PREPARATION AND EVALUATION OF IBUPROFEN TRANSDERMAL PATCH

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Summary

With the advent of new era of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Transdermal patches are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. Transdermal dosage forms, though a costly alternative to conventional formulations, are becoming popular because of their unique advantages. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery. Development of controlled release transdermal dosage form is a complex process involving extensive efforts. This research article describes the methods of preparation and evaluation of Ibuprofen patch by using Ethyl cellulose as an polymer.

Key words: Ibuprofen**,** Ethyl cellulose**,** Citric acid**,** PEG-400**,** Glycerin**,** Propylene glycol, Ethanol, Dibutyl pthalet**,** PEG-6000**,** Chloroform

Introduction

Transdermal Drug Delivery System:-

To provide continues drug infusion through an intact skin, several transdermal therapeutic systems have been developed for topical application on to the intact skin surface to control the delivery of drug & its subsequent permeation through the skin tissue. It is exemplified by the development & marketing of scopolamine releasing transdermal therapeutic system for 72hrs.

Advantages of transdermal drug delivery:

- Transdermal drug delivery systems offer several important advantages over more traditional approaches, including:
- Longer duration of action resulting in a reduction in dosing frequency Increased convenience to administer drugs which would otherwise require frequent dosing.
- Improved bioavailability.
- More uniform plasma levels.
- Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
- Flexibility of terminating the drug administration by simply removing the patch from the skin.
- Improved patient compliance and comfort via non-invasive, painless and simple application.

Some of the greatest disadvantages to transdermal drug delivery are:

- Possibility that a local irritation at the site of application.
- Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.

DRUG DELIVERY ROUTES ACROSS HUMAN SKIN

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, via the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum (Fig. 1).

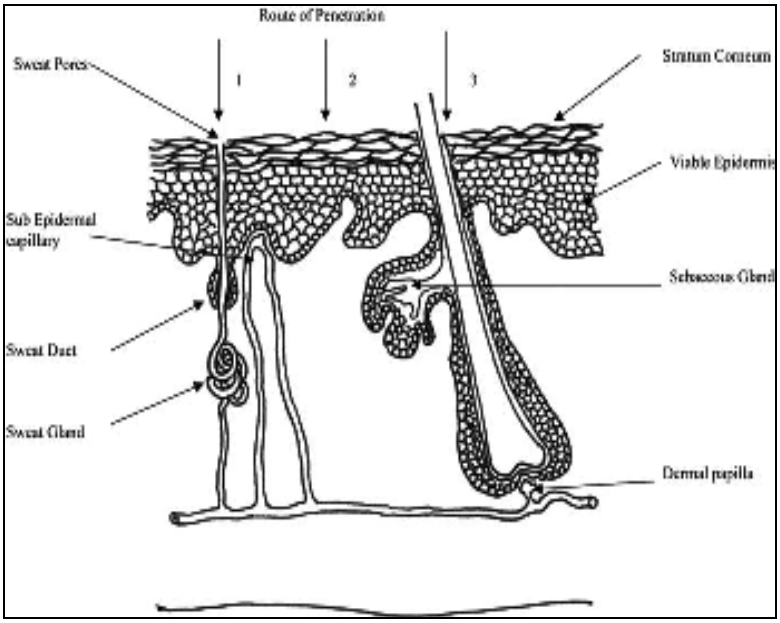


Fig. (1). Simplified representation of skin showing routes of penetration:

1. through the sweat ducts;

2. Directly across the stratum corneum;

3. via the hair follicles.

THEORY;

Basic Components Of TDDS

- Polymer matrix / drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (psa)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

Polymer matrix / drug reservoir:

Polymers are the backbone of tdds, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in tdds should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and psas.

Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status5.

- Natural polymers: e.g. Cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.
- Synthetic elastomers: e.g. Polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber etc.
- Synthetic polymers: e.g. Polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.

Drug:

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemiTransdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosingstry. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight (less than 500 daltons), have adequate solubility in oil and water (log p in the range of 1-3), a low melting point (less than 200°c) and are potent (dose in mg per day)19.

Permeation enhancers:

These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate20. Penetration enhancers interact with structural components of stratum corneum i.e., proteins or lipids. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability2

Pressure sensitive adhesives (PAS) :

A PAS is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue37-38. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in tddss39. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation.

Backing laminate:

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate41-42. Examples of some backing materials are vinyl, polyethylene and polyester films.

Release liner:

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. Typically, release liner is composed of a base layer which may be non-occlusive (e.g. Paper fabric) or occlusive (e.g. Polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for tdds release liner include polyester foil and metallized laminates38

Other excipients:

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoi. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

Different types of transdermal patches:

Several system designs have been used in development and fabrication of tddss. The systems that have been introduced in market can be classified into following types:

- Matrix type
- Reservoir type
- Membrane matrix hybrid
- Micro reservoir type
- Drug in adhesive type

Matrix type transdermal patch(s):

Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogenously dispersed in hydrophilic or lipophillic polymer. The required quantity of plasticizer like dibutylpthalate, triethylcitrate, polyethylene glycol or propylene glycol and permeation enhancer is then added and mixed properly. Commonly used polymers for matrix are cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose. Advantages of matrix patches include absence of dose dumping, direct exposure of polymeric matrix to the skin and no interference of adhesive. Design of matrix type patch is shown in figure (1).

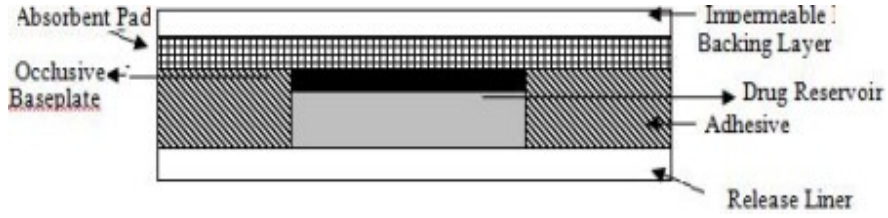


Fig 2 : design of matrix type transdermal patch

Reservoir type transdermal patch(s):

The drug reservoir is made of a homogenous dispersion of drug particles suspended in an unleachable viscous liquid medium (e.g. Silicon fluids) to form a paste like suspension or gel or a clear solution of drug in a releasable solvent (e. G. Ethanol). The drug reservoir formed is sandwiched between a rate controlling membrane and backing laminate

The rate controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid filled micropores in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of nonporous membrane, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the thickness. Figure 2 illustrates the design of reservoir type of patch

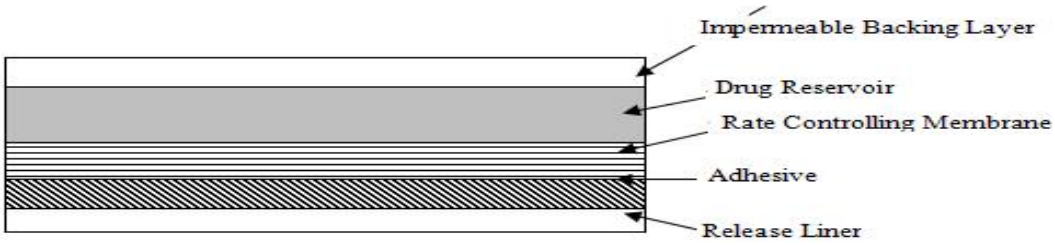


Fig 3: design of reservoir type transdermal patch

Micro reservoir type transdermal patch(s):

The drug reservoir is formed by suspending the drug solids in an aqueous solution of water miscible drug solubilizer e.g. Polyethylene glycol. The drug suspension is homogenously dispersed by a high shear mechanical force in lipophillic polymer, forming thousands of unleachable microscopic drug reservoirs (micro reservoirs). . This system is exemplified by development of nitrodisc. Micro reservoir type transdermal system is shown in figure 3.

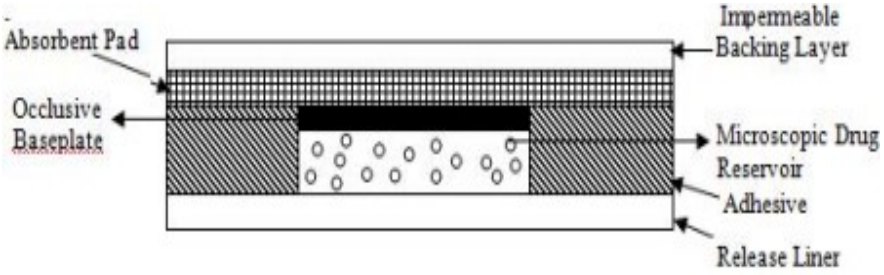


Fig 4: design of micro reservoir type transdermal patch

Drug in adhesive type transdermal patch(s):

The drug and other selected excipients, if any, are directly incorporated into the organic solvent based pressure sensitive adhesive solution, mixed, cast as a thin film and dried to evaporate the solvents, leaving a dried adhesive matrix film containing the drug and excipients. This drug in adhesive matrix is sandwiched between release liner and backing layer. Drug -in - adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane.Design of this system is shown in figure 4.

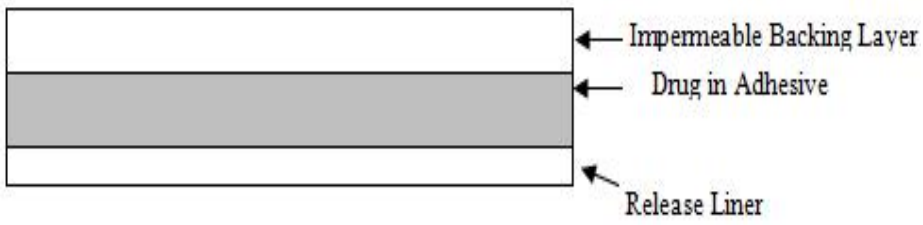


Fig 5: design of drug in adhesive type transdermal patch

Physicochemical evaluation

Thickness and weight variation

The thickness of the patches was assessed at 6 different points using screw gauze. For each formulation, three randomly selected patches used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.

Flatness

Longitudinal strips were cut from each film, one from the centre and two from either side. The length of each strip was measured and the variation in the length because of uniformity in flatness was measured by determining percent constriction, considering

Zero percent

constriction equivalent to 100% flatness.

$$\% \text{ constriction} = \frac{I1 - I2}{I1} \times 100 \quad (1)$$

I2 = final length of each strip

I1 = initial length of each strip

Folding endurance

The folding endurance was measured manually as per the reported method. Briefly, a strip of the film (4 x 3cm) was cut evenly and repeatedly folded at the same place till it broke. The thinner the film more flexible it is

Drug content determination

The patch (1 cm2) was cut and added to a beaker containing 100 ml of phosphate buffered saline pH 7.4(pbs). The medium was stirred (500 rpm) with teflon coated magnetic bead for 5 hours. The contents were filtered using whatman filter paper and the filtrate was analyzed by u.v.spectrophotometer at 269 nm for the drug content against the reference solution consisting of placebo films.

In vitro drug release studies

The in vitro release was carried out with the dialysis membrane using franz diffusion cell. The cell consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at 37 ± 0.5o c and receptor compartment was provided with sampling port. The diffusion medium used was pbs ph 7.4 solution.

The drug containing film with a support of backing membrane was kept in the donor compartment and it was separated from the receptor compartment by dialysis membrane with molecular weight cut off between 12000 to 14000. The dialysis membrane was previously soaked for 24 hours in pbs ph 7.4. The donor and receptor compartment hold together using clamp. The receptor compartment with 15 ml of pbs pH 7.4 was maintained at 37 ± 0.5 oc and stirred with magnetic capsule operated by magnetic stirrer, to prevent the formation of concentrated drug solution layer below the dialysis membrane. Samples of 3 ml, were collected at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by UV Spectrophotometrically .Cumulative percentage drug released were calculated and plotted against time.

Fig 6. schematic diagram of Franz diffusion cell preparation of skin

Stability studies:

The ability of vesicles to retain the drug (drug retention behavior) was assessed by keeping the proniosomal gel at three different temperature conditions, i.e., refrigeration temperature (4-80c), room temperature (25±20c) and oven (45±20c).throughout the study, proniosomal formulations were stored in aluminum foil-sealed glass vials. The samples were withdrawn at different time intervals over a period of one month and drug leakage from the formulations was analyzed for drug content

Moisture content:

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified

interval until they show a constant weight. The percent moisture content is calculated using following formula.

% moisture content = initial weight – final weight x 100

final weight

Moisture uptake:

Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below

% moisture uptake = final weight – initial weight x 100

initial weight

Tensile strength:

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

Tensile strength= f / a.b (1+l / e) (2)

Where,

f -the force required to break; a -width of film; b-thickness of film; l -length of film;

e- elongation of film at break point

In another study, tensile strength of the film was determined with the help of texture analyzer. The force and elongation were measured when the films broke.

Adhesive studies:

The therapeutic performance of tdds can be affected by the quality of contact between the patch and the skin. The adhesion of a tdds to the skin is obtained by using psas, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a tdds can be characterized by considering the following factors

- **Peel adhesion properties**: it is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° angle. The test is passed if there is no residue on the substrate
- **Tack properties**: it is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer75
- **Thumb tack test**: the force required to remove thumb from adhesive is a measure of tack.
- **Rolling ball test:** this test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.
- **Quick stick (peel tack) test:** the peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90◦ at the speed of 12 inch/min.
- **Probe tack test:** force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.
- **Shear strength properties or creep resistance :** shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate

In vivo studies

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 models
- Human volunteers

EXPEREMENTATION:

Materials & method:-

Ibuprofen **,**Ethyl cellulose**,**Citric acid**,**PEG-400**,**Glycerin**,**Propylene glycol, Ethanol, Dibutyl pthalet**,**PEG-6000**,**Chloroform

Fabrication of transdermal patch:

Method 1:

Transdermal patch was prepared by dissolvlvig ibuprofen (200mg) & ethyl cellulose (900mg) in ethanol (5ml). Then citric acid (10mg) was added to above solution. Add PEG-400(0.01ml), glycerin (0.01ml), propylene glycol(.01ml) to it. Then the solution was stirred well to dissolve completely. Then prepared solution was poured into prelubricated Petri plate. The patch was completely dried within 3 to 4 hrs.

Method 2:

Transderamal patch was prepared by dissolving ibuprofen (300mg), in chloroform (5ml), and then added the dibutyl phthalate (0.3ml). Then this prepared solution was added in polymeric solution i.s. ethyl cellulose (900mg) & PEG 6000(90mg) which was dissolved in chloroform (10ml). The volume was make up to 22ml.Prepared solution was poured in prelubricated patri plate. Patch was dried completely within 1/2hr.

Evaluation of polymeric film:

The films were evaluated for the following parameters:

Thickness: The thickness of film was measured by using micrometer screw gauze with a least count of 0.25 mm.Thickness was measured at five different points on the film and average of five readings was taken

Weight variation: Three films was selected & wet is taken individually & the average weight was calculated.

Flatness: Film was cut into strips, two from either end and one from the center. The length of these strips was measured to the nearest centimeter without applying any additional pressure. The percent flatness of the strips was selected as the average percent of length calculated from the 7cm strips.

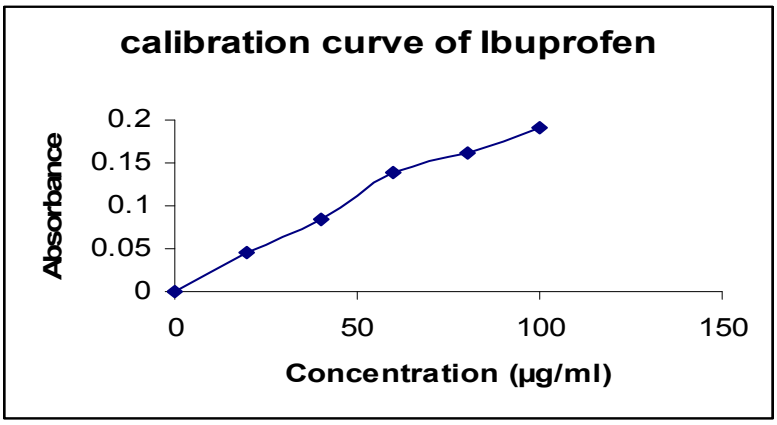
Folding endurance

The folding endurance was measured manually as per the reported method. Briefly, a strip of the film (4 x 3cm) was cut evenly and repeatedly folded at the same place till it broke. The thinner the film more flexible it is.

Drug content: Drug content was found out by cutting one patch & added in beaker containing 100ml of phosphate buffer (7.4pH). The medium was keep aside for 1hr. with occasional stirring. Then this solution was filtered using whatman filter paper. From that filtrate withdraw 1ml & it is diluted up to 10ml. then this solution was analyzed by U.V. spectrophotometer at 269nm for the drug content against the reference solution.

Calibration curve of Ibuprofen:-

Concentration	Absorbance
20µg/ml	0.045
40 µg/ml	0.083
60 µg/ml	0.138
80 µg/ml	0.162
100 µg/ml	0.190



Moisture content:

The prepared films was weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films was weighed again after 24h. interval. The percent moisture content was calculated by using following formula.

% moisture content = initial weight – final weight x 100

final weight

Moisture uptake:

Weighed film was kept in a desiccator at room temperature for 24 h. This was then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desiccator. % moisture uptake was calculated by using fowlling formula,

Results

NAME OF TEST	Formulation 1	Formulation 2
Thickness	67.4 µm	47.6µm
Weight variation	1.30gm	1.16 gm
Flatness	5.3%	8 %
Folding endurance	Patch was broken 3 times folding given at same place	Patch was broken 6 times folding given at same place
Drug content	93.95 %	94.76 %
Moisture content	4%	5.45%
Moisture uptake	8 %	4.54 %

Conclusion

Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery. Development of controlled release transdermal dosage form is a complex process involving extensive efforts. The present research article describes the methods of preparation and evaluation of Ibuprofen patch by using Ethyl cellulose as an polymer.

Attempts have been made to develop many new transdermal patches,Many advanced countries have developed transdermal patches for hypertension,diabetes mellitus,There is wide range of scope for the development for transdermal patches.

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