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TRANSDERMAL DRUG DELIVERY SYSTEM: REVIEW

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TDDS, Topical drug delivery, Systemic blood circulation, Types, method of preparation and evaluation parameters of Transdermal patches.

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ABSTRACT:
Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. This review article provides an overview of TDDS, its advantages over conventional dosage forms, drug delivery routes across human skin, penetration enhancers, various components of Transdermal patches, types of Transdermal patches, methods of preparation and its physicochemical methods of evaluation.

Introduction:
Currently, transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin [1]. Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation, oestradiol (alone or in combination with levonorgestrel or norethisterone) for hormone replacement and testosterone for hypogonadism.[2] Transdermal drug delivery systems (TDDS), also known as ―patches,‖ are dosage forms designed to deliver a therapeutically

effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered.

Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively.[3] 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. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel, particularly by sea. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.[4]

Advantages of transdermal drug delivery systems [5]

Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivery drugs across the skin to achieve systemic effects are:

- Avoidance of first pass metabolism
- Avoidance of gastro intestinal incompatibility
- Predictable and extended duration of activity
- Minimizing undesirable side effects
- Provides utilization of drugs with short biological half-lives, narrow therapeutic window
- Improving physiological and pharmacological response
- Avoiding the fluctuation in drug levels
- Inter and intra patient variations
- Maintain plasma concentration of potent drugs
- Termination of therapy is easy at any point of time
- Greater patient compliance due to elimination of multiple dosing profile
- Ability to deliver drug more selectively to a specific site
- Provide suitability for self-administration.
- Enhance therapeutic efficacy

MECHANISM OF ABSORPTION

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).
- The relative importance of the shunt or appendageal route versus transport across the stratum corneum has been debated by scientists over the years [6-8]) and is further complicated by the lack of a suitable experimental model to permit separation of the three pathways.
- In vitro experiments tend to involve the use of hydrated skin or epidermal membranes so that appendages are closed by the swelling associated with hydration. Scheuplein and colleagues [9, 10] proposed that a follicular shunt route was responsible for the presteady-state permeation of polar molecules and flux of large polar molecules or ions that have difficulty diffusing across the intact stratum corneum.
- However, it is generally accepted that as the appendages comprise a fractional area for permeation of approximately 0.1% [11], their contribution to steady state flux of most drugs is minimal. This assumption has resulted in the majority of skin penetration enhancement techniques being focused on increasing transport across the stratum corneum rather than via the appendages. Exceptions are iontophoretic drug delivery which uses an electrical charge to drive molecules into the skin primarily via the shunt routes as they provide less electrical resistance, and vesicular delivery.

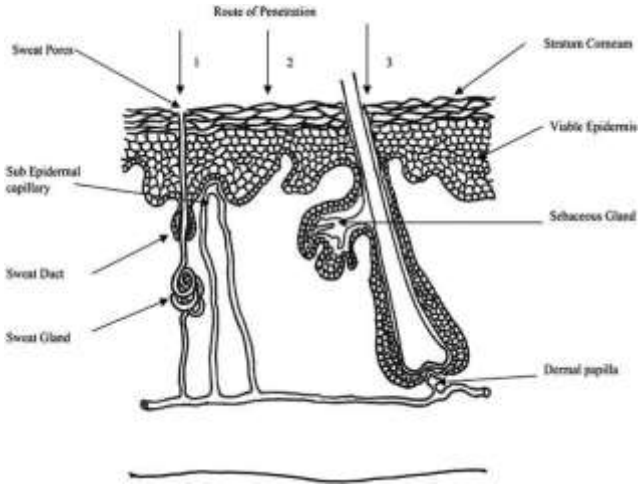

Fig. (1). Simplified representation of skin showing routes of penetration: 1. through the sweat ducts; 2. directly across the stratum corneum;

3. via the hair follicles.

- Considerable research effort has been directed towards gaining a better understanding of the structure and barrier properties of the stratum corneum. A recent review by Menon provides a valuable resource [12].
- The stratum corneum consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15 μm in the dry state to 40 μm when hydrated [13-14]. It comprises a multi-layered ―brick and mortar‖ like structure of keratin-rich corneocytes (bricks) in an intercellular matrix (mortar) composed primarily of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate and sterol/wax esters [15]. However it is important to view this model in the context that the corneocytes are not brick shaped but are polygonal, elongated and flat (0.2-1.5 μm thick, 34-46 μm in diameter).
- The intercellular lipid matrix is generated by keratinocytes in the mid to upper part of the stratum granulosum discharging their lamellar contents into the intercellular space. In the initial layers of the stratum corneum this extruded material rearranges to form broad intercellular lipid lamellae [16], which then associate into lipid bilayers [17, 18], with the hydrocarbon chains aligned and polar head groups dissolved in an aqueous layer (Fig. 2).
- As a result of the stratum corneum lipid composition, the lipid phase behaviour is different from that of other biological membranes. The hydrocarbon chains are arranged into regions of crystalline, lamellar gel and lamellar liquid crystal phases thereby creating various domains within the lipid bilayers [19]. The presence of intrinsic and extrinsic proteins, such as enzymes, may also affect the lamellar structure of the stratum corneum. Water is an essential component of the stratum corneum, which acts as a plasticizer to prevent cracking of the stratum corneum and is also involved in the generation of natural moisturizing factor (NMF), which helps to maintain suppleness. In order to understand how the physicochemical properties of the diffusing drug and vehicle influence permeation across the stratum corneum and thereby optimise delivery, it is essential to determine the predominant route of drug permeation within the stratum corneum.
- Traditionally it was thought that hydrophilic chemicals diffuse within the aqueous regions near the outer surface of intracellular keratin filaments (intracellular or transcellular route) while lipophilic chemicals diffuse through the lipid matrix between the filaments (intercellular route) (see Fig.2).

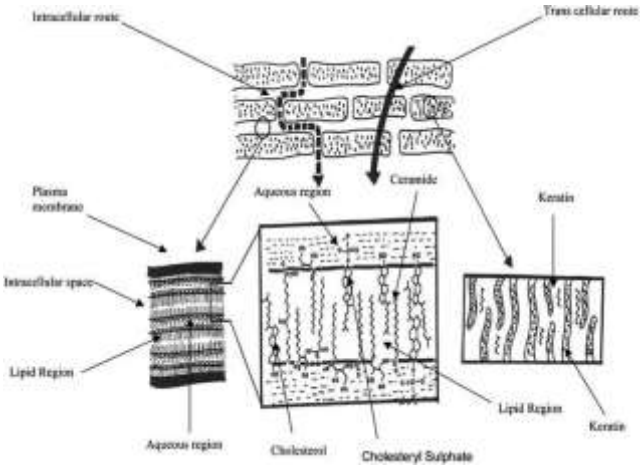

Fig. (2). Diagrammatic representation of the stratum corneum and the intercellular and transcellular routes of penetration.

However, this is an oversimplification of the situation as each route cannot be viewed in isolation. A molecule traversing via the transcellular route must partition into and diffuse through the keratinocyte, but in order to move to the next keratinocyte, the molecule must partition into and diffuse through the estimated

4-20 lipid lamellae between each keratinocyte. This series of partitioning into and diffusing across multiple hydrophilic and hydrophobic domains is unfavourable for most drugs. Consequently, based on more recent data for example [20-21] the intercellular route is now considered to be the major pathway for permeation of most drugs across the stratum corneum. As a result, the majority of techniques to optimise permeation of drugs across the skin are directed towards manipulation of solubility in the lipid domain or alteration of the ordered structure of this region (Fig. 3).

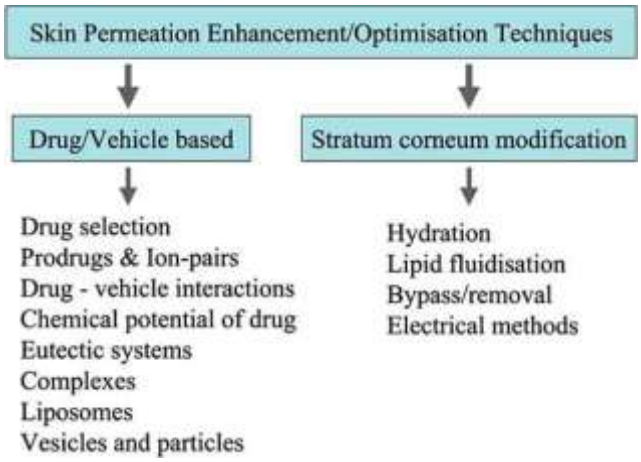

Fig. (3). Techniques to optimise drug permeation across the skin.

Factors affecting transdermal permeation 22, 23 Physicochemical properties of the penetrant molecules Partition coefficient

- A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability.
- It may be altered by chemical modification without affecting the pharmacological activity of the drug.

pH conditions

- Applications of solutions whose pH values are very high or very low can be destructive to the skin.
- With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

Penetrant concentration

- Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux.
- At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time.

Physicochemical properties of the drug delivery system Release characteristics

- Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors:
- Whether the drug molecules are dissolved or suspended in the delivery systems.
- The interfacial partition coefficient of the drug from the delivery system to the skin tissue.
- pH of the vehicle

Composition of the drug delivery systems

- The composition of the drug delivery systems e.g., boundary layers, thickness, polymers, vehicles not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or other sorption promoting effects e.g., benzocaine permeation decreases with PEG of low molecular weight.

Enhancement of transdermal permeation

- Majority of drugs will not penetrate skin at rates sufficiently high for therapeutic efficacy.
- In order to allow clinically useful transdermal permeation of most drugs, the penetration can be improved by the addition of a permeation promoter into the drug delivery systems.

TRANSDERMAL PATCH:

A transdermal patch or skin 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. Often, this promotes healing to an injured area of the body. 24

Development

Before these patches go into the market, they have to be carefully studied. One way to study these patches are through the use of Franz Diffusion Cell systems. This system is used to study the effects of temperature on the permeated amount of a specific drug on a certain type of membrane, which in this case would be the membrane that is used in the patches. A Franz Diffusion Cell system is composed of a receptor and a donor cell. In many of these research studies the following procedure is used. The donor cell is set at a specific temperature (the temperature of the body), while the receptor cell is set at different one (temperature of the environment).

Different runs are performed using different temperatures to study the impact of temperature on the release of a certain medicament through a certain type of membrane. Although different concentrations of the medicament are used in this study, they do not affect the amount permeated through the membrane (the process is constant). From Chemical kinetics it's concluded that these studies are zero order, since the concentration plays no role in the permeated amount through the membrane.

Some pharmaceuticals must be combined with substances, such as alcohol, within the patch to increase their ability to penetrate the skin in order to be used in a transdermal patch. Others can overwhelm the body if applied in only one place, and are often cut into sections and applied to different parts of the body to avoid this, such as nitroglycerin. Many molecules, however, such as insulin, are too large to pass through the skin.

Popular uses

The highest selling transdermal patch in the United States was the nicotine patch which releases nicotine to help with cessation of tobacco smoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007.

- Fentanyl, an analgesic for severe pain.
- Other skin patches administer estrogen for menopause. This also seems to prevent osteoporosis after menopause.
- Nitroglycerin patches for angina are available.
- Lidocaine patches, marketed as Lidoderm, relieve the peripheral pain of shingles (herpes zoster). It is also now commonly used off-label, for pain from acute injuries and chronic pain, although limited by its requirement to be removed for 12 hours, after 12 hours of use.
- Flector (Diclofenac epolamine) patch is an NSAID topical patch for the treatment of acute pain due to minor strains, sprains, and contusions. It is also being used in the treatment of pain and inflammation for chronic conditions benefiting from NSAIDs, including fibromyalgia and arthritis.
- Clonidine has also been administered transdermally.25 Buprenorphine, marketed as BuTrans, as analgesia for moderate to severe chronic pain Recent developments expanded their use to the delivery of hormonal contraceptives, antidepressants and even pain killers and stimulants for attention deficit hyperactivity disorder/ADHD.

Adverse events

- In 2005, the FDA announced that they are investigating reports of death and other serious adverse events related to narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain control. The Duragesic product label was subsequently updated to add safety information in June 2005.26
- In 2009, the FDA announced a public health advisory warning of the risk of burns during MRI scans from transdermal drug patches with metallic backings. Patients should be advised to removed any medicated patch prior to an MRI scan and replace it with a new patch after the scan is complete.27

Basic components of transdermal drug delivery systems:

Polymer matrix: Polymer is an integral and foremost important component of transdermal drug delivery systems. Different classes of polymeric materials have been used to achieve rate-controlled drug delivery. The mechanism of drug release depends upon the physicochemical properties of the drug and polymer used in the manufacture of the device. The following

criteria should be satisfied for a polymer to be used in a transdermal system.

- Molecular weight, glass transition temperature, chemical functionality or polymer must allow diffusion and release of the specific drug.
- The polymer should permit the incorporation of a large amount of drug.
- The polymer should not react, physically or chemically with the drug
- The polymer should be easily manufactured and fabricated into the desired product and in expensive.
- The polymer must be stable and must not decompose in the presence of drug and other excipients used in the formulation, at high humidity conditions, or at body temperature.
- Polymers and its degradation products must be non-toxic.
- No single material may have all these attributes; e.g., cosolvents such as ethanol, propylene glycol, PEG 400 could be added to increase drug solubility.

Various techniques which are employed to modify the polymer properties and thus drug release rates: [28, 29]

Techniques of matrix

- **Cross linked polymers:** The higher the degree of cross linking, the more dense the polymer and slower the diffusion of drug molecules through the matrix.
- **Polymer blends:** Polymers have been blended on varying ratios to combine the advantages of the individual polymers. Advantages of polymer blends include easy fabrication of devices, manipulation of drug loading and other devices properties such as hydration, degradation rate and mechanical strength.
- **Plasticizers:** Plasticizers have been known to reduce the stiffness of the polymer backbone, thereby increasing the diffusion characteristics of the drug. Commonly used plasticizers are polyethylene glycol, propylene glycol, glycerol, dibutyl phthalate.

Drug substance

Drug is in direct contact with release liner.

Ex: Nicotine, Methotrexate and Estrogen.

The selection of drug for transdermal drug delivery depends upon various factors.

Physicochemical properties [23, 30]

- The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml)
- The substance should have melting point less than 200 °F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point (in degree absolute of the drug). In order to obtain the best candidates for TDD, an attempt should be made to keep the melting point as low as possible.
- Substances having a molecular weight of less than 1000 units are suitable.
- A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD; because they get ionized rapidly at physiological pH and ionized materials generally penetrate the skin poorly.
- Hydrogen bonding groups should be less than 2.

Biological properties [31]

- Drug should be very potent, i.e., it should be effective in few mgs per day (ideally less than 25 mg/day)
- The drug should have short biological half life
- The drug should be non irritant and non allergic to human skin
- The drug should be stable when in contact with the skin
- The drug should not stimulate an immune reaction to the skin
- Tolerance to drug must not develop under near zero order release profile of transdermal delivery
- The drug should not get irreversibly bound in the subcutaneous tissue
- They should not get extensively metabolized in the skin

Penetration enhancers

- These are the compounds, which promote skin permeability by altering the as a barrier to the flux

of a desired penetrant and are considered as an integral part of most transdermal formulations. 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 [32].

- The penetration enhancer should be pharmacologically inert, non-toxic, non allergenic, non-irritating and ability to act specifically, reversibly and for predictable duration. It should not cause loss of body fluids, electrolytes or other endogeneous materials.

Ex: Terpenes, Terpenoids, Pyrrolidones.
Solvents like alcohol, Ethanol, Methanol.
Surfactants like Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.

Drug reservoir components

- It must be compatible with the drug and must allow for drug transport at the desired rate. If an ointment is used, the drug reservoir must possess the desired viscosity attributes to ensure reliable manufacturing process. It must possess the desired adhesive and cohesive properties to hold the system together. Materials used are: mineral oils, polyisobutylene, and colloidal silica, HPC.

Backing laminates

- The primary function of the backing laminate is to provide support. They should be able to prevent drug from leaving the dosage form through top. They must be impermeable to drugs and permeation enhancers. They 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. They must be relatively inexpensive and must allow printing and adhesive lamination. Type backing membranes are composed of a pigmented layer, an aluminium vapor coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) and a heat seal layer.

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. Recently composite poly-2-hydroxyethyl methacrylate (PHEMA) membranes have been evaluated as rate controlling barriers for transdermal application [33].

Adhesive layer

The fasting of all transdermal devices to the skin using a pressure sensitive adhesive that can be positioned on the face or in the back of device is necessary. It should not cause irritation, sensitization or imbalance in the normal skin flora during its contact with the skin. It should adhere to the skin aggressively. The three major classes of polymers evaluated for potential medical applications in TDDS include:

- Polyisobutylene type pressure sensitive adhesives
- Acrylic type pressure sensitive adhesives
- Silicone type pressure sensitive adhesives

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 nonocclusive or occlusive, and a release coating layer made of silicon or Teflon. Other materials include polyesters, foil, Mylar and metallized laminate

TYPES OF TRANSDERMAL PATCHES: [34,35, 36,37,38]

a) **Single layer drug in adhesive:** In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi -layer drug in adhesive: This type is also similar to the single layer but it contains a immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

c) **Vapour patch:** In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour. The vapour patches are new to the 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.

d) **Reservoir system:** In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the ratecontrolling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

e) Matrix system:

i. 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 (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. 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.

f) **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.

VARIOUS METHODS FOR PREPARATION OF TDDS:

a. **Asymmetric TPX membrane method:** [39] A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be 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. [Asymmetric TPX membrane preparation]: These are fabricated 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 to a pre-determined thickness with a gardner knife. After that the casting film is evaporated at 50°C for 30 sec, 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.

RECENT WORK

- **Da-Ming Wang et al,** have studied that asymmetric poly(4-methyl-1-pentene) (TPX) membranes, fabricated by the dry/wet inversion method, were applied to transdermal delivery of nitroglycerin (NTG), a drug for treating angina pectoris. The flux of NTG through the TPX membrane was measured in vitro by a Franz cell.

The results indicate that the NTG flux through asymmetric TPX membranes is strongly dependent on the membrane structure, which can be varied by adding non solvents in the casting solution. By adding different kinds of non solvents and adjusting the added amounts, membranes with different NTG release rates can be fabricated. It was also found that, with suitable drug formula, the NTG dissolution rate of a prototype TPX patch is comparable to that of a commercial patch, Transderm-Nitro.[40]

- **Shin SC et al,** have studied about Oral administration of triprolidine, antihistamines, may cause many adverse effects such as dry mouth, sedation, dizziness and transdermal drug delivery was considered. Poly(4-methyl-1-pentene) (TPX) membrane, which has good mechanical strength was fabricated by the casting method. TPX membranes was a little brittle and the plasticizers was added for preparing the membranes. The present study was carried out to evaluate the possibility of using the polymer TPX membrane as a controlling membrane and further develop a TPX matrix system for transdermal delivery of triprolidine. The effects of molecular weights of TPX, plasticizers, polyethylene glycol (PEG) 400, drug concentration, and temperature on drug release were studied. The solubility of triprolidine increased exponentially as the increased volume fraction of PEG 400 in saline, and the rate of permeation through TPX membrane was proportional to PEG 400 volume fraction. The release rate of drug from the TPX matrix increased with increased temperature and drug concentration. Among the plasticizers used such as alkyl citrates, phthalates and sebacate, tetra ethyl citrate (TEC) showed the best enhancing effects. Enhancement factor of TEC was 3.76 from TPX matrix at 37 degrees C. The transdermal controlled release of triprolidine system could be developed using the TPX polymer including the plasticizer.[41]

b. **Circular teflon mould method: [42]** 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. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butylphthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

RECENT WORK

- F.K. Alanazi et al, have studied about bioadhesive film containing ketorolac. Films were cast from organic and aqueous solvents using various bioadhesive polymers namely: sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) and Carbopol 934. The prepared films were subjected to investigations for their physical and mechanical properties, swelling behaviors, in vitro bioadhesion, drug permeation via bovine buccal mucosa and in vitro drug release. These properties were found to vary significantly depending on the preparation methods, the type of the polymers and the ratio of addition of both plasticizer (i.e. polyethylene glycol) and film forming agent (ethyl cellulose and polyvinylpyrolidene). The obtained results indicate that the concentration of ketorolac in the oral cavity was maintained above 4.0 μg/mL for a period of at least 6 h. This film shows promising results for using the ketrolac buccoadhesive route of administration topically and systemically, and thus it will be subjected to clinical evaluation in future work.[43]

c. Mercury substrate method: [44] In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10- 15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

RECENT WORK

- **Rathore RPS*et al**, have studied that Transdermal matrix type patches of terbutaline sulphate were fabricated using ethyl cellulose and cellulose acetate polymer. The transdermal patches of terbutaline sulphate were prepared by solvent casting technique employing a mercury substrate. In the present investigation various polymeric transdermal patches of terbutaline sulphate were prepared. The effect of permeability enhancer (PVP) on the permeability of drug from cellulose acetate and ethyl cellulose patches were studies. The polymeric combinations showed good film forming properties the method of casting on mercury substrate was found to give good films.[45]
- **Meenakshi Bharkatiya et al**, have studied that Matrix type transdermal patches containing Metoprolol tartrate were prepared by solvent casting method employing a mercury substrate by using the combinations of EC-PVP and Eudragit RL100-PVP in different proportions. concluded that Eudragit RL100-PVP polymers are better suited than EC-PVP polymers for the development of transdermal patches of Metoprolol tartrate.[46]
- **Shashikant D. Barhate*et al,** In these study ketoprofen transdermal patches was prepared by mercury substrate method using polymer Eudragit RS100, Eudragit RL100, HPMC K100M, HPMC E5 and HPMC K4M. Propylene glycol and oleic acid used as a skin permeation enhancer and dibutyl phthalate and polyethylene glycol-400 used as a plasticizer. It was observed that the formulation containing HPMC E5 showed ideal zero-order release kinetics.[47]
- **M.Bharkatiya et al,** the present investigation was taken up to prepare and evaluate drug free polymeric patches using different polymers and to study the effect of different plasticizers on physicochemical properties of the patches to explore their feasibility for transdermal application. Polyethylene glycol (PEG 400), Dibutylphthalate (DBP) and Propylene glycol (PG) were used as plasticizers at a concentration of 40 % w/w of dry polymer weight. Drug free polymeric patches were prepared by the casting method on mercury surface and evaluated for weight variation, thickness, flatness, tensile strength, folding endurance, surface pH, hardness, swellability, water vapour transmission rate and skin irritation studies. The mercury substrate method was found to give thin uniform patches.[48]
- **Raju.R.Thenge et al,** have studied Lercanidipine hydrochloride patches were prepared by using different concentration of Eudragit RS100, Hydroxypropyl methyl cellulose and ethyl cellulose using solvent casting techniques on a mercury substrate and the effect of polymer on the various physicochemical characteristics and in vitro drug release studies, ex vivo skin permeation studies. Formulations were prepared by taking 20 mg (Lercanidipine HCl), 10% w/w of propylene glycol and 10% w/w of dibutyl phthalate in ethanol. The formulations exhibited uniform thickness, weight and good uniformity in drug content The results of the study show that Lercanidipine HCl could be administered transdermally over a period of 24 h. through the matrix type TDDS for effective control of hypertension.[49]
- **Manish P. Patel et al,** have studied Transdermal patches containing glibenclamide (1.06 % w/v, i.e. 13.5 mg/cm2) were prepared by solvent casting techniqueemploying mercury as substrate2 to formulate transdermal patches using Eudragit RL 100, Eudragit RS 100, Polyvinyl pyrollidone (PVP) as polymers, glycerol and propylene glycol as a plasticizers and Span 80 as a permeation enhancer by solvent casting method , the formulation containing Eudragit RL 100 with propylene glycol as plasticizer showed complete and prolonged release with 98.02 % at the end of 24 hours.[50]

d. **By using "IPM membranes" method":[51]** In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer 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.

RECENT WORK

- **Honglei Xi et al,** have studied to prepare a drug-in-adhesive transdermal patch for anastrozole and evaluate this for the site-specific delivery of anastrozole. Different adhesive matrixes, permeation enhancers and amounts of anastrozole were investigated for promoting the passage of anastrozole through the skin of rats in vitro. The best in vitro skin permeation profile was obtained with the formulation containing DURO-TAK® 87-4098, IPM 8% and anastrozole 8%. For local tissue disposition studies, the anastrozole patch was applied to mouse abdominal skin, and blood, skin, and muscle samples were taken at different times after removing the residual adhesive from the skin. High accumulation of the drug in the skin and muscle tissue beneath the patch application site was observed in mice compared with that after oral administration. These findings show that anastrozole transdermal patches are an appropriate delivery system for application to the breast tumor region for site-specific drug delivery to obtain a high local drug concentration.[52]
- **Ting Li et al,** have studied to determine the formulation composition of a transdermal drug delivery system of indomethacin, MASCOS 10 (polyacrylic acid type) pressure sensitive adhesive was used to prepare a drug-in-adhesive type patch containing a variety of permeation enhancers (i.e. azone, L- menthol, 2-isopropyl-5 methylcyclohexyl heptanoate (M-HEP), isopropyl myristate (IPM), Tween-80 and oleic acid). It was notable that the presence of IPM, oleic acid and Tween 80 did not increase indomethacin permeation from the transdermal patches compared with the transdermal patches containing azone and L-menthol ($P > 0.05$). 5% azone and 5% L-menthol were the permeation enhancers of choice for the percutaneous absorption of indomethacin. The prepared patches showed good uniformity with regard to drug content and drug release.[53]
- **Uttam Budhathoki et al,** have studied the effect of combination of PG with DMSO, BC, IPM, Tween 80 and SLS on drug release rate was studied in vitro. The mechanism of drug release was also studied by using power law. Significant difference (One way ANOVA; $p<0.05$) in release rate among the 16 formulations was seen in the study. The release profiles of various formulations also showed that the added enhancers in individual batches affect the release rate of the drug. The concentration of DMSO and Tween 80 showed directly proportional where as concentration of BC and SLS showed inversely proportional relationship with drug release rate. The increase followed by decrease in drug release rate was seen with increase in IPM concentration.[54]
- **MALAY K. DAS et al,** have studied the transdermal dosage form of trazodone hydrochloride (TZN) may be useful in the treatment of moderate to severe depression in schizophrenic patients by providing prolonged duration of action. It will also improve patient compliance and bioavailability. Controlled input of TZN would attenuate fluctuating plasma level of TZN resulting from oral therapy. The aim of the current investigation was to evaluate its flux and the effects of various penetration enhancers, viz., isopropyl myristate (IPM), isopropyl palmitate (IPP), butanol and octanol on transdermal permeation from matrix-based formulations through the skin The highest enhancing effect was obtained with IPM followed by butanol, octanol and IPP.[55]

e. **By using "EVAC membranes" method:** [56] 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 specified 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.

RECENT WORK

- D.R. Friend et al, have studied the irritation of transdermal devices delivering levonorgestrel and

the permeation enhancer ethyl acetate with or without ethanol was evaluated in rabbits. Erythema and oedema were assessed 24, 48 and 72 hr and 7 days after application of the 24-hr delivery system. The devices were found to be mild to moderately irritating, with erythema the primary manifestation. No differences were observed between devices using pure ethyl acetate or ethyl acetate-ethanol (7:3, v/v) as enhancers. Devices using pure ethanol as an enhancer gave levels of irritation similar to those using ethyl acetate-ethanol (7:3) or pure ethyl acetate.[57]

- **Friend, D. R** et al, have studied the series of experiments were performed to evaluate the flux of levonorgestrel (LN), ethyl acetate (EtAc), and ethanol (EtOH) through excised rat skin, through a variety of synthetic membranes and through membranes supported on rat skin. Using a donor phase of EtAc:EtOH (7:3) containing excess solid LN, the flux of LN through rat skin was ~1.0 μg/cm2·h. The normalized fluxes of LN, EtAc, and EtOH through ethylene vinyl acetate (EVAc) copolymers of varying vinyl acetate (VAc) content (12 to 25%) were 1.3 to 3.1 × 108, 2.6 to 6.8 × 10—4, and 4.8 to 9.9 × 10—5 g·cm/cm2·h respectively. Permeability experiments were also performed with the EVAc membranes supported on rat skin. By selecting the VAc content and thickness of the EVAc membranes, it was possible to control the delivery of enhancer (EtAc:EtOH) through rat skin (membrane-rate control) or to let the skin control the overall delivery of enhancer.[58]
- **Liang et al,** (1990) studied controlled release of scopolamine through EVA membrane in transdermal patch formulations and release rates were compared with uncontrolled reservoirs. It was found that an EVA membrane patch released scopolamine at a constant rate for more than 72 hours.[59]
- **Krishna and Pandit** (1994) prepared three transdermal formulations containing propranolol hydrochloride in a hydrophilic polymer matrix, one without rate controlling membrane and other two with EVA rate controlling membranes of different thickness. It was found that increased thickness of EVA led to greater retention of the drug in device and zero order profile was observed with EVA.[60]

f. Aluminium backed adhesive film method: [61] Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

RECENT WORK

- **Christopher W. Jeans et al,** have investigated the permeation of primaquine across full-thickness excised human skin from two acrylate transdermal adhesives. Primaquine base was formulated with National Starch 387-2516 and 387-2287 to provide aluminium foil-backed 1-cm diameter patches, each loaded with 10 mg drug. The patches were applied to cadaver skin in Franz-type diffusion cells and the permeation of primaquine determined over a 24 h period. Relatively high fluxes were found.[62]
- **A Bagchi et al,** Present investigation was aimed at the formulation of transdermal therapeutic systems of losartan potassium for effective control over hypertension since losartan potassium shows considerable first pass metabolism when administered through oral route. Matrix type transdermal patches containing losartan potassium were prepared using different ratios of EC with PVP and acrycoat L100 with HPMC (Table 1) by solvent evaporation technique The bottom of the mould was wrapped with aluminum foil on which the backing membrane was cast by pouring 4 % w/v PVA solution followed by drying at 60ºC for 6 hr : Formulations containing higher proportion of hydrophilic polymer were found less consistent in comparison to the patches comprised of higher proportion of hydrophobic polymer.[63]
- **SANJAY DEY et al,** have studied Transdermal patches containing carvedilol were prepared by solvent casting method using aluminium foil as

the backing membrane. by using hydroxyl propyl methyl cellulose (HPMC) and eudragit RS100 polymers by incorporating dibutyl phthalate and propylene glycol as plasticizer and permeation enhancer, respectively. The invitro permeation studies indicated that matrix patches containing hydroxyl propyl methyl cellulose and eudragit RS100 in the ratio of 1:4 shown better release.[64]

g. **Preparation of TDDS by using Proliposomes: (65,66)** The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which 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 over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

- **Bhavana Vora et al,** have studied the proniosome based transdermal drug delivery system of levonorgestrel (LN) was developed and extensively characterized both in vitro and in vivo. The system was evaluated in vitro for drug loading, rate of hydration (spontaneity), vesicle size, polydispersity, entrapment efficiency and drug diffusion across rat skin. The effect of composition of formulation, amount of drug, type of Spans, alcohols and sonication time on transdermal permeation profile was observed. The stability studies were performed at 4°C and at room temperature. The biological assay for progestational activity included endometrial assay and inhibition with the formation of corpora lutea. The study demonstrated the utility of proniosomal transdermal patch bearing levonorgestrel for effective contraception.[67]

h. **By using free film method: [68]** Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be 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 petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

RECENT WORK

- **Arijit Das et al,** have studied Transdermal drug delivery system of MFH was prepared using combinations of a hydrophobic polymer, ethyl cellulose and hydrophilic polymer, polyvinyl pyrrolidone in different ratios (1:2, 1:4, 1:6, 1:8, 2:1, 4:1, 6:1 and 8:1 w/w) by solvent evaporation technique. Polyvinyl alcohol was used to prepare the backing membrane and dibutyl phthalate as plasticizer. The prepared polymeric films were characterized for various physiochemical parameters like film thickness, tensile strength, moisture content, moisture uptake, water vapour transmission rate. Permeation studies were carried out for patches through commercial semi-permeable membrane as well as rat abdominal skin using Keshary-Chien diffusion cell. Formulation FC6 showed 96.92% drug release from the patch within 24 h. [69]
- **F.K. Alanazi et al,** Films were cast from organic and aqueous solvents using various bioadhesive polymers namely: sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) and Carbopol 934. The obtained results indicate that the concentration of ketorolac in the oral

cavity was maintained above 4.0 µg/mL for a period of at least 6 h. This film shows promising results for using the ketrolac buccoadhesive route of administration topically and systemically, and thus it will be subjected to clinical evaluation in future work.[70]

- **MANISH KUMAR et al,** In the present investigation various concentration ratios of polymer were used for the fabrication of the matrix diffusion controlled transdermal drug delivery system by solvent evaporation technique. These transdermal drug delivery systems were characterized for their thickness, weight variation, folding endurance, swelling index, content uniformity, compatibility, in-vitro release and skin irritation studies of the drug from the polymeric matrix. In-vitro release studies were carried out with modified Franz diffusion cell using pH 7.4 phosphate buffer as receptor medium and it showed controlled release of drug.[71]
- **Madishetti S.K.et al,** studied about Bilayered matrix type transdermal drug delivery systems (TDDS) of DOM were prepared by film casting technique using hydroxypropyl methyl cellulose as primary and Eudragit RL 100 as secondary layers. Brij-35 was incorporated as a solubilizer, d-limonene and propylene glycol were employed as permeation enhancer and plasticizer respectively. All the formulations exhibited satisfactory physicochemical and mechanical characteristics.[72]

EVALUATION PARAMETERS:

1. **Interaction studies:** [73] Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can 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 commonly carried out inThermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.

2. **Thickness of the patch:** [74] The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

3. **Weight uniformity:** The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

4. **Folding endurance:** A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

5. **Percentage Moisture content:** The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

   Percentage moisture = [Initial weight- Final weight/ Final weight] ×100 content

6. **Percentage Moisture uptake:** The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

   Percentage moisture = [Final weight- Initial weight/ initial weight] ×100 uptake

7. **Water vapour permeability (WVP) evaluation: [75]**

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula

WVP=W/A

Where, WVP is expressed in gm/m2 per 24hrs,

W is the amount of vapour permeated through the patch expressed in gm/24hrs and

A is the surface area of the exposure samples expressed in m2.

8. Drug content: A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

9. Uniformity of dosage unit test: [76] An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was alysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

10. Polariscope examination: This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

11. Shear Adhesion test: This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of crosslinking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless-steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time, it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

12. Peel Adhesion test: In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and number of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless-steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured.

13. Thumb tack test: It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

14. Flatness test: [77] Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

15. Percentage Elongation break test: [78] The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.

    Elongation percentage = L1-L2 ×100
    L2

    Where, L1is the final length of each strip and L2 is the initial length of each strip.

16. Rolling ball tack test: [79] This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels

along the adhesive provides the measurement of tack, which is expressed in inch.

17. Quick Stick (peel-tack) test: [80] In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

18. Probe Tack test: In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

19. In vitro drug release studies: [73] The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

20. In vitro skin permeation studies: An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or H LC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated mg cm2 vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load mg cm2 .

21. Skin Irritation study: [76] Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

22. Stability studies: [73] Stability studies are to be conducted according to the 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 analyze suitably for the drug content. Ideal product requirements [81]

    - Shelf life up to 2 years
    - Small size patch (i.e., less than 40 cm2)
    - Convenient dose frequency (i.e., once a day to once a week)
    - Cosmetically acceptable (i.e., clear, white color)
    - Simple packaging (i.e., minimum number of pouches and steps required to apply the system)

- Easy removal of the release liner (i.e., for children and elderly patients)
- Adequate skin adhesion (i.e., no fall off during the dosing interval and easy removal without skin trauma)
- No residue i.e., ―cold flow‖ around the edge of the patch in storage or after application to skin or beneath the patch after removal)
- No unacceptable dermal reactions (i.e., contact dermatitis, skin sensitization, photo toxicity, photosensitization, erythema, itching, stinging, burning, etc.)
- Consistent biopharmaceutical performance (i.e., precision of the required pharmacokinetic and pharmacodynamic response between individuals and in the same individuals over time.

Limitations of transdermal drug delivery systems [82,83,84]

- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin
- Cannot administer drugs that require high blood levels
- Drug of drug formulation may cause irritation or sensitization
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- Not suitable for a drug, which doesn't possess a favourable, o/w partition coefficient
- The barrier functions of the skin of changes from one site to another on the same person, from person to person and with age.

CONCLUSION

This article provide an valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who are involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

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