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Formulation and Evaluation of Transdermal Patch of Doxylamine Succinate for long term Anti-Allergic effect in pregnancy

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ABSTRACT

Transdermal drug delivery is a appropriate method for controlled drug release, having several advantage. It allows for safe and pain free self administration, Transdermal patch is suitable for poly-medicated and those with difficulty in swallowing tablets or pills. It provides a constantprolongreleaseofmedicationandavoidingfirstpastmetabolismwhichissuitableforthe drug whose bioavailability is low. Transdermal drug delivery also increase the therapeutic effect ofdrugbybypassingtheissueoccurbyoraladministrationofdruglikepre-systemicmetabolism and GI irritation. Transdermal drug delivery not only allows controlled, continual release of medications but also permits constant delivery of drug with low biological half-life of drug. The benefit of transdermal drug delivery across other route of drug delivery such as topical, oral, intravenous, intramuscular etc., is that the patch gives a controlled release of medication to the patient. Transdermal patch are suitable for those drugs of low bioavailability and having short half life.
Objective:- The objective of the work is to prepare a transdermal patch of doxylamine succinate for the treatment of allergic effect as well as anti-emetic effect in pregnancy.

Key Words: *Transdermal patc , Doxylamine succinate, Sustain release, pregnancy.*

INTRODUCTION

In pregnancy approximately 70% of pregnant women suffers from complications of allergic effects like runny nose, congestion, insomnia etc., and about 30% of women experiences vomiting on daily basis which are occurs due to hormonal changes. These symptoms are occur from morning throughout the day and even into the night. Generally did symptomseffectsbetween4to9weeksandgetseverebetween7to12weeksanddecreasesdown from 12th week. In most of the pregnant women, these allergies of NVP resolve by week 20. However, in 10% of pregnant women, these symptoms shown in entire pregnancy.For the treatment of these allergic symptoms in pregnancy, Transdermal patch of Doxylamine succinate is suitable because, conventional oral doses form needs multiple doses to be given at definite time interval which is not suitable and safe for pregnant women.

Transdermal patch of doxylamine succinate is easy to use and decreases the risk of overdose of drug to patients. Doxylamine succinate is considered as safer drug use in pregnancy for treatment of allergic effects an NVP. The transdermal patch of Doxylamine succinate provides long term Anti-Allergic effect to the patient. The drug Doxylamine succinate has low bioavailability so it is not suitable for oral conventionalformbecausethetherapeuticeffectofdrugdecreaseduetofirstpastmetabolism.So, the transdermal patch bypasses the first pass metabolism and enhances the therapeutic action of drug.

Ideal properties of drugs for formulation of transdermal patch

- The drug dose must be smaller than 20mg per day.
- Molecular weight of drug must be below 400Da.
- Melting point of drug should be less than200°C.
- Oral bioavailability must be short.
- Drug pH should be in between 5-9.
- Half life of drug should be10hrs or lesser.

ANATOMYANDPHYSIOLOGYOFSKIN

Skin is the largest and primary defensive organ of the body. It covers the whole body externally and helping as first order physical obstacle against the external environment. It's function is to protect the body from ultraviolet(uv) light, external pathogens, toxins and temperature regulation. Skin also shows important character in sensorial approach as well as avoidance of unwanted water loss through the body and synthesis of vitamin D through sun light.[1]

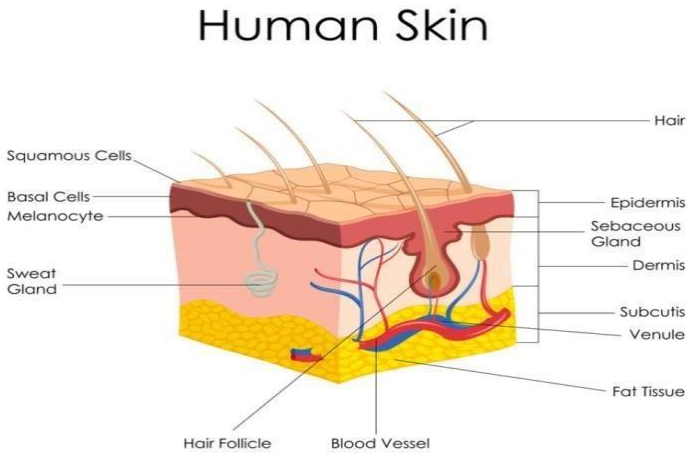

Fig:-Structure of human skin

Human skin is made up of three layers

1.The Epidermis–

It Is the outer most surface of the skin and is comprised of **stratified squamous epithelial cells.** The thickness of epidermis layer differ from 0.8mm on palm and soles low to 0.06mm on the eye lids.

The epidermis layer composed of different region :-

- **Stratum corneum:** It is the outer most surface of the skin and is about 10mm when dry but increases to few times when drenched. It consists of 10 to 30 layer of dead keratinized cells known as corneocytes. It is the principal barrier for penetration of drug.
  - **Stratum lucidum:** Smooth glassy surface of epidermis ,this fine surface of cell found in the dense skin of palms and soles.
  - **Stratum Granulosum :** Made up of 3 to 5 layer and undergoes apoptosis. It includes particles known as

keratohyalin , these particles secretes lipid rich excretion, acts as water repellent.

- **Stratum spinosum:** Includes 8 to10 surface of cells and is closely arranged.
- **Stratum basal :** Made up of one layer of columnar keratinicytes.

2.Dermis layer:

Dermis layer is 3 to 5 mm dense and is lies in the middle of the epidermis and subcutaneous layer and have blood vessels, lymph vessels, nerves and many type of sensory receptor for touch, pressure vibration, pain, touch, temperature etc., The kind of cells present in the dermis are Fibroblast, Mast cell, Histocytes

3 . Hypodermis :

The hypodermis is also known as subcutaneous tissue, gives support to the dermis and epidermis. It act as storage of fat. This surface aid in maintaining body temperature, providing dietary support, and providing external protection.[(1)]

Route of Drug Penetration from Skin

Drug penetration through the skin can happen by two ways :

- The transepidermal route ,which affects penetration from the epidermis
- Other is , the transappendegeal route, which affects penetration from appendages ie.,hair follicles and sweet glands.

Transepidermal Route: In this route,the medicaments, permits from skins outer most surface, known as stratum corneum. This surface is structurally complicated, multi-layered and multicellular barrier.

Transappendegeal Route : This route includes drugs passing through sweet glands and hair follicles in the skin.

So, when drugs requires to enter in the body by the skin, It can either enters from the outer layer of skin cell or use this small tunnels made by sweet gland and hair follicles. Every route has special features, Permitting different types of substances to enter the body.

PenetrationEnhancers

Penetration enhancers, also referred to as permeation enhancers, are substances engaged to increase the permeability of active compounds, such as drugs among the skin. They effect by temporary altering the structure and characterstics of stratum corneum the skin outermost layer. The changing allows for better penetration of the active ingredient into the blood stream or deeper layer of the skin increasing the effectiveness of topical medication.(18,21)

Transdermal patch:-

A transdermal patch is known as adhesive medicated patch that is placed on the skin which gives specific dose of drug by the skin into the systemic circulation at a predefined rate of release. These medicated patches are ease to use and self administrated.[(2,4,5,6)]

Advantages of transdermal patch:

- Delivery of medicine to the systemic circulation without any pain.
- Avoids GI incompatibility.
- Easy to use and having low side effects.
- More beneficial for those patients who are nauseated and unconscious.
- Transdermal patch are useful for the drugs that have low bioavailability and have poor oral uptake.
- Enhances the therapeutic effect of various drugs by avoiding problems related with drugs such as pre systemic metabolism, low absorption , GI irritation etc…
- The drug delivery can be stopped at any time by remove the transdermal patch.
- Transdermal patch are optional for people having problem to take drug orally.
- Decreases patient's drug dose.

- These are cost effective.
- It reduces systemic drug interactions.
- Improves patient acceptance due to ease of use.

Disadvantage of transdermal patch:

- Sometime it causes local skin irritation at the place of administration.
- Rarely dose dumping may occurs.
- It is not suitable for rapid therapeutic effect.
- Large level of drug dose can't be achieve by patch ie., more than 10-25mg/day
- Skin barrier function may varies from person to person or varies with age.

Formulation design:

The transdermal patch are composed of following constituents:-

- **Drug :** Doxylamine succinate
- **Polymer matrix:** Use to control drug release (eg .Eudragit, HPMC)
- **Plasticizer :**To ensure flexibility (eg.PEG**,** Glycerol)
- **Permeation enhancer:** To improve skin permeation (eg.DMSO, Isopropyl myristate).
- **Adhesive :**It ensures the patch remains in place and maintain its place (eg. Silicon adhesive)
- **Baking layer :**Prevent drug loss and maintain structure.[12,13,14]

Method of preparing Transdermal Patch:

Here, the transdermal patch of Doxylamine Succinate is prepared by **Solvent Casting Method.**

- The drug (Doxylamine Succinate)and polymer(eg Eudragit/HPMC) are dissolved in suitable solvent and mixed it slowly to make uniform mixture.
- After that plasticizer (eg PEG, Glycerol) and permeation enhancer(eg.DMSO, Isopropyl myristate) Are added to above mixture step by step and mixed homogeneously.
- The resulted homogeneous solution is cast into Petridish which was greased with glycerin and dried at room temperature for 24hrs.
- A inverted funnel is put on the Petridish to avoid fast evaporation.
- The dried film is removed with the help of sharp blade and wrapped in Butter paper and store in close container away from light in cool place[3].

Type of Transdermal:

- Single-layer drug in adhesive.
- Multi-layer drug in adhesive.
- Reservoir.
- Matrix.
- Vapour patch[2]

Evaluation of Transdermal Patch:

Physiochemical evaluation of the transdermal patch is examined by following methods:-

- **Physical Appearance –** The color, clarity, opacity, translucency, flexibility and smoothness of each patch are examined visually.
- **Thickness of patch –** To determine the thickness of the patch Digital micrometer, travellingmicroscope,micrometerscrewgaugesareusetomeasuredifferentspotsoneach patch to estimate its thickness.
- **Weight uniformity –** For identification of weight uniformity of patch each made patches are dried at 60°C before weighing, To find the weight uniformity $1cm^2$ pieces are cut from 3 patch and weighed individually.
- **Drug content uniformity** -The drug content uniformity of patch is determined by HPLC or GC.
- **Moisture content –** The made film are weighed separately and placed in desiccator containing calcium chloride at room temperature for 24hrs. The films are weighed again after a specific time interval until the show constant weight.
- **Folding endurance –** The prepared patch is cut from one region and then folded the patch repeatedly at same place until it breaks. Prior the patch breaks, the number of folds are recorded.
- **In vitro drug release–**The Invitro drug release is identified by Franz Diffusion Cell(1,6,8).

Conclusion :

This article provides information about the transdermal patch of Doxylamine succinate. In compared to more conventional oral delivery of drug, transdermal drug delivery is more suitable and offers a number of advantages including convenience, sustained release of medication and bypassing first pass metabolism. Transdermal delivery of doxylamine succinate provideslongtermAntiAllergiceffectaswellasNVPinpregnancy.Oraldeliveryofdoxylamine succinate is not suitable because of low bioavailability of drug and is safer drug which is use in pregnancy.

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