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Review Article of Transdermal Patch

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ABSTRACT

A transdermal patch is a medicated adhesive patch that is applied to the skin to allow a prescribed amount of medication to enter the bloodstream through the skin. One innovative drug delivery method that addresses issues with traditional dosage forms is the transdermal drug administration system. Introduction, GMP and GLP requirements, preformulation, excipient selection criteria, formulation, and preparation technique are all included in the domain formulation and characterisation of transdermal patches. and provides an overview of stability and assessment research. Documentation, labeling, packaging, and SOPS

KEY WORDS: transdermal patch

INTRODUCTION

Transdermal drug delivery systems, which are different from conventional topical drug administration methods, are used to administer drugs through the skin to provide a systemic impact. A transdermal drug delivery system is one that continuously administers medication via the skin to the systemic circulation. Transdermal dose forms involve the delivery of drugs into the skin's dermal or epidermal layers. Another name for a transdermal medicine delivery device is a patch. One innovative medicine delivery method is the transdermal system.

E.g. scopolamine –Motion sickness

Nitroglycerin –Angina pectoris

Advantages

1. It is a convenient method and requires only one weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy.

2. Transdermal drug delivery can be used as an alternative route of administration to accommodate patients who cannot tolerate oral dosage forms.

3. It is of great advantage in patients who are nauseated or unconscious.

4. Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on the stomach and intestine.

5. Drugs that are degraded by the enzymes and acids in the gastrointestinal system may also be good targets.

Disadvantages

1. Possibility of local irritation at the site of application.

2. A molecular weight less than 500 Da is essential

COMPONENTES OF TRANSDERMAL PATCH

• **Polymer matrix:** Backbone of TDDS, which controls the release of the drug. E.g.- cellulose derivatives, zein, gelatin, shellac, waxes, gums,

• **Drug;** For medications with the right physical chemistry and pharmacology, the transdermal route is a very alluring choice. Transdermal patches provide significant benefits for medications with a limited therapeutic window, high first pass metabolism, or short half-lives.E.g. Nitroglycerin

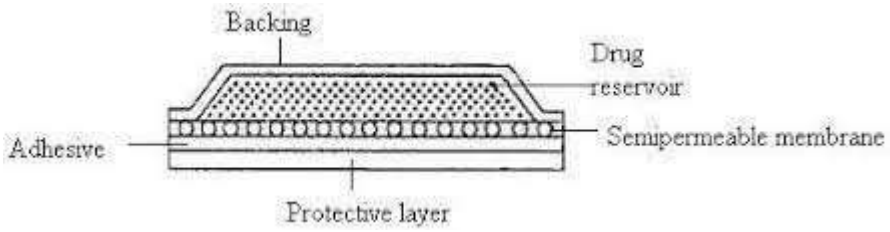


Fig:1 Components of Transdermal patches

• **Permeation enhancers:** Boost the stratum corneum's permeability to achieve greater therapeutic medication concentrations. These come in three varieties: two component systems, lipophilic solvents, and surface active agents.E.g. DMSO

• **Adhesive:** Increase permeability of stratum corneum to attain higher therapeutic levels of the drug that increase permeability of stratum corneum to attain higher therapeutic levels of the drug

• **Backing laminates:** Should have low modulus or high flexibility. Eg-vinyl, polyethylene

. • **Release liner:** Protect**s** the patch during storage. The liner is removed prior to use.

PREFORMULATION

The initial stage in creating a drug's dosage form is pre-formulation testing. It is the study of the physical and chemical characteristics of pharmacological compounds both by themselves and in combination with excipients. The main goal of the pre-formulation testing is to produce data that will help the formulator create dosage forms that are stable and bioavailable.

A) IDENTIFICATION AND CHARACTERISATION OF DRUG

a) Organoleptic properties: Organoleptic characteristics of the drug were investigated based on color, odor, taste and State.

b) Melting Point: Melting point determination of drug was done by using Melting Point Apparatus.

c) UV Absorption Maxima: The substance was identified using the UV spectrophotometric technique. λmax of the medication was observed from the spectra. This scan's spectral data was utilized to create the calibration curve.

d) Fourier Transform Infra-Red analysis: The FTIR analysis of the sample was carried out for compound identification (FTIR-8400S Shimadzu). The powdered drug was placed carefully over sample holder ensuring no air entrapment, there after the sample was scanned.

e) Solubility: The solubility analysis for drug was done in different solvents like Ethanol, Methanol, Water, etc.

B) Excipient drug compatibility studies

Study of drug excipient compatibility is an important phase in the preformulating stage of drug development.

Analytical Techniques Used to Detect Drug-Excipient Compatibility

Fourier Transform Infrared Spectroscopy (FT-IR)

Using the potassium bromide discs method, FT-IR spectra were acquired on an instrument Shimadzu FT-IR 8400S in the frequency range of 400–4000 cm (approximately 131.23 ft)-1 with a resolution of 4 cm-1. For one month, the medication and every chosen excipient (1:1 w/w) were kept at 40 ± 20C. Both the individual samples and the drug and excipient mixture were pulverized, fully combined with potassium bromide in a mortar for three to five minutes, and then compressed into a disc for five minutes under five tons of pressure. The sample's potassium bromide content should be between 0.2% and 1%. After the disc was put in the path of light, the spectrum was collected and examined for signs of any interactions.

Thermal methods of analyses:

Thermal analysis plays a critical role in compatibility studies and has frequently been employed for quick assessment of physicochemical incompatibility. We provide three different types of thermal analyses, which include:

Differential scanning calorimetry (DSC)

The DSC curves of pure components and those derived from a 1:1 physical combination are contrasted. Incompatibility is indicated by a notable change in the components' melting points, the emergence of a new exo- or endothermic peak, and/or changes in the associated enthalpies of reaction in the physical mixture.

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 a very small quantity of samples when performing compatibility studies.

C) CRITERIA FOR EXCIPIENTS SELECTION

Materials other than the active pharmaceutical ingredient (API) are known as pharmaceutical excipients. that have been properly assessed for safety before being incorporated into the medication administration system. Excipients are utilized to increase a drug's bioavailability and function as bulking and protecting agents.

Criteria

- They must be non-toxic
- low cost
- They must be physiologically inert
- They must be physically and chemically stable

Polymers

A polymer is a material or substance made up of several repeating subunits that combine to form a very large molecule known as a macromolecule.

1. The polymer should be chemically non-reactive, or it should be an inert drug carrier

;2. The polymer must not decompose on storage or during the life span;

3. Molecular weight, physical characteristic and chemical functionality of the polymer must allow the diffusion of the drug substance at desirable rate;

4. The polymer and its decomposed product should be nontoxic. It should be biocompatible with skin;

5. The polymer must be easy to manufacture and fabricate into the desired product. It should allow the incorporation of large amounts of active agent.

E.g. HPMC, acrylate copolymer, polyisobutylene

Permeation enhancers

The compounds called penetration enhancers are used to increase the mucosal permeability of skin. Also referred to as an absorption promoter or enhancer, penetration enhancers increase the amount of penetrant that is absorbed through the skin. Enhancers of penetration that raise a drug's permeability through skin.

Properties

- It should have no pharmacological activity within the body.
- It should be cosmetically acceptable.
- It should be odorless, tasteless, colorless and inexpensive
- These materials should be nontoxic, non-irritating, pharmacologically inert, non-allergic.
- It should be chemically and physically stable.

Eg, synthetic:.Sulphoxides and similar chemicals-dimethyl sulphoxide(DMSO), dimethyl formamide (DMF), dimethyl acetamide (DMAC), Azones , Pyrrolidones

Natural:.Terpens-Menthol, Linalool, Limonene, Carvacrol.

Adhesive

Serve to adhere the compound of the patch together along with adhering the patch to the skin

Properties

- Should not irritate the skin
- Should adhere to the skin aggressively
- Should easily removable

- Should have an intimate contact with skin
- Permeation of drug should not be affected

E,g,Rubber based pressure sensitive adhesives, acrylic PSA, etc.

Backing membrane

To protect layer and safeguard the stability of system

Properties

- Flexible and provide good bond to drug reservoir
- It should be impermeable

E,g metallic plastic laminate, plastic laminate with absorbent pad, occlusive base plate

Release liner

The film removed and discard prior to patch application that protect the transdermal drug delivery system by covering the adhesive side

Properties

- may be removed easily from the skin without leaving any residue on its surface
- Usually, a very light touch of a finger is sufficient to adhere them to a surface such as skin

Eg, polyacrylates (acrylates), polyisobutylene (PIB) or polydimethylsiloxane (silicone)

D)FORMULATION AND OPTIMIZATION TECHNIQUES

The definition of optimization is "to make perfect," which refers to creating the ideal object through a variety of methods and procedures. To create high-quality products, many medicine formulations employ optimization approaches. It deals with different drug product types and how they are made. A wide range of problems pertaining to the pharmaceutical process and product, including formulation, manufacturing, excipient selection, novel drug development, and other pharmacy-related difficulties, are solved through the application of optimization techniques. Because of the optimization method, we look at the different issues that arise while conducting research. Optimization techniques are helpful to make easy the process and formulation of pharmaceutical product and process

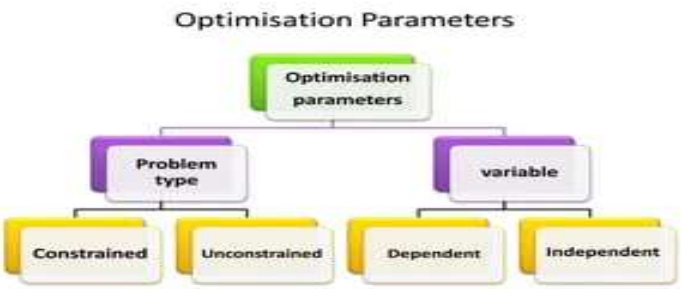


Fig.2 optimization parameter

PROBLEME TYPE

A) Unconstrained: In this system, the restriction is not based on physical limitations. For example, one might want to make an uncoated tablet possible for a specific pharmaceutical system.

B) Constrained: In this system the restriction is based on physical limitations. As a result, the constrained challenge is to make the uncoated tablet, but it should not be Disintegrate in the stomach.

VARIABLE TYPE

A) Independent variables: This type of variable is come under the supervision of a formulator like the force of compression, lubrication level, binder level etc.

B) Dependent variables: The formulator has no direct control over this type of variable. They are reliant on an unrelated variable. These are responses like hardness, flow property, and friability, among others

FORMULATION

A transdermal therapeutic system is essentially a multilaminate structure that is composed of following

constituents:

1. Drug;

2. Polymer matrix;

3. Penetration enhancers;

4. Adhesives;

5. Backing membrane

6. release liner

Constituents	use	example
Drug	For the pharmacological action	Scopolamine nitroglycerin
Polymer	It is a outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane	Hydroxy propyl methylcellulose (HPMC) acrylate copolymer polyisobutylene
Penetration enhancers	They are promoting permeation through skin poorly penetrating drug molecules	,Synthetic:Sulphoxides and similar chemicals-dimethyl sulphoxide(DMSO), dimethyl formamide (DMF), dimethyl acetamide (DMAC) 2.Azones 3.Pyrrolidones Natural: Terpens-Menthol, Linalool, Limonene, Carvacrol. 2.Essential oil-Basil oil, Neem oil, Eucalyptus, Chenopodium, Ylang- Ylang
Adhesive layer	It must possess sufficient property to firmly secure the system to the skin surface and to maintain it in position for as long as desired	Rubber based pressure sensitive adhesives, acrylic PSA,
Backing layer	The backing membrane serves the purpose of holding the entire system together and at the same time protecting the drug reservoir from exposure to the atmosphere.	Polyester Aluminized polyethylene terephthalate Siliconized polyethylene terephthalate
Release liner	The peel strip prevents the loss of the drug that has migrated into the adhesive layer during storage and protects the finished device against contamination	Polyester foils Metalized laminates

Method of preparation

1. Membrane permeation-controlled system
2. Adhesive dispersion type system
3. Matrix diffusion-controlled system
4. Micro reservoir diffusion-controlled system

1.membrane permeation-controlled system

This kind of system uses a homogeneous dispersion of drug molecules suspended in a viscous liquid to create a transparent drug solution in a solvent or a gel, paste-like suspension. The drug reservoir is fully contained within a shallow compartment constructed of backing laminate, which is composed of a drug-impermeable polymeric membrane with rate-controlling properties. Metallic plastic, silicone rubber, or polyurethanes are the main materials used to make the rate-controlling membrane, which can be either nonporous or microporous and made of ethylene vinyl acetate (EVA) copolymer.

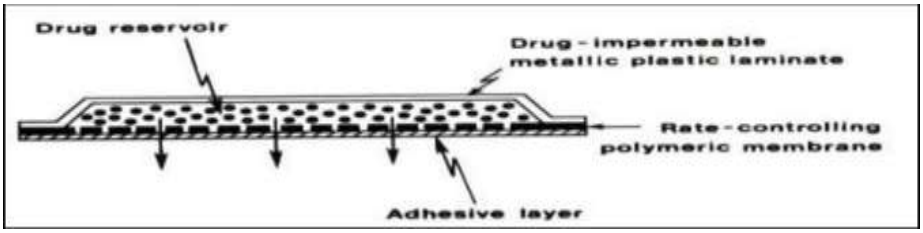
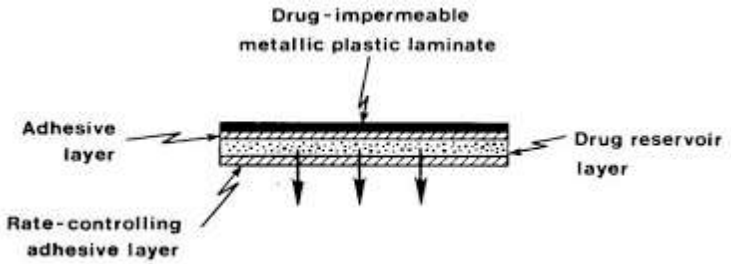


Fig: 3 Membrane Permeation controlled system

2. Adhesive Dispersion –Type Systems

This is a streamlined version of systems controlled by membrane permeability. The medication and other carefully chosen excipients are mixed right into the glue solution in this technique. After mixing and casting them into thin films, the solvent is eventually removed by drying the film. After that, the backing laminate and rate-controlling adhesive polymer membrane are placed on top of the film, which serves as the drug reservoir.



Fig;4 Adhesive Dispersion controlled system

3.Matrix Diffusion controlled systems

This kind of drug reservoir is made by uniformly dissolving or dispersing the finely ground drug particle in a highly viscous base polymer or a hydrophilic/lipophilic liquid polymer. The drug mixture is then thoroughly mixed before the necessary amount of plasticizer, such as propylene glycol or polyethylene glycol, and permeation enhancer are added.After that, the polymer matrix is mounded into discs with a predetermined surface area and thickness.The medicated disc is then positioned within a drug-impermeable backing compartment on an occlusive base plate.Lastly, instead of adhering to the medicated disk's surface directly, the sticky polymer is dispersed around the film.

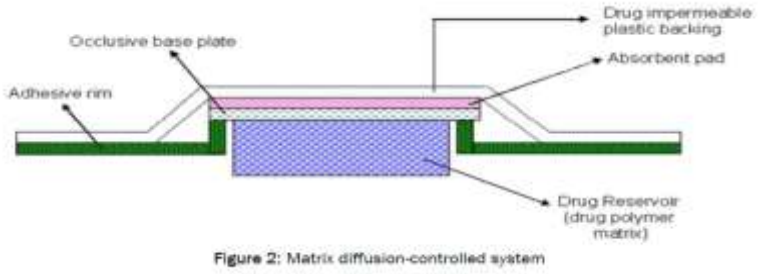


Fig:5 Matrix Diffusion controlled system

4. Micro reservoir diffusion-controlled system

It is possible to think of this kind of TDDS as a hybrid of matrix and reservoir type systems. The solid drug particle is first suspended in an aqueous solution of a water-soluble liquid polymer, such as polyethylene glycol, to produce the drug reservoir in this system. The drug suspension is then uniformly distributed by strong mechanical force in a lipophilic polymer, such as silicone elastomer, creating thousands of impervious miniature drug reservoir spheres, or "micro reservoirs."

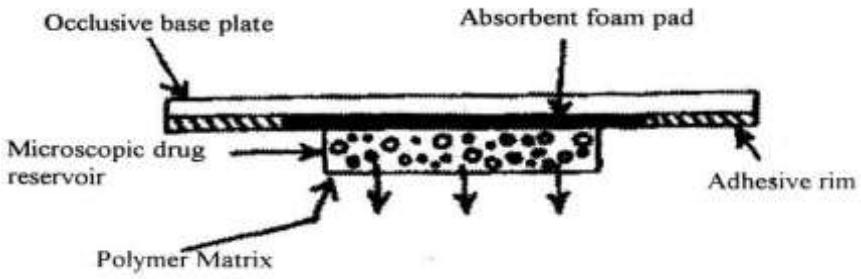


Fig.6 micro reservoir diffusion-controlled system

EVALUATION OF FORMULATION

1.Evaluation of physical parameters

A. Physical Appearance and surface texture: Physical appearance and surface texture include visual inspection of patch and evaluation of texture by feel or touch

B**. 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

C. Weight variation test: It determines the unform distribution of drug. Weight variation was calculated using the formula

(Initial weight - Average weight)/Average weight X 100

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

E. Percentage moisture content: The prepared patches are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature. After 24 hrs. the films are to be reweighed and determine the percentage moisture content by below formula

Percentage moisture content = [(Initial weight- Final weight) / Final weight] ×100.

F. moisture absorption: The patches were weighed accurately and placed in desiccators containing 100 ml of saturated solution of aluminum chloride which maintains humidity. After 3 days the films were taken out and weighed. The percentage moisture absorption was calculated using the formula

Moisture absorption = [final weight –initial weight/initial weight x 100]

G. Swelling studies: Each of the prepared transdermal patches was weighed (W1) and incubated in an agar gel (2%) plate at 37±0.5 °C independently. Every 15 minutes to an hour, the patches were taken out of the petri dish, and any extra water on the surface was carefully wiped away with filter paper. The swelling index was computed using the formula after the swelled patches were reweighed (W2).

Swelling index = W2 − W1 /W1 x 100

H. Peel adhesion test: The measure of patch strength between an adhesive and a substrate is defined as adhesion. The force required removing adhesive coating from the steel used as test substrate. The type and amount of polymer molecular weight and the composition of polymers determine the adhesive properties. The single patch is adhering to test substrate (Steel) and it pulled from the substrate at 1800 angle. No residue on the test substrate indicates failure of adhesive.

I. Drug content : A 2x2 cm size transdermal patch was dissolved in 100 ml methanol and shaken continuously for 24 h. The whole solution was then ultrasonicated for 15 min. After filtration, the drug's content was measured using spectrophotometry at a wavelength of 292 nm

J. Tensile Strength:The tensiometer was used to assess the patch's tensile strength (Erection and instrumentation, Ahmedabad). Two load cell grips make up this device. One was mobile on top and one was stationary at the bottom. These cell grips were attached with 2 × 2 cm film strips, and force was applied incrementally until the film snapped. Right off the dial, the tensile strength was determined in kilograms.

2. Invitro studies

Franz diffusion cell: Locally made Franz diffusion cells with a 25 ml receptor volume were utilized for the permeation investigations. The defrosted rat skin was placed onto a diffusion cell such that the receptor solution was constantly in touch with the dermis side. A patch was placed on the stratum corneum that faces the donor compartment. A magnetic stirrer was used to agitate the receptor fluid at a speed of 100 rpm while maintaining a temperature of 32±0.5°C. For eight hours, a 1 ml sample was taken out at prearranged intervals, and the drug content was measured using a UV-VIS double beam spectrophotometer set to 267.6 nm.

3. In vivo studies

In vivo evaluation of TDDS can be carried out using Animal Models, Human volunteers

a.Skin irritation study: Testing for skin sensitivity and irritation can be done on healthy rabbits weighing between 1.2 and 1.5 kg on average. The rabbit's dorsal surface, which measures 50 cm2, needs to be cleansed. The hair should be shaved off of the clean surface, and rectified spirit should be used to clean the surface after applying representative formulations to the skin. After 24 hours, the patch is to be taken off, the skin examined, and the degree of the skin injury is to be graded into five categories.

STABILITY STUDIES

Type of Stability of drug substance

Physical Stability:

The original physical properties, including appearance, palatability, uniformity, dissolution and suspend ability are retained. Physical stability affects drug uniformity and release rate hence it is important from safety and efficiency point of view.

Chemical Stability:

Each active ingredient retains its chemical integrity and labelled potency within the specified limits. The Chemical stability of drug is of great importance since it becomes less effective as it undergoes degradation. Also, drug decomposition may yield toxic by-products that are harmful to the patient

Microbiological Stability:

Sterility or resistance to microbial growth is retained according to the Specified requirements. Antimicrobial agents retain effectiveness within specified limits. Microbiological instability of a sterile drug product could be hazardous.

Therapeutic Stability: The therapeutic effect remains unchanged.

Toxicological Stability: No significant increase in toxicity occurs

stability testing procedures have been categorized into the following four types.

Real-time stability testing:

Under suggested storage circumstances, real-time stability testing is typically conducted for a longer period of time to allow for considerable product degradation. The length of the test depends on the product's stability, which needs to be sufficient to show unequivocally that no detectable deterioration takes place and to allow one to discern degradation from inter-assay variance. Data is gathered during testing at a suitable frequency to enable a trend analysis to differentiate between daily ambiguity and instability. In addition to the reagents' stability, the reference material's stability also refers to the instrument's performance consistency during the course of the stability testing. Nevertheless, system performance and control for discontinuity and drift brought on by adjustments to the reagents and instrumentationmust be monitored

Accelerated stability testing:

Accelerated stability testing involves stressing a product at multiple high (higher than ambient) temperatures in order to calculate the minimum amount of heat input necessary for the product to fail. This is done in order to put the product in an environment that speeds up deterioration. Next, shelf life is estimated using this data, or it can be used to contrast the relative stability of different formulations. This typically reduces the development schedule by giving an early indication of the product shelf life. During accelerated stability testing, stress factors such as moisture, light, agitation, gravity, pH, and packing are applied in addition to temperature.

Retained sample stability studies

This is standard procedure for any product that is commercialized and needs stability data. Stability samples are chosen for this investigation in order to be kept in storage for at least one batch per year. It is advised to gather stability samples from two batches if there are more than 50 batches being marketed. Stability samples of each batch may be obtained when the product is first introduced to the market; however, at a later time, this percentage may be lowered to only 2% to 5% of marketed batches. The stability samples in this study are examined at pre-arranged intervals, thus if a product has a five-year shelf life.

Cyclic temperature stress testing:

For marketed items, this is not a standard testing procedure. This approach uses cyclic temperature stress tests that are created based on product knowledge to simulate typical storage conditions found in marketplaces. Since the diurnal rhythm of the earth is 24 hours, which the marketed medications are most likely to experience during storage, the time of cycle that is primarily examined is 24 hours. It is advised that the lowest and maximum temperatures for the cyclic stress testing be chosen product by product, taking into account things like the product's suggested storage temperature and unique physical and chemical degradation characteristics. It's also advised that the examination.

PACAKAGING AND LABELLING

PACKAGING

a) a product package substantially moisture impermeable comprising a thermoplastic material configured in the shape of a container having one opening, and further having a substantially moisture impermeable cover sheet comprising a thermoplastic material coextensive to said container opening and affixed to the opening edges by means of heat or adhesive;

(b) one or more child-resistant pouches which are preferentially permeable to moisture consisting essential

(i) a primary layer of a nitrile rubber modified acrylonitrile-methyl acrylate copolymer; and

(ii) a secondary layer of polyester affixed to said primary layer by means of heat or an adhesive;

(iii) a transdermal system comprising a therapeutically effective amount of methylphenidate in a non-aqueous carrier composition, said transdermal system being sealed within a child-resistant pouch; wherein the child-resistant pouches are sealed within the product package; and

(c) a desiccant capable of absorbing at least 1.5 grams of moisture over a one year period of storage, wherein the desiccant is sealed within the product package.

LABELLING

Required information for labels

Information on the main label

The main label is the portion of the label where the name of the medicine is more or most conspicuously shown.

the main label must include:

- name of the medicine
- name of the active ingredients
- quantity or proportion of active ingredients
- name of the dosage form
- quantity of medicine

Specific requirements

There are specific requirements related to different properties of a medicine product. For any product, you need to check the requirements for:

- type of medicine
- specific routes
- specific ingredients
- type of medicine
- batch number and batch number prefix
- expiry date and expiry date prefix
- storage conditions
- name and contact details of sponsor – required to be updated within a year of any change
- declaration of any substances in Schedules
- any required warning statements
- directions for use
- instructions for medicine preparation
- shelf life of product

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Noven Pharmaceuticals (Hisamitsu Pharmaceutical Company Incorporated)

Original Assignee

Noven Pharmaceuticals (Hisamitsu Pharmaceutical Company Incorporated)

Inventors

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