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Overview of Transdermal Medicated Patches with its research updates in preceding years

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ABSTRACT

Innovations in transdermal drug delivery systems (TDDS) is an important influence to medical practice by providing advances in the delivery of treatment with existing conventional drugs and novel drugs. Transdermal drug delivery is one of the most promising methods for drug application. It has several benefits over conventional system to offer sustained drug release, avoidance of first pass effect, patient compliance, ease of application and removal in case of toxicity as well as decrease in the side effects as compared with conventional therapy. Transdermal patches are dosage forms which transport drug to viable epidermal and dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery. The purpose of this review is to introduce transdermal patches including type of transdermal patches, components of transdermal patches, method of preparation of TDDS, evaluation parameters, researches and development done on TDDS in last decade etc.

Keywords: Transdermal Drug Delivery System, Permeation Enhancers, Transdermal Patch, Polymer Matrix.

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1. INTRODUCTION

The conventional oral drug delivery systems are associated with numerous difficulties such as pass metabolism, fluctuation in plasma level, drug degradation in gastrointestinal tract due to enzymes, pH etc. These difficulties are overcome by introduction of novel drug delivery systems one of them is transdermal drug delivery systems. The most common transdermal system available in the market is called patches [Sachan *et. al.* 2013]. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. It (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream [Patel *et. al.* 2012]. The main objective behind transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation. [Jalwal *et. al.* 2010]

The basic components of any transdermal delivery system include the drug(s) dissolved or dispersed in a reservoir or inert polymer matrix; an outer backing film of paper, plastic, or foil, and a pressure-sensitive adhesive that anchors the patch to the skin. The adhesive is covered by a release liner which needs to be peeled off before applying the patch to the skin. Drugs administered via skin patches include scopolamine, nicotine, estrogen, nitroglycerin, and lidocaine. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives, and eliminates pulsed entry into systemic circulation which often causes undesirable side effects [Gaikwad *et. al.* 2013].

1.1 IDEAL PROPERTIES OF TDDS

The ideal properties of transdermal drug delivery system are as follows

1. They have optimum partition coefficient required for the therapeutic action of drug.

2. They have Shelf life up to 2 years.

3. They have Low melting point of the drug is desired which is less than 200°C.

4. Patch size should be < 40cm^2

5. The pH of the saturated solution should be between 5 to 9 [Chauhan *et. al.* 2015].

ADVANTAGES OF TDDS

- Avoid first pass metabolism and gastro intestinal incompatibility.
- Predictable and extended duration of action and Minimizes undesirable side effects.
- Provides utilization of drugs with short biological half-lives and narrow therapeutic window.
- Improves physiological and pharmacological response.
- Avoids the fluctuation in drug levels and Inter and intra patient variations.
- Maintain plasma concentration of potent drugs.
- Termination of therapy is easy at any point of time.
- Provides greater patient compliance due to elimination of multiple dosing profiles.
- Ability to deliver drug more selectively to a specific site.
- Provide suitability for self-administration [Jalwal *et. al.* 2010].

DISADVANTAGES OF TDDS

- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability.
- Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable [Mali *et. al.* 2015].

1.2 TRANSDERMAL PATCHES AND CONDITION OF USAGE

Transdermal patch is used when the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery. It is used where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia. It can be used in combination with other enhancement strategies to produce synergistic effects [Patel *et. al.* 2012].

1.3 ROUTES OF DRUG PENETRATION THROUGH SKIN

The diffusants has two potential entry routes to the blood vasculature; through the epidermis itself or diffusion through shunt pathway, mainly hair follicles with their associated sebaceous glands and the sweat ducts. Henceforth there are two major routes of penetration

1.3.1 Transcorneal Penetration

a) **Intracellular penetration**: Drug molecule passes through the cells of the stratum corneum. It is generally seen in case of hydrophilic drugs. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water.

b) **Intercellular penetration**: Non-polar substances follow the route of intercellular penetration. These molecules dissolve in and diffuse through the non-aqueous lipid matrix imbibed between the protein filaments.

1.3.2 Trans-appendegeal Penetration

It is also known as the shunt pathway. In this route, the drug molecule may transverse through the hair follicles, the sebaceous pathway of the pilosebacious apparatus or the aqueous pathway of the salty sweat glands. The transappendegeal pathway is considered to be of minor importance because of its relatively smaller area (less than 0.1% of total surface). However, this route may be of some importance for large polar compounds [Gaikwad *et. al.* 2013].

1.4 BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEMS

Various components of a transdermal drug delivery system A transdermal therapeutic system is essentially a multilaminate structure that is composed of following constituents:

1.4.1 Drug Substance

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

a. **Physiochemical Properties**: The drug should have a molecular weight less than 1000 Daltons, should have affinity for both lipophilic and hydrophilic phases and have a low melting point.

b. **Biological Properties**: The drug should be potent with a daily dose of the order of a few mg/day, half-life (t½) should be short, must not produce allergic response and Tolerance must not develop under the near zero-order release profile of transdermal patches [Mali *et. al.* 2015].

Table 1 Ideal Properties of Drug for Transdermal Drug Delivery

[Tanwar *et. al.* 2016]

S. No.	Parameters	Properties
1.	Dose	Less than 20mg/day
2.	Half life	< 10 hrs
3.	Molecular weight	<400 Daltons
4.	Melting point	<200°C
5.	Partition coefficient	1 to 4
6.	Aqueous solubility	>1mg/mL
7.	pH of the aqueous saturated solution	5-9
8.	Skin Permeability Coefficient	$>0.5\times10^{-3}$ cm/h
9.	Skin Reaction	Non irritating and non-sensitizing
10.	Oral Bioavailability	Low

1.4.2 Polymer Matrix

The polymer controls the release of the drug from the device following criteria should be satisfied for a polymer to be used in transdermal patches are Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it. The polymer should be stable, nontoxic, easily manufactured, inexpensive and its degradation product must be non toxic or non-antagonistic to the host.

Types of Polymer:

a) **Natural polymers**: Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.

b) **Synthetic Elastomers**: Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.

c) **Synthetic polymers**: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamide, polyurea, epoxy [Mali *et. al.* 2015].

1.4.3 Permeation Enhancers

These are the compounds, which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant and are considered as an integral part of most transdermal formulations. Mainly to achieve and maintain therapeutic concentration of drug in the blood, the resistance of skin to diffusion of drugs has to be reduced in order to allow drug molecules to cross skin and to maintain therapeutic levels in blood. They can modify the skin's barrier to penetration either by interacting with the formulation that applied or with the skin itself [Jalwal *et. al.* 2010].

Table 2 Types of Absorption Enhancers [Tanwar *et. al.* 2016]

S. No.	Class	Examples
1.	Surfactants	Na-lauryl sulfate Polyoxyethylene-9-laurylether, Bile salts, Na-deoxycholate
2.	Fatty acids	Oleic acid, Short fatty acids
3.	Cyclodextrins	a-, b- and g cyclodextrins, Methylated b cyclodextrins
4.	Chelating agents	EDTA, Polyacrylates
5.	Positively charged polymer	Chitosan salts, Trimethyl chitosan

1.4.4 Drug Reservoir Components

It must be compatible with the drug and must allow for drug transport at the desired rate. It must possess the desired adhesive and cohesive properties to hold the system together. Materials used are: mineral oils, Polyisobutylene, and colloidal silica, HPC.

1.4.5 Backing Laminates

The primary function of the backing laminate is to offer support, should be able to prevent drug from leaving the dosage form through top, impermeable to drugs and permeation enhancers. should a low moisture vapor transmission rate. They must have optimal elasticity, flexibility, and tensile strength. They must be chemically compatible with the drug, enhancer, adhesive and other excipients, relatively inexpensive and must allow printing and adhesive lamination. The backing membranes are composed of a pigmented layer, an aluminum vapor coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) and a heat seal layer.

1.4.6 Rate Controlling Membrane:

Rate controlling membranes in transdermal devices govern drug release from the dosage form. Membranes made from natural polymeric material such as chitosan show great promise for use as rate controlling membranes.

1.4.7 Adhesive

Pressure sensitive adhesive is a material that helps to adhere transdermal devices to the skin over long periods of time. These adhesives can be placed on the face of device known as face adhesive system (or) peripherally at the back of device known as peripheral adhesive system [Sirisha *et. al.* 2018].

The adhesive layer should not be irritant, leave an un washable residue on the skin and should be easily removable, have excellent contact with the skin, Physical & chemical compatibility with the drug. It should not be effect permeation of drug [Mali *et. al.* 2015].

The three major classes adhesive for potential applications in TDDS includes Polyisobutylene type pressure sensitive adhesives, Acrylic type pressure sensitive adhesives and Silicone type pressure sensitive adhesives

1.4.8 Release Liners:

The release liner has to be removed before the application of transdermal system, and it prevents the loss of the drug that has migrated into the adhesive layer during storage. It also helps to prevent contamination. It is composed of a base layer, which may be non-occlusive or occlusive, and a release coating layer made of silicon or Teflon. Other materials include polyesters, foil, Mylar and metallized laminates [Jalwal *et. al.* 2010].

1.5 TYPES OF TRANSDERMAL PATCH

1.5.1 Adhesive Dispersion Type System

The system consists of drug-impermeable backing membrane, the drug reservoir which is prepared by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or hot melting onto a flat sheet of drug-impermeable backing to form a thin drug reservoir layer. On top of this, a layer of rate-controlling adhesive polymer (non-medicated) of constant thickness is spread to produce an adhesive diffusion-controlled drug delivery system with detachable release liner which in an ideal situation is removed and the patch is applied to the skin for a required period of time. (Sachan) Illustration of this type of system is exampled by development and marketing of transdermal therapeutic system of angina pectoris and Valsartan as angiotensin II type 1 selective blocker for one-day medication

a) Single-Layer Drug-In-Adhesive

The adhesive layer of this system also contains the drug. In this type of patch, the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi-Layer Drug-In-Adhesive

The multi-layer drug in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-in adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing [Mali *et. al.* 2015].

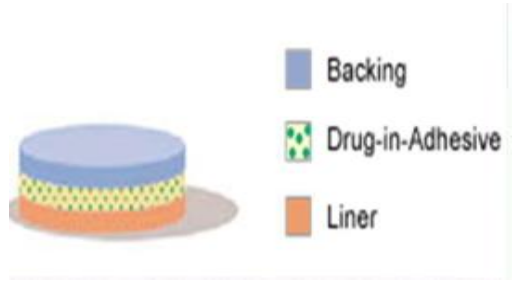

Fig. No. 1 Single layer in adhesive

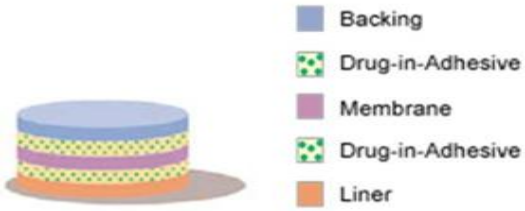

Fig. No. 2 Multi-layer in adhesive

1.5.2 Membrane Permeation Controlled System

In this system the drug reservoir is totally embedded in a compartment molded between a drug-impermeable backing laminate and a rate controlling polymeric membrane The drug molecules are permitted to release across the rate controlling membrane simply by diffusion process through the pores. In the reservoir compartments the drug solids are dispersed homogenously in a solid polymeric matrix (e.g. Polyisobutylene) suspended in the unleachable viscous liquid medium (e.g. silicon fluid) to form a gel-like suspension, or dissolved in a releasable solvent (e.g. alkyl alcohol) to form a gel like in solution. In this type of system the rate of release is zero order.

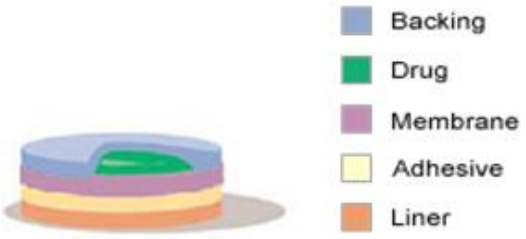

Fig. No. 3 Membrane permeation controlled system (Reservoir system)

1.5.3 Matrix

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it. These type of patches are also known as monolithic device [Tanwar *et. al.* 2016].

Types of Matrix

a) Drug-In-Adhesive System

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

b) Matrix-Dispersion System

In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

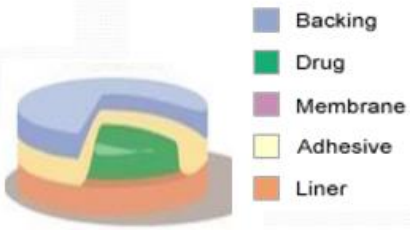

FIG. NO. 4 Matrix Drug Delivery System

1.5.4 Microreservoir System:

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

1.5.5 Vapour Patch

In this type of patch, the role of adhesive layer not only serves to adhere the various layers together but also serves market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions [Chauhan *et. al.* 2015].

1.6 METHODS OF PREPARATION OF TRANSDERMAL PATCH

[KADAM *ET. AL.* 201] [TANWAR *ET. AL.* 2016] [CHAUHAN *ET. AL.* 2015]

a) Asymmetric TPX membrane method

b) Circular Teflon mould method

c) Mercury substrate method

d) By using "IPM membranes" method

e) By using "EVAC membranes" method

f) Preparation of TDDS by using Proliposomes

g) By using free film method

a) Asymmetric TPX membrane method: A prototype patch can be fabricated by a heat sealable polyester lm (type 1009, 3m) with a concave of 1cm diameter used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. These are prepared by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°c to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate. Then casting film is evaporated at 50°C for 30 secs, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs].

b) Circular Teflon Mould Method: Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Plasticizer added into drug polymer solution. The total contents are to be stirred and then poured into a circular Teflon mould. And rate of solvent vaporization controlled with placing inverted glass funnel on Teflon mould. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored in desiccators.

c) Mercury substrate method: In the polymeric solution drug &plasticizer get dissolved. It is kept for 10-15min stirring to produce homogenous dispersion then it is poured into leveled mercury surface, covered with inverted funnel to control solvent evaporation.

d) By Using IPM Membranes Method: In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

e) By using "EVAC membranes" method: In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specied area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device

f) Preparation of TDDS by using Proliposomes: By carrier method using film deposition technique Proliposomes are prepared. Drug and lecithin ratio should be 0.1:2.0 taken as an optimized one from previous references. For the preparation of Proliposomes in 100ml round bottom flask take 5mg of mannitol powder, then it is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20- 30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing Proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (Proliposomes) are placed in a desiccator overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

g) By using free film method: Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is prepared by using chloroform. Plasticizers are incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petridish. The lm formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry lm will be separated out and stored between the sheets of wax paper in desiccators until use. Free films of different thickness can be prepared by changing the volume of the polymer solution

1.7 EVALUATION METHODS:

[Gaikwad *et. al.* 2013] [Tanwar *et. al.* 2016] [Chauhan *et. al.* 2015] [Kadam *et. al.* 201] [Sachan *et. al.* 2013]

a) **Physicochemical Evaluation:** Interaction studies the drug and the excipients must be compatible with one another to produce a product that is stable. The interaction between drug and excipients affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are taken out by Thermal analysis, Fourier transform infrared spectroscopy (FTIR), ultra violet (UV) and chromatographic techniques by comparing their physicochemical properties like assay, melting point, wave numbers, and absorption maxima

b) **Thickness of the patch:** At different points the thickness of the patch is measured by using digital mirometer& determine average thickness & standard deviation of the same.

c) **Weight of uniformity:** Before testing the patch is dried at 60 c for 4 hrs. Cut that patch in different parts & weighed in digital balance. Take average weight & calculate standard deviation from individual weight.

d) **Folding endurance:** A specific area of strip is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of folding 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 h, the films are to be reweighed and the percentage moisture content determined by

below formula: Percentage moisture content (%) = [Initial weight - Final weight / Final weight] ×100

f) **Percentage moisture uptake:** The prepared patches are to be weighed individually and to be kept in a desiccator containing saturated solution of potassium chloride in order to maintain 84% Rhesus factor (RH). After 24 h, the films are to be reweighed and the percentage moisture uptake determined by the formula

Percentage moisture uptake (%) = (Final weight - Initial weight / initial weight) × 100

g) **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

h) **Determination of surface pH:** Specific number of patches are kept in contact with distilled water and excess water is drained and pH noted by pH meter.

i) **Peel adhesion test:**Here peel adhesion is the force required to remove an adhesive coating from a substrate. A single tape is applied to a stainless steel plate then tape is pulled from the substrate at a 180° angle, and the required to pull the tape is measured.

j) **Thumb tack test:**This test determines the tack property of adhesive .Thumb is pressed on adhesive & tack property is determined.

k) **Flatness test:** Three longitudinal strips are cut from different portions of the films. The length of the each stripis measured and the variation in length because of non-uniformity in flatness is measured bydetermining percentage constriction, with 0% constriction equivalent to 100% flatness

l) **Percentage elongation break test:** Percentage elongation can be determined by using following formula:

Elongation percentage = L1-L2*100/L2

Where L1 is the final length of each strip & L2 is the initial length of each strip.

m) **Rolling ball tack test:** This test determines the softness of the polymer that relates the talk. Here the stainless steel ball of size 7/16 inches in diameter is released on an inclined track so that it rolls down & comes in contact with horizontal, upward facing adhesive .Distance travelled by ball along adhesive track gives the measurement of tack expressed in inch.

n) **Quick stick (Peel-tack) test:** The Peel force required to break the bond between on adhesive and substrate is measured by pulling the force away from the substrate at 90o at a speed of 12inch/min.

o) **Probe tack test:**Here the probe with specific surface kept in contact with adhesive so as to form bond between them. Then probe is remove so that it mechanically break it.The force required to pull the probe is the tack measured in terms of grams

p) **Flatness:**A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

% constriction = I1 – I2 X 100

I2 = Final length of each strip

I1 = Initial length of each strip

q) **Folding Endurance:** Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value

r) **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.

s) **Shear strength properties:** Shear strength is the measurement of the cohesive strength of an adhesive polymer. Adequate cohesive strength of a device will mean that the device will not slip on application and will leave no residue on removal. It is determined by measuring the time it takes to pull on adhesive coated tape off a stainless steel plate when a specified weight is hung from the tape which pulls the tape in a direction parallel to the plate.

t) **Drug content:** Take the patch with specific area dissolve it in specific volume of solvent. Solution is then filtered and the drug content analyzed with the suitable method (UV or HPLC technique).Then take the average of three different samples.

u) **Uniformity of dosage unit test:**Take ten patches and content determined for individual patches. If 9 out of 10 patches have content between 85 to 115% of the specified value and one has content not less than 75 to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75 to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85 to 115%, then the transdermal patches pass the test

v) **Polariscope examination:** The instrument polariscope used to study the crystal structure of drug in a patch. A specifiec area of patch is cut and kept on the slide to observe that drug present in crystalline form or amorphous form.

w) **Stability studies:** Stability studies were conducted according to the International Conference on Harmonization (ICH) guidelines by storing the TDDS samples at 40 ± 0.5°C and 75 ± 5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyzed suitably for the drug content.

x) **Skin irritation test:**This study is performed on healthy rabbits (average weight 1.2-1.5kg). Remove the dorsal surface of rabbit by shaving & clean by using spirit. Formulation applied on skin surface & remove

after 24hrs & skin is to be observed & classified in to 5 grades on the basis of severity of skin injury.

y) *In-vitro* permeation studies K-C cell (Keshary –chein) diffusion cell is used if skin of rats are used. Hairless skin is used and skin is thoroughly cleaned of any adhering tissues or blood vessels and equilibrated for an hour in pH 7 buffer before running for experiment. The K.C. cell or skin piece was mounted between the compartment of the diffusion cell and donor compartment and epidermal part of skin upward or toward donor compartment. The patch to be tested was placed on skin. Specific butter media at 37^0 C + 1^0 C is used as receptor phase and stirred with magnetic stirrer. Specific amount of sample withdrawn at regular period through the sampling port and fresh receptor fluid was added. Absorbance of sample is measured spectrophotometrically at against blank. The cumulative amount of drug permeated is ploted against time in hours.

z) ***In-vitro* drug release studies** A modified dissolution apparatus consisting of a jacketed vertical glass beaker 18cm long and 48cm in diameter was used for assessment of the release of drug from patches. The specific amount of formulation of buffer solution. The patch to be evaluated is struck on to the depression (15mm internal diameter and 1.5mm depth) on a teflon block fabricated for the purpose and is put into the glass beaker containing the dissolution medium. The apparatus was equilibrated to 37 + 20 C and operated at 50 rpm. Specific amount of sample pipette out of reguler interval of time. Sample are filtered out through filter paper and finally membrane filtered the sample is analyzed by the HPLC or U.V. spectrophotometer.

aa) ***In-Vivo* methods:** *In-vivo* evaluation of trandermal patch can be carried out using – i) Animal models ii) Human Volunteers Animal models In Vivo animals models are preferred because considerable time and resources are required to carry out studies in humans. Some of the species are used : mouse, rat, guinea pig, rabbit, rat, cat, dog, pig, house, monkey small hairy animals (e.g. rat, rabbit) or rhesus monkey is most reliable or in vivo evaluation of transdermal patches standard radiotracer methodology used. The application site is generally the abdomen which are the least hairy site on the animals body. The compound is applied after light clipper showing of the site.

1.8. RESEARCH UNDERTAKEN ON LAST DECADE

Kriplani Priyanka, *et. al.* (2018), formulated transdermal films of non-steroidal anti-inflammatory drug Diclofenac sodium using mercury substrate method and evaluated for physicochemical parameters like thickness, weight variation, moisture uptake, moisture content, folding endurance, and drug content values. Three transdermal patches were prepared using different concentrations of ethyl cellulose by solvent casting method. They concluded that as the concentration of polymer increases the thickness of patch, weight uniformity and folding endurance increases, percentage moisture content and percentage moisture uptake decreases with increase in polymer concentration.

Asha *et. al.* (2017), developed a transdermal patch of Indomethacin using patchouli oil as a natural enhancer to increase transdermal permeation of the drug from the matrix system across rat epidermis.The transdermal flux obtained of the different concentration of patchouli oil tend to increase with increasing concentration of the oil and the maximum transdermal flux of 61.92 ± 0.89 µg/cm2/hr was obtained with formulation F7 (containing 1% w/v of patchouli oil). They concluded that a potential enhancing effect of patchouli oil on the transdermal permeation of the model drug Indomethacin and may be used as natural permeation enhancer in transdermal drug delivery systems.

Bhagyeshwar G., *et. al.* (2017), prepared and evaluated transdermal drug delivery (TDDS) of Metformin Hydrochloride (MFH) using combinations of polyvinyl pyrrolidone K30 and Hydroxypropylmethylcellulose E50 in different ratios by solvent evaporation technique. Polyvinyl alcohol was used to prepare the backing membrane and dibutyl phthalate as plasticizer. They concluded that Metformin hydrochloride that released from the transdermal patches of F7 (PVP K30- HPMC E50 2.5:1) are best suited for once a day drug delivery.

Ahmed Tarek A. *et. al.* (2016), developed an ethosomal formulation of Glimepiride then formulated transdermal films to offer lower drug side effect, extended release behavior and avoid first pass effect. Four formulation factors were optimized for their effects on vesicle size (Y1), entrapment efficiency (Y2) and vesicle flexibility (Y3). The optimized ethosomal formulation showed observed values for Y1, Y2 and Y3 of 61 nm, 97.12% and 54.03, respectively. Ethosomal formulation could be considered a suitable drug delivery system especially when loaded into transdermal vehicle with possible reduction in side effects and controlling the drug release.

Vishvesh B Kanabar, *et. al.* (2015), prepared transdermal patches of Cefdinir using various polymers such as Cellulose derivatives, polyvinyl alcohol, Polyethylene, Polypropylene, Polyvinylpyrrolidone and Polymethyl methacrylate with their different concentration by the solvent evaporation technique by using PEG-400 as plasticizer. They concluded that among various polymers HPMC K100M was found to be the best polymer used to prepare transdermal patches.

Ahmed Tarek A.*et. al.* (2014), developed Rabeprazole (RP)-alginate core coated chitosan nanoparticles (NP) utilizing water-in-oil (W/O) nanoemulsion technique and formulated transdermal patches loaded with RP-NP that avoid drug per-oral acid sensitivity and first pass effect. Chitosan, oil phase and surfactant to oil ratios had significant effects on Y1, while Y2 was significantly affected by the same variables affecting Y1 and span80-tween80 ratio. Patches loaded RP-NP exhibited substantial skin permeability and controlled drug release, and were in favor of Fickian diffusion.

Zhao Lili *et. al.* (2014), prepared and evaluated a Ropivacaine-loaded microemulsion (ME) formulation and microemulsion-based carbopol gel (ME-gel) for transdermal delivery. The optimal ME formulation was comprised of 15 % Capryol 90, 53 % Smix and 32 % water, respectively. The results of *ex vivo* permeation study showed that Ropivacaine had a significant higher cumulative amount from ME than that from ME-gel. ME and ME-gel presented a remarkable analgesic activity on acetic acid-induced writhing in mice. They concluded that ME could be a promising formulation for Ropivacaine transdermal administration.

Madan Jyotsana R., *et. al.* (2014), formulated transdermal patches of Donepezil for improving patient compliance, therapeutic efficacy and to reduce the frequency of dosing and side effects and to avoid its extensive first pass metabolism. The system containing Eudragit S -100, Eudragit E -100 and HPMC as matrix forming agent and glycerin as plasticizer was the best formulation. Tween-80

(0.83 % w/w) was found to be the best among all penetration enhancers.

Yang Zhen *et. al.* (2013), designed and evaluated a reservoir-type transdermal delivery system (TDS) of Bufalin for various formulation variables like different penetration enhancers, formulation matrix, rate controlling membranes as well as biopharmaceutical characteristics. Transdermal drug delivery of Bufalin provide sustained release rate and avoids the peak concentration, which prolong the duration of action and decrease the risk of side effect. They demonstrated that transdermal administration can deliver adequate Bufalin across skin on rodent models. Both in vitro and in vivo studies showed consistent results that with optimized chemical enhancer and formulation components, Bufalin can achieve sustained and sufficient delivery across skin.

Sun Lin,*et. al.* (2012), formulated adhesive transdermal patch containing Azasetron andevaluated the correlation between *in vitro* and *in vivo* release. The effects of different adhesives, permeation enhancers, and loadings of Azasetron used in patches on the penetration of Azasetron through rabbit skin were investigated using two-chamber diffusion cells *in vitro*. For *in vivo* studies, Azasetron pharmacokinetic parameters in Bama miniature pigs were determined according to a noncompartment model method after topical application of transdermal patches and intravenous administration of Azasetron injections. The best permeation profile was obtained with the formulation containing DURO-TAK 87-9301 as adhesive, 5% of isopropylmyristate as penetration enhancer, and 5% of Azasetron. The permeation profiles through porcine skin *in vitro* and *in vivo* suggested that Azasetron could effectively penetrate through the skin and pass into the systemic circulation.

Maheshwari Rahul G.S.*et. al.* (2012), formulated, evaluated and compared the transdermal potential of novel vesicular nanocarriers; ethosomes and ultradeformable liposomes, containing clotrimazole(CLT), an anti-fungal drug. The ethosomal formulation (ET4) and ultradeformable liposomal(UL) formulation (TT3) showed highest entrapment 68.73±1.4% and 55.51±1.7%, optimalnanometric size range 132±9.5 nm and 121±9.7 nm, and smallest polydispersity index0.027±0.011 and 0.067±0.009, respectively. Their results suggested that ethosomes to be the most proficient carrier system for dermal and transdermal delivery of clotrimazole.

Patel Kunal N. *et. al.* (2011), formulated adhesive transdermal patches of diclofenac acid using Pressure Sensitive Adhesive (PSA) like acrylic adhesive by the solvent evaporation technique. Different concentrations of Labrasol, oleic acid and triacetin were used to enhance the transdermal permeation of diclofenac acid. 12 formulations were formulated. All prepared formulations indicated good physical stability. *In vitro* skin permeation studies of formulations were performed by using Franz diffusion cells. Formulation F3 containing 5% drug, 85% adhesive solution and 10% triacetin as permeation enhancer showed best *in vitro* skin permeation through human cadaver skin as compared to all other formulations.

PrajapatiShailesh T.,*et. al.* (2011), formulated and evaluated of transdermal patch of Repaglinideto sustain the release and improve bioavailability of drug and patient compliance. Nine formulations were prepared by varying the grades of HPMC and concentration of PVP K30 by solvent casting method. The prepared formulations were evaluated for various parameters like thickness, tensile strength, folding endurance, % elongation, % moisture content, % moisture uptake, % drug content, in vitro drug release, in vitro permeation, and drug excipient compatibility. Batch F6 was considered optimum batch which contained HPMC K100 and PVP (1.5%), showed release 92.343% up to 12 hr, and was more similar to the theoretical predicted dissolution profile ($f2$ = 69.187).

Shah Samip S., et. al. (2010), formulated and evaluated transdermal patches of Papaverine hydrochloride by solvent casting method using ethyl cellulose:PVP, PVA:PVP, and Eudragit RL-100:Eudragit RS-100 in different ratios. The formulation containing PVA: PVP as polymers showed faster release rate (hydrophilic polymers) compared to Eudragit RL-100: Eudragit RS-100 (hydrophobic polymers) or combination of hydrophilic and hydrophobic polymers (ethyl cellulose and PVP). The formulated patches containing the hydroplilic polymers showed best release rate of drug.

Jamakandi V.G. *et. al.* (2009), formulated and evaluated matrix-type transdermal patches of Nicorandilan antihypertensive drugusing different polymeric grades of hydroxy propyl methyl cellulose (6cps, 15cps, and K4M).They evaluated matrix-type patches for their physicochemical characterization followed by *in vitro* evaluation. Among the six different HPMCformulations they had formulated, transdermal patch with 6 cps and 6% w/vDMSO as permeation enhancer showed maximum releaseand offered least resistance to the movement of the drugmolecule due to its high hydrophilic nature and high waterpermeability value to water.

Murthy etal, 2008 studied the Influence of polymers on the release of Carvediol from transdermal films and revelated many interested and important factors related to release rate of the drug due to polymers.

REFERENCES:

1. Ahmed T. A. and Khalid M. (2014). Development of alginate-reinforced chitosan nanoparticles utilizing W/O nanoemulsification/internal crosslinking technique for transdermal delivery of rabeprazole. *Life sciences*, *110*(1), 35-43.
2. Ahmed T. A., Khalid M., Aljaeid B. M., Fahmy U. A. and Abd-Allah F. I. (2016). Transdermal glimepiride delivery system based on optimized ethosomal nano-vesicles: Preparation, characterization, in vitro, ex vivo and clinical evaluation. *International journal of pharmaceutics*, *500*(1-2), 245-254.
3. Bhagyeshwar G., Ramu B. and Rajkamal B. (2017) Formulation and evaluation of transdermal patches of metformin hydrochloride. *World Research Journal of Pharma Technology.;* 2:1-20.
4. Das A. and Ahmed A. (2017). Formulation and Evaluation of Transdermal Patch of Indomethacin Containing Patchouli Oil As Natural Penetration Enhancer. *Asian Journal of Pharmaceutical and Clinical Research*, 10(11), p.320.
5. Dhiman S., Singh T. G. and Rehni A. K. (2011). Transdermal patches: a recent approach to new drug delivery system. *Int J Pharm Pharm Sci*, *3*(5), 26-34.
6. Gaikwad A. K. (2013). Transdermal drug delivery system: Formulation aspects and evaluation. Compr J Pharm Sci. Feb;1(1):1-0.
7. Jalwal P., Jangra A., Dahiya L., Sangwan Y. and Saroha R. (2010). A review on transdermal patches. *The Pharma Research*, *3*, 139-149.
8. Jamakandi V. G., Mulla J. S., Vinay B. L. and Shivakumar H. N. (2009). Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug. *Asian Journal of Pharmaceutics (AJP):* from Asian J Pharm. Aug 28; 3.
9. Kadam A. S., Ratnaparkhi M. P. and Chaudhary S. P. (2014). Transdermal drug delivery: An overview.
10. Kanabar V. B., Patel V. P. and Doshi S. M. (2015). Formulation and evaluation of transdermal patch of Cefdinir with various polymers. *The Pharma Innovation*, *4*(6, Part B), 74.

11. Kriplani P., Abhishek S. and Ashwani D. (2018) Formulation and Evaluation of Transdermal Patch of Diclofenac Sodium, *Global Journal of Pharmacy and Pharmaceutical Sciences;* 4(5): 001-004.
12. Madan J., S Argade N. and Dua K. (2015). Formulation and evaluation of transdermal patches of donepezil. *Recent patents on drug delivery and formulation*, *9*(1), 95-103.
13. Maheshwari R. G., Tekade R. K., Sharma P. A., Darwhekar G., Tyagi A., Patel R. P. and Jain D. K. (2012). Ethosomes and ultradeformable liposomes for transdermal delivery of clotrimazole: a comparative assessment. *Saudi Pharmaceutical Journal*, *20*(2), 161-170.
14. Mali A. D. (2015). An updated review on transdermal drug delivery systems. *Skin*, *8*, 9.
15. Murthy T.E.G.K., Ramana R.V., Kishore B.M., (2008), Influence of polymers on the release of Carvediol from transdermal films, *Indian Drugs*, 45(12), 970- 974.
16. Patel K. N., Patel H. K. and Patel V. A. (2012). Formulation and characterization of drug in adhesive transdermal patches of diclofenac acid. *Int. J. Pharm. Pharm. Sci*, *4*(1), 296-299.
17. Prajapati S. T., Patel C. G. and Patel C. N. (2011). Formulation and evaluation of transdermal patch of repaglinide. *ISRN pharmaceutics*, *2011*.
18. Sachan R. and Bajpai M. (2013). Transdermal drug delivery system: a review. *IJRDPL*, *3*.
19. Shah S. S., Rahul J. and Prabhakar P. (2014). Formulation and evaluation of transdermal patches of papaverine hydrochloride. *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm*, *4*(1).
20. Shubhangi C., Piyush S., Ajay A. and Shiv G. K. (2015). International Journal of Current Research In Chemistry and Pharmaceutical Sciences. *Int. J. Curr. Res. Chem. Pharma. Sci*, *2*(2), 64-79.
21. Sirisha V. and Sailaja A. K. (2018) Review on Recent Approaches in Transdermal Drug Delivery System. J Nurs Patient Health Care 1(1): 103
22. Sun L., Cun D., Yuan B., Cui H., Xi H., Mu L. and Fang L. (2012). Formulation and in vitro/in vivo correlation of a drug-in-adhesive transdermal patch containing azasetron. *Journal of pharmaceutical sciences*, *101*(12), 4540-4548.
23. Tanwar H. and Sachdeva R. (2016). Transdermal drug delivery system: A review. *Int. J. Pharm. Sci. Res*, *7*, 2274-2290.
24. Tanwar H. and Sachdeva, R. (2016). Transdermal drug delivery system: A review. *Int. J. Pharm. Sci. Res*, *7*, 2274-2290.
25. Yang Z., Teng Y., Wang H. and Hou H. (2013). Enhancement of skin permeation of bufalin by limonene via reservoir type transdermal patch: formulation design and biopharmaceutical evaluation. *International journal of pharmaceutics*, *447*(1-2), 231-240.
26. Zhao L., Wang Y., Zhai Y., Wang Z., Liu J. and Zhai G. (2014). Ropivacaine loaded microemulsion and microemulsion-based gel for transdermal delivery: Preparation, optimization, and evaluation. *International journal of pharmaceutics*, *477*(1-2), 47-56.