Development and Evaluation of Irbesartan transdermal patches.

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Introduction

Transdermal drug delivery system is an advanced and non invasive system which facilitates the administration of therapeutics through the transdermal route as skin being the largest organ in the human body by mass covering an area between 1.5 to 2.0 sq.m in adults .These medicated patches are applied to the skin surface for treatment of superficial disorders or to treat and manage systemic ailments or are used as cosmetics.It is a polymeric drug delivery system containing drug either in a reservoir with a rate controlling membrane or dispersed in polymer matrix. Approximately 74% of drugs are administered orally and are not able to exhibit its desired action. In order to attain its desired action this system was emerged which differs from the traditional oral route by delivering the drugs systemically via skin.Hence this system has now become a great zone of interest and a highly researched field among various drug delivery systems.

The bypassing of first- pass metabolism and intermediate permeation properties make it even more attractive for drugs which are highly sensitive to enzymatic degradation and pH. This interest in novel routes of administration of drugs occurs from their ability of enhancing the bioavailability of drugs which is impaired by the narrow absorption window in the gastrointestinal tract.

Drug delivery through the transdermal route using offers such a novel route of drug administration. This route has been used successfully for the delivery of number of drugs.Moreover, transdermal drug delivery offers a safe and very easy method of drug utilization, because absorption of drug can be terminated very easily in cases of toxicity exerted by simply removing the dosage form from the skin. It is considered as an alternative route to administer drugs to patients who find the oral administration of drug difficult. [1]

Advantages

- This system bypasses the hepatic first pass effect and hence suitable for delivery of drugs that are extensively metabolized in the liver.It is also suitable for drugs which are degraded in the stomach acids.
- This system also reduces the chances of dose dumping and dosing inflexibility thereby preventing drug toxicity.
- These medicated patches extend the activity of drugs with shorter half lives through the drug reservoir in the therapeutic delivery system and its controlled release.
- This system also minimizes the chances of adverse drug reactions such as GIT disorders.
- The termination of drug action is also possible at any point of time by easily peeling off the patch if any adverse reaction is observed. [2]

Limitations

- Skin irritation such as eczema,erythema or edema may be possible due to the components of delivery system.
- There is also a possibility of dose dumping.
- This system is suitable for certain potent drug delivery only and the drugs with a daily dose of more than 25mg makes the transdermal delivery difficult.
- This system is not suitable for the delivery of ionic drugs.
- This system is not suitable for delivery of drugs with a molecular weight greater than 1000 daltons

Components of tdds (Figure 1)

Polymer matrix

The polymer controls the rate of drug release from the device and hence being referred as to the backbone of the TDDS.It is prepared by dispersing the drug either in a liquid or solid state synthetic polymer base.As the polymer concentration is increased more denser matrix is formed and with the decrease in its concentration less denser matrix if formed.

Examples Natural polymers – Cellulose derivatives, gelatine, proteins, shellac, starch.Synthetic elastomers – Silicon rubber, acrylonitrile, neoprene, chlorprene.Synthetic polymers – Poly vinyl alcohol, poly vinyl chloride, polyamide [3].

Drug

The physicochemical,pharmacokinetic and pharmacological properties of a drug should be considered for the development of a transdermal system.The drug crosses the lipophilic stratum corneum layerwhichactsabarriereitherthroughthehairfollicles,sweatglands or sebaceous glands.The transdermal delivery system is suitable for drugs with narrow therapeutic window, short half lives and which undergo hepatic first pass effect [4].

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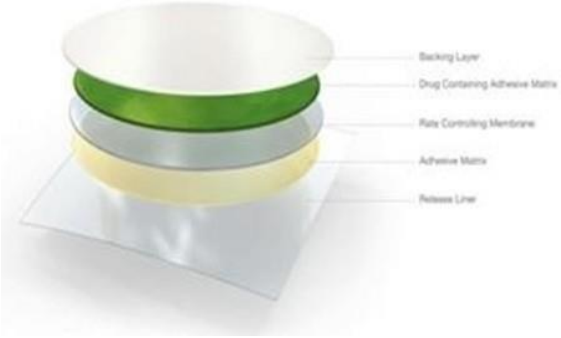

Figure 1: *Components of TDDS.*

Permeation enhancers

They are substances which are employed to increase the drug permeation and absorption by improving the diffusivity and solubility of drugs through the skin which acts by reversibly reducing the barrier resistance of the skin.Thus allows the drug to penetrate to the viable tissues and enter the systemic circulation.They also referred to as absorption promoters or accelerants.

a. **Chemical enhancers-** Sulphoxides and similar chemicals, azone, fatty acids, essential oils,
b. **Physicalenhancers**-Solvents-alcohols**,**Surfactant's SLS,pluronics,terpenes, pyrollidones

Pressure sensitive adhesive

They help in acquiring an intimate contact between the skin surface and medicated patch.It is placed either on the face or back of the device.It is selected based on patch design and drug formulation.It carries the drug which is dissolved or dispersed either in a solution or suspension form [5].

Examples- Acrylicsandsilicons, polysobutylene, polyacrylates

Backing membrane

It's primary function is to provide support to the system. It is the outermost layer of the patch which provides protection to the formulation when it is being worn out.

Examples-Plastic film (polyethylene, poly vinyl chloride, polyeseter), heat seal layer, aluminium vapour coated layer.

Release liner

It is regarded as primary packaging material substance which prevents the loss of drug upon migration into the adhesive layer and also prevents contamination.The patch is covered by a protective liner during its storage until it is used.It is then removed and discarded just before the application of patch over the skin since it forms an intimate contact with the transdermal system and hence should be physically and chemically inert.It consists of a base layer which may be non-occlusive(paper fab ric),occlusive(polyethylene,poly vinyl chloride) and a release coating layer made up of either Teflon or silicon [6].

Types of transdermal patch

Single layer drug in adhesive

It is characterized by the drug inclusion directly within the skin contacting adhesive which not only helps to affix the system to the skin, but also serves as the foundation of the formulation containing the drug and all the other components of the system under a single backing film. The drug release rate from this type of system depends on the diffusion across the skin (Figure 2).

Multi-layer drug in adhesive

It resembles the single layer drug in adhesive.However, the multi-layer encompasses either the addition of a membrane between the two distinct drugs in adhesive layers or the addition of multiple drugs in adhesive layers under a single backing film (Figure 3).

Drug reservoir in adhesive

It involves the inclusion of a liquid compartment with a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for adhesion of the skin can either be added as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane [7] (Figure 4).

Drug matrix in adhesive

It involves the inclusion of semisolid matrix which contains a drug solution or suspension which is in a direct contact with the release liner. The component responsible for adhesion of the skin is added in an overlay and forms a concentric configuration around the semisolid matrix (Figure 5).

Factors affecting tdds

Physicochemical properties of the permeate

1. Partition coefficient
2. Molecular size
3. Solubility/melting point
4. Ionization

Physiological & pathological skin conditions

1. Reservoir effect of horny layer
2. Lipid film
3. Skin hydration
4. Skin temperature

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Figure 2: *Single layer drug in adhesive.*

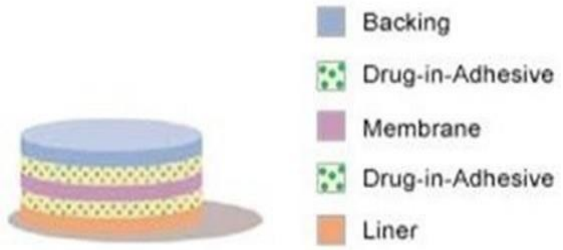

Figure 3: *Multi-layer drug in adhesive.*

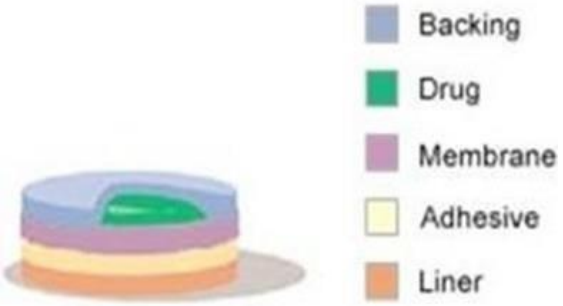

Figure 4: *Drug reservoir in adhesive.*

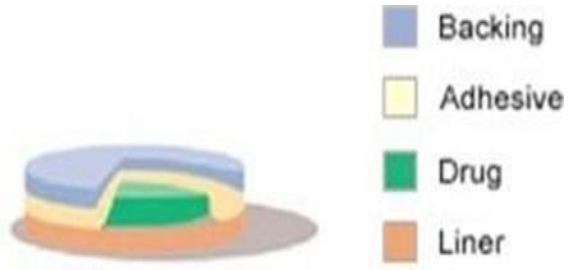

Figure 5: *Drug matrix in adhesive.*

5. Regional variation
6. Pathological injuries to the skin

Physicochemical properties of the permeate Partition coefficient

The hydrophilic and lipid soluble drugs are easily absorbed via the skin.TheIntercelluler route is suitable for drugs with intermediate partition coefficient (logK 1 to 3) and high lipophilicity.The transcellular route usually predominates the hydrophilic molecules (logK< 1).

Molecular size

An inverse relationship exists between the transdermal flux and the molecular weight of the molecule.The drug molecules which are selected for transdermal delivery tends to lie within a narrow molecular weight range (100-500 Dalton).

Solubility

The lipophilicity is a required property of transdermal candidates as lipophilic molecules which tend to permeate via the skin faster than more hydrophilic ones.Drugs with a high melting point have a relatively low aqueous solubility at normal pressure and temperature conditions.

Ionization

According to pH-partition hypothesis, only the unionized form of the drug can cross through the lipohilic barrier of the skin in significant amounts.

Physiological & pathological conditions of skin

Reservoir effect of horny layer

It is a deeper layer whose reservoir effect is due to irreversible binding of an applied drug with the skin.

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Lipid film

The lipid film on the surface of the skin acts as a protective layer which helps in preventing the moisture loss from the skin and also helps in maintaining the barrier property of the stratum corneum layer.

Skin hydration

The hydration of the skin can be achieved easily by covering or occluding the skin with plastic sheeting which causes accumulation of sweat and thereby enhances the penetration by opening the closely packed skin cells and results in increasd porosity.

Skin temperature

The increase in skin temperature causes an increase in the rate of skin permeation which is due to availability of energy that is required for diffusivity.

Regional variation

The differences in nature and thickness of the skin barrier causes variation in drug permeability.

Pathological injuries to the skin

The injuries which disrupt the continuity of the stratum corneum causes an increase in the permeability due to increased vasodilatation produced by removal of the barrier layer.

Cutaneous self-metabolism

The catabolic enzymes found in the epidermis may render the drug inactive by means of the metabolism and thus the topical bioavailability of the drug [8].

Evaluation of transdermal drug delivery system

1. Interaction studies
2. Thickness of the patch
3. Weight uniformity
4. Folding endurance
5. Percentage moisture content
6. Percentage moisture uptake
7. Drug content
8. In vitro drug release studies
9. Stability studies 10.Peel adhesion test 11.Rolling ball tack test

Interaction Studies

The drugs and excipients used in the formulation must posesscompatability in order to produce stable products. The drug-excipient interaction will have an effect on the stability,bioavailability of the resulting final product. These studies are carried out by Thermal analysis, Fourier transform infrared spectroscopy (FTIR), ultra violet (UV) and chromatographic techniques which work by comparing the physicochemical properties like assay, wave numbers, absoprtion maxima and Melting point [9].

Thickness of the patch

The thickness of a patch is measured at various points and its average thickness and standard deviation is measured. The thickness is measured using an instrument such as digital micrometer.

Weight uniformity

The patch is dried at a temperature of about 60^0C for 4 hours and then tested.The patch is cut at different places and weighed in a digital balance.The average weight and standard deviation is then calculated.

Folding endurance

A strip with known area is cut from a patch and is folded repeatedly till it breaks and the number of times required to break it gives the value of folding endurance.

Percentage moisture content

The patches are weighed individually and placed in a desicator containing calcium chloride for about 24hrs and then reweighed.The percentage moisture content is calculated using the below formula

Formula of Percentage moisture content (%) = [Initial weight - Final weight / Final weight] ×100

Percentage moisture uptake

The Patches are weighed seperatelyandn then placed in a desicator containing saturated kcl to maintain 84% rhesus factor (RF). The patches are then reweighed and percentage moisture content is known using the

following formula Formula of

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

Drug content

The patch with known area is taken and dissolved in a known solvent.The solution is then filtered and its drug content is analyzed with suitable methods (UV or HPLC technique).The average of three different samples is then calculated.

Peel adhesion test (Figure 6)

The peel adhesion is defined as forced which is required to remove the adhesive coating from the substrate.The tape is applied onto a substrate and is pulled in a direction of 180° angle.The force required to remove it gives the peel adhesion test value.

Rolling ball tack test (Figure 7)

This test helps in determining the softness of the polymer. A stainless steel ball of diameter 7/16 inches is allowed to move on an inclined plane and come in contact with the horizontal upward facing adhesive. The distance travelled by the ball gives the value of tack which is expressed in inches [10].

In vitro drug release studies

The patch of known area was subjected to study using franz diffusion cell apparatus.The patch is placed on the membrane

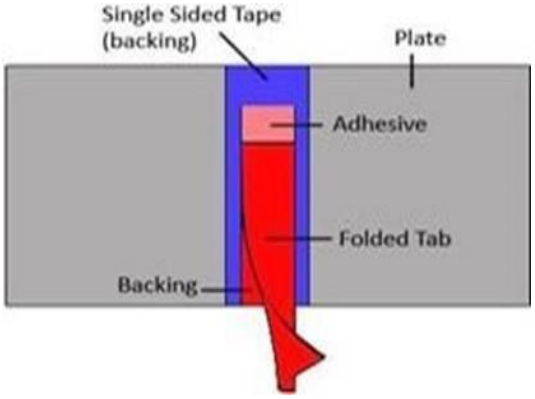

Figure 6: *Peel adhesion test.*

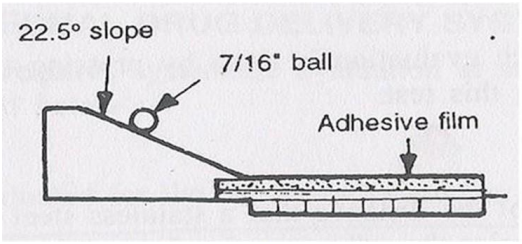

Figure 7: *Rolling ball tack test.*

in the donor compartment and the temperature in the receptor medium is maintained at 37 ±2ºC throughout the experiment. The amount of drug permeated through the membrane is determined by withdrawing samples at regular time intervals and immediately replacing it with equal volume of buffer.The samples withdrawn were filtered and then subjected to a UV visible spectrophotometer (Figure 8).

Stability studies

The stability studies were carried out in otder to determine the effect of different temperatures on drug content in different formulations of the prepared patches. Effect of temperature: All the six formulations of prepared patches were exposed to different temperatures of 30 ± 1ºC and 70 ± 1ºC in separate hot air ovens. The prepared patches were then analyzed for drug content at a period of about regular time intervals of 24 hours for about a week [11].

Physiology and anatomy of skin (Figure 9)

Epidermis

It is the outermost layer of the skin which provides a waterproof barrier.They contain cells called keratinocytes which are responsible for producing keratin which in turn provides the waterproof property to the skin and makes it tough [12]. The lower portion of this layer produces immature cells which rapidly divide keratin as they mature by loosing water and gets flattened and eventually move upwards towards the stratum corneum layer by the end of their cycle (Figure 10).

Dermis

It is also called as corium which is the middle layer present between the epidermis and hypodermis.It occupies a region of about 90% of the total layer of the skin. This layer of the skin contains the hair follicles,sweat glands which produce sweat and thereby regulates the body temperature,sebaceous glands which produces sebum and prevents the skin from drying,bloodvessels,lymph vessels and tough connective tissue. These blood vessels give nourishment and cause removal of waste from both dermal and epidermal cells [13]. This layer of the skin is tightly attached to the epidermis layer through a basement membrane. Apart from the cells,dermis also consists of the matrix components such as collagen which helps in providing strength, elastin which helps in providing elasticity and extrafibrillar matrix, an extracellular gel substance primarily consisting of glycosaminoglycans, proteoglycans, and glycoproteins.

Hypodermis

It is also called as a subcutaneous layer. The hypodermis consists of well- vascularized, loose, areolar connective tissue and adipose tissue, which acts as a mode of storing fat and provides insulation and cushioning effect for the integument. It also helps in temperature regulation and acts as a nutritional support (Figure 11).

Sites for drug entry through skin

The drug enters into the skin via

Appendageal route

- **Trans cellular route**
- **Inter cellular route**

Appendageal route

It includes permeation through sweat glands, sebaceous glands or hair follicles. Skin appendages provide a continuous channel directly across the stratum corneum barrier.

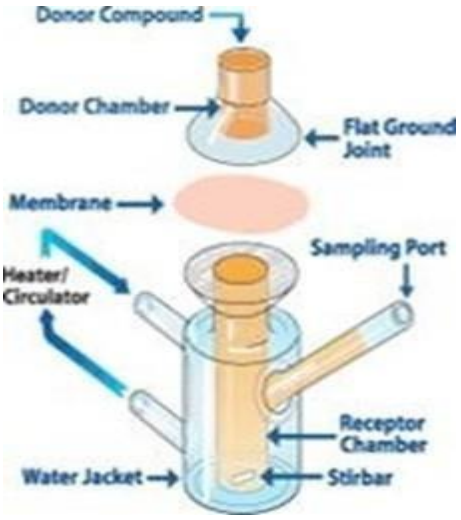

Figure 8: *Franz diffusion cell.*

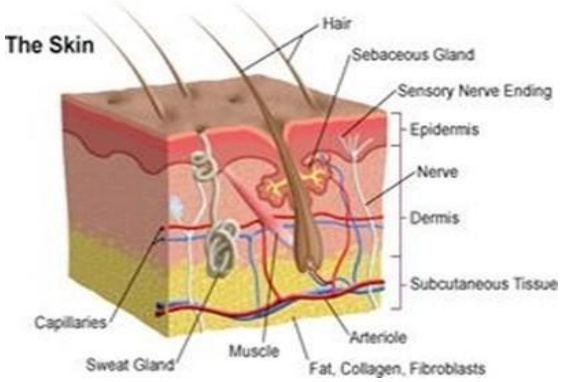

Figure 9: *Structure of skin.*

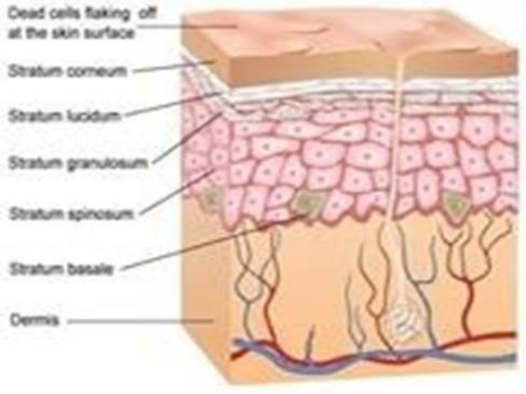

Figure 10: *Layers of skin.*

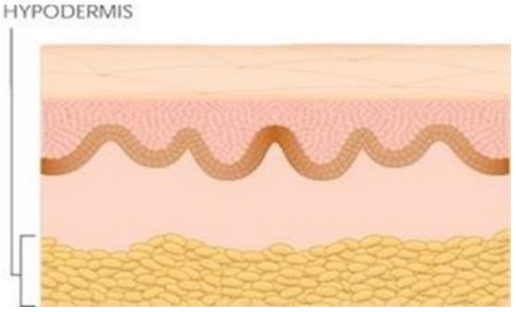

Figure 11: *Structure of hypodermis.*

Trans cellular route

It includes permeation through corneocytes. The corneocytes with highly hydrated keratin helps in providing an aqueous environment through which the hydrophilic drug substances move [14].

Inter cellular route

It includes diffusion across the lipid matrix continuously. This route is generally considered as the most common route for unchargeg small molecules which are penetrating into the skin (Figure 12).

Kinetics of transdermal drug delivery (Figure 13)

The rate of drug permeation across the skin is governed by following equation: Ps(Cd–Cr) .Where,Cd=concentration of penetrate in the donor phase(on the surface of skin)Cr= penetrate concentration in the receptor phase(body); and Ps is the overall skin permeability coefficient Where,K= penetrant partition coefficient, Dss- penetrant apparent diffusivity, hs= skin thicknessA constant rate of drug permeation achieved,if Cd >Cr now the equation is reduced as: dQ/dT=Ps.Cd

The rate of skin permeation (dQ/dt now becomes a constant, if the C value remains fairly constant throughout the time of skin permeation. To maintain the Cd at a constant value, it is critical to make the drug to be released at a rate (Rr) which is always greater than the skin uptake rate (Ra), i. e., Rr>>RaBy doing so, the concentration of the drug on the surface of the skin (Cd) is maintained at a level which is always higher than the equilibrium (or saturation) solubility of the drug in the stratum corneum (Ce s) Cd>>C; maximum rate of skin permeation(dQ/dt)m is expressed by the equation dQ/dT]m= PsCse. Apparently, the magnitude of (dQ/dt)m is determined by the skin permeability coefficient (Ps) of the drug and its equilibrium solubility in the stratum corneum [15].

Aim and objectives

Transdermal drug delivery system provides avoidance of first pass effect and enhance the bioavailability of drug substances by delivering it directly into the systemic circulation. It also

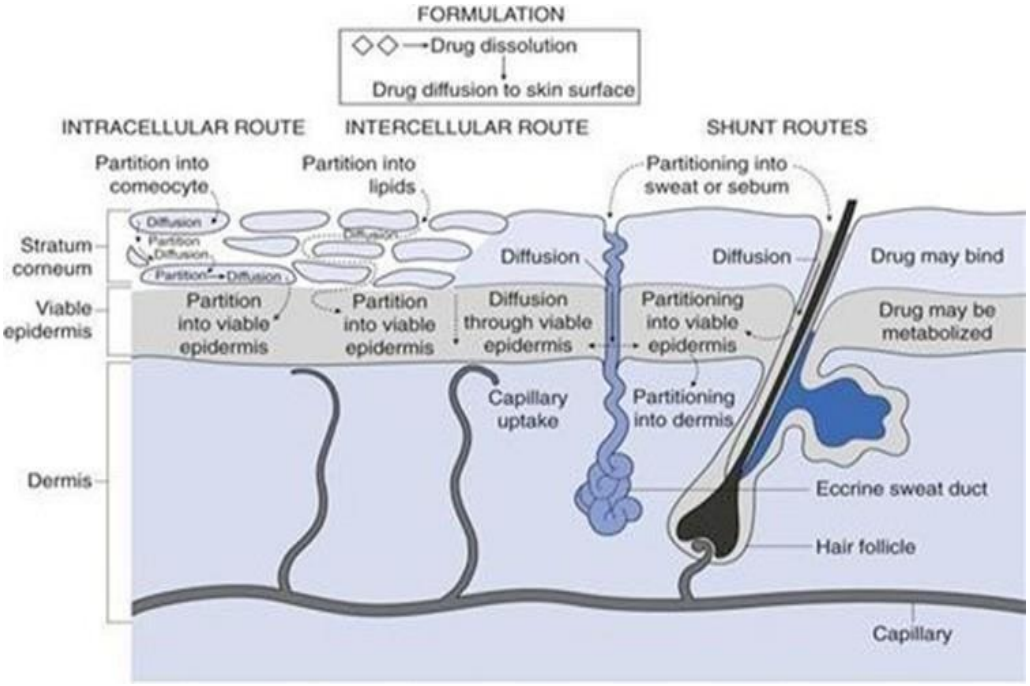

Figure 12: *Routes of drug entry into skin.*

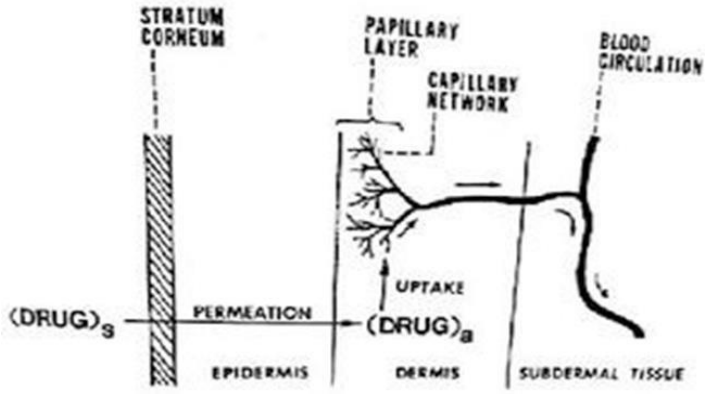

Figure 13: *Kinetics of TDDS.*

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offers various advantages over the other traditional methods of delivering drugs.

IRBESARTAN is an anti-hypertensive drug belonging to a class of angiotensin II receptor-blocking agents.It works by blocking the action of angiotensin which in turn causes vasodilation and helps in lowering the blood pressure. The oral bioavailability of IRBESARTAN is about 60-70%.It undergoes metabolism in the liver primarily by cytochrome P450 coenzyme to inactive metabolite.

In this study the transdermal patches of IRBESARTAN were prepared by following solvent casting method using ethyl cellulose as a main polymer in all six formulations. Theco-polymers such as polyvinyl pyrrolidone , hydroxy propyl methyl cellulose and carbopol were used in combination with main polymer by dissolving in sufficient amount of alcohol. The backing membrane was prepared using 2.5 % w/v of aqueous PVA which was poured into the glass bangles in petri dishes containing mercury followed by drying at 600 C for 5hrs.

Tween 80 and propylene glycol were used as penetration enhancer and plasticizer in each formulation. In vitro studies were performed using a dialysis membrane and other physicochemical parameters were also evaluated.

Literature review

1. Bhabani Shankar Nayak et.al.; prepared twelve transdermal patches of nebivolol using ethyl cellulose as a main polymer,hpmc and pvp as co-polymers by following solvent casting technique method. The backing membrane was prepared using poly vinyl alcohol. The prepared patches were subjected to in vitro characterization and the formulation with ethyl cellulose and hpmc in 1:4 ratio showed maximum skin permeation in comparison with other formulations.
2. Ashwini s. kadam et.al.; gave a complete review on the transdermal drug delivery system which includes the advantages, disadvantages, anatomy and physiology of skin, factors affecting transdermal drug delivery and its components, types, methods of preparation and evaluation.
3. Richa sachan provides a detailed review on transdermal drug delivery system which covers the types of transdermal drug delivery,its concept, components, evaluation, advantages, disadvantages and recent advancements made in the system .
4. Sonia Dhiman et.al, provides a detailed review on transdermal drug delivery which gives elaborate information on various methods of enhancing skin permeation,various sites of drug entry into the skin, components of transdermal system and its evaluation.
5. Nirav s sheth conducted a study on formulation, and evaluation of transdermal patches of propranolol Hcl. The permeation enhancement effect of eugenol was compared with commercially available DMSO. The permeation studies of optimized batches were carried out using rat abdominal skin as permeating membrane in franz diffusion cell. The polymers used were EC,HPMC and PVP.The data obtained showed promising results using eugenol as permeation enhancer and with the increase in polymer concentration, the rate of drug release decreased.
6. Amandeep singh et.al, performed formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride with or without a plasticizer and different grades of hpmc(15 CR,100 M, and 4 M) were used.In vitro and ex vivo drug release studies for all the formulations have showed that drug release equivalent to first drug dose was obtained within 2 to 3 hours and nearly complete release (94%) was achieved in 24 hrs.

Methodology

Materials and methods

Materials (Table 1)

Equipments (Table 2)

Drug profile-irbesartan

Candesartan is an angiotensin II receptor blockade that is routinely used in the care of hypertension and heart failure. Candesartan is an angiotensin II receptor antagonist prodrug created from benzimidazole and has antihypertensive action. Candesartan competes with angiotensin II for binding of the angiotensin II receptor subtype 1 (AT1) in vascular smooth muscle, limiting angiotensin II-mediated vasoconstriction and causing relaxation. Furthermore, restricting AT1 in the adrenal gland decreases angiotensin II-stimulated aldosterone synthesis and secretion by the adrenal cortex; salt and water excretion increase, followed by a reduction in plasma volume and blood pressure (Figure 14, Table 3).

Analytical method for irbesartan

Reagents

0.2M Sodium Hydroxide

8gms of NaOH dissolved and made up to 1000ml with distilled water.

0.2M Potassium Dihydrogen Ortho Phosphate

27.22gms of Potassium dihydrogen ortho phosphate was dissolved and diluted with distilled water to 1000ml.

Preparation of phosphate buffer of ph 7.4

To 50ml of 0.2M Potassium dihydrogen ortho phosphate solution, 39.1ml of 0.2M sodium hydroxide solution was added and the volume was made up to 1000ml with distilled water.

Preparation of standard stock solution

Accurately weighed 100mg of IRBESARTAN was dissolved in 100ml of Phosphate Buffer pH 7.4 to give 1000 microg/ml.

Determination of λ max

The stock solution of IRBESARTAN was scanned in UV visible spectrophotometer in the range of 200-300 nm.

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Table 1: *List of Materials.*

S.No	Materials	Source
1	IRBESARTAN	Nicholas piramal
2	Hydroxy propyl methyl cellulose (HPMC)	S.D Fine Chem Ltd, Mumbai
3	Polyvinyl pyrrolidone (pvp-30)	S.D Fine Chem Ltd, Mumbai
4	Ethyl cellulose (EC)	S.D Fine Chem Ltd, Mumbai
5	Carbopol	S.D Fine Chem Ltd, Mumbai
6	Propylene glycol	S.D Fine Chem Ltd, Mumbai
7	Tween 80	S.D Fine Chem Ltd, Mumbai
8	Ethanol	Market

Table 2: *List of Equipments.*

S.NO	EQUIPMENTS	SOURCE
1	C.V Spectrophotometer (double beam)	Thermo scientific
2	Digital balance	Sartorius
3	Magnetic stirrers	Secor scientific Engg.Corp, Delhi.
4	Glass Rings	Mitutoyo, Japan
5	Screw Gauge	Market

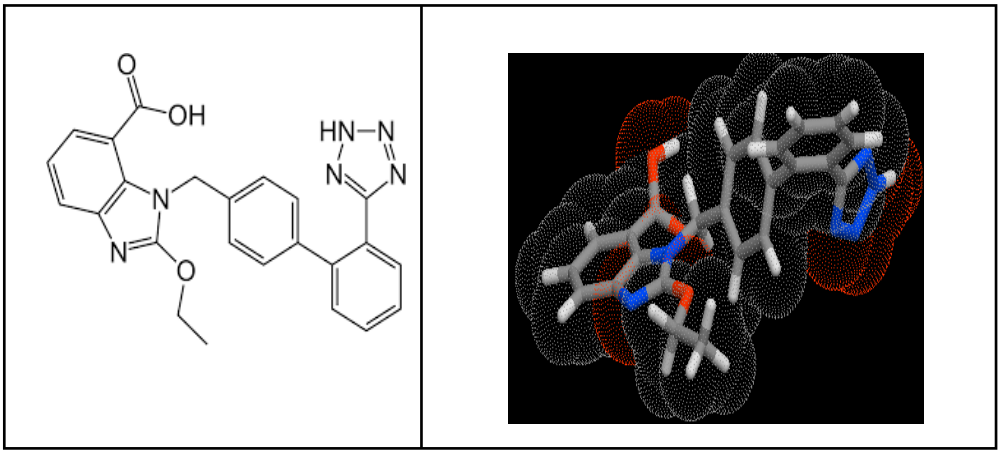

Figure 14: *Kinetics of TDDS.*

Wavelength of 248nm was selected and utilized for further studies in this work.

Standard graph of irbesartan

From the stock solution, 1ml was pipetted out and diluted to 100ml. From the solution 2, 4, 6, 8 and 10ml were pipetted out in different 10ml volumetric flasks and the volume was made up to the mark (10ml) using phosphate buffer 7.4. The absorbance of the solutions was measured at 248 nm [16]. The data for the standard curve is given in the following table. A graph was plotted by taking the concentration on X-axis and absorbance on Y-axis (Table 4).

Standard graph of Irbesartan (Figure 15)

Phosphate Buffer at ph-7.4

Method of Preparation of Transdermal patches

The patches were prepared by using 300mg of EC in all 6 formulations as main polymer. 50mg and 100mg of carbopol was used in F1and F2, which was dissolved in ethanol after neutralization with triethanolamine.50mg and 100mg of HPMC was taken in F3 and F4 after dissolving in sufficient quantity of ethanol.50mg and 100mg of PVP was taken in F5 and F6 after dissolving in ethanol. In all the six formulations, propylene glycol was added as plasticizer (40%w/w of polymer) and tween 80 as permeation enhancer (40%w/w of polymer). 50mg of drug was added to each formulation. The backing membrane was prepared using 2.5 % w/v of acqeous PVA which was poured into the glass bangles in petri dishes containing mercury followed by drying at 600 C for 5hrs. The polymeric solution was poured onto the dried backing membrane. Drying was carried out under low temperatures. The drying rate was controlled by placing an inverted glass funnel to control the drying rate. After complete drying, the films were removed from Petri dishes containing mercury. These films were used throughout the work. The films were found to be smooth, flexible and could be cut to any desired size and shape [17,18].

Formulation (Table 5)

Evaluation of transdermal patches of irbesartan

1. Physical appearance - It includes visual inspection of the prepared patches.
2. Surface texture - The prepared patches were evaluated by simply touching the prepared patches.

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Table 3: *Physicochemical Properties IRBESARTAN.*

Physicochemical Properties	
Formula	C24H20N6O3
Molecular weight	440.45 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	26
Fraction Csp3	0.12
Num. rotatable bonds	7
Num. H-bond acceptors	7
Num. H-bond donors	2
Molar Refractivity	122.35
TPSA	118.81 Å²
Lipophilicity	
Log Po/w (iLOGP)	2.44
Log Po/w (XLOGP3)	4.07
Log Po/w (WLOGP)	4.03
Log Po/w (MLOGP)	3.51
Log Po/w (SILICOS-IT)	3.61
Consensus Log Po/w	3.53
Water Solubility	
Log S (ESOL)	-5.26
Solubility	2.44e-03 mg/ml ; 5.55e-06 mol/l
Class	Moderately soluble
Log S (Ali)	-6.27
Solubility	2.37e-04 mg/ml ; 5.37e-07 mol/l
Class	Poorly soluble
Log S (SILICOS-IT)	-7.93
Solubility	5.22e-06 mg/ml ; 1.19e-08 mol/l
Class	Poorly soluble
Drug-likeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.56

Table 4: *Standard graph of Irbesartan.*

S.NO	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.185
3.	4	0.345
4.	6	0.534
5.	8	0.689
6.	10	0.88

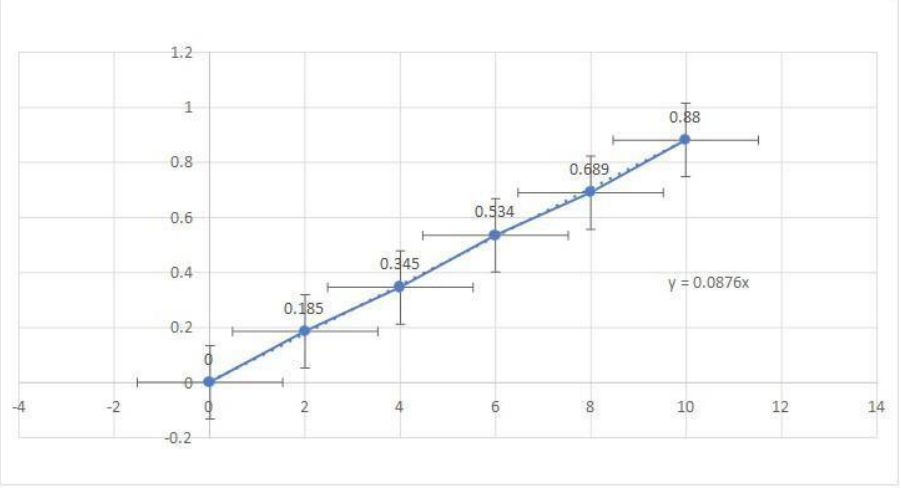

Figure 15: *Calibration Graph of Candesartan in Potassium Dihydrogen.*

Table 5: *Formualtions.*

	Ingredients	F1	F2	F3	F4	F5	F6
1.	IRBESARTAN (in mg)	50	50	50	50	50	50
2.	Ethyl cellulose (mg)	300	300	300	300	300	300
3.	Carbopol (in mg)	50	100	-	-	-	-
4.	HPMC (in mg)	-	-	50	100	-	-
5.	PVP (mg)	-	-	-	-	50	100
6.	Ethanol (in ml)	q.s	q.s	q.s	q.s	q.s	q.s
7.	Triethanolamine (ml)	q.s	q.s	q.s	q.s	q.s	q.s
8.	Tween 80(in ml)	0.2	0.2	0.2	0.2	0.2	0.2
9.	Propylene glycol (in ml)	0.2	0.2	0.2	0.2	0.2	0.2

3. Folding endurance - It was determined by repeated folding a small strip of patch at the same place till it is broken. The patch is folded at the same place until it breaks with which it gives the value of folding endurance.
4. Thickness - The thickness of prepared patches is measured simply by using a digital micrometer screw gauge.
5. Drug Content - A patch of area 1cm square was placed in a volumetric flask containing 50 ml of phosphate buffer of pH 7.4 and kept aside for some time to release the total drug present in it and the volume was made up to 100 ml with the same buffer. Then the absorbance was measured after suitable dilution at 248nm against drug devoid polymer blank solution in phosphate buffer of pH 7.4.The content of IRBESARTAN was calculated using standard graph.
6. Surface pH - The surface pH of the patches was determined to know if any side effects were present or not.A combined glass electrode was used for this purpose and each film was allowed to swell by keeping it in contact with an ml of distilled water for a period of about 30 mins at room temperature and the pH was noted down by bringing the electrode in contact with surface of the patch and allowing it to equilibrium for a min.
7. In-vitro evaluation - The In-vitro release studies of the patches were carried out using Sigma dialysis membrane attached to one end of franz diffusion cell which acts as a donor compartment. The patches of 1cm square area were used for each formulation and the sigma dialysis membrane was previously hydrated by soaking it in distilled water for a time period of about 30 minutes. Which was then fixed to the donor compartment. The patch was placed over the dialysis membrane in the donor compartment. The receptor compartment was then filled with 100 ml of phosphate buffer of pH 7.4. A Teflon coated magnetic bead was placed in receptor compartment.The whole assembly was then placed on the magnetic stirrer and the temperature was maintained at 37±0.5ºC. The Buffer was stirred at 50 rpm in case of all formulations. The samples of 5 ml were withdrawn at regular intervals and followed by suitable dilution.The absorbance was then measured at 248nm.
8. Water vapour transmission studies - Accurately weighed transdermal patches were placed on a glass slide which was kept in a dessicator containing 200ml of saturated potassium chloride and saturated sodium bromide solutions.The dessicators were kept closed tightly and the humidity inside it was measured using an instrument called hygrometer.It was found to be 56% RH and 84% RH.The patches were then weighed daily for about a week.
9. Water vapour absorption studies - Accurately weighed amount (1g) of calcium chloride was placed in dried empty vials having equal diamater.The prepared patches were pasted over the brim with the help of an adhesive. The dessicator containing 200ml of saturated potassium chloride and saturated sodium bromide solutions were kept closed tightly and the humidity inside it was measured using an instrument called hygrometer.It was found to be 56% RH and 84% RH.The patches were then weighed daily for about a week.
10. Stability studies - The stability studies were carried out in otder to determine the effect of different temperatures on drug content in different formulations of the prepared patches. Effect of temperature: All the six formulations of prepared patches were exposed to different temperatures of 30 ± 1ºC and 70 ± 1ºC in separate hot air ovens. The prepared patches were then analyzed for drug content at a period of about regular time intervals of 24 hours for about a week.

Results and Discussion

The main objective of this study was to prepare and evaluate the transdermal patches of IRBESARTAN using a combination of hydrophobic and hydrophilic polymers like HPMC, EC, PVP and Carbopol.

Physical evaluation of IRBESARTAN transdermal patches

++ = flexibile

Surface pH: Surface (Table 6, Figure 16)

In vitro drug release of Formulation F (Table 7, Figure 17)

In vitro drug release of Formulation F2 (Table 8, Figure 18)

In vitro drug release of Formulation F3 (Table 9, Figure 19)

In vitro drug release of Formultion F4 (Table 10, Figure 20)

In vitro drug release of Formulation F5 (Table 11)

In vitro drug release of F5 (Figure 21)

Citation: *Sushma S. Development and Evaluation of Irbesartan transdermal patches. Asian J Biomed Pharm Sci. 2024;14(103):213*

In vitro drug release of Formulation F6 (Table 12, Figure 22, 23)

Among all the 6 formulations prepared, F6 has shown maximum amount of drug release of about 86% in a time period of 24hrs **(**Figure 24, 25).

Kinetic values for optimized Formulation – F6 (Table 13)

Stability studies

The stability studies were carried out in otder to determine the effect of different temperatures on drug content in different formulations of the prepared patches. Effect of temperature:

All the six formulations of prepared patches were exposed to different temperatures of 30 ± 1ºC and 70 ± 1ºC in separate hot air ovens. The prepared patches were then analyzed for drug content at a period of about regular time intervals of 24 hours for about a week.

At 30o C Temperature (Table 14, 15)

It is clearly seen that the drug content in all the six formulations are less affected at 300 C whereas at higher temparature of 700 C ,the six formulations underwent degradation.

Water vapour absorption studies (Table 16, Figure 26)

Table 6: *Physical evaluation of TDDS.*

S.NO	Formulation code	Color	Surface Texture	Folding Endurance	Thickness (mm)	Drug content
					Mean	
1.	F1	White	Smooth	++	0.34	96.72
2.	F2	White	Smooth	++	0.34	97.4
3.	F3	White	Smooth	++	0.33	95.62
4.	F4	White	Smooth	++	0.32	98.20
5.	F5	White	Smooth	++	0.30	98.54
6.	F6	White	Smooth	++	0.32	96.13

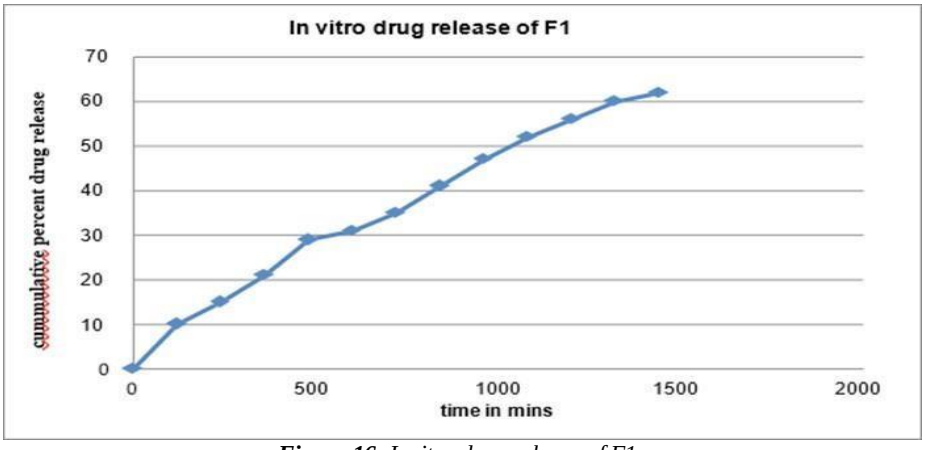

Figure 16: *Invitro drug release of F1.*

Table 7: *Formulations.*

Formulation	pH
F1	7.3
F2	7.3
F3	7.4
F4	7.3
F5	7.5
F6	7.3

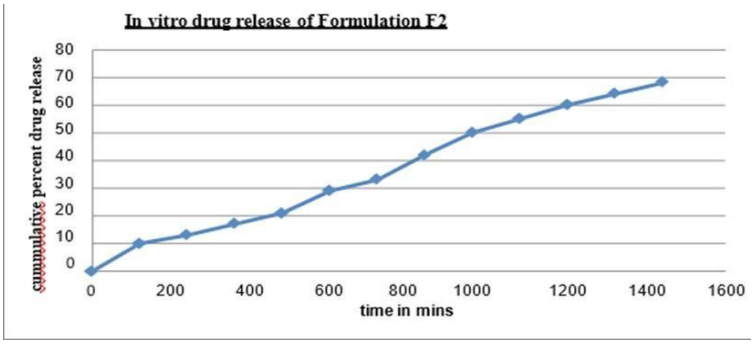

Figure 17: *Invitro drug release of Formulation F2.*

Citation: *Sushma S. Development and Evaluation of Irbesartan transdermal patches. Asian J Biomed Pharm Sci. 2024;14(103):213*

Table 8: *Invitro drug release of Formulation F1.*

Time (mins)	Abs	Conc.	Cum% Released	log	Cum% retained	log	T1/2	Log T1/2
0	0	0	0	0	0	0	0	0
120	0.113	1.3	10	1	90	1.95	10.95	1.03
240	0.171	2	15	1.17	85	1.92	15.49	1.19
360	0.246	2.8	21	1.32	79	1.89	18.97	1.27
480	0.321	3.9	29	1.46	71	1.85	21.9	1.34
600	0.351	4.1	31	1.49	69	1.83	24.49	1.38
720	0.391	4.6	35	1.54	65	1.81	26.83	1.42
840	0.462	5.4	41	1.61	59	1.77	28.98	1.46
960	0.534	6.2	47	1.67	53	1.72	30.98	1.49
1080	0.596	6.9	52	1.71	48	1.68	32.86	1.51
1200	0.646	7.5	56	1.74	44	1.64	34.64	1.53
1320	0.683	8	60	1.77	40	1.60	36.33	1.56
1440	0.712	8.3	62	1.79	38	1.57	37.94	1.57

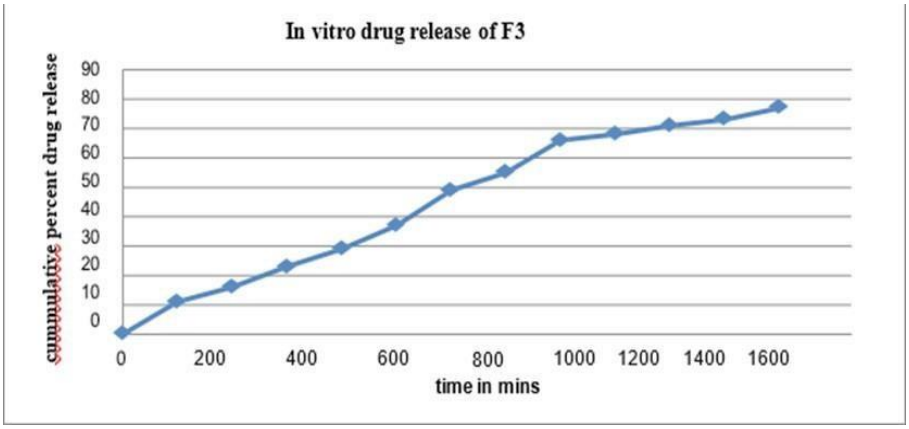

Figure 18: *In vitro drug release of F3.*

Table 9: *Invitro drug release of Formulation F2.*

Time (mins)	Abs	Conc.	Cum% Released ed	Log cum % relead	Cum % retained	Log cum % retaind	T1/ 2	Log T 1/2
0	0	0	0	0	0	0	0	0
120	0.110	1.3	10	1	90	1.95	10.95	1.03
240	0.145	1.7	13	1.11	87	1.93	15.49	1.19
360	0.196	2.2	17	1.23	83	1.91	18.97	1.27
480	0.246	2.8	21	1.32	79	1.89	21.9	1.34
600	0.336	3.9	29	1.46	71	1.85	24.49	1.38
720	0.376	4.4	33	1.51	67	1.82	26.83	1.42
840	0.485	5.6	42	1.62	58	1.76	28.98	1.46
960	0.573	6.7	50	1.69	50	1.69	30.98	1.49
1080	0.621	7.3	55	1.74	45	1.65	32.86	1.51
1200	0.683	8	60	1.77	40	1.60	34.64	1.53
1320	0.732	8.5	64	1.80	36	1.55	36.33	1.56
1440	0.758	8.8	68	1.83	32	1.50	37.94	1.57

Citation: *Sushma S. Development and Evaluation of Irbesartan transdermal patches. Asian J Biomed Pharm Sci. 2024;14(103):213*

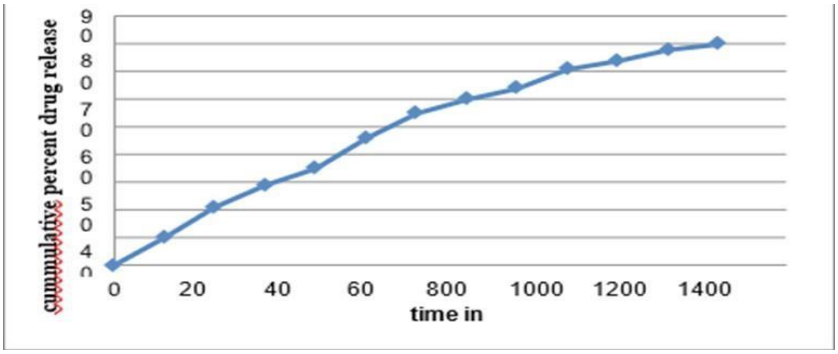

Figure 19: *In vitro drug release of F4.*

Table 10: *In vitro drug release of Formulation F3.*

Time (mins)	Abs	Conc.	Cum% Released	log	Cum% retained	Log	T1/2	Log T1/2
0	0	0	0	0	0	0	0	0
120	0.132	1.5	11	1.04	89	1.94	10.95	1.03
240	0.172.	2.1	16	1.20	84	1.92	15.49	1.19
360	0.268	31	23	1.36	77	1.88	18.97	1.27
480	0.336	3.9	29	1.46	71	1.85	21.9	1.34
600	0.426	4.9	37	1.56	63	1.79	24.49	1.38
720	0.551	6.5	49	1.69	51	1.70	26.83	1.42
840	0.621	7.3	55	1.74	45	1.65	28.98	1.46
960	0.758	8.8	66	1.81	34	1.53	30.98	1.49
1080	0.772	9	68	1.83	32	1.50	32.64	1.51
1200	0.813	9.5	71	1.85	29	1.46	34.23	1.53
1320	0.835	9.7	73	1.86	27	1.43	26.23	1.56
1440	0.873	10.2	77	1.88	23	1.36	37.94	1.57

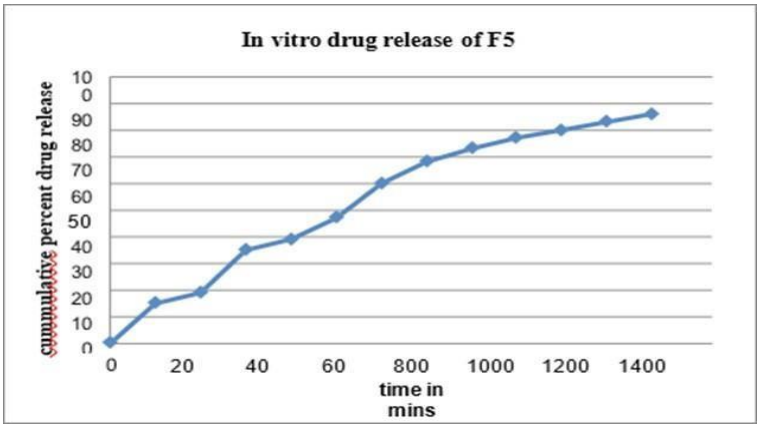

Figure 20: *In vitro drug release of F5.*

Table 11: *In vitro drug release of Formulation F4.*

Time (mins)	Abs	Conc.	Cum% Released	log	Cum% retained	log	T1/2	Log T1/2
0	0	0	0	0	0	0	0	0
120	0.110	1.3	10	1	90	1.95	10.95	1.03
240	0.246	2.8	21	1.32	79	1.89	15.49	1.19
360	0.336	3.9	29	1.46	71	1.85	18.97	1.27
480	0.391	4.6	35	1.54	65	1.81	21.9	1.34
600	0.512	6.1	46	1.66	54	1.73	24.49	1.38
720	0.621	7.3	55	1.74	45	1.65	26.83	1.42
840	0.683	8	60	1.77	40	1.60	28.98	1.46
960	0.732	8.5	64	1.80	36	1.55	30.98	1.49
1080	0.813	9.5	71	1.85	29	1.46	32.86	1.51
1200	0.856	9.9	74	1.86	26	1.41	34.64	1.53
1320	0.891	10.4	78	1.89	22	1.34	36.23	1.56
1440	0.921	10.6	80	1.90	20	1.30	37.94	1.57

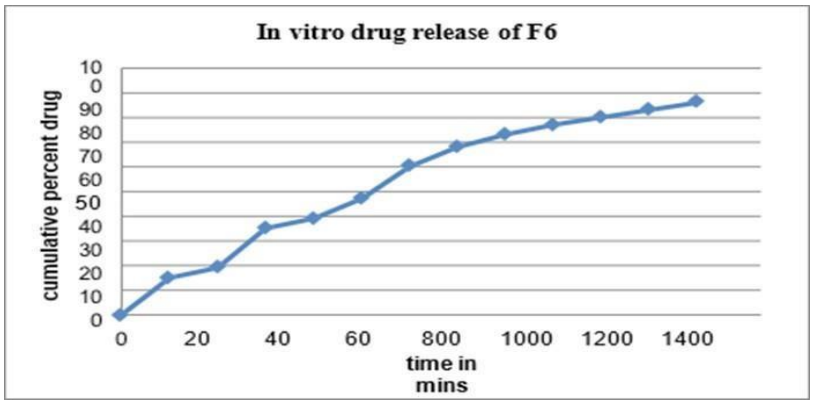

Figure 21: *In vitro drug release of F6.*

Table 12: *In vitro drug release of Formulation F5.*

Time (mins)	Abs	Conc.	Cum% released	log	Cum% retained	log	T1/2	LogT1/2
0	0	0	0	0	0	0	0	0
120	0.145	1.7	13	1.11	87	1.93	10.95	1.03
240	0.246	2.8	21	1.32	79	1.89	15.49	1.19
360	0.336	3.9	29	1.46	71	1.85	18.97	1.27
480	0.391	4.6	35	1.54	65	1.81	21.9	1.34
600	0.462	5.4	41	1.61	59	1.77	24.49	1.38
720	0.573	6.7	50	1.69	50	1.69	26.83	1.42
840	0.683	8	60	1.77	40	1.60	28.83	1.46
960	0.758	8.8	66	1.81	34	1.53	30.96	1.49
1080	0.835	9.7	73	1.86	27	1.43	32.86	1.51
1200	0.873	10.2	77	1.88	23	1.36	34.64	1.53
1320	0.921	10.6	80	1.90	20	1.30	36.23	1.56
1440	0.962	11.2	84	1.92	16	1.20	37.94	1.57

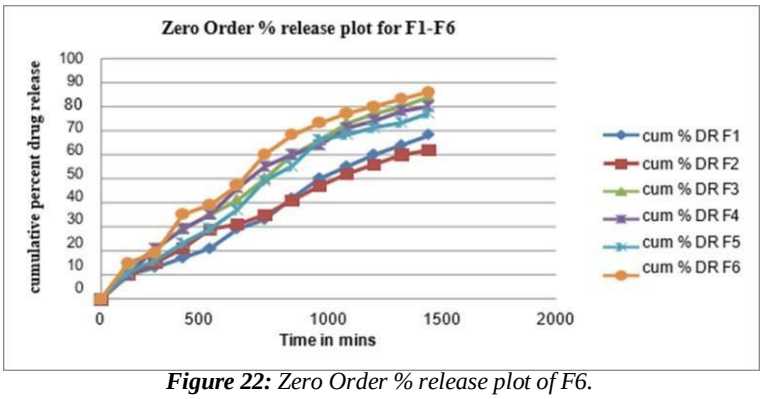

Figure 22: *Zero Order % release plot of F6.*

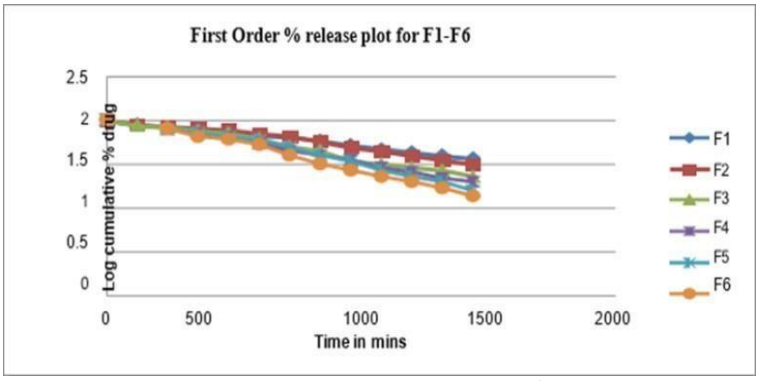

Figure 23: *First Order % release plot of F1-F6.*

Citation: *Sushma S. Development and Evaluation of Irbesartan transdermal patches. Asian J Biomed Pharm Sci. 2024;14(103):213*

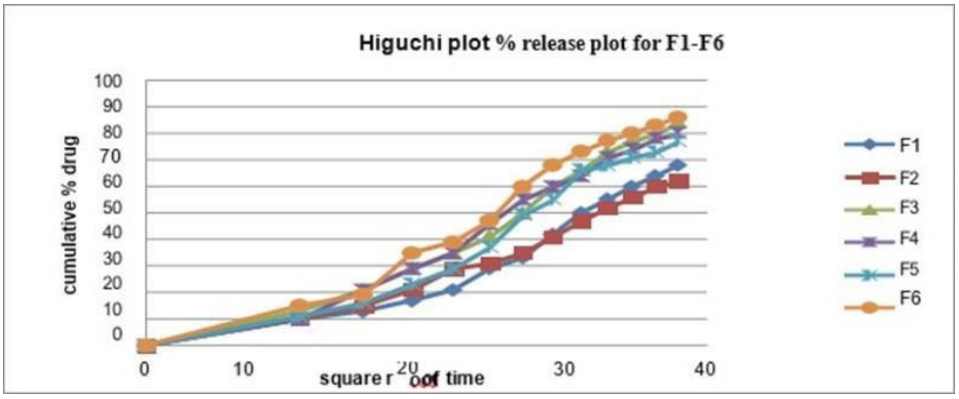

Figure 24: *Higuchi plot %release plot for F1-F6.*

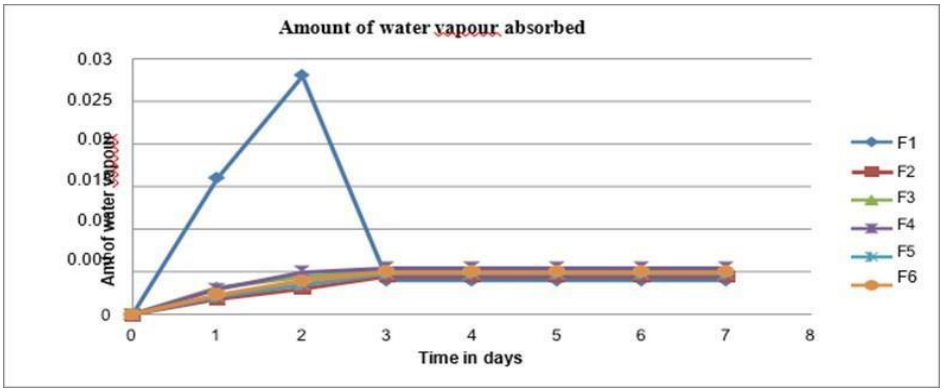

Figure 25 *Higuchi plot %release plot for F1-F6.*

Table13: *In vitro drug release of Formulation F6.*

Time (mins)	Abs	Conc.	Cum% released	Log	Cum% retained	log	T1/2	Log T1/2
0	0	0	0	0	0	0	0	0
120	0.161	2	15	1.17	85	1.92	10.95	1.03
240	0.211	2.4	19	1.27	81	1.90	15.49	1.19
360	0.391	4.6	35	1.54	65	1.81	18.97	1.27
480	0.441	5.2	39	1.59	61	1.78	21.09	1.34
600	0.534	6.2	47	1.67	53	1.72	24.48	1.38
720	0.683	8	60	1.77	40	1.60	26.83	1.42
840	0.772	9	68	1.83	32	1.50	28.98	1.46
960	0.835	9.7	73	1.86	27	1.43	30.98	1.49
1080	0.873	10.2	77	1.88	23	1.36	32.86	1.51
1200	0.921	10.6	80	1.90	20	1.30	34.64	1.53
1320	0.942	11	83	1.91	17	1.23	36.33	1.56
1440	0.982	11.5	86	1.93	14	1.14	37.94	1.57

Table 14: *Kinetic values for optimized Formulation – F6.*

	ZERO ORDER	FIRST ORDER	HIGUCHI
SLOPE	0.0709	-0.0007	2.567
INTERCEPT	9.1109	2.0434	-10.456
R2	0.9569	0.9990	0.9231

Table 15: *Temperatures at 30o C.*

Formula		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	% DC	100.00	99.64	99.64	99.06	98.11	97.12	96.45	96.16
2	% DC	100.00	98.82	98.45	98.17	97.23	97.03	96.01	95.23
3	% DC	100.00	99.98	99.78	99.50	98.61	97.54	96.45	96.21
4	% DC	100.00	99.97	99.87	99.21	98.50	97.34	97.21	96.33
5	% DC	100.00	98.45	98.31	98.12	98.01	97.93	97.67	97.37
6	% DC	100.00	97.65	97.45	97.23	97.01	96.65	96.30	96.01

Table 16: *Temperatures at 70o C.*

Formula		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	% DC	100.00	99.45	99.31	99.06	98.14	97.21	95.23	94.11
2	% DC	100.00	99.82	98.45	97.45	96.23	96.11	95.01	94.23
3	% DC	100.00	99.98	99.78	99.78	98.61	97.54	96.45	95.21
4	% DC	100.00	99.97	99.87	99.87	98.50	97.34	96.21	94.34
5	% DC	100.00	98.45	98.31	96.41	96.05	95.90	95.67	95.37
6	% DC	100.00	98.65	97.45	97.95	97.03	97.05	96.22	95.89

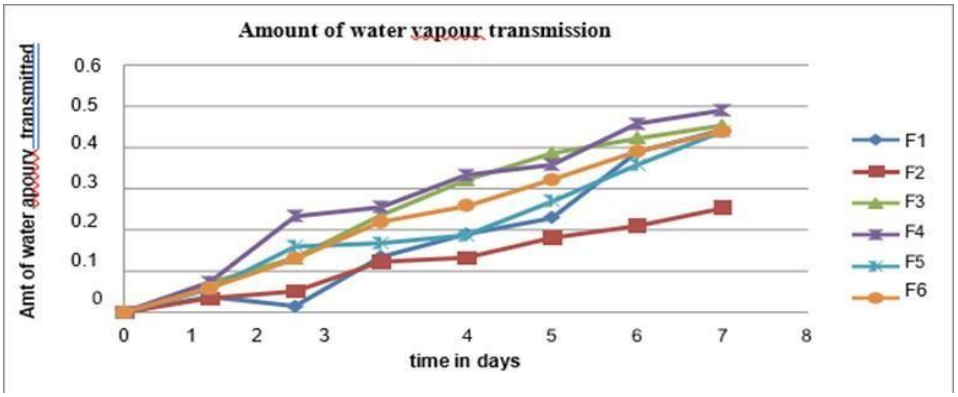

Figure 26: *Amount of water vapour transmission.*

Summary and conclusion

The transdermal drug delivery system is an extremely effective approach to enhancing the bioavailability of drugs going through systemic hepatic first-pass metabolic process. This is due to the fact that the medicine straight penetrates the skin using the epidermis, which after that promotes the straight entrance of medication particles into the systemic flow. Though the dental route is the most generally preferred route of medicine management, it is not always suitable for medications that are very susceptible to gut/hepatic metabolic rate as well as additionally for drugs that trigger stomach irritation or side effects. The transdermal drug shipment system is well accepted by individuals as the skin is conveniently obtainable for self-medication and is a noninvasive method. Additionally, the spots likewise permit medication absorption to be terminated in case of any negative response. In the here and now study, an attempt was made to produce as well as assess transdermal patches of IRBESARTAN by utilizing Ethyl Cellulose as a major polymer and various other co-polymers particularly PVP K30, carbopol-934, and also HPMC. 6 formulations were prepared as well as reviewed for their physical attributes such as look, surface appearance, folding endurance, thickness, and surface pH. The in-vitro launch research studies were performed by using Franz diffusion cell and also a dialysis sac was used as a membrane. Prepared patches of area 1 cm square were utilized for researches. The outcomes acquired from the above examinations motivated us to acquire the following final thoughts.

1. The medicine material of the films was found to be in was discovered the range of 95.62 to 98.54%.
2. Thickness of the patches was discovered to be in the variety of 0.30 to 0.34 mm.
3. In-vitro launch profiles for formulations were in the order of: F6 > F5 > F4 > F3 > F2>F1.
4. The surface ph was located to be in the variety of 7.3 to 7.5
5. Among the 6 solutions prepared, formulation F6 has shown an optimal percentage release of 86% in twenty-four hours and also therefore was selected as a maximized formulation. Medicine kinetic studies were performed for enhanced formula F6 and also based on the kinetic information, it was ended that the device of medicine release was diffusion complied with by first- order kinetics. The outcomes acquired indicated the suitability of the system for shipment of improperly soluble medications, extremely healthy protein bound, and also have a short half-life and low bioavailability upon oral administration.
6. Among the 6 solutions prepared, formula F4 has shown a maximum quantity of water vapor absorption in a week.
7. Among the 6 formulations prepared, formulation F4 has actually shown the optimum amount of water vapor transmission in a week.

References

1. Srilakshmi A, Teja VR, Lakshmi K, Thippesh M, Salma SU, et al (2017) Formulation and evaluation of transdermal patches of Irbesartan. Indian J Res Pharm Biotechno. 5: 212-215.
2. Tambe, BD (2018) Formulation design and evaluation of transdermal film of irbesartan using hydrophilic and hydrophobic polymers. Int J.Info Res Rev 5: 5597-5601.
3. Srilakshmi A, Teja VR, Lakshmi K, Thippesh M, Salma SU, et al (2017) Formulation and evaluation of transdermal patches of Irbesartan. Indian J Res Pharm Biotechno. 5: 212-215.
4. Patil CC, Patel B, Vijapure VK (2016) Formulation and evaluation of transdermal drug delivery system of Ramipril. Indian J Res Pharm Biotechno. 9: 2127-2134.

Citation: *Sushma S. Development and Evaluation of Irbesartan transdermal patches. Asian J Biomed Pharm Sci. 2024;14(103):213*

5. Gaur S, Sharma AK, (2013) Development and Evaluation of Transdermal Drug Delivery System of Ivabradine Hydrochlride. Indian J Res Pharm Biotechno.

6. Almazan EA, Castañeda PS, Torres RD, Escobar-Chavez JJ, (2020) Design and evaluation of losartan transdermal patch by using solid microneedles as a physical permeation enhancer. Iran J Pharmac Res: IJPR. 19: 138.

7. Tadhi N, Chopra H, Sharma GK, (2021) Formulation and Evaluation of Transdermal patch of Methimazole. Indian J Res Pharm Biotechno. 14: 4667-4672.

8. Qadri R, Ahad A, Aqil M, Imam SS, Ali A et al (2017) Invasomes of isradipine for enhanced transdermal delivery against hypertension: formulation, characterization, and in vivo pharmacodynamic study. Artif Cells Nano Medici Biotechnol. 45: 139-145.

9. Kamble RN, Gaikwad S, Maske A, Patil SS, (2016) Fabrication of electrospun nanofibres of BCS II drug for enhanced dissolution and permeation across skin. J Advan Res. 7:483-489.

10. Sharma K, (2016) Skin permeation of Candesartan Cilexetil from transdermal patch containing Aloe Vera gel as penetration enhancer. Asian J Pharmace. 10.

11. Dubey J, Mishra A, Dubey V, Lariya N, (2018) Formulation development and evaluation of transdermal patch of diclofenac–tizanidine. World J Pharmacel Res. 7: 945-958.

12. Tirunagari M, Jangala VR, Khagga M, et al, (2010) Transdermal therapeutic system of isradipine: effect of hydrophilic and hydrophobic matrix on in vitro and ex vivo characteristics. Archi Pharm Res. 33: 1025-1033.

13. Ramkanth S, (2017) Fabrication and characterization of transdermal drug delivery using Losartan potassium. Internat Res J Pharmace Applied Sci. 7: 23-30.

14. Hardainiyan SWATI, Kumar KRISHAN, Nandy BC, et al (2017) Design, formulation and in vitro drug release from transdermal patches containing imipramine hydrochloride as model drug. Int J Pharm Pharm Sci. 9: 220-5.

15. Srikanth A, (2005) Permeation studies of few antihypertensive drugs for transdermal delivery Doctoral dissertation, Rajiv Gandhi Unive Heal Sci.

16. Kshirsagar SJ, Bhalekar MR, Mohapatra SK, (2012) Development and evaluation of carvedilol-loaded transdermal drug delivery system: In-vitro and in-vivo characterization study. Drug Develop Industr Pharm. 38: 1530-1537.

17. Dey BK, Kar PK, Nath LK (2009) Formulation design, preparation and in vitro–in vivo evaluation of propranolol hydrochloride transdermal patches using hydrophilic and hydrophobic polymer complex. Res J Pharma Technol, 2(1),155-160.

18. Bagchi A, Dey BK, (2010) Formulation, in-vitro evaluations and skin irritation study of losartan potassium transdermal patches.

Citation: *Sushma S. Development and Evaluation of Irbesartan transdermal patches. Asian J Biomed Pharm Sci. 2024;14(103):213*