

## PROMETHAZINE HYDROCHLORIDE ORODISPERSIBLE FILM: REVIEW

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Article Received on 12/10/2021

Article Revised on 02/11/2021

Article Accepted on 23/11/2021

## ABSTRACT

Promethazine hydrochloride phenothiazine derivative with histamine H1-blocking, antimuscarinic, and sedative properties. It is used as an antiallergic, in pruritus, for motion sickness and sedation, and also in animals. In transdermal drug delivery system (TDDS) the drug is mainly delivered through the skin with the aid of transdermal patch which is a medicament adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and to the blood stream. Now a day TDD is a well-accepted means of delivering many drugs to the systemic circulation in order to achieve a desired pharmacological outcome.

**KEYWORDS:** Promethazine hydrochloride, Transdermal drug delivery system, Transdermal Patch, Histamine H1-blocking, Pruritus, Motion sickness.

## INTRODUCTION

**Human skin** The skin plays an important role in the transdermal drug delivery system. The skin of an average adult body covers a surface area of approximately 2 sq. m. and receives about one third of the blood circulating through the body and serves as a permeability barrier against the transdermal absorption of various chemical and biological agent. The main three layers of skin play an important role in transdermal drug delivery system (Shridevi and Krishna, 1991).

**Transdermal drug delivery system** Transdermal drug delivery system is self contained, discrete dosage form (Arunachalam *et al.*, 2010) in which drug stick to the body surface and delivers the drug, across the skin at controlled rate in to the blood stream. Till now total 16 active ingredients and more than 35 Transdermal drug delivery products have been approved for use globally and for sale in the US market. By statistics analysis it has been found that there is an increase in transdermal market which was \$ 21.5 billion in the year 2011 and will be \$31.5 billion in the year 2015 (Bhargava *et al.*, 2011) as compare to \$ 12.7 billion in year 2005. Oxybutinin drug molecule patch is largest (359 Da) and nicotine drug molecule patch is smallest (162Da) (Saroha *et al.*, 2011) Transdermal drug delivery permits controlled release of the drug into the patient, it enables a steady blood level profile which causes reduced systemic side effects and improved efficacy over other dosage forms (Soni *et al.*, 1992) (Chong *et al.*, 1989) The main

aim of transdermal drug delivery system is to administer drugs into systemic circulation through skin at predetermined rate with minimal inter and inpatient variation with user friendly, convenient, painless, and is multi day dosing, it offer improved patient compliance too1. Patch formulation is a complex process. The rate and amount of transdermal absorption depend on factors like nature of the drug, the drug's concentration in the reservoir or matrix, area of skin covered by the patch. The formulations used are identical but the patches have different surface areas for different strengths of delivered drug when several dose strengths of a drug patch are marketed (e.g., estradiol patches). Drug is placed in large amount in the patches to keep the concentration gradient suitable for absorption because the active ingredients act at low dosage and are inexpensive, the cost of wasted excess drug is not economically significant (Jain *et al.*, 1997; Storm *et al.*, 1990; Banker *et al.*, 1982; Swarbrick *et al.*, 2002; Valenta *et al.*, 2001; Morgan *et al.*, 1998) New advanced technologies like chemical enhancers (Osborne *et al.*, 1997) iontophoresis, electroporation, (Preat *et al.*, 2004). Pressure waves generated by ultrasound or photoacoustic effects (Doukas *et al.*, 2004; Mitragotri *et al.*, 2004) have been developed to enhance transdermal drug delivery for therapeutic and diagnostic purposes (Ilana *et al.*, 2004).

**Uses of transdermal drug delivery system** The highest selling nicotine transdermal patches decrease the tobacco smoking. In Europe 2007 the first commercially

available vapor patch to decrease degree of smoking was approved. Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans) are two opioid medications used for intense pain are administered in patch form. To treat menopausal symptoms as well as postmenopausal osteoporosis estrogen patches are used. Other transdermal patches for delivery of certain hormones include the contraceptive patch (marketed as Ortho Evra or Evra) and testosterone patches for both men (Androde) and women (Intrinsa). For the treatment of angina Nitroglycerin patches are sometimes prescribed instead of sublingual pills. Transdermal scopolamine is commonly used for treatment of motion sickness (Nachum *et al.*, 2006). Antihypertensive drug Clonidine is available in market in form of transdermal patch (Berner *et al.*, 1996) named as Catapres-TTS23. First transdermal patch used as antidepressant approved for use in the U.S. in March 2006 (Peck *et al.*, 2006) was of the MAOI (monoamine oxidase inhibitor) selegiline (brand name Emsam). A transdermal delivery patch (Daytrana) used for Attention (ADHD), drug used methylphenidate (other names Ritalin or Concerta), was approved for market sell by the FDA in April 2006 (Cabray *et al.*, 2006). Vitamin B12 is also administered in the form of transdermal patch. Cyanocobalamin, stable form of vitamin B12 is used in the patch. Transdermal patch of Rivastigmin (market name Exelon) was commercially introduced in

#### Limitations of transdermal drug delivery systems

Transdermal delivery is not suitable for delivery of large doses of drugs. It cannot administer drugs that require high blood levels (Govil *et al.*, 1998). Drug which may cause irritation or sensitization are not given by this route. This route is limited when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin (Misra, *et al.*, 2002). For a drug, which doesn't possess a favourable o/w partition coefficient this route cannot be used. From one site to another on the same person, from person to person and with age the barrier functions of the skin changes which hinders transdermal drug penetration (Monkhouse *et al.*, 1988).

**Care taken while applying transdermal patch** The part of the skin should be properly cleaned before application of patch. Cutting the patch destroys the drug delivery system therefore patch should not be cut. It should be made sure that the old patch is removed from the site before applying a new patch. Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch. The patch should be applied accurately to the site of administration.

**Main components of transdermal drug delivery system** **Polymer matrix** Polymer act as a backbone and important component of transdermal drug delivery systems. Polymeric materials of different classes have been used to require rate controlled drug delivery. The physicochemical properties of the drug and polymer used

in the manufacture of the device act as mechanism of drug release. The criteria to be satisfied for a polymer to be used in a transdermal system are molecular weight, glass transition temperature, chemical functionality or polymer must allow diffusion and release of the specific drug, the polymer should permit the incorporation of a large amount of drug, the polymer should not react physically or chemically with the drug, polymer should be easily manufactured and fabricated into the desired product and inexpensive (Misra, *et al.*, 2002).

#### Drug substance

The selection of drug for transdermal drug delivery depends upon various factors. The drug should have degree of solubility greater than 1 mg/ml in both oil and water. Melting point should be less than 200 °F for the drug (Jayaswal *et al.*, 1987). Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point. The melting point should be as low as possible to obtain the best candidates for transdermal patch (Finnin, *et al.*, 1999).

**Drug reservoir components** It should allow drug transport at the desired rate and compatible with the drug. The drug reservoir must possess the desired viscosity attributes to ensure reliable manufacturing process if an ointment is used. It must possess the desired adhesive and cohesive properties to hold the system together. Mineral oils, polyisobutylene, colloidal silica, HPC are the examples of drug reservoir component.

**Backing laminates** Backing laminate function is to provide support. They prevent drug from leaving the dosage form through top. They are impermeable to drugs and also to permeation enhancers. Backing laminates should be chemically compatible with the drug, enhancer, adhesive and other excipients (Patani *et al.*, 1999).

**Rate controlling membrane** Drug release from the dosage form is controlled by rate controlling membranes in transdermal devices. Poly-2-hydroxyethyl methacrylate (PHEMA) membranes have been evaluated as rate controlling barriers for transdermal application which is discovered recently (Sun *et al.*, 1997).

**Adhesive layer** The main function of adhesive layer is it should not cause irritation, sensitization or imbalance in the normal skin flora during its contact with the skin and should stick to the skin aggressively (Aslani *et al.*, 1996).

**Penetration enhancers** To enhance permeability of stratum corneum to achieve higher therapeutic levels of the drug penetration enhancers are used. They interact with structural components of stratum corneum which include proteins or lipids. They change the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier function which improved permeability.

**Penetration enhancers mechanical methods Iontophoresis** The application of a low level electric current either directly to the skin or indirectly via the dosage form enhance permeation of a topically applied drug (Wang *et al.*, 1993; Turner *et al.*, 1997; Banga *et al.*, 1999; Guy *et al.*, 2000).

**Electroporation** The application of high voltage pulses to the skin that induce the formation of transient pores. High voltages of 100 V and short treatment durations of milliseconds are most implemented.

**Microneedle-based Devices** The very first microneedle systems was invented in 1976. It consist of drug reservoir and plurality of projections which are microneedles of 50 to 100 mm long and they extend from reservoir which penetrate the stratum corneum and epidermis to administer the drug (Gerstel *et al.*, 1976).

**Skin Abrasion** The direct removal or disruption of the upper layers of the skin to enhance the permeation of topically applied drugs. It is a device based on techniques uses by dermatologists for superficial skin resurfacing like microdermabrasion which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes.

**Needle-less Injection** This method is based on firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. Compressed gas like helium is injected through the nozzle which contain drug particle too and the drug is permeated inside body through skin.

**Ultrasound (sonophoresis and phonophoresis)** The use of ultrasonic energy to increase the transdermal delivery of solutes is the mechanism of this method. It uses low frequency ultrasound of 55 kHz for an average time of 15 seconds to inject drug inside body (Kost *et al.*, 2003).

**Laser Radiation** Direct and controlled exposure of a laser to the skin causing ablation of the stratum corneum without significantly destroying the underlying epidermis is the method of this process. The delivery of lipophilic and hydrophilic drugs is done by removal of the stratum corneum using this method (Jacques *et al.*, 1988).

**Carriers or vehicles Micro or nanocapsules** They contain multiple concentric bilayers of surfactant separated by a polar liquid medium, generally water in which the hydrophilic additives are added. Good skin affinity leading to cutaneous penetration and good hydration is created by their multi-lamellar structure and lipid core allows encapsulation of lipid additives.

**Nanoemulsions or Sub-micron emulsions (SMEs) or Mini-emulsions** Nanoemulsion are oil-in-water emulsions having average droplet size ranging from 100 to 500 nm. They have very good stability and during storage they do not undergo phase separation. They give

support to the barrier function of the skin by reducing transepidermal water loss which is shown in many studies (Muller *et al.*, 1998).

**Multiple emulsions** These are W/O/W emulsions constaining dispersion of a W/O emulsion in an aqueous phase under several conditions (Tadros *et al.*, 1992). One can incorporate different water-soluble ingredients even if they are incompatible and also oil soluble additives.

**Miscellaneous Techniques Prodrugs and Ion-Pairs** To enhance dermal and transdermal delivery of drugs with unfavourable partition coefficients the prodrug approach is used (Sloan *et al.*, 2003). This technique involves addition of a promoity to increase partition coefficient and solubility which increase the transport of the drug in the stratum corneum. By hydrolysis esterases release the active drug thereby optimising concentration in the epidermis viable epidermis.

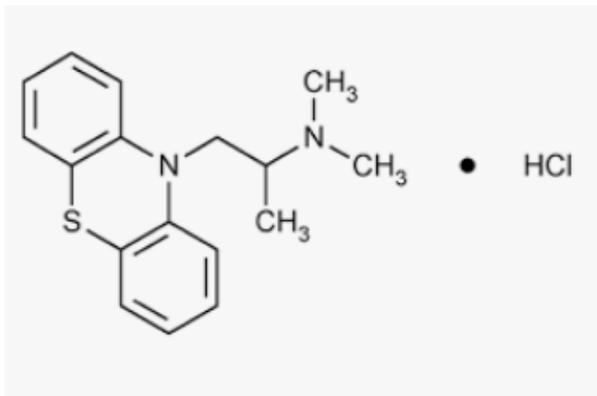
**Vehicle – Saturated and Supersaturated Solutions** When a drug is at its highest thermodynamic activity like supersaturated solution maximum skin penetration rate is obtained. Due to evaporation of solvent or by mixing of cosolvents supersaturated solutions can occur (Vollmer *et al.*, 1994).

**Eutectic Systems** Solubility and hence skin penetration is influenced by melting point of a drug. According to solution theory, lower the melting point, greater the solubility of a material in a given solvent, including skin lipids. The melting point of a drug delivery system can be lowered by formation of a eutectic mixture, which is a binary system. At a constant ratio, the components inhibit the crystallization process of each other, such that the melting point of the two components in the mixture is less than that of each component alone.

**Complexes** Cyclodextrins are large molecules, with molecular weights greater than 1000 Da, therefore it would be expected that they would not readily permeate the skin. To enhance aqueous solubility and drug stability complexation of drugs with cyclodextrins is used. Cyclodextrins contain 6, 7 or 8 dextrose molecules bound in a 1,4- configuration to form rings of various diameters. Complexation with cyclodextrins is used to increase and decrease skin penetration of drugs (Legendre *et al.*, 1995).

#### **Drug: Promethazine hydrochloride**

A phenothiazine derivative with histamine H1-blocking, antimuscarinic, and sedative properties. It is used as an antiallergic, in pruritus, for motion sickness and sedation, and also in animals.



**Figure 5.1: Structure of Promethazine hydrochloride.**

**Molecular Formula:** C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>S

**Molecular Weight:** 320.88

**IUPAC Name:** dimethyl[1-(10H-phenothiazin-10-yl)propan-2-yl]amine hydrochloride.

### PHARMACOLOGY

**Indication:** For the treatment of allergic disorders, and nausea/vomiting.

**Pharmacodynamics:** Promethazine, a phenothiazine, is an H<sub>1</sub>-antagonist with anticholinergic, sedative, and antiemetic effects and some local anesthetic properties. Promethazine is used as an antiemetic or to prevent motion sickness.

**Mechanism of action:** Like other H<sub>1</sub>-antagonists, promethazine competes with free histamine for binding at H<sub>1</sub>-receptor sites in the GI tract, uterus, large blood vessels, and bronchial muscle. The relief of nausea appears to be related to central anticholinergic actions and may implicate activity on the medullary chemoreceptor trigger zone.

**Absorption:** On average, 88% of a promethazine dose is absorbed after oral administration; however, the absolute bioavailability is only 25% because of first-pass clearance.

**Route of elimination:** Promethazine hydrochloride is metabolized in the liver, with the sulfoxides of promethazine and N-desmethylpromethazine being the predominant metabolites appearing in the urine.

**Half life:** 16-19 hours

### Uses

Promethazine is used to prevent and treat nausea and vomiting related to certain conditions (such as before/after surgery, motion sickness). It is also used to treat allergy symptoms such as rash, itching, and runny nose. It may be used to help you feel sleepy/relaxed before and after surgery or to help certain narcotic pain relievers (such as meperidine) work better. It may also be used for a short time to treat a runny nose due to the common cold.

### Side effects

- Drowsiness,
- Dizziness,
- Constipation,

- Blurred vision,
- Dry mouth

### Evaluation of transdermal patch Interaction studies

Excipients are essential constituents of all pharmaceutical formulations. Compatibility of the drug with the excipient is the factor which controls the stability of a formulation. The drug and the excipient must be compatible with one another to produce a product that is stable. It is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug.

**Thickness of the patch** The thickness of the drug loaded patch is measured by using a digital micrometer which also determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

**Drug content** A specified area of patch is dissolved in a suitable solvent in specific volume, the solution is filtered through a filter medium and the drug content is analyzed with the suitable method like UV or HPLC technique.

**Polariscope examinations** It involves examining drug crystals from patch by polar scope. A specific surface area of patch is kept on the object slide and we have to observe whether the drug is present in crystalline or amorphous form.

**Thumb tack test** This test is for tack property determination of adhesives. The thumb is simply pressed on the adhesive and the relative tack property is detected.

**Percentage Elongation break test** By noting the length just before the break point the percentage elongation break is determined. The mathematical formulae used for this method is  $\text{Elongation percentage} = \frac{L1 - L2}{L2} \times 100$ . Where, L<sub>1</sub> is the final length of each strip and L<sub>2</sub> is the initial length of each strip

**In vitro drug release studies** The release of the drug from the prepared patches is done by the paddle over disc method or USP apparatus V. Dry films of known thickness are cut into definite shape, weighed and fixed over a glass plate with an adhesive. The glass plate is placed in a 500- mL of the dissolution medium or phosphate buffer pH 7.4. The apparatus was equilibrated to 32 ± 0.5°C. The paddle is then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. 5- mL aliquots sample are withdrawn at 24 hrs time interval and UV spectrophotometer or HPLC is used to analyze the sample.

**In vitro skin permeation studies** In vitro permeation study is done in diffusion cell. Full thickness abdominal skin of male Wistar rats of weights 200 to 250g is taken. By using an electric clipper hair from the abdominal region is removed and dermal side of the skin is cleaned

with distilled water to remove tissues and blood vessels. It is equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment. Then we place it on magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. By using a thermostatically controlled heater the temperature of the cell is maintained at  $32 \pm 0.5^\circ\text{C}$ . The isolated rat skin piece is mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is replaced. Samples are filtered through filtering medium and checked in HPLC.

**Skin Irritation study** Healthy rabbits of average weight 1.2 to 1.5 kg are taken and skin irritation and sensitization testing is performed. The dorsal surface 50cm<sup>2</sup> area of the rabbit is cleaned, hairs are removed from the clean dorsal surface by shaving and cleaning the surface by rectified spirit and the representative formulations is applied over the skin. The patch is removed after 24 hr and the skin is observed and classified into 5 grades on the basis of the severity of skin injury.

**Stability studies** According to the ICH guidelines, stability studies are conducted in which samples are stored at  $40 \pm 0.5^\circ\text{C}$  and  $75 \pm 5\%$  RH for 6 months. The samples are taken at 0,30,60,90,180 days and drug content is analyzed. Future of transdermal therapy Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness and estradiol for estrogen deficiency, all through patches. At that time, biotech medicinal was still being developed. During the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. The reason is the only a limited number of drugs fit the molecular weight, and potency requirements for transdermal absorption.

## CONCLUSION

Promethazine hydrochloride has all of the properties needed for a controlled drug delivery method in the form of transdermal films. When combined with the medicine and excipient, the polymers used were non-toxic, non-absorbable, and did not lose their film forming capabilities. Because of its larger concentration of hydrophilic quaternary groups, the ERL polymer swells more than the ERS polymer. Transdermal films of diverse polymeric combinations had little or no influence on the physicochemical characteristics from one another. HPMC and Eudragit RSPO polymers were used to develop suitable, smooth, and transparent films.

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