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REVIEW OF MATRIX TYPE TRANSDERMAL PATCHES OF BENAZEPRIL HYDROCHLORIDE

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Abstract:

Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the circulation (Monkhouse and Huq, 1988). FDA approved the primary skin patch products in 1981. These delivery systems provided the controlled systemic absorption of scopolamine for the prevention of sickness (TransdermScop, ALZA Corp.) and nitroglycerine for the prevention of angina related to arterial blood vessel disease (Transderm-Nitro). Over the last twenty years, over 35 transdermal products are approved generating sales of $3.2 billion in 2002, which is predicted to rise to $4.5 billion in 2008. More recently, such dosage forms are developed and/or modified so as to reinforce the actuation of drug diffusion (thermodynamic activity) and/or increase the permeability of the skin. These approaches include the employment of penetration enhancers, supersaturated systems, prodrugs, liposomes and other vesicles (Bhavna yadav et al., 2011).

KEYWORDS- Transdermal Patches, Benazepril Hydrochloride, Eudragit L100.

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1. INTRODUCTION:

A drug is any substance or product that's used or is meant to be wont to modify or explore physiological systems or pathological states for the advantage of the recipient (Tripathi K.D., 2004)

Routes of Drug Administration (Tripathi K.D., 2004)

- Local routes
- Topical Deeper Tissues Arterial supply
- Systemic routes
- Oral
- Sublingual or buccal Rectal
- Cutaneous – Transdermal therapeutic systems Inhalation
- Nasal Parenteral

Drug Delivery System

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of medicine to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables, as drug carriers. this kind of drug delivery system is understood to produce a prompt release of drug. Therefore, to realize additionally on maintain the drug concentration within the therapeutically effective range needed for treatment, it's often necessary to require this kind of drug delivery system several times on a daily basis. This ends up in a major fluctuation in drug levels. they need resulted within the development of latest techniques for drug delivery.

These techniques are capable of controlling the speed of drug delivery, sustaining the duration of therapeutic activity, and/or targeting the delivery of drug to a tissue.

Sustained release

The term sustained release is understood to possess existed within the medical and pharmaceutical literature for several decades. it's been constantly wont to describe a pharmaceutical dosage form formulated to retard the discharge of a therapeutic agent such its appearance within the circulation is delayed and/or prolonged and its plasma profile is sustained in duration. The onset of its pharmacologic action is usually delayed, and therefore the duration of its therapeutic effect is sustained.

Controlled release

The term-controlled release on the opposite hand, encompasses a meaning that goes byond the scope of sustained drug action. It also implies a predictability and reproducibility within the drug release kinetics, which implies that the discharge of drug ingredients from a controlled release drug delivery system proceeds at a rate profile that's not only predictable kinetically, but also reproducible from one unit to a different (Chein Y. W., 2005).

Advantages of Controlled Drug Delivery System

- Decreased incidence and/or intensity of adverse effects and toxicity
- Better drug utilization
- Controlled rate and site of release
- More uniform blood concentration
- Improved patient compliance
- Reduced dosing frequency
- More consistant and prolonged therapeutic effect
- A greater selectivity of pharmacological activity (Jain N. K., 2004)

Disadvantage of Controlled Drug Delivery System

- Increase variability among dosage units
- Stability problems
- Toxicity due to dose dumping
- Increased cost
- More rapid development of tolerance
- Need for extra patient education and counseling (Jain N. K., 2004)

Requirements of Controlled Drug Delivery System

- Extended drug action at a predetermined rate
- Localize the drug action
- Target drug action
- Therapeutically based drug release (Remington., 2006)

Factors Governing the Design of Controlled Release Dosage Forms

- **Drug related**
- Aqueous solubility
- Partition coefficient
- Molecular size
- Protein binding
- **Biological**
- Absorption
- Distribution
- Excretion
- Duration of action
- Margin of safety
- Side effects
- **Physiological**

- Prolonged drug absorption
- Variability in gastro intestinal emptying and motility
- Gastro intestinal blood flow

➢ **Pharmacokinetic**

- First pass metabolism
- Variability in urinary pH
- Enzyme induction/inhibition (Vyas S.P. and Roop K. Khar. 2008)

Advantages of Transdermal Drug Delivery System (TDDS)

- Transdermal drug delivery systems offer several important advantages over more traditional approaches, including (Sampath kumar K.P. et al., 2010)
- Longer duration of action leading to a discount in dosing frequency
- Increased convenience to administer drugs which mightotherwise require frequent dosing
- Improved bioavailability
- More uniform plasma levels
- Reduced side effects and enhanced therapy due to maintenance of plasma levels up to the end of the dosing interval
- Flexibility of dismissing the drug administration by simply removing the patch from the skin
- Enhanced patient compliance and comfort via non-invasive, painless and simple application

Limitations of Transdermal Drug Delivery System

Some of the greatest disadvantages to transdermal drug delivery are (Sampath kumar K.P. et al., 2010)

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

Structure of the Skin

The skin is one in all the foremost extensive and readily accessible organs of the material body. It receives about one-third of the blood circulation through the body (Jain N. K., 2004). The skin may be a very effective barrier for the permeation of most xenobiotics. Only a awfully little drug actually arrives at the positioning action.

Skin could be a multilayered tissue consisting of epidermis, dermis and hypodermis as shown in Figure 1.

Stratum corneum (or) corneum is that the outermost layer of epidermis, which restricts the inward and outward movement of chemical substances. These are compacted, flattened, dehydrated and keratinized cells which are physiologically inactive.

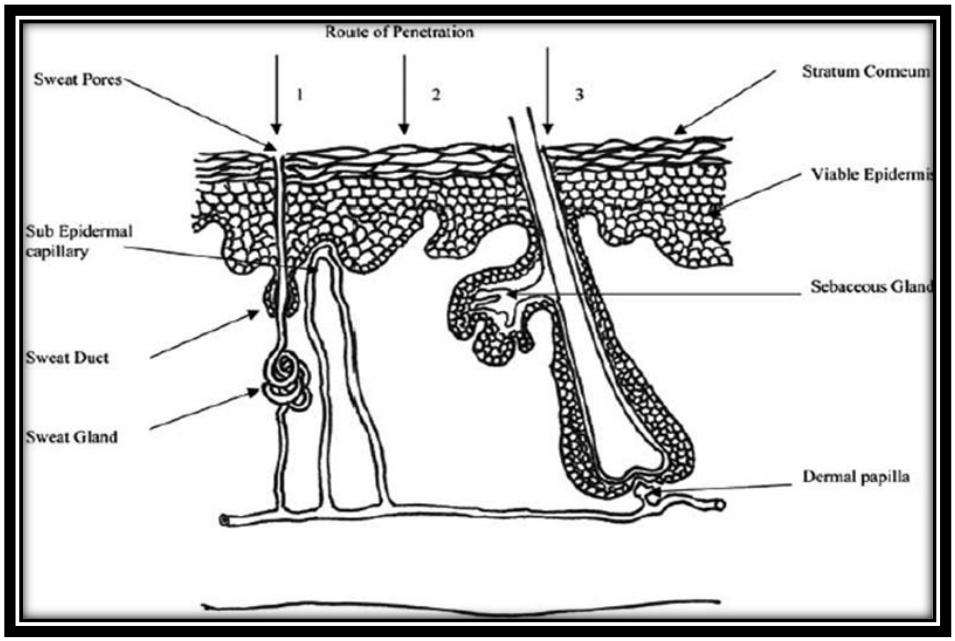


Figure 1 Structure of skin

Stratum corneum has two distinct chemical regions (Jain N. K., 2004) as shown in Figure 2
The mass of intracellular (Transcellular) protein
The intercellular lipoidal medium.

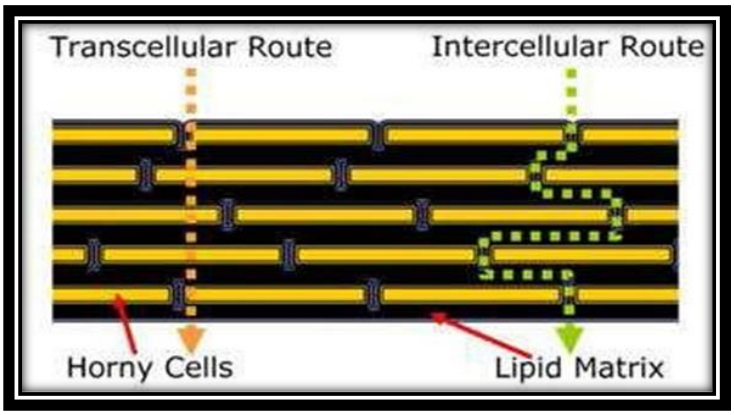


Figure 2 Structure of stratum corneum

The epidermis rests on the much thicker (2000 µm) dermis. The dermis essentially consists of about 80% proteins during a matrix of mucopolysaccharide ground substance (Jain N. K., 2004). Also contained within the dermis are lymphatics, nerves and epidermal appendages like hair follicles, sebaceous glands and sweat glands.

Percutaneous Absorption

Percutaneous absorption involves passive diffusion of drugs through the skin. The mechanism of permeation can involve passage through the epidermis itself (transepidermal absorption) or diffusion through shunts, particularly those offered by the relatively cosmopolitan hair follicles and eccrine glands (transfollicular or shunt pathway absorption) (Jain N. K., 2004).

Trans epidermal absorption

Transepidermal (or Transcorneal) penetration includes intracellular and intercellular penetration, hydrophilic drugs generally seen to permeate through intracellular pathway. As stratum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to labor under this immobilized water. Non polar substances permeate through intercellular penetration. These molecules diffuse into the non-aqueous lipid matrix imbibed between the protein filaments as shown in Figure 3.

Trans follicular (shunt pathway) absorption

In Transappendegeal permeation (shunt pathway) the drug molecule may transverse through the hair follicles, the sebaceous pathway of pilosebaceous apparatus or the aqueous pathway of the salty sweat glands as shown in Figure 3.

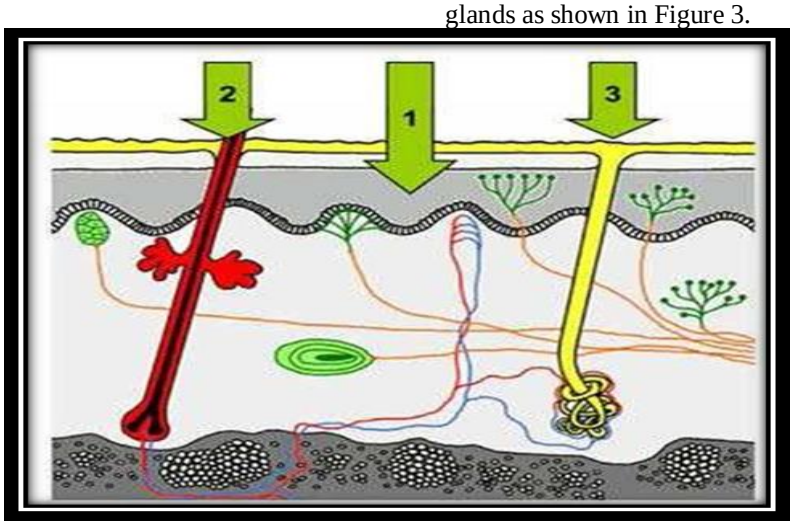


Figure 3 Percutaneous absorption

1. Across the intact horny layer,
2. through the hair follicles with the associated sebaceous glands
3. via the sweat glands

Principles of transdermal permeation

Earlier skin was considered as an impermeable protective barrier, but later investigations were disbursed which proved the utility of skin as a route for systemic administration. Skin is that the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. the assorted steps involved in transport of drug from patch to circulation are as follows (Bhavna yadav et al., 2011)

- Diffusion of drug from drug reservoir to stratum
- Sorption by stratum corneum and penetration through viable epidermis
- Uptake of drug by capillary network within the dermal papillary layer
- Effect on the right track organ.

Factors Affecting Permeability

Physiological factors

- Stratum corneum layer of the skin
- Anatomic site of application on the body
- Skin condition and disease
- Age of the patient
- Skin metabolism
- Desquamation (peeling or flaking of the surface of the skin)
- Skin irritation and sensitization
- Race

Formulation factors

- Physical chemistry of transport
- Vehicles and membrane used
- Penetration enhancers used
- Method of application
- Device used

Physicochemical properties of enhancers

- Partition coefficient of 1 or greater is required.

  pH value should be moderate, the flux of ionizable drugs may be plagued by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.
- Concentration of penetrant higher than solubility, excess solid drug functions as a reservoir and helps in maintaining constant drug concentration for extended time (Jalwal P et al., 2010).

Methods of Preparation of TDDS

Asymmetric TPX membrane method

A prototype patch are often fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter are going to be used because the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX 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 an exceedingly mixture of solvent (cyclohexane) and nonsolvent additives at 60°c to create a polymer solution. The polymer solution is kept at 40°C for twenty-four hrs and sew together a glass plate to a pre- determined thickness with a gardner knife. at that time 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 are often removed, air dry in an exceedingly circulation oven at 50°C for 12 hrs].

Circular Teflon mould method

Solutions containing polymers in various ratios are utilized in an organic solvent. Calculated amount of drug is dissolved in half the number of same organic solvent. Enhancers in numerous concentrations are dissolved within the partner of the organic solvent and so added. Di-N-butyl phthalate is added as a plasticizer into drug polymer solution. the full contents are to be stirred for 12 hrs and so poured into a circular teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to manage solvent vaporization during a streamline flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for twenty-four hrs. The dried films are to be stored for an additional 24 hrs at 25±0.5°C in a very desiccators containing colloid before evaluation to eliminate aging effects. the sort films are to be evaluated within one week of their preparation.

Mercury substrate method

In this method drug is dissolved in polymer solution together with plasticizer. The above solution is to be stirred for 10 - quarter-hour to supply a regular dispersion and poured in to a leveled mercury surface, covered with inverted funnel to manage solvent evaporation. By using “IPM membranes” method

In this method drug is dispersed in an exceedingly

mixture of water and antifreeze 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 will be employed in order to get solution gel, if the drug solubility in solution is incredibly poor. The formed gel are going to be incorporated within the IPM membrane.

By using "EVAC membranes" method

In order to arrange the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes may be used as rate control membranes. If the drug isn't soluble in water, propanediol is employed for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin are going to be added to the above solution and neutralized by using 5% w/w caustic soda solution. The drug (in gel form) is placed on a sheet of backing layer covering the desired area. A rate controlling membrane is placed over the gel and also the edges are sealed by heat to get a leak proof device.

Aluminum backed adhesive film method

Transdermal drug delivery system may produce unstable matrices if the loading dose is bigger than 10 mg. Aluminium backed adhesive film method may be a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs likewise as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive are going to be added to the drug solution and dissolved. A custom made aluminium former is lined with tin foil and also the ends blanked off with tight-fitting cork blocks.

Preparation of TDDS by using Proliposomes

The proliposomes are prepared by carrier method using film deposition technique. From the sooner reference drug and lecithin within the ratio of 0.1:2.0 will be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a very 100 ml round bottom flask which is kept at 60-70°c temperature and therefore the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for half-hour. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved during 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 answer is to be added. After the last loading, the flask containing proliposomes are connected in a very lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed during a desiccator over night and so sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

By using free film method

Free film of cellulose ester is ready 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 amount of 40% w/w of polymer weight. Five ml of polymer solution was poured during a glass ring which is placed over the mercury surface in an exceedingly glass petridish. the speed of evaporation of the solvent is controlled by placing an inverted funnel over the petridish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film are going to be separated out and stored between the sheets of paper during a desiccator until use. Free films of various thickness may be prepared by changing the quantity of the polymer solution (J. Ashok kumar et al., 2009).

Types of Transdermal Patches

Polymer membrane permeation-controlled TDDS

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane (Figure 4). The drug releases only through the speed controlling membrane, which may be micro porous or non-porous. within the drug reservoir compartment, the drug is within the variety of an answer, suspension, or gel or dispersed in solid polymer matrix. On the outer surface of the polymeric membrane a skinny layer of drug-compatible, hypoallergenic adhesive polymer may be applied. the speed of drug release from this kind of Transdermal drug delivery system will be tailored by varying the polymer composition, permeability coefficient and thickness of the speed controlling membrane.

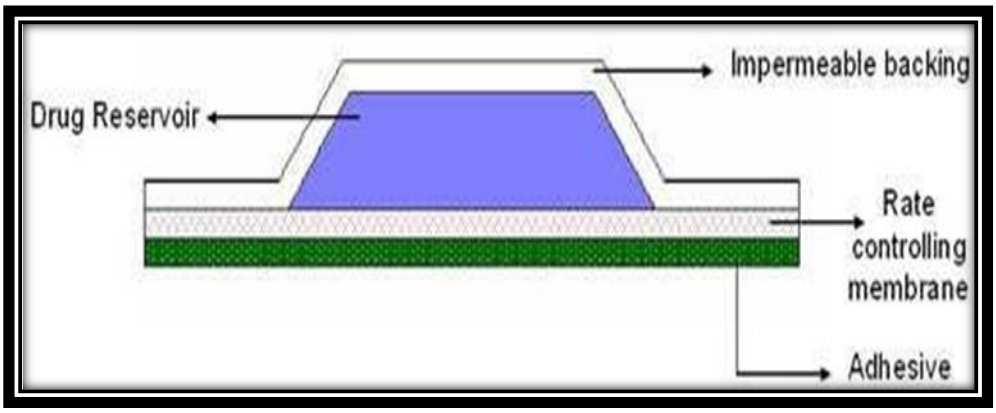


Figure 4: Polymer membrane permeation-controlled TDDS

Examples

TransdermScop (Scopolamine) for 3 days protection of motion sickness and

TransdermNitro (Nitroglycerine) for once-a-day medication of angina pectoris.

Adhesive diffusion controlled TDDS

The drug reservoir is made by dispersing the drug in an adhesive polymer so spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in case of hot-melt adhesives) onto an impervious backing layer (Figure 5). The drug reservoir layer is then covered by a non-medicated rate controlling adhesive polymer of constant thickness to provide an adhesive diffusion controlling drug delivery system.

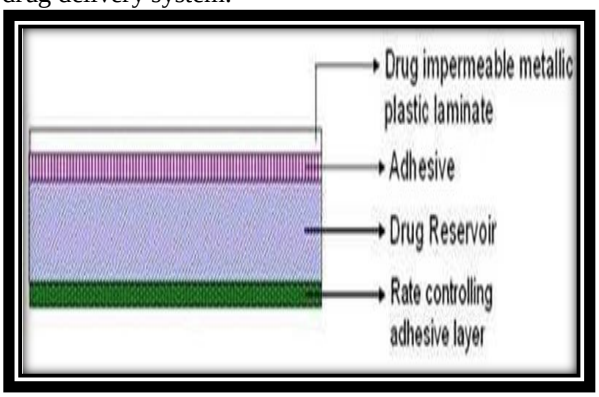


Figure 5: Adhesive diffusion controlled TDDS

Example

Deponit (Nitroglycerine) for once-a-day medication of angina pectoris.

Matrix diffusion controlled TDDS

The drug is dispersed homogeneously in a very hydrophilic or lipophilic polymer matrix. This drug containing polymer disk then is fixed onto an occlusive base plate during a compartment fabricated from a drug-impermeable backing layer (Figure 6). rather than applying the adhesive on the face of the drug reservoir, it's spread along the circumference to make a strip of adhesive rim.

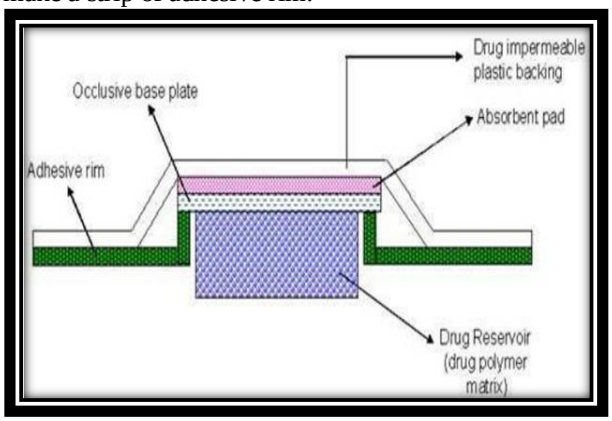


Figure 6: Matrix diffusion controlled TDDS

Example

Nitro Dur (Nitroglycerine) used for once each day medication of heart disease.

Micro reservoir controlled TDDS

This drug delivery system could be a combination of reservoir and matrix-dispersion systems (Figure 7). The drug reservoir is made by first suspending the drug in an exceedinglyn solution of water-soluble polymer then dispersing the answer homogeneously in a lipophilic polymer to make thousands of unreachable, microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross linking the polymer in place. A transdermal system therapeutic system thus formed as a medicated disc positioned at the center and surrounded by an adhesive rim (Dipen M. Patel and Kavitha K., 2010).

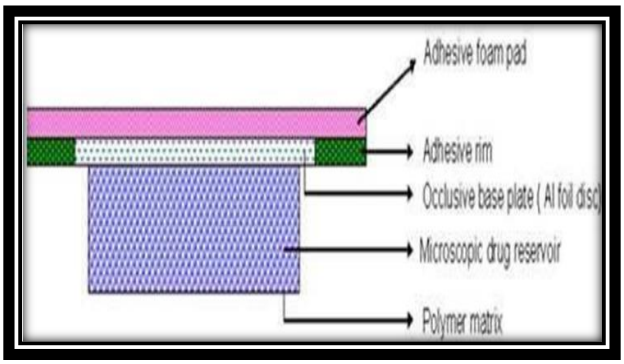


Figure 7: Microreservoir controlled TDDS

Example

Nitro-dur® System (Nitroglycerin) for once a day treatment of angina pectoris.

Evaluation of Transdermal Patches

Transdermal patches are developed to boost clinical efficacy of the drug and to boost patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important so as to confirm their desired performance and reproducibility under the specified environmental conditions (Bhavna Yadav et al., 2011). These studies are predictive of transdermal dosage forms and may be classified into following types:

- Evaluation of adhesive
- Physicochemical evaluation
- In vitro drug release evaluation
- Effect of skin uptake and metabolism
- In vivo evaluation
- Cutaneous toxicological evaluations

Evaluation of adhesive

Pressure sensitive adhesives are evaluated for the following properties (Jain N. K., 2004)

1. Peel adhesion properties
2. Tack properties
- Thumb tack test
- Rolling ball tack test
- Quick stick test (peel tack test)
- Probe tack test
3. Shear strength properties

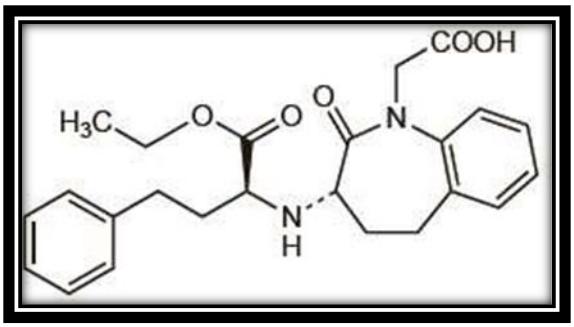
Physicochemical evaluation (Bhavna yadav et al., 2011)

- Physical Appearance
- Weight variation
- Thickness of the patch
- Folding Endurance
- Flatness
- Percentage Moisture Content
- Estimation of drug content

2. DRUG PROFILE

Benazepril Hydrochloride

Structural Formula



Synonyms:

Benazepril HCl Benazepril Hydrochloride Benazeprilum (Latin) (Drug Bank: Benazepril).

Empirical Formula:

C24H28N2O5, HCl

Mechanism of Action:

Benazepril and benazeprilate inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE may be a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, Hypertensin. Hypertensin also stimulates aldosterone secretion by the ductless gland.

Inhibition of ACE ends up in decreased plasma angiotensin, which results in decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may lead to alittle increase of serum potassium.

While the mechanism through which benazepril lowers force per unit area is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-rennin hypertension (Drug Bank: Benazepril).

Pharmacokinetics:

Absorption:

Peak in plasma within 0.5-1.0 Hours. The extent of absorption is atleast 37% as determined by urinary recovery and isn't significantly influenced by the presence of food within the gastrointestinal tract.

Distribution in blood:

Benazeprilate is not extensively distributed into extravascular sites with minimum passage across the blood/brain barrier.

Metabolism:

Peak in plasma within 0.5-1.0 Hours. The extent of absorption is atleast 37% as determined by urinary recovery and isn't significantly influenced by the presence of food within the gastrointestinal tract.

Excretion:
Benazepril and benazeprilate are cleared predominantly by renal excretion in healthy subjects with normal renal function. Nonrenal (i.e., biliary) excretion accounts for about 11%-12% of benazeprilat excretion in healthy subjects (Colin Dollery., 1999, Drug Bank: Benazepril).

Indications and Usage:
Control of arterial hypertension
Treatment of congestive heart failure (Colin Dollery., 1999)

Dose:
An initial dose of 10 mg once daily is usually recommended in patients with creatinine clearance ≥30 ml /min and people not receiving diruetics.
Hypertensive patients with heart failure and those with a creatinine clearance ≥ 30 ml /min are recommended an initial daily dose of 5 mg (Anthony C Moffat., 2004, Colin Dollery., 1999).

Adverse Effects
Serious Reactions

- angioedema, head/neck
- angioedema, intestinal
- hypotension, severe
- hyperkalemia
- renal impairment/failure
- hepatotoxicity
- neutropenia
- agranulocytosis
- anemia, hemolytic
- thrombocytopenia
- pancreatitis
- Stevens-Johnson syndrome
- pemphigus
- oligohydramnios (in utero exposure)
- fetal/neonatal harm or death (in utero exposure)
- congenital malformations, major (1st trimester use)

Common Reactions

- Cough
- Hypotension
- Dizziness
- Fatigue
- Hyperkalemia
- nausea/vomiting
- elevated Cr
- musculoskeletal pain
- photosensitivity

Drug Interactions:
Potentially hazardous interactions:
Increased hypotensive effects occur when benazepril is combined with thiazide diuretics or dihydropyrimidine calcium antagonist (Colin Dollery., 1999).

Contraindications:
Angioedema
Pregnancy (Colin Dollery., 1999).
Storage:
Preserve in well closed container store below 30º C.

3. MATERIALS

Sr. No	Material
1.	Benazepril Hydrochloride
2.	Ethyl cellulose
3.	Eudragit L100
4.	Eudragit S100
5.	Dibutyl phthalate
6.	Poly ethylene glycol
7.	Dimethyl sulfoxide
8.	Ethanol
9.	Potassium dihydrogen phosphate
10.	Disodium hydrogen phosphate
11.	Sodium chloride
12.	Formaldehyde solution
13.	Surgical spirit

4. CONCLUSION:

The transdermal route of administration has been recognized as one of the highly potential routes. Transdermal drug delivery is the delivery of drugs across epidermis to achieve systemic effects. Transdermal patches control the delivery of drugs at controlled rates by employing an appropriate polymer. This route allows controlled release of the drug at rates approaching zero-order simulating those provided by intravenous infusion.

The aim of this study is to develop suitable transdermal patches of benazepril hydrochloride by employing ethyl cellulose, Eudragit S100 and Eudragit L100 as a film former and to investigate the effect of polymers, plasticizer and permeation

enhancer on in vitro release of transdermal patches of benazepril hydrochloride.

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