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Preparation and Evaluation of Transdermal Films Containing Diltiazem Hydrochloride

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Abstract: ***Diltiazem Hydrochloride is an antihypertensive drug belongs to the category of calcium channel blockers. The half-life is 3.7 hr, metabolised mainly in the liver and undergoes significant first pass metabolism. The present study is carried out to develop and evaluate a matrix-type transdermal formulation containing Diltiazem hydrochloride with different ratios of HPMC and PVP combination plasticized with PEG (Polyethylene Glycol) by the solvent evaporation technique. The prepared patches were evaluated for their physicochemical characteristic such as thickness, weight variation, drug content uniformity, moisture content, folding endurance, tensile strength. Data of in-vitro release from patches were fit into different equation and kinetic models to explain release of kinetics. The model used were zero order and first order equations and Higuchi and Korsmeyer-peppas models. The promising formulation is subjected to short term stability studies and found to be stable with respect to the physical parameters and drug content. IR studies showed that there is no interaction between drug and polymer and they are found to be compatible.***

Keywords: Diltiazem Hydrochloride, HPMC, PVP, PEG

1. Introduction

Transdermal drug delivery has made an important contribution to medical practice, but it has yet to fully achieve its potential as an alternative to the oral delivery and hypodermic injections. An advantage of a transdermal drug delivery route over other types of delivery systems such as oral, topical, intravenous, intramuscular, etc. is that the patch may essentially can provide a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. First-generation transdermal delivery systems have continued their steady increase in clinical use for delivery of small, lipophilic, low-dose drugs. Second-generation delivery systems using chemical enhancers, non-cavitational ultrasound and iontophoresis have also resulted in clinical products; the ability of iontophoresis to control delivery rates in real time provides added functionality. Third generation delivery systems target their effects to skin's barrier layer of stratum corneum using microneedles, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound. Using these novel second- and third-generation enhancement strategies, transdermal delivery is poised to significantly increase impact on medicine[1].

1.1 Transdermal Drug Delivery System[2]

Topical formulations containing drugs showing systemic action are called transdermal delivery systems (TDS) or transdermal therapeutic systems (TTS). Transdermal delivery may be defined as the delivery of a drug through 'intact' skin so that it reaches the systemic circulation in sufficient quantity, to be beneficial after administration of a therapeutic dose. Transdermal systems are ideally suited for diseases that demand chronic treatment. Hence, anti-diabetic agents of both therapeutic and prophylactic usage have been subjected to transdermal investigation.

Advantage[1]

a) Can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.
b) Can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.
c) To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.
d) Noninvasive, avoiding the inconvenience of parenteral therapy.
e) e) They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Transdermal clonidine 7 day.
f) The activity of drugs having a start half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
g) Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

Disadvantages[4]

a) Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
b) Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability.
c) Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
d) Long time adhere is difficult.

1.2 Structure of Skin

Skin is one of the most extensive organ of the body covering an area of about $2m^2$ on in an average human adult. This multilayered organ receives approximately one third of all blood circulating through the body. With thickness of only a millimeter, the skin separates the underlying blood circulation network from outside environment. Human skin comprises of three distinct but mutually dependent tissues:
A) The stratified, vascular, cellular epidermis,
B) Underlying dermis of connective tissues and
C) Hypodermis

Epidermis: it results from an active epithelial basal cell population and is approximately 150 micrometers thick. It is the outermost layer of skin and process of differentiation results in migration of cells from basal layer towards the skin surface. The end result of this process is the formation of a thin, stratified and extremely resilient layer (the stratum corneum) at the skin surface.

Stratum corneum: This is the outermost layer of skin, also called horny layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface, lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nature of the horney layer depends critically on its constituents: 75 to 80% proteins, 5 to 15% lipids, and 5 to 10% ondansetron material on a dry weight basis. Protein fractions predominantly contain alpha-keratin (70%) with some betakeratin (10%) and cell envelope (5%). Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane.

Viable epidermis: This is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms.

Dermis: electron microscopic examination shows that the dermis is made up of a network of robust collagen fibers of fairly uniform thickness with regularly spaced cross striations. It is about 3 to 5 mm and contains the blood vessels, lymph vessels, and nerves. It also provides oxygen and nutrients to the skin while removing toxins and waste products.

Hypodermis: The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanic protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery, only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

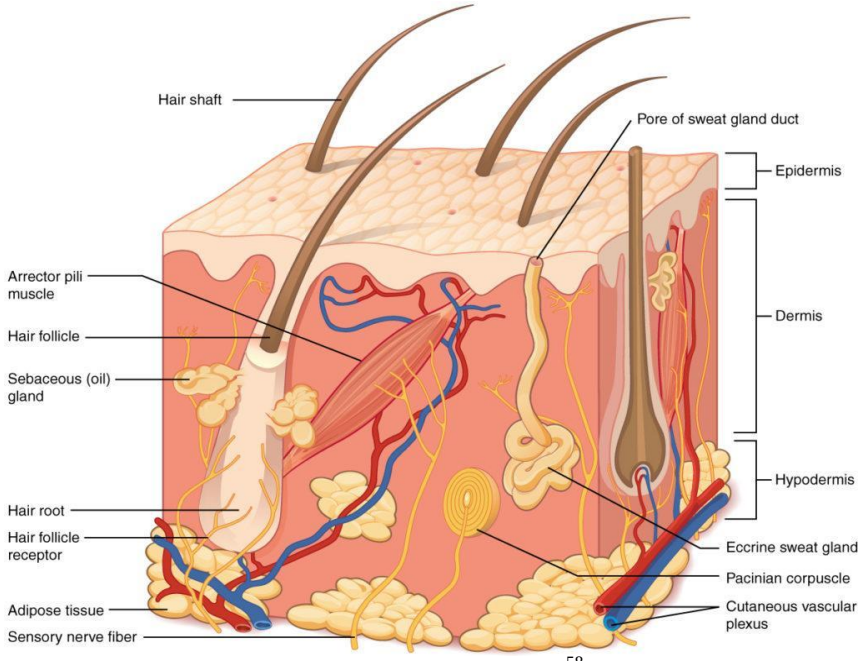

Figure 1: Structure of skin[58]

Factors that influence transdermal drug delivery[5]:

Biological factors include:

1) Skin condition
2) Skin age
3) Blood flow
4) Regional skin sites
5) Skin metabolism
6) Species differences

Physiological factors include:

1) Skin hydration
2) Temperature and pH
3) Diffusion coefficient
4) Drug concentration
5) Partition coefficient
6) Molecular size and shape

Basic Components of TDDS[7]:

1) Drug
2) Polymer matrix
3) Permeation enhancers
4) Adhesive
5) Backing layer.

1) Drug

The drug is in direct contact with release liner.

Ex: Nicotine, Methotrexate, and Estrogen. Some of the desirable properties of a drug for transdermal delivery:

a) The drug molecule should possess an adequate solubility in oil and water.
b) The drug should have a molecular weight less than approximately 1000 Daltons.
c) The drug should have low melting point.

d) Along with these properties the drug should be potent, having short half-life and be non- irritating.

2) Polymer Matrix

The Polymer controls the release of the drug from the device. Possible useful polymers for transdermal devices are:

a) Natural Polymers: e.g., cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.
b) Synthetic Elastomers: e.g., polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrene butadiene rubber, Neoprene etc.
c) Synthetic Polymers: e.g., polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Poly acrylate, Polyamide, Poly urea, Polyvinyl pyrrolidone, Polymethyl methacrylate, Epoxy etc.

3) Permeation Enhancers[48]

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. These may conveniently be classified under the following main headings:

a) **Solvents**: These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols-methanol and ethanol; alkyl methyl sulfoxides-dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolid- ones- 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone), miscellaneous solvents- propylene glycol, glycerol, silicone fluids, isopropyl palmitate.
b) **Surfactants:** These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.
c) **Anionic Surfactants:** e.g. Dioctylsulpho- succinate, Sodium lauryl sulphate, Decodecyl- methyl sulphoxide etc. Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.
d) **Bile Salts:** e.g. Sodium mstaurocholate, Sodium deoxycholate, Sodium tauro glycocholate.
e) **Binary system**: These systems apparently open up the heterogeneous multi laminate pathway as well as the continuous pathways. e.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.
f) **Miscellaneous chemicals**: These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide calcium thioglycolate anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein[3].

4) Adhesives

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

a) Should adhere to the skin aggressively, should be easily removed.
b) Should not leave an un washable residue on the skin.
c) Should not irritate or sensitize the skin.

The face adhesive system should also fulfill the following criteria;

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

5) Backing membrane

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

1.3 Kinetics of Transdermal Permeation[40]

Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems. Transdermal permeation of a drug involves the following steps:

1) Sorption by stratum corneum.
2) Penetration of drug through epidermis.
3) Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physiochemical properties. The rate of permeation across the skin is given by:

$$\frac{dQ}{dt} = Ps\,(Cd - Cr)$$

Where Cd and Cr are the concentration of the skin penetrant in the donor compartment i.e. on the surface of stratum corneum and in the receptor compartment i.e. body respectively. Ps is the overall permeability coefficient of the skin tissue to the penetrant. This permeability coefficient is given by the relationship:

$$Ps = \frac{D_{ss}\,Ks}{hs}$$

Where Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum, Dss is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and hs is the overall thickness of skin tissues.

As Ks, D_{ss} and hs are constant under given conditions the permeability coefficient Ps for a skin penetrant can be considered to be constant.

From equation (1)

It is clear that a constant rate of drug permeation can be obtained only when Cd >> Cr i.e. the drug concentration at the surface of the stratum corneum Cd is consistently and substantially greater than the drug concentration in the body Cr. The equation becomes

$$\frac{dQ}{} = Ps\ Cd\ dt\ .$$

The rate of skin permeation is constant provided the magnitude of Cd remains fairly constant throughout the course of skin permeation. For keeping Cd constant the drug should be released from the device at a rate Rr i.e. either constant or greater than the rate of skin uptake Ra i.e. Rr>> Ra. Since Rr>> Ra, the drug concentration on the skin surface Cd is maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum Cs.i.e. Cd>>Cs. Therefore a maximum rate of skin permeation is obtained and is given by the equation:

$$(dQ/dt)\ m = PsCs$$

From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient Ps and is equilibrium solubility in the stratum corneum Cs. Thus skin permeation appears to be stratum corneum limited[3].

1.4 Transdermal Patch[5]

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 blood stream. Often, this promotes healing to an injured area of the body. The basic components of transdermal patch consists of polymer matrix / Drug reservoir, active ingredient (drug), permeation enhancers, pressure sensitive adhesive (PSA), backing laminates, release liner, and other excipients like plasticizers and solvents.

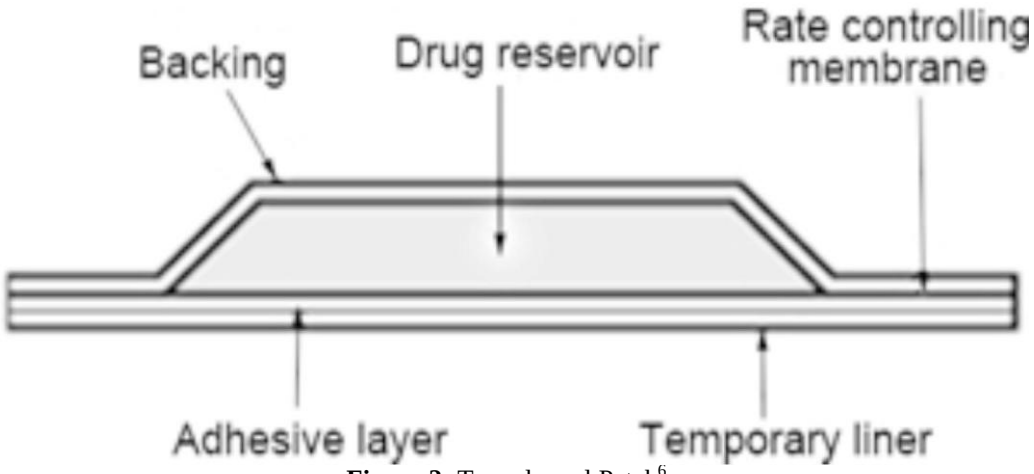

Figure 2: Transdermal Patch[6]

Types of Transdermal Films

1) 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.

2) Multi -layer drug in adhesive

This type is also similar to the single layer but it contains an 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. Vapour patch: The patch containing the adhesive layer not only serves to adhere the various surfaces together but also serves as to release the vapour. The vapour patches are new to the market, commonly used for releasing the essential oils in decongestion. Various other types of vapour patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

3) Reservoir system[8]

In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling 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.

4) Matrix system[10]
a) Drug-in-adhesive system

This type of patch is formulated by mixing the drug with adhesive polymer to form drug reservoir. It then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by an unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-in-adhesive. The system is considered to be compatible with a wide variety of drugs. Moreover the system is competent to deliver more than one drug in a single patch. It offers advantages in reduced size and thickness and improved

conformability to the application site, helping drive patient preference.

b) Matrix-dispersion system

The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with the definite shape and thickness. 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.

5) Micro reservoir system

The system consists of microscopic spheres of drug reservoirs which releases drug at a zero order rate for maintaining constant drug levels. Micro reservoir system is a combination of reservoir and matrix-dispersion system. The aqueous solution of water soluble polymer is mixed with drug to form a reservoir. It is then followed by dispersing the solution homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross linking agents are added to stabilize thermodynamically unstable dispersion by in-situ cross-linking the polymer.

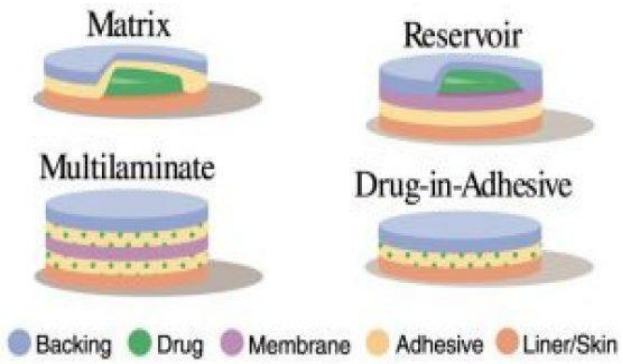

Figure 3: Types of transdermal patch[44]

Various methods for preparation of TDDS[48]

1) **Solvent casting technique:** Transdermal patches containing drug will be prepared by solvent casting technique. The patches will be prepared by incorporation glycerin (15% w/w of dry polymer) as a plasticizer and polyethylene glycol 400 (PEG 400, 10% w/w of dry polymer) as a permeation enhancer. The polymeric casting solution will be prepared by dissolving HPMC (hydroxypropyl methylcellulose) in a chloroform: methanol (1:1) mixture by using a magnetic stirrer. Glycerin 15% (w/w of dry polymer) and PEG 400 is added into the above mixture. The drug 50mg will be added slowly to the solution and dissolved by continuous stirring for 30min. This polymeric solution will be poured in the laboratory fabricated moulds. The moulds will be kept on a horizontal surface and covered by a inverted funnel to control the rate of evaporation. The polymeric solution is allowed to dry for 24hrs. After 24hrs the dried films/patches will be then detached and cut to generate transdermal patches of 1cm2 diameter. The formulated patches will be stored in dessicator until further evaluation. A thin layer of hydroallergenic adhesive polymer is applied on the external surface of transdermal patches to provide contact between transdermal patches and skin.[47]
2) **Asymmetric TPX membrane method:** 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. [48]
3) **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 hr and cast on a glass plate to a predetermined 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 min of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hr.
4) **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. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butyl phthalate is added as a plasticizer into of the organic solvent and then added. Di-N-butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hr 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 hr. The dried films are to be stored for another 24 hr at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. These type of films are to be evaluated within one week of their preparation.
5) **Mercury substrate method:** In this method, drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 min to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation[45].
6) **By using "IPM membranes" method:** In this method, drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hr 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.
7) **By using "EVAC membranes" method:** In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (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 thespecified 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.

8) **Aluminium backed adhesive film method:** 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 custom made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.
9) **Preparation of TDDS by using Proliposomes:** 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 min. 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 desiccators 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[46].
10) **By using free film method:** 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. 5 ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petridish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petridish.

2. Aim & Objectives

2.1 Aim & Objectives

Transdermal films with their unique nature of convenience in dosing and portability of thin films gained a quick acceptance in administering drugs in young and geriatric patients effectively.

Diltiazem hydrochloride is a calcium channel blocker is widely used in the management of angina pectoris and hypertension. It has short biological half life and low oral bioavailability. The biological half-life of diltiazem is 3- 4.5 hrs. It produces GIT disturbances such as nausea, vomiting, constipation and intestinal pseudo- obstruction.

Diltiazem is not completely absorbed on oral administration but due to extensive first pass effects its bioavailability decreases to 30-40%. So Diltiazem Hcl transdermal film is a suitable dosage form to avoid first pass effect and improving the bioavailability of the drug and expected to be safe with negligible side effects.

The design of transdermal film of Diltiazem Hydrochloride should be primarily aimed to achieve more predictable and increased bioavailability and improve patient compliance.

2.2 Plan of work

1) To carry out the Pre -formulation study for drug and excipient.
2) Formulation of transdermal film by suitable method.
3) Characterization of developed formulation by,
   - Physical evaluation
   - Film thickness
   - Folding endurance
   - Tensile strength
4) Weight variation
5) Drug content
6) Percentage of moisture content
7) Kinetic studies
8) Entrapment efficiency and In- vitro release pattern.
9) Stability studies as per ICH Guidelines.

3. Review of Literature

Rohit Tiwari*, Manish Jaimini, Shailender Mohan[1], Sanjay Sharma reviewed the patch may essentially can provide a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.

J. Ashok kumar et.al.[49] 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 article provides an overview of types of Transdermal patches, methods of preparation and its physicochemical methods of evaluation
Audumbar Digambar Mali.et.al[2]. 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. The TDDS review articles provide valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS. With the advancement in technology Pharma industries have

trendified all its resources. Earlier we use convectional dosage form but now we use novel drug delivery system. One of greatest innovation of novel drug delivery is transdermal patch. The advantage of transdermal drug delivery system is that it is painless technique of administration of drugs.

Shweta Srivastava*.et.al.[3] one of the most sophisticated and innovative approaches of drug deliveries. The transdermal drug delivery system has attracted considerate attention because of its many potential advantages, including better patient compliance, avoidance of gastrointestinal disturbances, hepatic first-pass metabolism and sustained delivery of drugs to provide steady plasma profiles, particularly for drugs with short half-lives, reduction in systemic side effects and enhanced therapeutic efficacy. This review article covers a brief outline of the transdermal drug delivery system.

Pawan Jalwal*et.al[4]. The administration of drugs by transdermal route offers the advantage of being relatively painless. The appeal of using the skin as a portal of drug entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the noninvasive nature of drug delivery. Delivery of drugs through the skin for systemic effect, called transdermal delivery was first used in 1981, when Ciba-Geigy marketed Transderm V (present day marketed as Transderm Scop) to prevent the nausea and vomiting associated with m.otion sickness. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation.

Md. Intakhab Alam.et.al.[5] 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, permeation enhancers, and various components of transdermal patches, types of transdermal patches, methods of preparation and its methods of evaluation This review article provides an overview of TDDS, its advantages over conventional dosage forms, drug delivery routes across human skin, permeation enhancers, and various components of transdermal patches, types of transdermal patches, methods of preparation and its methods of evaluation.

Nirav S Sheth, Rajan B Mistry[7], The polymers selected for sustaining the release of drug were polyvinylpyrrolidone, Hydroxypropylmethycellulose (HPMC) and Ethyl cellulose (EC). The patches were formulated using combination of polymers and propylene glycol as plasticizer. The physicochemical evaluation of the polymer matrices was performed for suitability. In vitro permeation studies were performed using rat abdominal skin as the permeating membrane in Franz diffusion cell. The result indicated that maximum release was obtained at 2% solution of EC. Optimized batch was evaluated for permeation enhancement through rat skin using natural permeation enhancer Eugenol and it was concluded that permeation enhancement through Eugenol was comparable to the commercially available permeation enhancer Dimethyl sulfoxide 1% (DMSO). All the films were found to be stable at 37ºC and 45ºC with respect to their physical parameters and drug.

Sandhu Premjeet et.al.[50] studied Characterization of transdermal patch to check it's quality, size, time of onset & duration, adhesive property, thickness, weight of patch, moisture of content, uniformity & cutaneous toxicological studies. The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future.

V.N.L. Sirisha et.al.[7] was developed a matrix-type transdermal therapeutic system containing drug propranolol hydrochloride with different ratios of hydrophobic (eudragit's) polymeric systems by the solvent evaporation technique by using 30 % Md. Intakhab Alamw/w of di-butyl phthalate to the polymer weight, incorporated as plasticizer.

Priyanka Kriplani et.al[40] 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.

Himabindu Peddapalli.et.[511]. Effect of permeation enhancers such as oleic acid was studied. The interference of the polymers was ruled out by Fourier transform infrared and ultraviolet-spectroscopic methods. In vitro release studies of buspirone HCL-loaded patches in phosphate buffer (pH, 7.4) were performed using a modified diffusion cell and showed first-order release rate. Skin studies for the transdermal patches were assessed and were found to be free of irritation. In vivo drug release studies had shown release up to 24 h with the release of 73.82% and it was correlated with in vitro studies. The patches were subjected to short-term stability studies and were found stable. Conclusion: It is concluded from the present studies that the transdermal patches.

Irfan newaz khana et.al[52]. The present study was designed to develop a suitable matrix type transdermal drug delivery system (TDDS) of Aceclofenac using blends of three different polymeric combinations of Polyvinyl pyrrolidine (PVP) and ethylcellulose (EC). Physical studies including moisture content, moisture uptake, flatness to study the stability of the formulations and in vitro dissolution of the experimental formulations were performed.

Amandeep Singh and Alka Bali[53] prepared formulations and were uniform in their physical characteristics with low water vapor absorption, moisture loss and water vapor transmission implying excellent quality and uniformity in patch characteristics. The patches were devoid of

hypersensitivity reactions on rat skin. The in-vitro and ex-vivo drug release studies for all the formulations showed that the first dose of the drug was released in 2.0-3.0 h and nearly complete release (94%) was achieved in 24 h.

Renuka Das et.al.[54] evaluated the transdermal patches of Cissus Quadrangularis extract. Cissus Quadrangularis Aquous extracts was prepared using Maceration method. The transdermal patch was prepared by the solvent evaporation method using hydroxy propyl methyl cellulose (HPMC E -15) in different concentrations Di butyl Phthalate and DMSO were used as plasticizers and permeation enhancer. The prepared transdermal patches were evaluated for their physiochemical characteristics such as physical appearance, weight uniformity, thickness, folding endurance; moisture content.

Lalita Chauhan, Saloni Vashisht et.al[49]. formulated and evaluated the Transdermal Drug Delivery System of an antidiabetic herbal drug and to increase the efficacy and to improve the patience compliance of the herbal medicine which can be achieved by developing alternative drug delivery system.

André Luís Morais Ruela.et.al.[55] In vitro and in vivo evaluations of these novel drug delivery systems are necessary to characterize their quality and efficacy. This review covers the most well-known methods for assessing the cutaneous absorption of drugs as an auxiliary tool for pharmaceutical formulation scientists in the design of drug delivery systems. In vitro methods as skin permeation assays using Franz-type diffusion cells, cutaneous retention and tape-stripping methods to study the cutaneous penetration of drugs, and in vivo evaluations as pre-clinical pharmacokinetic studies in animal models are discussed. Alternative approaches to cutaneous microdialysis are also covered. Recent advances in research on skin absorption of drugs and the effect of skin absorption enhancers, as investigated using confocal laser scanning microscopy, Raman confocal microscopy, and attenuated total reflectance Fourier-transform infrared spectroscopy, are reviewed

Amit Kumar Singh, Richa PandeyKuldeep Singh [56]evaluated for physicochemical parameter in vitro release and ex vivo permeation. Release of the drug from the films followed anomalous transport ($0.5 < n < 1$). Polymeric combination containing in ratio (ERS100: ERL: 2:1) (F 2) was considered as the best formulation with maximum drug release of 92% after 12 hrs. The flux of formulation F2 was found to be greater than the other formulations.

Pallavi Vadlamudi et.al.[57] prepared Glibenclamide transdermal patches and to studied the effect of different polymer combination and polymer ratios on physiochemical parameters including in-vitro drug release profile. Matrix type Glibenclamide transdermal patches were prepared using Ethyl Cellulose (EC) and Hydroxy propyl methyl cellulose (HPMC) in different ratios.

Beedha. Saraswathi et.al.[40] Transdermal patches of Tramadol HCl were prepared by solvent casting method using different polymers i.e. HPMCK4M, HPMCK15M, HPMCE5.Propyleneglycol was used as plasticizer and methanol was used to dissolve the drug. Water was used as solvent to dissolve the polymer. The prepared formulations were evaluated for drug content uniformity, *in vitro* diffusion study, thickness, tensile strength, moisture content, folding endurances etc. Amongst all formulation, formulation F3 had more desirable characteristic & shows 88.36% drug release in 12hr. Release kinetic can be described by Higuchi model with anomalous diffusion as a release mechanism.

4. Materials and Methods

4.1 Drug profile[29]

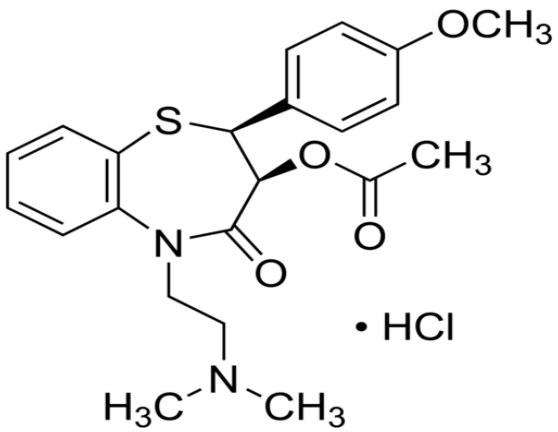

Figure 4: Structure of Diltiazem hydrochloride

IUPAC name:
-5-[2-(dimethylamino)ethyl]-2-(4- methoxyphenyl)-4-oxo-2, 3-dihydro-1, 5-benzothiazepin-3-yl] acetate;hydrochloride

Molecular formula: $C_{22}H_{27}ClN_2O_4S$

Molecular weight: 450 g/mol

Description: Calcium channel blocker, it works by relaxing blood vessels in the body and heart and lowers the heart rate.

Solubility: Soluble in water (50mg/ml), methanol, Formic acid.

pH: 3.6

Bioavailability: 44%

Protein binding: 80%- 90%

Metabolism: liver

Half-life: 3-4.5

Excretion: 35% in urine and 65% as bile

Mechanism of action: It has a role as a calcium channel blocker, a vasodilator agent and an antihypertensive agent.

Clinical use: used to prevent chest pain (angina). It may help to increase your ability to exercise and decrease how often you may get angina attacks.

Side effects: Dizziness, light headedness, weakness, nausea, upset stomach, flushing (warmth, redness, or tingly feeling), sore throat.

4.2 Excipient Profiles

4.2.1 Hydroxy propyl methylcellulose

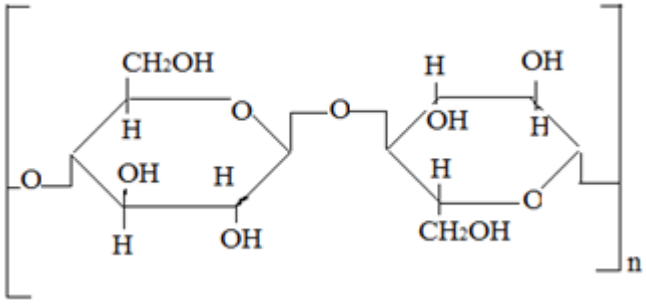

Figure 5: Structure of HPMC

Nonproprietary name
BP: Hypromellose
JP: Hydroxypropylcellulose
PhEur: Hypromellosum
USP: Hypromellose Hypromellose

Synonym
Benecel MHPC, Cellulose, hydroxypropylmethylether, methocel, methylcellulose propylene glycol ether, methylhydroxypropyl cellulose, metolose, Pharmacoat, HPMC.

Functional categories
Coating agent, film former, rate -controlling polymer for sustained release stabilizing agent, suspending agent, tablet binder, viscosity -increasing agent.

Description
Odorless and tasteless, white or creamy white, fibrous or granular powder.

Classification of HPMC
USP distinguishes four different type of HPMC
HPMC1828
HPMC2208
HPMC2906
HPMC2910

Table 1: Viscosity grades of HPMC

Grades	type	Viscosity
Low viscosity grades	Methocel E5	5
	Methocel E15	15
	Methocel E 50 LV	50
	Methocel K100LV	100
Medium viscosity	Methocel E4 M	4000
	Methocel K4M	4000
High viscosity grade	HPMC K 15M	15000
	HPMC K 100 M	100000

Table 2: Typical Properties of HPMC

Chemical name	Cellulose Hydroxypropyl methyl ether
CAS registry no.	[9004-65-3]
Empirical Formula	$C_8H_{15}O_8$-($C_{10}H_{18}O_6$)n-$C_8H_{15}O_8$
Appearance	White or creamy white
Molecular weight	Approximately 10000-15000
Particle size	40 -60
Melting point	Browns at 190-200^{0}C
Acidity /alkanity	5.5 -8.0 for 1%w/w aqueous solution
True density	1.326g/cm^3
Bulk density	0.341g/cm^3
Tapped density	0.557g/cm^3
Angle of repose	39-46^0
Glass transition temperature	170-180^0
Degradation temperature	280-300^{0}C
Auto ignition temperature	360^{0}C
Loss on drying	Not more than 5%
pH	5.5-8.0
Specific gravity	1.26

Solubility
Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol and other organic solvents.

Moisture content
Hypermellose absorbs moisture from the atmosphere ; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Stability and storage condition
Hypermellose powder is a stable material, although it is hygroscopic after drying.Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypermellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 50-90^{0}C, depending upon the grade and concentration of material.

Incompatibilities
Hypermellose is incompatible with some oxidizing agents, since it is non -ionic hypermellose will not complex with metallic salt or ionic organics to form insoluble precipitates.

Safety
HPMC is widely used as an excipient in oral and topical pharmaceutical formulation. It is used extensively in cosmetics and food products.

Regulatory status
GRAS listed. Accepted as a food additive in Europe. Included in the FDA inactive ingredients guide (ophthalmic preparations, oral capsules, suspensions syrup and tablets, topical and vaginal preparations) included in non-parentral medicines liscensed in UK.

Applications
Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.
1) In oral products it is used as tablet binding and film coating.
2) In the case of extended release formulation of tablets it is used in concentration between 2% and 5%w/w as binder either in wet or dry granulation process.

3) High viscosity grades may be used to retard the release of drug from the matrix at levels of 10-80%w/w in tablet and capsules.
4) depending upon the viscosity grade concentration of 2-20%w/w are used for film forming solution to film coat tablets.

Lower viscosity grades are used in aqueous film coating solution, while higher viscosity grades are used with organic solvents
Hypermellose is used as suspending and thickening agent in topical formulations.

Compared with methylcellulose, hyperomellose produces aqueous solution of greater clarity, fewer undispersed fibres present, and in therefore preferred in formulations for ophthalmic use.

Hypermellose at concentrations between 0.45-1.0%w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

4.2.2 PVP[30]
Polyvinyl pyrrolidine

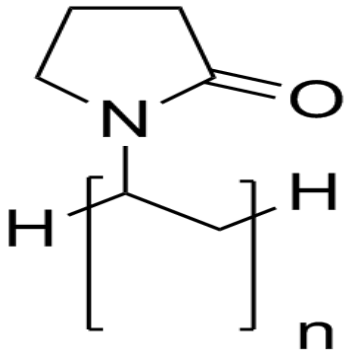

Figure 6: Structure of PVP
IUPAC name: 1-ethenylpyrrolidin-2-one
Synonym: polyvidone or povidone
Molar mass: 2, 500-2, 500, 000 g·mol^{-1}
Chemical formula: ($C_6H_9NO)_n$
Melting point : 150 to 180 °C
Appearance: white to light yellow, hygroscopic, amorphous powder
CAS Registry No. 9003-39-8
Functional categories: Emulsifier, disintegrant, binder, thickening agent.
Solubility: PVP is soluble in water and other polar solvents.
pH: 3-5
Stability and storage: Stable. Incompatible with strong oxidizing agents. Light sensitive, Hygroscopic.

Safety
Povidone is commonly used in conjunction with other chemicals. Some of these, such as iodine, are blamed for allergic responses, although testing results in some patients show no signs of allergy to the suspect chemical. Allergies attributed to these other chemicals may possibly be caused by the PVP instead.

Applications
PVP added to iodine forms a complex called povidone-iodine that possesses disinfectant properties.
PVP is used as a lubricant in some eye drops.
PVP was used as a plasma volume expander for trauma victims after the 1950s.

4.4 Instruments/ Equipments Used

Table 3: List of instrument /equipments used

Name of the equipment	Name of the supplier
Digital weighing balance	Infra digit
Screw gauge	Dollar
pH meter	Elicopvt Ltd Hyderabad
Tensile strength equipment	Fabricated
Mechanical stirrer	Rotek laboratory Instruments
Dissolution test apparatus	Electrolab, Bangalore
Double beam UV spectrometer	Systronics
FTIR	Jasco model FT/IR4100

4.5 Experimental Work

4.5. Pre formulation study
Pre formulation testing was an investigation of physical and chemical properties of drug substance alone. It is the first step in rational development of dosage form.

4.5.1. Identification of drug
The melting point of diltiazem Hydrochloride was determined by capillary fusion method. A capillary was sealed at one end filled with small amount of diltiazem Hydrochloride and the capillary was kept inverted that is sealed end towards into the melting point apparatus.

4.5.2 Physicochemical properties
Organoleptic properties
The organoleptic properties include the colour, odour and feel of the drug and all other excipients used in the formulation.

Solubility
The solubility of diltiazem Hydrochloride was determined by adding small amount of diltiazem hydrochloride in 5ml of different solvents in a beaker and was shaken well. The solutions were examined physically for the absence or presence of diltiazem Hydrochloride.

4.5.3 Analytical method
Determination of λmax of diltiazem Hydrochloride
UV absorption spectrum of Diltiazem drug sample in phosphate buffer pH 7.4 shows maximum at 237 nm specified in the range of 220 to 280 nm. Thus 237 were found to be in specification of drug. So further selected as λ_{max} diltiazem Hydrochloride.

Preparation of calibration curve
The present analytical method obeyed Beer's law in the concentration range 2-10 µg/ml and is suitable for the estimation of Diltiazem from different solutions. The correlation coefficient (r) was found to be 0.9993, indicating a positive correlation between the concentration of Diltiazem and corresponding absorbance values.

4.5.4Drug excipient compatibility studies
While designing the formulation of a transdermal films, it is important to give consideration on drug polymer interaction

within the system. So it is necessary to find out that if there is any interaction between diltiazem Hydrochloride and polymers used in the formulation. The study was conducted using fourier Transform Infrared Spectroscopy (FTIR).

The physical mixtures of the samples were subjected to experimental condition (40-+50 and 75-+5%RH) for 4 weeks. The physical changes like discoloration, liquefaction and clumping of material were observed after regular interval of a week. The infrared absorption spectra of 4 week aged physical mixture are run between 400-500cm$^{-1.}$

4.6 Formulation of transdermal film of Diltiazem Hydrochloride

Solvent casting method

The transdermal patches were prepared by solvent casting method. Different polymers (HPMC and PVP) alone and in combination were accurately weighed and dissolved in 20 ml of solvent known volume of Polyethylene glycol was used as plasticizer and tween 80 is used as penetration enhancer and mixed thoroughly with help of magnetic stirrer. 10mg of drug dissolved in the solution and mixed for 10 minutes. The resulted uniform solution was poured into Petri dish and kept for the evaporation after 24 hrs a dried film was out and stored in desiccators.

4.7 Experimental Design

Seven formulations namely F1 to F7 were prepared with 2 different polymer HPMC & PVP effect on drug action.

Table 3: Experimental design

Ingredients	Formulation Code						
	F1	F2	F3	F4	F5	F6	F7
Diltiazem Hydrochloride	10mg	10mg	10mg	10mg	10mg	10mg	10mg
HPMC(mg)	250	-	250	200	150	100	300
PVP(mg)	-	250	100	150	200	250	300
PEG (%)	36	36	36	36	36	36	36
Tween 80(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Chloroform	1:1						
Methanol							

4.9 Evaluation of transdermal films

4.9.1 Visual inspection of film and film formulation

The prepared films were evaluated visually for its clarity, transparency and stickiness. If it is satisfactory, then it was taken for further evaluation. If formed films were not satisfactory they are discarded.

4.9.2 Thickness[43]

The thickness of the film was measured using micrometer screw gauge with least count 0.01mm at three different locations of the film. The thickness is measured and the average was taken and the standard deviation was calculated.

4.9.3 Weight variation[43]

This test ensures that the uniformity of the formed films. From the whole film three small film of area 4cm^2(2cm*2cm) were taken and are weighed individually and the standard deviation from the value was calculated.

4.9.4 Folding endurance[42]

Folding endurance of the prepared films was determined by repeatedly folding a small strip (2cm*2cm) until the film is broken. The number of times the film could be folded at the same place without breaking gives the folding endurance value.

4.9.5 Determination of Tensile strength[44]

Tensile strength is determined as stretching force applied to the sample at which point it breaks. These measurements were performed on a dumb well shaped specimen. A specified weight was hung from the film through the specimen such that a pulling force was created the force applied on the load cell of the apparatus was measured in kg/cm^2.

Tensile strength can be calculated by formula

$$\text{Tensile strength} = \frac{[\text{break force}]\ [1+\Delta]}{a \times b\ L}$$

Where a is the thickness of the patch
b Is the width of the patch.
Δ L is the length of elongation
L is the length of the film.

Figure 6: Tensile strength apparatus

4.8.6 Percentage of moisture content[31]

The films are weighed accurately and placed in a dessicator containing 100ml of saturated solution of aluminium chloride, which maintains 79.50% RH. After three days, the films were taken out and weighed.

$$\text{Percentage of moisture content} = \frac{\text{Final weight-initial weight}}{\text{Initial weight}} \times 100$$

4.8.7 Drug content

The films (1.5 cm^2) were cut and added to a beaker containing 100 ml of phosphate buffer saline of pH 7.4. The medium was stirred with magnetic stirrer for 6 hrs. Then, 1ml sample pipette out and diluted up to 10ml with phosphate buffer pH 7.4. The resulting solution was filtered

through 0.45 µm What man filter paper. The drug content was determined at 237 nm using U.V spectrometer.

4.8.8 Preparation of phosphate buffer pH 6.8[37]
Dissolve 2.38 g of disodium hydrogen orthophosphate, 0.19g of potassium hydrogen phosphate and 8g of Nacl in sufficient water to produce 1000ml and adjust the ph if necessary (I.P -2010).

4.8.9 In -vitro Drug release studies[34]
The fabricated film was placed on the semi permeable membrane and attached to the modified diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 6.8at 37±1^{0}C. The elution medium was stirred magnetically. The aliquots (5ml) were withdrawn at predetermined time interval and replaced with the same volume of phosphate buffer of pH 6.8. The sample were analyzed for the drug content using UV spectrophotometer at 237 nm.

4.8.10 Kinetics of drug release[38]
To examine the drug release kinetics and mechanism, the cumulative release data were fitted to model representing zero order, First -order, Higuchi's square root of time and koresemeyer Peppas double log plot respectively, where Q is the cumulative percentage of drug released at time and cumulative percentage of drug after time t.

4.8.11. Stability studies[33]
The purpose of stability is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. One formulation was selected for stability studies on the basis of physiochemical characteristics, in vitro drug release of the formulations. The formulation was subjected to accelerated stability studies as per ICH guidelines. The most satisfactory formulation was sealed in an aluminum foil and stored at 30±2^{0}C, 65±5% RH and 75±5% RH for 6 months. Patches were periodically removed and evaluated.

5. Results

5.1 Pre formulation studies

Identification of drug

The identification is done by determining the melting and by performing FTIR Studies.

Determination of melting point

The temperature at which the solid changes to liquid was noted and it is found to be 212±0.0054 ^{o}C.

5.1.2. Physicochemical properties

Table 4: Organoleptic properties of Diltiazem Hydrochloride

Physical appearance	Powder
Colour	White
Odour	Odorless
Feel	Non-sticky

Table 5: Solubility profile of Diltiazem Hydrochloride

Solvent	Solubility
Methanol	Practically soluble
Chloroform	Practically soluble
Water	Soluble in water
Ether	Practically insoluble

5.1.3 Determination of ƛ max of Diltiazem Hydrochloride
The absorption maximum of Diltiazem Hydrochloride was found to be 237 and is shown in figure.no.8

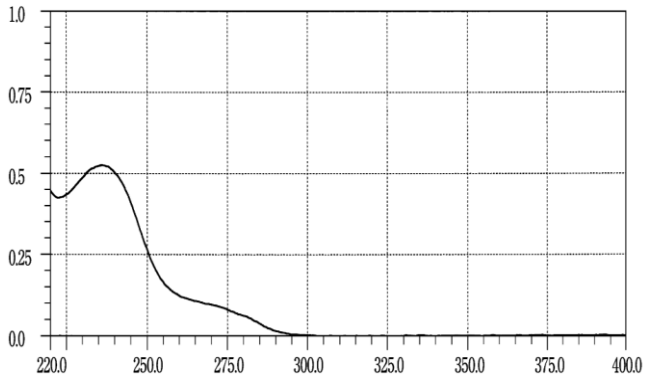

Figure 8: Absorption spectra of diltiazem Hcl

5.1.4 Calibration curve of Diltiazem Hydrochloride in phosphate buffer

The prepared aliquots 2, 4, 6, 8, 10µg/ml were scanned in phosphate buffer at pH 6.8. The absorbance of the above concentration is shown in table no.6. The above curve was found to be linear and solutions obeyed beers lambert's law in above concentration range. The standard plot of Diltiazem Hydrochloride is shown below in figure.9.

Table 6: Calibration curve of Dilitiazem Hydrochloride

Concentration (ug/ml)	Absorbance at 237nm
2	0.125± 0.012
4	0.221± 0.131
6	0.328±0.150
8	0.426±0.0142
10	0.529±0.0112

All values are expressed as mean ± SD, n = 3.

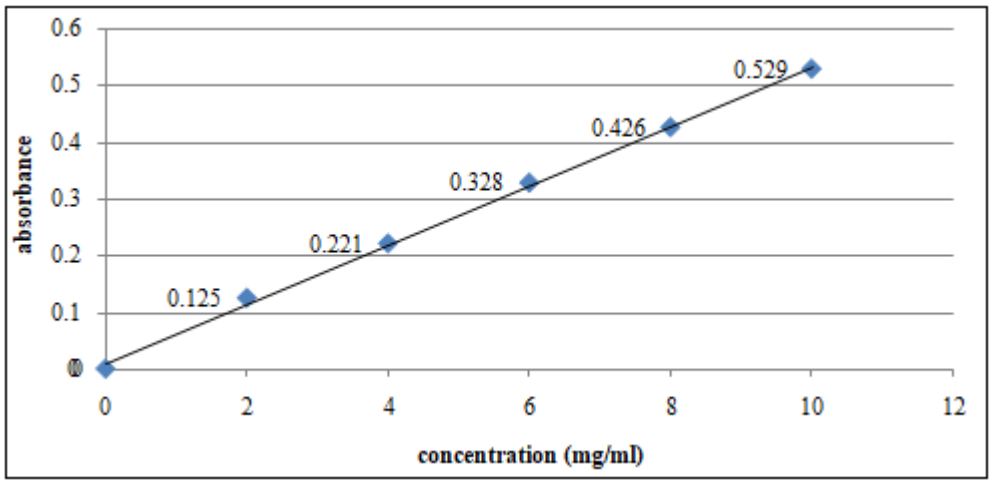

Figure 9: Caliberation curve of dilitazem hydrochloride

Compatibility Studies

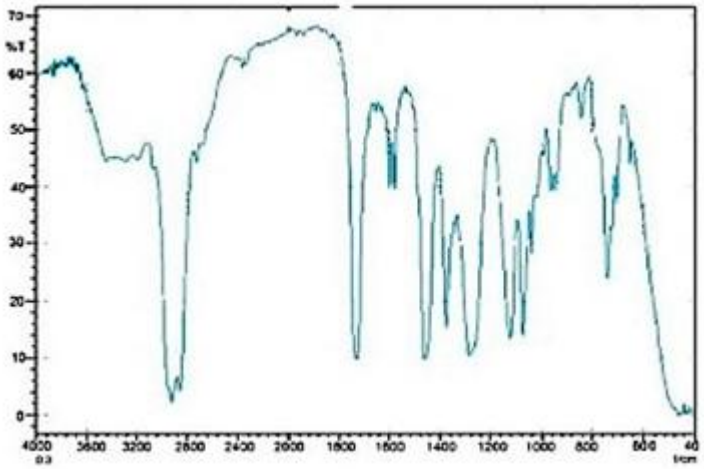

Figure 10: FTIR of HPMC Studies

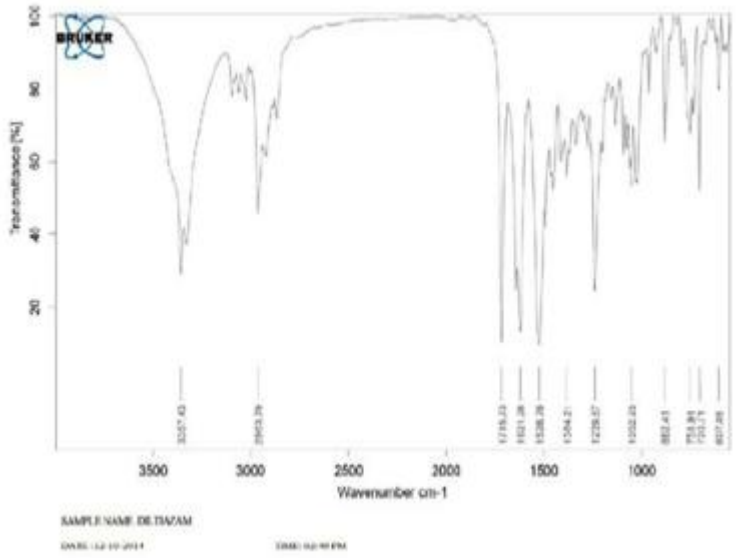

Figure 12: FTIR of Diltiazem Hcl+HPMC+PVP

Table 7: Peaks of FTIR

Peak	Groups
3357.43	N-H stretch
2963.79	CH-stretch
1621.96	C=C stretch
1052.93	C-N stretch

Compatibility studies are performed using FTIR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and the polymer were studied. The characteristic absorption peaks of diltiazem Hydrochloride were obtained at different wave numbers in different samples.

From the FTIR spectra of the drug and polymers it is found that, no major difference was seen in the characteristic absorption peaks of pure drug.

5.2 Evaluation of transdermal patch

Seven formulation (F1 to F7) were prepared from diltiazem Hydrochloride by solvent casting method. The prepared films were evaluated for the visual inspection, surface pH, Folding endurance, tensile strength, drug content and uniformity, in vitro disintegration time and in vitro dissolution time.

5.2.1Visual inspection of the formulation

The prepared Transdermal patch was evaluated visually and for their patch forming property. The result is shown in the table

Table 8: Visual inspection of the formulation

Formulation Code	Appearance	Stickiness
F1	Transparent, brittle	Non sticky
F2	Semitransparent, tough	Sticky
F3	Transparent, flexible	Non sticky
F4	Semitransparent,, flexible	Sticky
F5	Transparent, tough	Non sticky
F6	Transparent,, flexible	Non sticky
F7	Transparent, tough	Non sticky

From the visual studies it was found that as the concentration of polymer increases the flexibility decreases. Film with low concentration of polymer are sticky and brittle in nature. The films with optimum concentration of polymer were found have good, flexible patch forming property.

5.2.2. Surface pH of the patch

The surface pH of the patch prepared from Diltiazem Hydrochloride was determined in order to investigate the possibility of any side effects in vivo.

The pH of the formulation are shown in table 9 and figure.13

Table 9: Surface pH of the formulation

Formulations	pH value
F1	6.3±0.1528
F2	6.3+ 0.1330
F3	6.7±0.0577
F4	6.5±0.1534
F5	6.6±0.1000
F6	6.53 ±0.1155
F7	6.47 ±0.1155

All values are mean± SD, n=3.

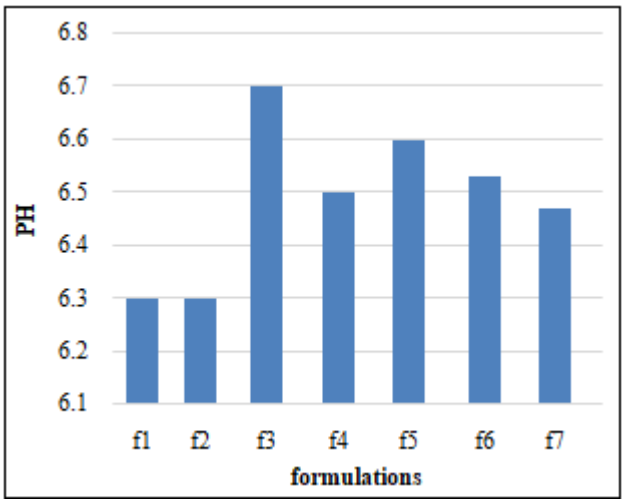

Figure 14: Surface pH value of formulation

5.2.3 Folding Endurance

The folding Endurance of the patches was done. The folding Endurance was found to be in the range of 98.66±4.041 to 140±2.642 for the patches prepared from HPMC and PVP. The folding endurance of prepared patches are shown in the table 10.

Table 10: Folding endurance of formulation

Formulation	Folding Endurance
F1	105±0.332
F2	98.66±4.041
F3	102±2.443
F4	114±4.556
F5	105±4.996
F6	125±4.099
F7	140±2.642

Value are mean± SD, n=3.

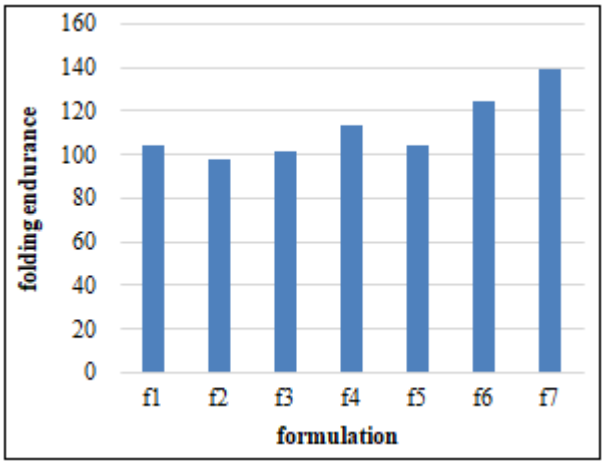

Figure 15: Folding endurance of formulation

5.2.4 Weight Variation

The weight variation test was performed on the selected samples were found to be in the range of 6.17 ± 0.008 to 7.213 ±0.008 for HPMC and PVP containing patches. The weight variations of films are tabulated in table no.11.

Table 11: Weight variation of formulation

Formulation	Weight variation
F1	6.17 ± 0.008
F2	6.172 ± 0.007
F3	7.152 ± 0.005
F4	6.181± 0.006
F5	7.152 ± 0.005
F6	7.12 ± 0.009
F7	7.213 ±0.008

All values are expressed as mean ± SD, n=3.

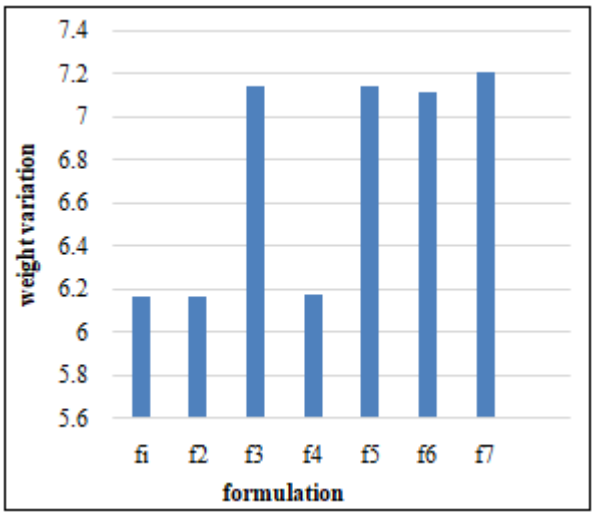

Figure 16: Weight variation of formulation

5.2.5 Film thickness of patch

The Thickness of the patch was evaluated. The thickness of the patches was found to be in the range between 0.050 ± 0.0037 to 0.056 ± 0.0036mm for HPMC and PVP containing patches. The thicknesses of the patches are shown in table 12.

Table 12: Film thickness of patch

Formulation	Thickness Of Patch
F1	0.050 ± 0.0037
F2	0.037 ± 0.0038
F3	0.045 ± 0.0039
F4	0.050 ± 0.0038
F5	0.050 ± 0.0039
F6	0.056 ± 0.0036
F7	0.054± 0.035

All values are expressed as mean ± SD, n=3.

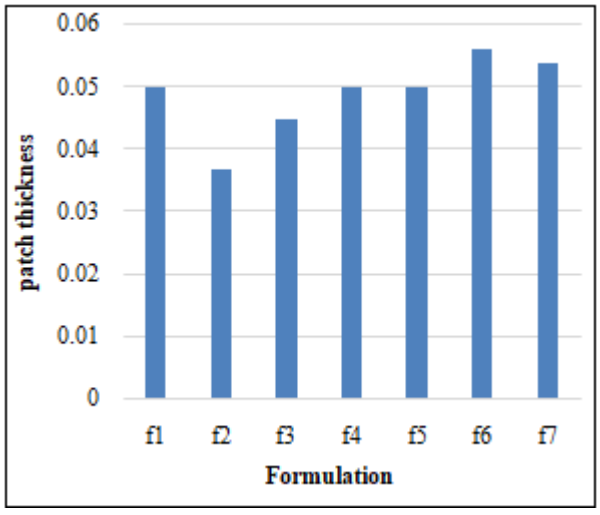

Figure 17: Film thickness of formulation

5.2.6 Tensile strength

Tensile strength of the prepared formulations was determined. Tensile strength of the patches found to lie between 0.285 ± 0.20 to 0.326 ± 0.10 for HPMC and PVP patches. Tensile Strength is found to increase with increase in concentration of polymer.

Table 13: Tensile strength of formulation

Formulation code	Tensile strength
F1	0.294 ± 0.14
F2	0.285 ± 0.20
F3	0.285 ± 0.20
F4	0.293 ± 0.16
F5	0.311 ± 0.120
F6	0.315 ± 0.23
F7	0.326 ± 0.10

All mean values are expressed as mean ± SD, n=3.

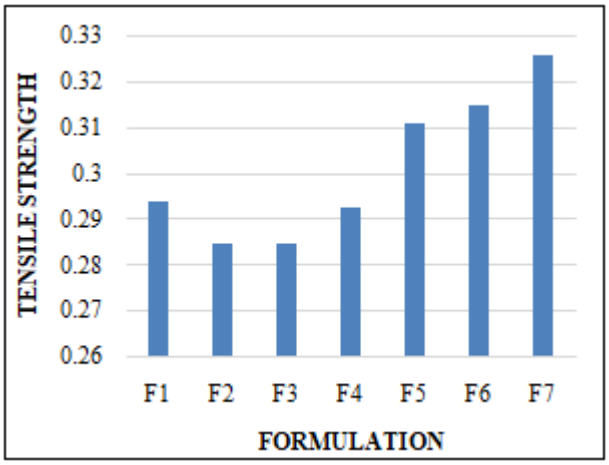

Figure no. 18. Tensile strength of formulation

5.2.7 Drug content and Uniformity Test

Drug content uniformity test was done on the prepared patches to ensure that the drug has been distributed uniformly throughout the transdermal patch. The drug content of the patch was found to be 74.3±0.007 to 94.3±0.028% shown in the table no.14.

Table 14: Drug content of formulation

Formulation	Drug Content
F1	90.2 ±0.006
F2	74.3±0.007
F3	94.3±0.028
F4	86.66±0.090
F5	75.09±0.010
F6	80.6±0.007
F7	89.7±0.009

All mean values are expressed as mean ± SD, n=3.

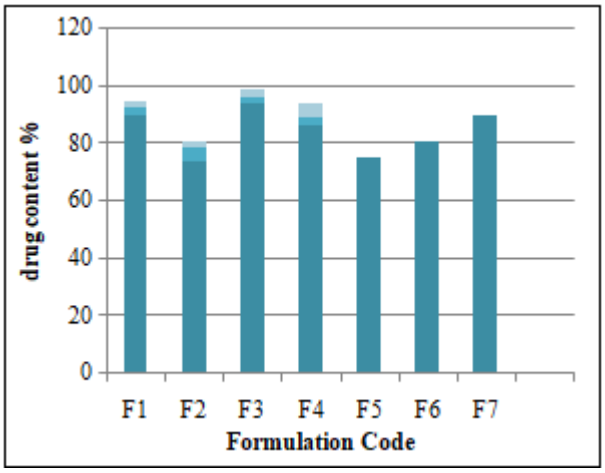

Figure 19: Drug content of formulation

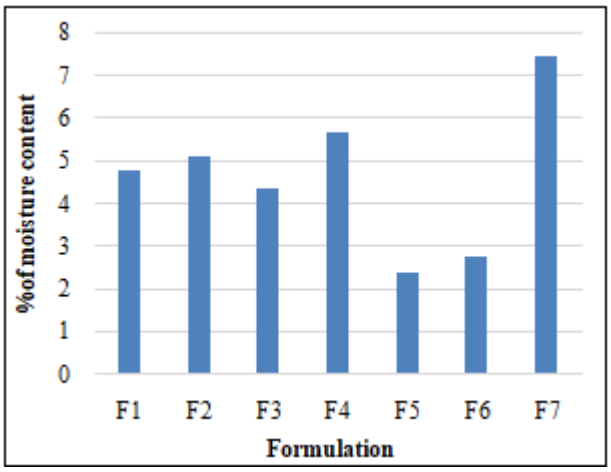

Figure 20: Percentage of moisture content

5.2.8. Percentage of moisture content

Percentage of moisture content was evaluated. The percentage of moisture content range lies between 3.38± 0.008 to 5.47± 0.068% for patches containing HPMC and PVP. The % of moisture content increases with increase in concentration.

Table 15: Percentage of moisture content

Formulation	% Moisture Content
F1	4.8±0.009
F2	5.15 ± 0.010
F3	4.39 ± 0.004
F4	4.69± 0.002
F5	3.38± 0.008
F6	3.78± 0.006
F7	5.47± 0.068

All mean values are expressed as mean ± SD, n=3.

5.2.9 In- vitro drug release study

The In-vitro drug release study was done for 24 hours. F3 formulation showed highest In-vitro drug release of 99%. The In vitro drug release was shown in figure no.21.

Table 16: In- vitro drug release study

Cumulative percentage of drug release

Time (HRS)	F1	F2	F3	F4	F5	F6	F7
1	18.9	20	20.3	21.2	25.45	26.7	30.31
2	20.78	21.3	40.65	25.6	42.15	28	38.09
3	24.5	25.7	50.68	28.9	48.46	34.5	39.78
4	26.8	26.1	57.13	30.8	50.56	38.3	48.09
5	27.8	28.2	62.15	35.8	58.79	40.5	58.9
6	30.89	34.37	69.28	42.3	59.22	46.8	60.98
7	35.9	36.45	71.56	46.9	62.88	48.09	63.89
8	38.89	40.85	76.21	50.89	70.22	50.2	72.91
9	40.89	42.8	85.07	60.8	72.88	52.9	75.56
10	44.78	45.6	97.07	70.8	76.22	56.8	77.68
11	51.2	48.9	98.93	72.9	78.12	60.8	83.61
12	58.89	54.3	98.95	76.8	85.91	78.6	92.37
24	70	57	99.0	78	88.92	82.15	95.0

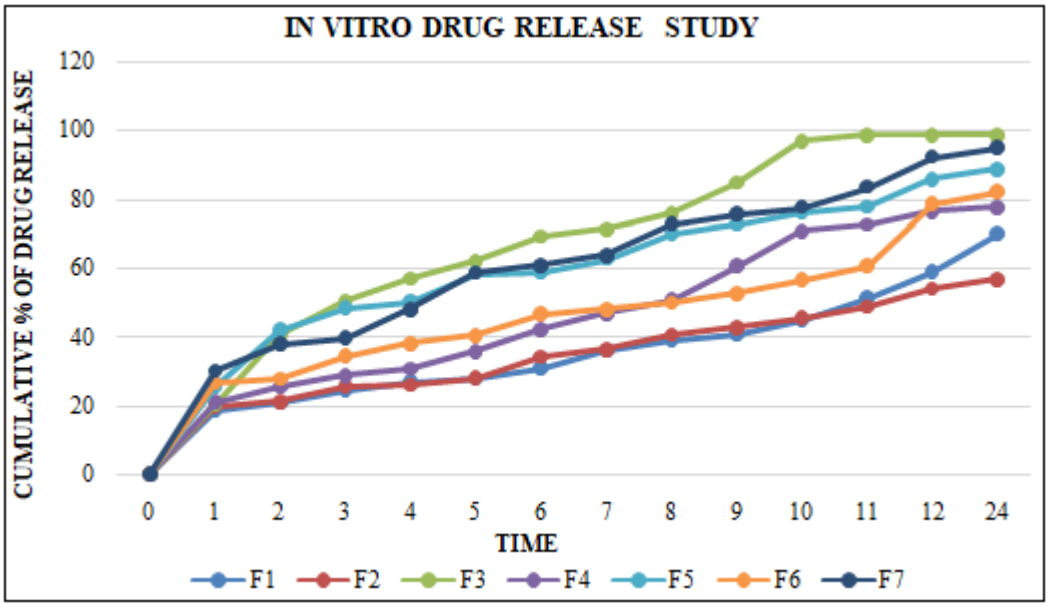

Figure 21: In vitro drug release study of formulation

5.2.10. Kinetic studies

For analyzing the mechanism of drug release kinetic of the patch F3, the data obtained were fitted to various kinetic equation of zero order, first order, Higuchi model and Koresmeyer Peppas model. The regression coefficient was calculated. Graphs of kinetic models were plotted with suitable data as shown in figure no.22-25.

Table 17: Zero order release model

Time (hours)	Cumulative % drug release
0	0
1	20.3
2	40.65
3	50.65
4	57.18
5	62.15
6	69.28
7	71.56
8	76.21
9	85.07
10	97.07
11	98.93

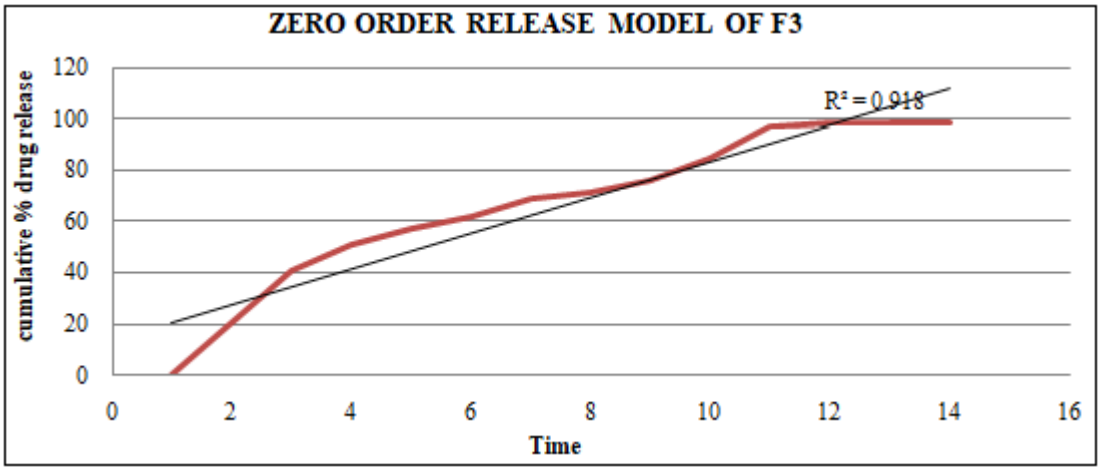

Figure 22: Zero order drug release of patch

First Order Release Model

A plot time Vs Cumulative percentage of drug release

Table 18: First order model drug release

Time in hours	Log of cumulative %drug release
0	0
1	1.3074
2	1.6090
3	1.704
4	1.756
5	1.793
6	1.840
7	1.854
8	1.882
9	1.929
10	1.987
11	1.995

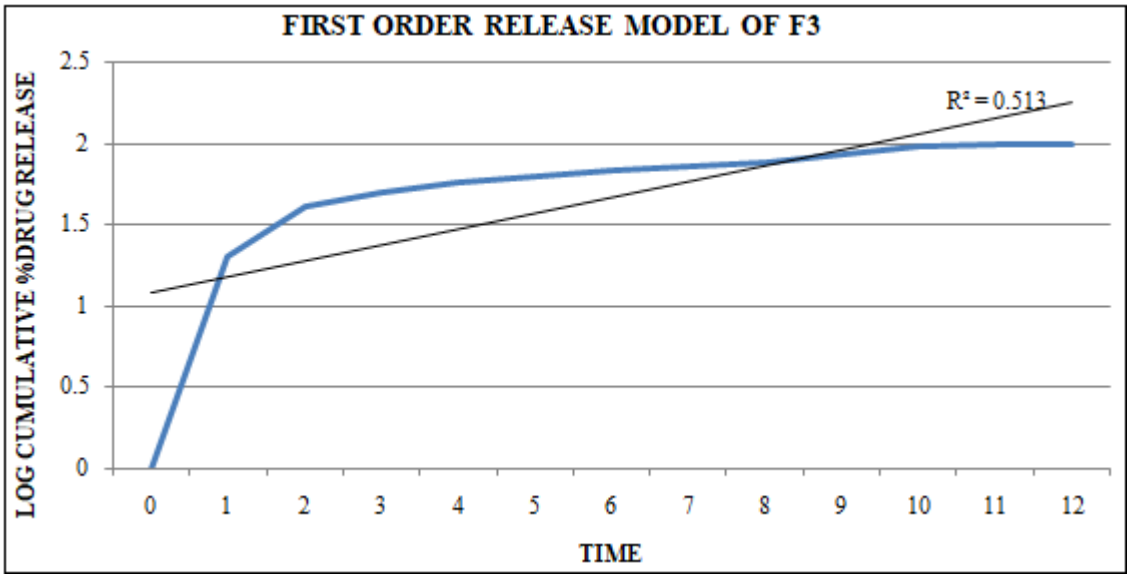

Figure 23: First order release model of F3 formulation

Higuchi release model

A plot on square root of time Vs Cumulative percentage of drug release

Table 19: Higuchi release model

Square root of time in hrs	% Cumulative Drug Release
0	0
1	20.3
1.414	40.65
1.732	50.68
2.0	57.13
2.236	62.15
2.449	69.28
2.645	71.56
2.828	76.21
3.16	85.07
3.46	97.07

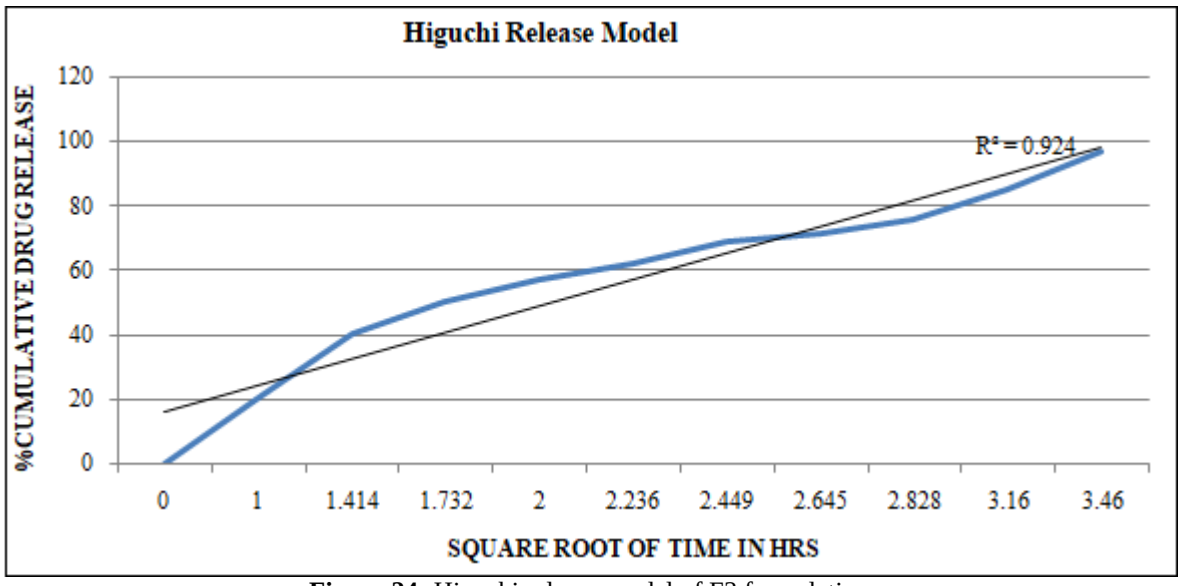

Figure 24: Higuchi release model of F3 formulation

Koresmeyer-peppas model

A plot on log time Vs log cumulative percentage drug release

Table 20: Koresmeyer-peppas model of f3 formulation

Log time	Log % cumulative drug release
0	0
0	1.3074
0.301	1.6090
0.4771	1.704
0.6020	1.756
0.698	1.793
0.778	1.840
0.845	1.854
0.903	1.882
1.000	1.929
1.079	1.987

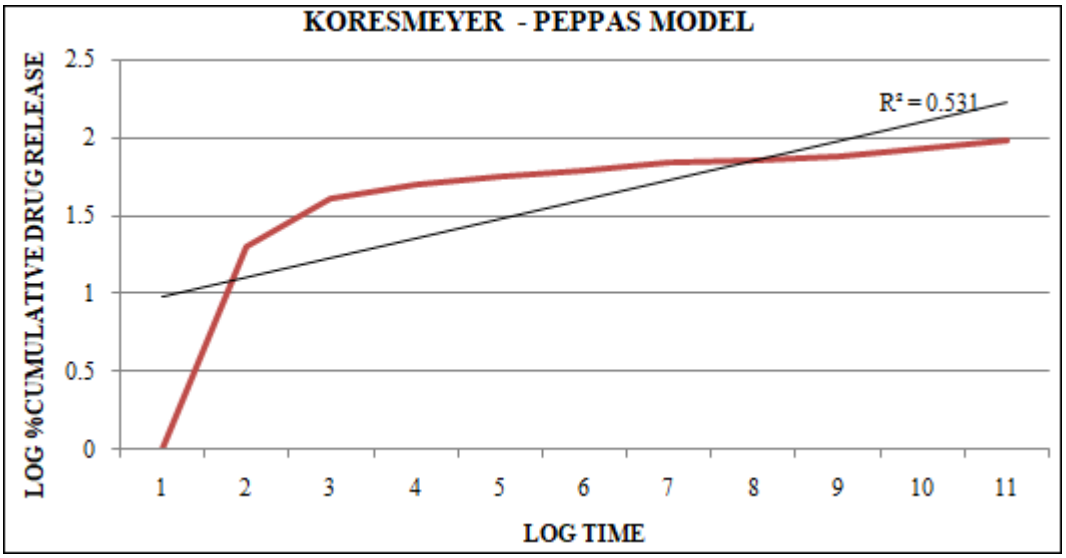

Figure 25: Koresmeyer peppas model of patch

Table 21: Data regression coefficient of different kinetic models

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer - peppas (R^2)
F3	0.918	0.513	0.924	0.531

5.4 Stability studies

From in vitro release studies of prepared formulation of transdermal patch. The best formulation F3was selected for the stability studies.

Table 22: Stability studies

Parameters studied	Initial			1 month			3 month		
	R.T	40 °C*	4°C**	R.T	40°C*	4°C**	R.T	40°C*	4°C**
Appearance	Smooth and elegant	Smooth and elegant	Smooth and elegant	Smooth and elegant	Smooth and elegant	Smooth and elegant	Smooth and elegant	Smooth and elegant	Smooth and elegant
pH	5.1	5.3	4.9	5	5.2	4.8	4.9	5.1	4.7
Drug content	95%	95%	94.5%	94.5%	94.3%	93.5%	93.8%	93.5%	93.0%
Disintegration Time	10sec	13sec	14sec	12sec	14sec	15sec	13sec	15sec	16sec

RT -Room temperature:30±2°C; RH-60±5%.*-Temp-40±2°C;RH-70±5%,
** -Refrigerated temperature.

6. Discussion

6.1.1 Identification of the drug

The identification of the drug was done by performing the melting point and FTIR studies. From the result obtained the melting point is found to be 212±0.0054 degree Celsius which complies with the official standards indicating the purity of sample.

6.1.2 Physicochemical Properties

Organoleptic and solubility studies were carried out and results obtained indicate that both the parameters of the drug comply with pharmacopeal standards.

6.1.3 Analytic Methods

Determination of ƛ max of Diltiazem Hydrochloride. The drug was scanned in UV spectrophotometer for determining the absorption maxima ƛmax was found to be 237 nm. The

standard caliberation curve of Diltiazem Hydrochloride was developed at this wavelength.

Caliberation curve of Diltiazem Hcl was determined at pH at 6.8 at 237 nm by plotting absorbance against concentration. The caliberation curve is shown in figure no.9 was found to be linear between 1-6µg/ml and obey s beer-lambert s law. The calculation of drug content uniformity, in vitro drug release and stability studies were based on standard graph.

6.1.4 Drug Excipient Compatibility Studies

The FTIR spectra of the drug and polymer showed that no interaction had taken place between the drug and polymer. Hence there is no interaction between drug and the polymer.

6.2 Evaluation of the Formulation

6.2.1 Visual inspection of the patch

The visual inspection of the prepared patch was done. From the visual inspection studies it was found that films in low concentration of polymer were brittle in nature and was also non-sticky.

6.2.3 Surface pH of the Transdermal patch

The surface pH's of the patch from Diltiazem Hcl was determined in order to investigate the possibility of any side effects in vivo. The pH is of the film were found to be in the range between 6.3±0.1528 to 6.7±0.0577. Since the pH's of the films was around neutral pH, there will not be any kind of irritation on the outer skin.

6.2.4 Weight variation

The weight variation test was performed on the selected samples. The weight variations of the sample were found to be in the range from 6.17 ±0.007 to7.213± 0.008. It was observed that slight increase in the weight of films was due to increase in concentration of the polymer indicating that as the concentration of the polymer increases, the weight of the film increases.

6.2.5 Folding endurance

The folding endurance was performed. The folding endurance of the patch was found to be in the range 98.66±4.041 to 140± 2.642 for patch prepared PVP and HPMC the folding endurance was found to increase with increase in concentration of polymer.

6.2.6 Tensile strength

Tensile strength was performed on the formulations. The tensile strength of the prepared patch was found to be increase with increase in concentration. 0.054±0.0036 for F7 formulation containing patch. Tensile strength was found to increase in increase in concentration of polymer.

6.2.7 Drug content and uniformity test

Drug content uniformity test was done on the prepared patches to ensure drug has been distributed uniformly throughout the transdermal patch. Homogenous distribution of drug is an important characteristic for transdermal patch that ensures the uniform reproducible release of drug from the film. Drug content of the film with all polymers was found to be in the range of 74.3±0.028 to 94.3 ±0.007. Film containing films estimation of drug content indicated that drug is uniformly distributed throughout the patch for most of the patch evidenced by the low value of standard deviation.

6.2.8 In vitro dissolution study

In vitro dissolution studies was conducted on formulations F1 to F7 using USP apparatus -II(paddle) using pH 6.8 phosphate buffer as dissolution medium. The volume of buffer used was 500ml. For the entire polymer used in the formulation, it was observed that the drug release was found to decrease with increase in concentration of polymer. It indicates that increase in level of polymer, result in formation of high viscous gel layer caused by more intimate contact between the particles of polymers resulting in decreased mobility of drug particles in a swollen matrix, finally leading to decreased release rate.

The patch prepared from HPMC was found to release more quickly than patch prepared by PVP.

6.2.9. Stability studies

F3 formulation was evaluated for the stability studies which was stored at 3 different temperature condition ie, at room temperature (30±2C), 40+2C/75% and refrigerated temperature; 4C for three months. For the evaluation, it is found that there is no significant change in appearance pH, folding endurance, Drug content and percentage of drug release.

6.2.10. % of moisture content

Moisture content was performed on the formulation. The % of moisture content is ranging from 3.38±0.008 to 5.47±0.068. % of moisture content increases with increase in concentration of patch.

6.2.11. Entrapment efficacy and in vitro release patch

The *in vitro* drug release of F1 was 70%, F2 was 57%, F3 was 99%, F4 was 78% F5 was 88.92%, F6 was 82.15% and F7 was found to be 95%. From the prepared seven formulations, F3 was selected as best formulation as it showed greater drug release (99%) than all other formulations. Hence the data obtained was fitted to various kinetic models and also stability studies were conducted on selected formulation as per ICH Guidelines.

7. Summary

Transdermal patches were prepared from Diltiazem Hcl using HPMC and PVP as polymer, PEG as plasticizer and tween 80 is used as penetration enhancer and solvent used were chloroform and methanol in 1:1 ratio by solvent casting method. From the pre formulation studies conducted, it was found that no interaction between drug and the excipients from the FTIR studies. The prepared film F1 to F7 were then evaluated for their visual appearance and thickness, folding endurance, tensile strength, pH stability, drug content uniformity, in vitro disintegration time and percentage drug release.

From the evaluation it was found that the film prepared from HPMC and PVP were semitransparent and flexible than films from PVP was transparent and less flexible than films from HPMC. It was seen concentration that when the

concentration of polymer increases the flexibility of the film decreases leading to the formation of tough films.

The thickness of the patch was found to increase with increase in concentration of patch forming polymer in the patch. The patches prepared from PVP were found to have more thickness than film prepared from HPMC with same concentration of polymer. Tensile strength of the patches was found to increase with increase in concentration of polymer.

The tensile strength was found to be maximum for patch containing higher concentration of polymer. The films prepared by PVP were found to have higher tensile strength than patch prepared from HPMC.

From the present work it is was found that the transdermal patch can be innovative and promising approach for the delivery of Diltiazem Hcl with improved bioavailability, enhanced dissolution.

8. Conclusion

Diltiazem Hcl transdermal patch was prepared by solvent casting method containing HPMC and PVP as polymers, tween 80 as penetration enhancer, methanol and chloroform used as solvent.

Formulation F3 showed suitable satisfactory physicochemical properties with melting point, tensile strength, folding endurance showing maximum in vitro release of 99%in 10 min.

From the present work it is concluded that the transdermal patch can be innovative and promising approach for the delivery of Diltiazem Hcl with improved bioavailability, enhanced dissolution rate.

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