qualified and experienced.

7. Health, Clothing and Sanitation of Workers

Need for special protective clothing. Personnel should not move between areas producing different products. Garments need to be cleaned. The personnel handling beta-lactum antibiotics shall be tested for penicillin sensitivity.

8. Raw Materials

There shall be adequate separate area for materials “under test”, “approved “, and “rejected” with arrangement and equipment. Only raw materials which have been released by the quality control department and which are within their shelf- life shall be used. It shall be ensured that all the

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containers of raw materials are placed on the raised platforms/racks and not placed directly on the floor.

PART 1 B

1. Sifting Mixing and Granulation

Unless operated as a closed system, mixing, sifting and blending equipment's shall be fitted with dust extractors. Residues from sieving operation shall be examined properly. Filter bags fitted to fluid-bed drier shall not be used for different products.

2. Packaging

The strips coming out of the machine shall be inspected for defects such as misprint.

PART 2

Deals with requirements of plants and equipments.

1. Equipments

Equipments shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of the equipment shall aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross- contamination. Defective equipment shall be removed. Balance and other measuring equipment of an appropriate range, accuracy and precision shall be available in the raw material stores, production and in process control operation.

2. Labels and Other Printed Materials

Necessary for identification of drug and their use. Printed in bright colours and legible manner. All containers and equipment shall bear appropriate labels. Different color-coded labels can be used. Printed packaging materials & leaflets shall be stored separately to avoid mix-up.

GOOD LABORATORY PRACTICES

- The laboratory should be located designed, customized and maintained to suit the performance of all Q.C. test and analysis required.
- As far as possible there must be separate wings for analytical, instruments, microbiology and sterility etc. And all wings may be interconnected with the internal door.
- There must be an effective air lock, provisions for A.C. and fumigation chamber, the laboratory should be so designed that not only adequate provision of space but provision for utility, water, solvent storage, extraction dust collection etc. were covered.

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- Laboratory furniture so designed to provide for adaptability, tabletop must be covered properly resistant to acid, alkali and solvent. The floor should be smooth, easy to clean and adequate drainage facility.

Equipment

There must be written SOP for each instrument. The instrument should be located with an adequate place in a separate room under controlled temperature. The calibration and maintenance record must be done periodically. All the necessary instruction regarding operating, handling and care should be display near the instruments. The light should be adequate.

Chemical Reagents

Storage of chemicals and reagent should be done in a manner it involved in the use, the container of all chemicals and reagents must be properly labeled. Transfer of chemical must be done almost care. All analytical reagents and a prepared solution must be labeled. Records of Molar Solutions entered in the register prepared for the same.

Organization And Personnel

Every individual have the requisite educational qualification, training, and experience to enable the individual to perform the assigned function. There shall be sufficient and a number of personnel for the proper conduct of the studies in accordance with protocols. The personnel should take adequate precautions to avoid contamination of test and control article of the test systems.

Documentation

The document is a critical factor of the good laboratory practice. Documentation is the accepted method of recording information for future reference. The major documents that need to be provided are protocols, logbook for usage, maintenance, and calibration of equipment there should be well established SOPs.

Quality Control

There must be a well-defined procedure, which covers all the aspects pertaining to the sample i.e., receipt of the consignment, sampling techniques to be adopted, storage and handling of samples recording and reporting of analysis. Every sample that is received must have a distinctive number, which should appear on the label of the sample and should be stored in the prescribed conditions.

Records And Reports

Every laboratory should maintain records of all the tests performed any of the graphs pertaining to IR, HPLC, etc. should be stored along with the raw data. For a quick reference, the access to records should be restricted to an authorized person and these records are preferably stored under lock and key.

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Safety

There should be adequate facilities and accessories to provide safety for personnel involved in drug testing.

PREFORMULATION STUDIES

Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form.

- To generate useful data needed in developing stable and safe dosage forms that can be manufactured on a commercial scale.
- To provide in-depth knowledge and understanding of the physical characteristics of a candidate drug molecule prior to dosage form development.
- To generate useful information on how to design a drug delivery system with good bioavailability.

Preformulation Studies of drug includes Identification, Melting point, calibration curve, Fourier Transform Infra-Red analysis, Solubility Studies, Partition coefficient, thin layer chromatography and Drug- Excipient Interaction, Lamda max.

(A) IDENTIFICATION AND CHARACTERISATION METHODS FOR DRUGS

Organoleptic properties: Organoleptic characteristics of the drug were investigated on the basis of colour, odour, taste and State.

- **Melting Point:** It was determined by taking a small amount of drug in a capillarytube closed at one end and was placed in melting point apparatus and temperature at which the drug meltswere noted.
- **UV Absorption Maxima:** The identification of drug was done by UV spectrophotometric method. From the spectra, λmax of drug was identified. The spectral data from this scan was used for the preparation of calibration curve of the drug.
- **Fourier Transform Infra-Red Analysis:** The FTIR analysis of the sample was carried out for compound identification. The powdered drug was placed carefully over sample holder ensuring no air entrapment, thereafter the sample was scanned. The technique is based upon the identification of functional groups within molecules where such groups vibrate (either through stretching or bending in various ways) when irradiated with specific wavelengths of light. spectrum.
- **Solubility:** The solubility analysis for drug was done in different solvents like Ethanol, Methanol, Water.

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- **NMR:** It is well suited for determining the identity of most organic substances, even for such cases where reference substances/spectra are not available. NMR spectroscopy is also an excellent technique for quantification of any substance in the sample. Examples include determination of the purity of APIs as well as quantification of active ingredients, excipients and impurities in pharmaceutical products.

(B) EXCEPIENT DRUG COMPATIBILITY STUDY

Study of drug-excipient compatibility is an important phase in the pre-formulation stage of drug development. The potential interactions between drugs and excipients have effects on the chemical, physical, bioavailability and stability of the dosage form.

Differential Scanning Calorimetry (DSC)

DSC curves of pure components are compared to the curves obtained from 1:1 physical mixture. A significant shift in the melting of the components or appearance of a new exo/endothermic peak and/or variation in the corresponding enthalpies of reaction in the physical mixture indicate incompatibility.

Isothermal Microcalorimetry

It allows determination of minute amounts of evolved or absorbed heat. The thermal activity of API, excipient and their mixtures are measured individually in the calorimeter and the thermal activity (heat flow) at a constant temperature is monitored.

Hot Stage Microscopy (HSM)

HSM is a visual thermal analysis technique, which allows efficient monitoring of solid-state interactions that could be erroneously interpreted as incompatibility by DSC. This technique only requires very small quantity of sample when performing compatibility studies.

(C) CRITERIA FOR EXCIPIENTS SELECTION

Excipient used in transdermal patches are polyethylene, polystyrene, PVC, silicones, paper fabrics, Acrylates.

a) They must be non-toxic and acceptable to the regulatory agents in all countries where the product is to be marketed.
b) They must be commercially bioavailable in an acceptable grade in all countries where the product is to be manufactured.
c) Their cost must be acceptably low.
d) They must be physiologically inert.
e) They must be physically and chemically stable by themselves and in combination with the drugs and other tablet components.

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f) They must be free of any unacceptable microbiological load.
g) They must be colour comparable (not produce any off colour appearance).

Polymer Matrix:

- Chemical functionality of the polymer should be such that specific drug diffuses properly and get released through it. It should be stable, non-reactive with the drug, easily manufactured.

  Eg: Liquid or solid synthetic polymer base.

Adhesives:

- It should not leave any un washable residue. It should be easily removed
- Adhere to the skin during the dosing interval.
- Do not irritate or sensitize the skin.

  Eg: polyacrylate, polyisobutylene

Face Adhesive:

- It should be physically and chemically compatible with the drug, excipients and the enhancers.
- The delivery of the permeation enhancers should not be affected.
- Permeation of the drug should not be affected.

  Eg: Silicones

(D) FORMULATION AND OPTIMIZATION TECHNIQUES

- The term Optimize is defined as to make perfect, effective, or as functional as possible.
- It is the process of finding the best way of using the existing resources while taking into the account of all the factors that influences decisions in any experiment.
- Traditionally, optimization in pharmaceuticals refers to changing one variable at a time, so to obtain solution of a problematic formulation.
- Modern pharmaceutical optimization involves systematic design of experiments (DoE) to improve formulation irregularities.
- In the other word we can say that – quantitate a formulation that has been qualitatively determined. It's not a screening technique.

Optimization Parameters

(1) UNCONSTRAINED

- In unconstrained optimization problems there are no restrictions.
- For a given pharmaceutical system one might wish to make the hardest tablet possible.
- The making of the hardest tablet is the unconstrained optimization problem.

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(II) CONSTRAINED

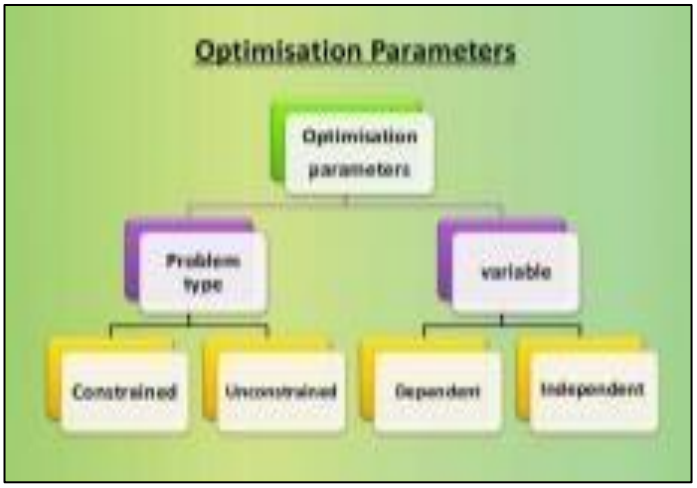
- The constrained problem involved in it, is to make the hardest tablet possible, but it must disintegrate in less than 15 minutes.

(III) INDEPENDENT VARIABLES

- The independent variables are under the control of the formulator. These might include the compression force or the die cavity filling or the mixing time.

(IV) DEPENDENT VARIABLES

- The dependent variables are the responses or the characteristics that are developed due to the independent variables. The more the variables that are present in the system the more the complications that are involved in the optimization.



FORMULATIONS

Ingredients	Example
Drug reservoir	Liquid or solid synthetic polymer base
Drug	Rivastigmine
Permeation enhancers	Dimethylsulphoxide, propylene glycol
Adhesives	Polyacrylate, polyisobutylene
Backing laminates	Polyesterfilm, polypropylene resin
Release liner	Paperfabric, polyethylene
Solvents	Chloroform, acetone

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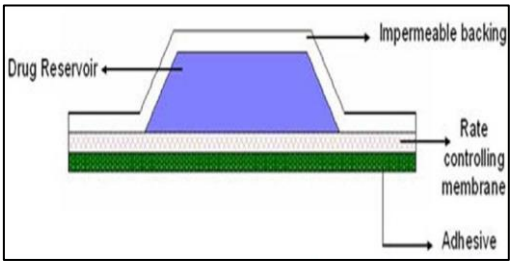
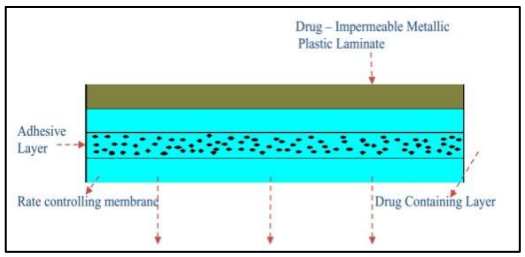
1. Polymer Membrane Permeation Controlled TDDS

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be microporous or non- porous. In drug reservoir compartment, the drug can be in the form of solution, suspension, or dispersed in solid polymer matrix.



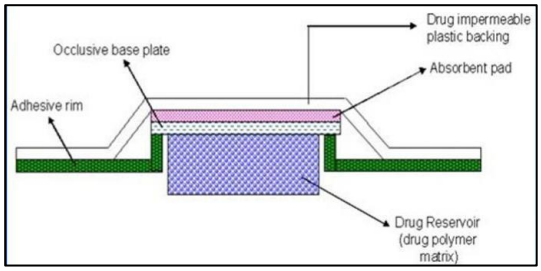
2. Adhesive Diffusion Controlled TDDS

The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesives by solvent casting or by melting the adhesive on to an impervious backing layer. The drug reservoir layer is then covered by a non-medicated rate controlling adhesives polymer of constant thickness. Eg: Deponit (nitroglycerine).



3. Matrix Diffusion Controlled TDDS

The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk then is fixed on to an occlusive base plate in a compartment fabricated from a drug – impermeable backing layer. Eg: Nitrodur (nitroglycerine).



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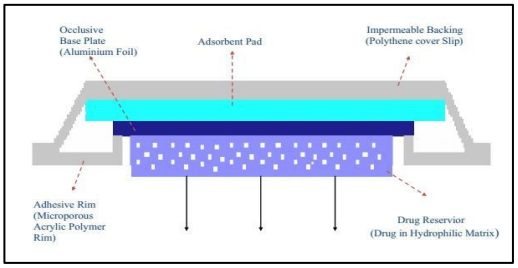
4. Micro Reservoir Controlled TDDS

This is the combination of reservoir and matrix dispersion system. The drug reservoir is formed by suspending the drug in an aq. solution of water-soluble polymer and then dispersing the solution homogenously in a lipophilic polymer to form microscopic spheres of drug reservoir.



EVALUATION OF FORMULATION

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. The study is predictive of transdermal dosage forms and can be classified into different types including physicochemical evaluation, in-vitro evaluation, and in-vivo evaluation.

A. EVALUATION OF PHYSICAL PARAMETERS

Thickness Of the Patch

The thickness of the drug prepared patch is measured by using a digital micrometer at different point of patch and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Weight Uniformity

The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Folding Endurance

A specific area of strip is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of endurance.

Percentage Moisture Content

Water vapour permeability (WVP) evaluation

WVP=W/A W is the amount of vapour permeated through the patch expressed in gm/24 hrs and A is thesurface area of the exposure samples expressed in m

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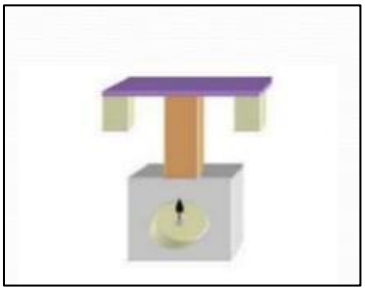
Drug Content

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique).

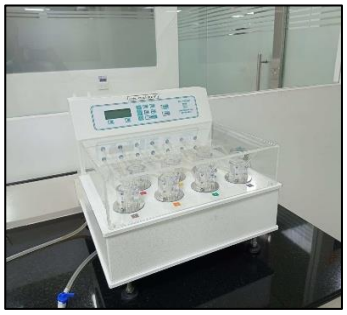
Probe Tack Test

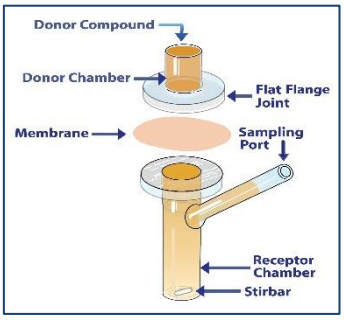
In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.



B. INVITRO EVALUATION

Invitro evaluation can be performed by using Vertical Franz diffusion cell. The Franz diffusion cells consist of a donor chamber and a receptor chamber, separated by a membrane – e.g., skin or a skin equivalent. Sample introduction is done at the top, in the donor compartment. In a flow diffusion cell, the receptor medium is circulated at the bottom from which samples are extracted for analysis over a time interval. The vertical franz diffusion cell is a simple reproducible test for measuring the in vitro drug release from creams, ointments and gels. The transdermal diffusion cell apparatus is remarkably simple to operate the system is supplied with; Six stage magnetic stirrer with digital RPM indicator, Water heater and water circulation system, Cell holders, Diffusion cells, Teflon coated stirring bars.





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C. INVIVO EVALUATION

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 model and Human volunteers

❖ Animal Model

Considerable time and resources are required to carry out 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 rehsus etc. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in animals.

Hair was removed from the dorsal skin with the aid of an electric shaver. After that, animals were sacrificed, skin was excised and examined for integrity using a lamp-inspecting method. The fresh skin was maintained in phosphate buffer pH 7.4 containing 0.02% sodium azide as preservative in a refrigerator at 4 °C overnight to be used at the next morning.

The permeation experiment was conducted by using modified Franz diffusion cell. The skin samples were mounted on the donor half-cells so that SC side was towards the donor and the dermal side was facing the receptor compartment. One hundred milliliters of phosphate buffer (pH 7.4, 0.02% sodium azide) was added to the receptor compartment. The diffusion cells were maintained at 37 ± 0.5 °C and agitated at 100 rpm for about 30 min to attain equilibrium. The patches were placed in the donor compartment so that the drug supply layer was facing SC. A similar set was run simultaneously using the placebo patches as control systems to avoid the influence of any material leached from the patch or skin.

At predetermined time intervals, aliquots of one ml each were sampled and replaced with equal volume of fresh buffer. Samples were analyzed spectrophotometrically at 272 nm versus blank of the placebo patches. At the end of permeation experiment, the skin surface facing the patches were inspected for any visible damage or abnormalities and compared to that of the control set.

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.
- 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.

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- Phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Human studies require considerable resources but they are the best to assess the performance of the drug.

STABILITY STUDIES

Stability of a TDDS is a very important factor to be considered while formulating such system because it affects therapeutic efficacy of the system as well as patient compliance. Here, formulated patches were wrapped in aluminium foil and kept at room temperature for a period of 30 days. After completion of 30 days, patches were analyzed for their drug release profile across rat's skin. Formulation P1 was selected for this study as this formulation seemed quite promising throughout all evaluation studies performed previously on this formulation.

TYPES OF STABILITY STUDIES ON DRUG SUBSTANCES

Physical Stability

The original physical properties such as appearance, colour, dissolution, palatability, suspendability are retained. The physical stability may affect the uniformity and release rate, hence it is important for the efficacy and safety of the product.

Chemical Stability

It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.

Microbiological Stability

The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The antimicrobial agents used in the preparation retain the effectiveness within specified limits. This microbiological instability could be hazardous to the sterile drug product.

Therapeutic Stability

The therapeutic effect (Drug Action) remains unchanged.The patch were packed in aluminium foil and kept in different condition and analysed for weight, thickness, drug condition, content uniformity, peel strength, moisture content,skin condition.

Toxicological Stability

Toxicological stability has no significant increase in the toxicity occurs.

Animal models: Acute dermal toxicity, Sub chronic dermal toxicity, Dermal irritation, Skin corrosion test, Skin sensitization test, Phototoxicity.

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Non-animal models: In vitro skin irritation assay, In vitro skin corrosion test, In vitro skin sensitization test, Phototoxicity and photoallergy, Skin genotoxicity.

STABILITY TESTING METHODS

Stability testing is a procedure performed for all the pharmaceutical products at various stages of the product development.

1. Real-Time Stability Testing

Real-time stability testing is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period of time for the test of the product depends on the stability of the product which clearly tells that the product is not degraded or decomposed for a long time.

2. Accelerated Stability Testing

This type of stability testing is done at higher temperatures and that decomposition the product is determined. The information is used to predict the shelf life or used to compare the relative stability of alternative formulations. The accelerated stability studies are easily predicted by the Arrhenius equation,

K = Ae -Ea/RT Log, Where
K= Specific rate constant
A= Frequency factor or Arrhenius factor
Ea= Energy of activation
R= Real gas constant 4.184 j/mol. K
T= Absolute temperature

In this method the drugs are stored at different temperatures such as 40°C, 60°C, 70°C, 80°C, 100°C etc.

3. Retained Sample Stability Testing

These studies are to be done at room temperature and at refrigerator temperatures. In this type of testing, the stability is done by selecting one batch for a year. If the number of samples exceeds more than 50 then they are divided into two batches. The samples stability studies help to predict the shelf life. The maximum shelf life of every product predicted could be 5 years which is conventional to the test samples at 3, 6. 9, 12, 18, 24, 36, 48 and 60 months. This method of testing is also known as constant interval method.

4. Cyclic Temperature Stress Testing

This method is not so much used to the sampling of the products. In this method, cyclic temperature stress tests are designed knowledge of the product so as to mimic likely conditions in the market

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place storage. In this testing the sampling is considered to be conducted by a cycle of 24 hours which is known as the rhythm of the earth is 24 hours.

PACKAGING AND LABELLING

Packaging

Compositions and methods for producing laminate materials in packaging a transdermal drug delivery system comprising a rubber modified acrylonitrile methyl acrylate copolymer film, alone or in combination with a polyester film, wherein the active drug incorporated in the transdermal system remains substantially solubilized and stable in the system during storage prior to use.

1) An inner layer comprising a thermoplastic polymer film, wherein said layer is free of polyolefins, metal foil and vinyl acetate.
2) An outer layer affixed to said inner layer; providing a non-aqueous carrier composition of a transdermal system comprising a chiral drug or active enantiomers thereof that degrades or is unstable when exposed to vinyl acetate and metal foilmaterials; placing said carrier composition within a pouch of the laminate packaging material; and sealing said pouch along one or more edges of the inner layer.

- Wherein the inner layer of the laminate packaging material is self-sealing.
- Wherein the inner layer is a film of rubber modified acrylonitrile methyl acrylate copolymers.
- Wherein the outer layer comprises at least one polyester film affixed to the inner layer.
- Wherein the outer layer is affixed to the inner layer by means of an adhesive.
- Wherein the laminate packaging material is child resistant.
- Wherein the laminate packaging material is translucent.
- Wherein the chiral drug is selected from the group consisting of methylphenidate, a pharmaceutically acceptable salt or base of methylphenidate, and active enantiomers thereof.
- A laminate packaging material for inhibiting degradant formation of methylphenidate or active enantiomers thereof in a non-aqueous carrier composition of a transdermal system comprising: an inner layer of rubber modified acrylonitrile methyl acrylate copolymers, and an outer layer comprising at least one polyester film affixed to said inner layer; whereby both said layers are affixed by means of an adhesive and formed into a pouch.

Labelling

Particulars to appear on the outer packaging and minimum particulars to appear on pouch for individual patch sachet.

1. Name Of the Medicinal Product
2. Statement Of Active Substance(S)
3. List Of Excipients

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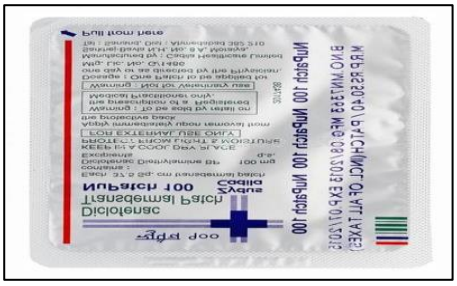
4. Pharmaceutical Form and Contents
5. Method And Route(S) Of Administration
    - Transdermal use.
    - Read the package leaflet before use.
6. Special Warning That the Medicinal Product Must Be Stored Out of The Sight and Reach of Children.
    - Keep unused and used patches out of children's sight and reach.
7. Other Special Warning(S), If Necessary
8. Expiry Date
9. Special Storage Conditions
    - Do not store above 25ºC.
    - Store in the original sachet in order to protect from moisture
10. Special Precautions for Disposal of Unused Medicinal Products or Waste Materials Derived from Such Medicinal Products, If Appropriate
11. Name And Address of The Marketing Authorisation Holder
12. Marketing Authorisation Number(S)
13. Batch Number
14. General Classification for Supply
15. Instructions On Use
16. Information In Braille



CONCLUSION

Transdermal drug delivery systems are defined as self-contained, discreate dosage forms which when applied to the intact skin deliver the drug at a controlled rate to the systemic circulation.

In this study we describe GMP and GLP requirements of patch. The pre-formulation studies like identification and characterization method of drug, excipient drug compatibility studies, criteria for excipient selection, formulation and optimization techniques and formulation were also studied. The

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method of preparation is like membrane diffusion-controlled system, adhesive dispersion-controlled system, matrix diffusion-controlled system, micro reservoir system are studied. And we studied stability studies, SOPs, packaging and labelling of transdermal patches.

After completing 150 hours of practice school training in the domain "Formulation and characterization of Transdermal Patches" enables to implement the knowledge acquired in a practical or realistic way. During the period of practice school, achieved a lot of knowledge that employs new production technology, GMP, formulation, evaluation, documentation and labelling and packaging criteria of transdermal patches. Utilized the 150 hours for scientific collection, analysis and interpretation of data leading to valid conclusion.

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