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Formulation and evaluation of transdermal patches and to study permeation enhancement effect of eugenol

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ABSTRACT

Since oral bioavailability of Propranolol Hydrochloride is poor due to high first pass metabolism different matrix- type transdermal patches incorporating Propranolol Hydrochloride were formulated with an objective to study the effect of polymers on transdermal release of the drugs. The polymers selected for sustaining the release of drug were polyvinylpyrrolidone, Hydroxypropylmethycellulose (HPMC) and Ethyl cellulose (EC). The patches were formulated using combination of polymers and propylene glycol as plasticizer. The physicochemical evaluation of the polymer matrices was performed for suitability. In vitro permeation studies were performed using rat abdominal skin as the permeating membrane in Franz diffusion cell. The result indicated that maximum release was obtained at 2% solution of EC. Optimized batch was evaluated for permeation enhancement through rat skin using natural permeation enhancer Eugenol and it was concluded that permeation enhancement through Eugenol was comparable to the commercially available permeation enhancer Dimethyl sulfoxide 1% (DMSO). All the films were found to be stable at 37ºC and 45ºC with respect to their physical parameters and drug content.

Key words: Transdermal patches, Propranolol Hydrochloride, Polyvinylpyrrolidone, Hydroxypropylmethycellulose (HPMC), Ethyl cellulose.

INTRODUCTION

There are two important layers in skin: Dermis and Epidermis. The outermost layer, the epidermis, is approximately 100 to 150 micrometers thick, has no blood flow and includes a layer within it known as the stratum corneum. This is the layer most important to transdermal delivery. Its composition allows it to keep water within the body and foreign substances out. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body. If the drug is able to penetrate the stratum corneum, it can enter the blood stream. A process known as passive diffusion, which occurs too slowly for practical use, is the only means to transfer normal drugs be both water-soluble and lipid soluble. Transdermal drug delivery systems are topically administered medicaments in form of patches that deliver the drug for systemic effects at a predetermined controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow pharmaceuticals to be delivered across the skin barrier (Aquil M et al.,2004) A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. The best mixture is about fifty percent of the drug being each hydrophilic and lipophillic. This is because “Lipid-soluble substances readily pass through the intercellular lipid bi- layers of the cell membranes whereas water-soluble drugs are able to pass

limiting steps in transdermal drug delivery system. Sweat ducts and hair follicles are paths of entry, but they are considered rather insignificant. (Arabi H et al., 2002)

BASIC COMPONENTS OF T. D. D. S (Baker RW et al., 1989)

1. Polymer Matrix

The Polymer controls the release of the drug from the device.

a) Natural Polymers: Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b) Synthetic Elastomers: Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

c) Synthetic Polymers: Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy etc.

2. Drug

For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

- Physicochemical properties

1. The drug should have a molecular weight less than approximately 1000 daltons.
2. The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
3. The drug should have low melting point.

Along with these propertiesthe drug should be potent, having short half life and be non irritating.

3. Permeation Enhancers (Cal K et al., 2000)

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant.

These may conveniently be classified under the following main headings:

a) Solvents

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids.

Examples

Water alcohols – methanol and ethanol;
Alkyl methyl sulfoxides : dimethyl sulfoxide,
alkyl homologs : methyl sulfoxide dimethyl acetamide
pyrrolidones : 2 pyrrolidone,

Mechanism of permeation enhancer

- These are the chemical compounds that increase permaeblity of stratum corneum so as to attain higher therapeutic level of drug.
- Permeation enhancers interact with structural components of stratum corneum that is proteins and lipids.
- They alter protein and lipid packaging of stratum corneum thus chemically modifying barrier function leading to increased permeability.

Natural permeation enhancer Eugenol:

- It is having less toxicity profile.
- Irritation is not produced.

b) Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

- Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate
- Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.
- Bile Salts: e.g. Sodium ms taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

c) Miscellaneous chemicals

These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents.

Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein.

4. Other excipients

a) Adhesives:

The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive systems should fulfill the following criteria:

- Should adhere to the skin aggressively, should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should not irritate or sensitize the skin.

The face adhesive system should also fulfill the following criteria.

- Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
- Permeation of drug should not be affected.
- The delivery of simple or blended permeation enhancers should not be affected.

b) Backing membrane:

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc.

Desirable features for transdermal patches

- Composition relatively invariant in use.
- System size reasonable.
- Defined site for application.
- Application technique highly reproducible.
- Delivery is (typically) zero order.
- Delivery is efficient

TYPES OF T.D.D.S (Godbey KJ., 1996)

Single-layer Drug-in-Adhesive

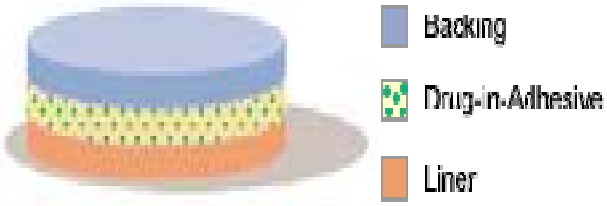

Figure 1: Single-layerdrug-in-adhesive

The Single-layer Drug-in-Adhesive system is characterized by the inclusion ofthe drug directly within the skin-contacting adhesive. In this transdermal systemdesign, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin.

Multi-layer Drug-in-Adhesive

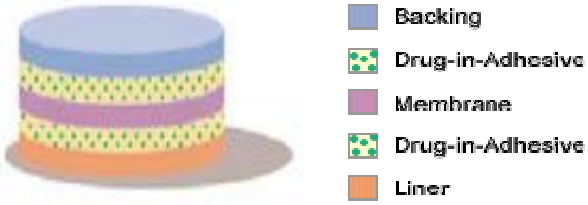

Figure 2: Multi layer drug in adhesive

The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.

Drug Reservoir-in-Adhesive (Bromberg L., 1996)

Figure3:Drug-reservoir-in-adhesive

The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

Drug Matrix-in-Adhesive

Figure4:Drug-matrix-in-adhesive

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.

EVULTION PARAMETRER OF TDDS (Costa P et al., 1997)

Adhesive strength determination (Dodou K et al., 2007)

This is done with the help of tensiometer. TDD unit is applied on the hand and the force required to pull the applied patch away from hand is measured, more the force required to pull the patch away from hand indicates more adhesive strength.

Strategies of skin permeation

Dermatological and cosmetic preparations frequently contain active principles which can only act when they penetrate at least the outermost layer of the skin. However, the efficacy of the skin is slow due to the resistance of the outermost layer of the skin, the stratum corneum. Most small water-soluble non-electrolytes therefore diffuse into the systemic circulation a thousand times more rapidly when the horny layer is absent. Thus, a variety of means have been studied in attempts to overcome this barrier. Such strategies include physical, biochemical, and chemical methods.(Desai SJ et al., 1997)

Physical approach (Izumoto T et al., 1992)

- Stripping of stratum corneum,
- Hydration of stratum corneum,
- Iontophoresis
- Phonophoresis,
- Thermal energy.

Chemical approach (Izumoto T et al., 1992)

- Synthesis of lipophilic analogs
- Delipidization of stratum corneum
- Coadminitration of skin permeation enhancer

Biochemical approach

- Synthesis of bioconvertable prodrugs,
- Co-administration of skin metabolism inhibitors.

Structure of the skin barrier

The skin is the largest human organ and consists of three functional layers: epidermis, dermis, and subcutaneous tissue. It has a wide variety of functions. One major task of the skin is to protect the organism from water loss and mechanical, chemical, microbial, and physical influences. The protective properties are provided by the outermost layer of the skin, the epidermis. Although its thickness measure on average only 0.1 mm (from 0.02 mm on the face up to 5 mm on the soles of the feet) it is specially structured to fulfill this challenging task. Out of the five layers of the epidermis, it is mainly the upper most layer (horny layer; stratum corneum) which forms the permeability barrier. The stratum corneum consists of horny skin cells (corneocytes) which are connected via desmosomes (protein-rich appendages of the cell membrane). The corneocyte are embedded in a lipid matrix. Thus the structure of the stratum corneum can be roughly described by a "brick and mortar" model. (Elias PM., 1981)

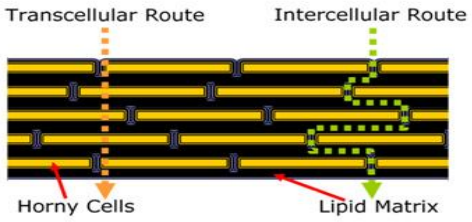

Figure 5: brick and mortal model

Routes of penetration

Illustrates the possible pathway for a panetrant to cross the skin barrier. Accordingly, a molecule may use two diffusional routs to penetrate normal intact human skin: the appendageal route and the transepidermal route. The appendageal route comprises transport via the sweet glands and the hair follicles with their associated sebaceous glands. The routes circumvent penetration through the stratum corneum and are therefore known as shunt routes. Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1 % of the total skin area. The appendageal route seems to be most important for ions and large polar molecules which hardly permeation the stratum corneum. (Dimas DA et al., 2000)

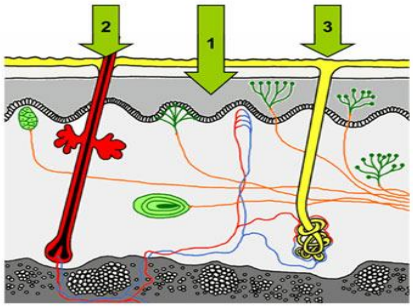

Figure 6: Possible pathways for a reentrant to cross the skin barrier.

(1) Across the intact horny layer, (2) through the hair follicles with the associated sebaceaous glands, or (3) via the sweat glands

MATERIAL AND METHODS

Preparation of transdermal patch containing drug and polymer matrix

- Matrix type transdermal patches compose of different ratio of metoprolol, Polyvinylpyrrolidone(PVP),Ethyl cellulose , Glycerin and PEG400 where prepared by solvent evaporation techniques using bangles. The bottom of the bangle was wrapped with aluminium foil on which backing membrane was cast by pouring 5%w/v aqueous PVA solution followed by drying at 50°C for 8hrs.
- Drug matrix was prepared by dissolving requisite amount of drug(Propranolol) and EC in methanol. To this solution PEG400 (40%w/w of polymer composition) was added and stirred.
- The uniform dispersion obtained was casted on PVA backing membrane and dried at room temperature for 24hrs.
- The dry films were removed and wrapped in aluminum foil and kept in a dessicator until used, which is shoe in the figure no.7
- The so prepared films were stick to adhesive layer of bandage which was purchased from local market.

Figure 7: Prepared Transdermal patch of Propranolol hydrochloride

1. Extraction and isolation of Eugenol:

- Clove powder (10g) was mixed with 100ml of solvent ether and was shaken with 3 successive quantities of 100ml of 10% potassium hydroxide solution.
- Regenerate Eugenol by acidifying the aqueous layer with excess of sulphuric acid and extracting the acidified layer with 3 successive quantities of 50ml of solvent ether.
- Distill off the solvent with care to ensure minimum loss of Eugenol and dry residue in dessicater.

EVALUATION OF TRANSDERMAL PATCHES

Calibration Curve

1. Stock solution 100µg/ml was prepared in phosphate buffer pH 7.2 .

Table 1: Formulation table of transdermal patches of propranolol hydrochloride

S No	ING	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	Drug(mg)	80	80	80	80	80	80	80	80	80	80	80
2	Methanol(ml)	3	3	3	3	3	3	3	3	3	3	3
3	PEG-4000 (%)	40	40	40	40	40	40	40	40	40	40	40
4	PVA (%)	5	5	5	5	5	5	5	5	5	5	5
5	EC (%)	2	5	10	-	-	-	-	-	-	5	5
6	PVP (%)	-	-	-	2	5	10	-	-	-	-	-
7	HPMC (%)	-	-	-	-	-	-	2	5	10	-	-
8	Eugenol (1%)	-	5	-	-	-	-	-	-	-	5	-
9	DMSO(1%)	-	-	-	-	-	-	-	-	-	-	5

2. Using this solution dilutions were done and solutions of comcentration 2,4,6,8,10 and 12µg/ml were prepared and there absorbance was measured in u.v spectrophotometer at λmax 280nm,these calibration curve show in figure no.9

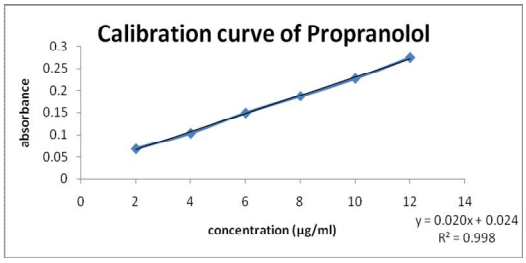

Figure 8: Clibration curve of Propranolol

In vitro skin permeation studies with polymeric matrix

The *in vitro* skin permeation of Propranolol Hydrochloride from various transdermal patches using locally fabricated franz type of diffusion cell. The diffusion cell consists of two parts; the upper part that is donor compartment and contain active ingredient and the carrier patch; the bottom part contains the receptor solution, the water jacket for temperature control, and the sampling port. The effective permeation area of the diffusion cell and receptor and cell volume was 1cm^2 and 20ml, respectively. The temperature was maintain at 37± 2`c. the receptor compartment contained 20ml of phosphate buffer IP PH 7.2 stirred by magnetic stirrer. The permeability studies were carried out across rat skin. Sample 5ml were withdraw and replace with the same volume of fresh receptor solution, to the sampling port of the diffusion cell predetermine time intervals till 6hrs.the absorbance of withdrawn samples were measured at 280nm for Propranolol Hydrochloride. Find out the %Cumulative Drug release of each formulation. Plot the graph between %Cumulative Drug release v/s time, which is present in figure no.10 (A, B, C). The experiments were done in triplicates, simultaneously blanks were also run and the average value reported. (Franz TJ., 1991)

Figure 9: Diffusion study of prepared TDS

Thickness:

The thickness of the patch was determine by using vernial calipers, recording mean of 6 determinations, thickness is present in figure no. 11

RESULT AND DISCUSSION

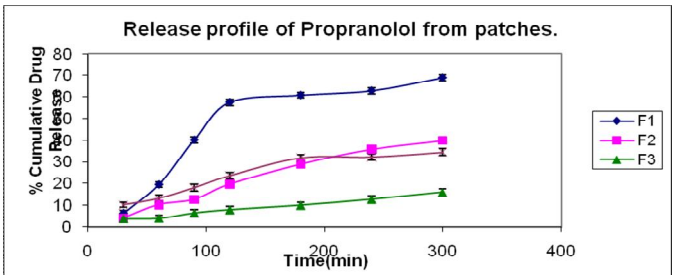

Figure.10 (A): Release profile of Propranolol from patches(F1-F4)

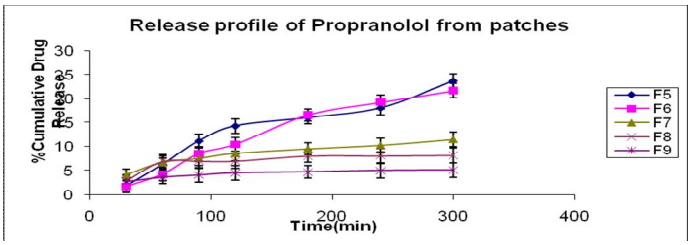

Figure 10(B): Release profile of Propranolol from patches(F5-F9)

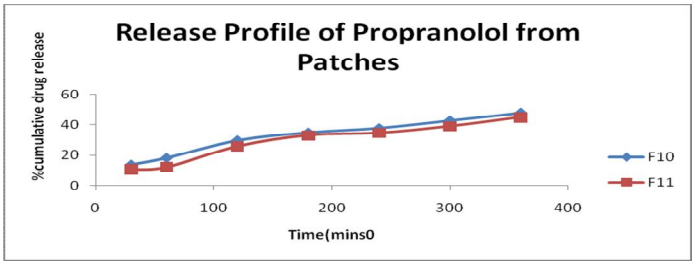

Figure 10(C): Release profile of Propranolol from patches(F10-F11)

THICKNESS

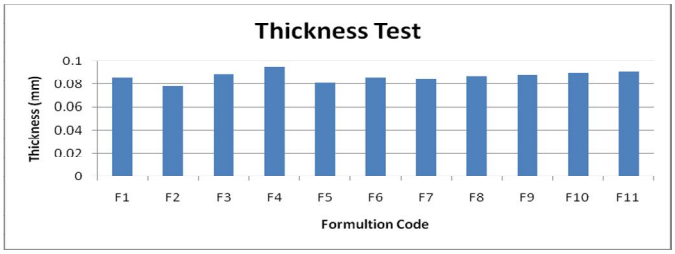

Figure 11:Thickness of the prepared TDP

DISCUSSION

From above graph we can conclude that %cumulative release of drug depends on the concentration of PVP, HPMC and EC. If concentration of polymers increases there would be decrease in the release of drug. We can draw the conclusion that %cumulative release of EC was greater than the %cumulative release of PVP.

CONCULSION

Thin, flexible, smooth and transparent films were obtained with PVP, HPMC and EC polymers using glycerin as plasticizers. Thickness of all the formulations remained uniform with low SD values. All the system containing EC polymer showed good release than that of PVP systems. Optimized batch was evaluated for permeation enhancement through rat skin using natural permeation enhancer Eugenol and it was concluded that permeation enhancement through Eugenol was comparable to commercially available permeation enhancer DMSO. The systems were found to be stable at 37 ºC and 45 ºC. Studies have shown promising results; hence, there is a scope for further pharmacodynamic and pharmacokinetic evaluation.

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