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Formulation and Evaluation of Transdermal Patches of Antihypertensive Drug

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ABSTRACT

Transdermal therapeutic system are defined as self-contained, discrete dosage forms, which when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation so that it can improve the therapeutic efficacy and safety of the drugs. Through a diffusion process the drug enters the bloodstream, directly through the skin. The main disadvantages to transdermal delivery systems stems from the fact that the skin is a very effective barrier, as a result only medications whose molecules are small enough to penetrate the skin can be delivered. The purpose of this study was to develop suitable matrix transdermal therapeutics system of atenolol with different proportions of Ethyl cellulose (EC) and Hydroxy Propyl Methyl cellulose (HPMC). Five formulations were prepared by solvent casting method. The prepared patched showed satisfactory physiochemical characteristics of weight uniformity, thickness, folding endurance, moisture lost, moisture absorption for stability of the formulation and drug content were uniform in all patches. *Invitro* study done by using Franz diffusion cell having cellophane membrane to determine the amount of drug present in the formulation patch. In different formulation on the basis of evaluation parameters and by optimization study formulation F4 shows satisfactory drug release pattern.

Key-words: Transdermal delivery system, Ethyl cellulose, Hydroxy Propyl Methyl Cellulose, solvent casting method, In-vitro study, Franz diffusion Cell.

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INTRODUCTION

Transdermal drug delivery system is defined as the topically administered medications in the form of patches which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate. Transdermal patches are delivered the drug through the skin in controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduced side effect of drug. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver the drug via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time[1]. For effective Transdermal drug delivery system, the drug are easily able to peneterate the skin and easily reach the target site. TDDS increase the patient compliance and reduces the load as compared to oral route. FDA approved the first Transdermal system Transderm-SCOP in 1979. FDA approved this for the prevention of nausea and vomiting associated with ravel, particularly by sea[2] Transdermal therapeutic systems are also defined as a self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at control rate to the systemic circulation. Transdermal formulation maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration[3,4].

Transdermal drug delivery offers the following potential advantages[5,6]:-

1. Avoid the risks and inconveniences of intravenous therapy and of varied conditions of absorption and metabolism associated with the oral therapy.
2. Continuity of drug administration in TDDS permits the use of a drug with short biological half-life.
3. Transdermal drug delivery improves the bioavailability that reduces the total daily dose.
4. Avoids first-pass hepatic metabolism.
5. Less chances of over or under dosing as the result of prolonged pre programmed delivery of drug at the required therapeutic rate.
6. Decrease gastrointestinal side effects.
7. Elimination drug food interactions.
8. Increased patient compliance in following manner
    - Provisions of simplified therapeutic regimen.
    - Painless delivery of drug.
    - Eliminates swallowing.
    - No chances of forgetting the dose once the device is applied on skin.
    - Easy to carry a patch in wallet or ladies purse.
9. Patches offer less friability problems of wear and tear than the tablets.
10. In a multi drug regimen TDDS avoids drug interaction in GIT.
11. It is easy to terminate the medication simply by removing the dug delivery device from the skin surface.
12. TDDS system can be taken without any aid, which makes it most suitable formulation; for instance, tablet and capsule need little water. Liquid oral preparation needs teaspoon and parentaral delivery needs specialized person whereas if a patient is told to apply TDDS patch, he/she can do it any where e.g. in office, in theatre, in club, in house without any aid.
13. Chance of toxicity due to additives e.g. preservatives, stabilizing agent antioxidants etc. are less as compared to other dosage forms.
14. Problem of dose dumping is least in TDDS, because stratum corneum is more resistant than the inner membranes (i.e. mucous membrane in case of oral controlled release delivery systems) and stratum corneum itself is a rate limiting factor.
15. Need not to be sterile, obviates processing problem.

Disadvantages of transdermal drug delivery system[7]:-

1. The limitation of transdermal drug delivery is principally associated with skins barrier function, which severely constrains the absolute amount of drug that can be absorbed across reasonable area of skin during the dosing period. Thus, the major disadvantage of the method is that it is limited to potent drug molecule typically those requiring a daily dose on the order of 20 mg or less.
2. Even if the drug is sufficiently potent, it must yet satisfy other criteria to be considered a viable candidate for transdermal drug delivery. For example its physiochemical properties must allow to be absorbed percutaneously. This mean that its molecular weight should ideally be less than 500 Daltons and it should have

adequate solubility in both lipophillic and aqueous environments since, to reach dermal micro circulation and gain access to systemic
circulation, the molecule must cross that stratum corneum (a lipid barrier) and then transfer through the much-more-aqueous-in-nature viable epidermis and upper dermis. Absence of either oil or water solubility altogether, will preclude permeation at a useful rate.
3. The pharmacokinetic and pharmacodynamic characteristic of the drug must be such that relatively sustained and slow input provided by transdermal delivery makes sense. Tolerance inducing compounds are not intelligent choice for this mode of administration unless until an appropriate "wash out" period is programmed into the dosing regimen.

PENETRATION ENHANCER[8, 9, 10]

Penetration enhancers increases the penetration ability of permeant by breaking the stratum corneum structure. Breaking may be done by chemical which affects both extracellularly and intracellularly. Fluidization and randomization of intercellular lipids, protein denaturation may also cause disruption of stratum corneum. Enhancers of transdermal drug delivery system are physical enhancers, perticulate systems and chemical enhancers.

1. Physical enhancers:

Iontophoresis, electroporation, microneedle, magnetophoresis and ultra sound (also known as phonophoresis or sonophoresis) techniques are the physical enhancers of TDDS used for increasing the penetration of drugs.

2. Perticulate system:

liposomes, microemulsion, transfersome, niosomes and nanoparticles are the enhancers of TDDS.

3. Chemical enhancers:

sulphoxides, glycols, alkanols, terpenes, azones etc. are the chemical enhancers of TDDS.

FACTORS AFFECTING TRANSDERMAL PERMEABILITY[2,11]

Passive diffusion is the main transport mechanism across skin.

Factors affecting the permeability of skin can be grouped into three categories:

1. Physicochemical properties of the penetrant:

i) Partition co-efficient: Both water and lipid soluble drugs are absorbed across the skin. Changing the penetrant changes the lipid/water partition co-efficient of the molecule.
ii) pH condition: pH effects the rates of penetration of alkaline and acidic drugs. Ionizable species from aqeous solutions have very strong dependence on its transportation.
iii) Drug concentration: Since transdermal drug transportation is mainly via passive diffusion. Therefore concentration of drug effects the permeability.

2. Physicochemical properties of the drug delivery system:

i) The affinity of the vehicle for the drug molecules: It influences the release of drug from the medium and solubility determines its release.whether the drug is dissolved or suspended in the delivery system and its partition co-efficient from the delivery system are the factors on which the release of drugs depends.
ii) Composition of drug delivery system: Rate of release of drug and permeability of stratum corneum are affected by the composition of drug delivery system.
iii) Enhancement of transdermal permeation: Stratum corneum have very low permeability. Penetration enhancers can be used to increase the penetration and permeation ability of drugs across the skin.

3. Physicochemical and pathological conditions of the skin:

i) Skin age: Infant and foetal skin is more permeable than the adult skin but permeability of water is same for both adult and children.
ii) Lipid film: Lipid fim on skin formed from the excretion of sebaceous glands, sebum and epidermal cell containing emulsifying agents which provide a protection and felp in maintaining the barrier function of stratum corneum.
iii) Skin hydration: More hydrated the stratum corneum, more will be the permeability of the skin.

iv) Skin temperature: Rise in temperature increases the rate of skin permeation and subcutaneous absorption by increasing vasodilation of blood vesel.
v) Cutaneous drug metaboilsm: Drug either reaches the systemic circulation in active form or inactive form. Some of the drugs passing through the skin layers get motabolised by the metabolic enzymes present inside the skin.
vi) Species differences: mammalian skin shows differences in the anatomy from different species.
vii) Pathological injury to the skin: permeability increases after skin getting injured. Injury causes disturbances in stratum corneum.

CLASSIFICATION OF TRANSDERMAL DRUG DELIVERY SYSTEM[12, 13]

1. According to the transportation of drug molecule through the skin:

a. Passive:

i. Matrix
ii. Reservoir

b. Active:

i. Iontophoresis
ii. Electroporation
iii. Sonophoresis
iv. Heat or thermal energy
v. Microneedles

2. Based on their technical sophistication:

a. Rate pre programmed drug delivery system:

i. Polymer membrane permeation controlled drug delivery system
ii. Polymer matrix diffusion controlled drug delivery system
iii. Microreservoir partitioned controlled drug delivery system

b. Activation modulated drug delivery system:

i. Physical means:
- Hydrodynamic pressure controlled drug delivery system
- Vapour pressure activated drug delivery system
- Hydration activated drug delivery system

ii. Chemical means
iii. Biological means

c. Feadback regulated drug delivery system:

i. Bio-erosion regulated drug delivery system
ii. Bio-resposive drug delivery system

d. Carrier based drug delivery system:

i. Colloidal perticulates carrier system

COMPONENT OF TRANSDERMAL DRUG DELIVERY SYSTEM[2,14, 15-22]

1. Drug

Drug should be selected with extreme care and precision for successful development of TDDS. Different properties on which the selection of drug for transdermal drug delivery system depends are dose, molecular weight, partition co-efficient, pH melting point, oral bioavailability, half life, therapeutic index, skin reaction, skin permeability co-efficient.
Captopril, Clonidine, Propranolol hydrochloride, Carvedilol, Atenolol, Nicardipine hydrochloride, Metaprolol tartrate, Nitrendipine, Verapamil hydrochloride etc are the few examples of drugs which are suitable for transdermal drug delivery system.

2. Polymer matrix

It is the primary part of TDDS. It is called as the backbone of TDDS and regulate the release of drug in the skin.
Types of polymers used in TDDS are:
i) Natural polymers: Starch, rubber, gum, cellulose, waxes, proteins etc.
ii) Synthetic elastomers: Acrylonitrite, neoprene, nitrile, silicon rubber etc.

iii) Synthetic polymers: Polyvinyl chloride, polyethylene, polypropylene etc.

3. Permeation enhancers

They are also called as accelarant which increases the permeability of drugs across the skin.

i) Solvents: Methanol, ethanol, propylene glycol, glycerol etc.

ii) Surfactants:

- Anionic: Sodium lauryl sulphate diacetyl sulphosuccinate.
- Nonionic: Pluronic F68, pluronic F127.
- Bile salts: Sodium deoxycholate, sodium taurocholate.

iii) Miscellaneous chemicals: Calcium thioglycolate, urea.

4. Other excipients

i) Adhesives: They are also called pressure sensetive adhesives (PSA). PSA adhere to the skin due to the interatomic and intermolecular forces between the surfaces.

ii) Liner: It is used for the protection of transdermal patch during storage and is removed just before use. It is said to be a part of packing material more than a component of TDDS. It composed of base layer (paper fabric, polyvinylchloride) and release layer (teflon. Silicon).

iii) Backing: it gives protection to the patch from environment. Examples are polyester films, polyurethylene etc.

Table 1: Ideal properties of transdermal drug delivery system

S. No.	Properties	Range
1	Shelf life	Should be upto 2.5 years
2	Patch size	Should be less than 40cm^2
3	Dose frequency	Once a daily- once a week
4	Appearance	Should be clear or white clear
5	Packaging properties	Should be easily removable of release liner
6	Skin reaction	Should be non-irritating
7	Release properties	Should have consistent pharmacokinetic and pharmacodynamic profiles over time
8	Packaging properties	Should be easily removable of release liner

Table 2: Ideal properties of drug for TDDS

S.No.	Parameter	Properties
1	Dose	Should be low
2	Half life in hr	Should be 10 or less
3	Molecular weight	Should be less than 500
4	Partition coefficient	Log P (octanol-water) between -1 and 3
5	Skin permeability coefficient	Should be less than 0.5×10^{-3} cm/hr
6	Skin reaction	Should be non-irritating
7	Oral bioavailability	Should be low
8	Therapeutic index	Should be low
9	Concentration	Minute
10	pH of saturated aqueous solubility	5-9
11	Dose deliverable	<10mg/day

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM [5, 7, 23, 14, 24]

There are four main type of transdermal patches (TDDS) they are:

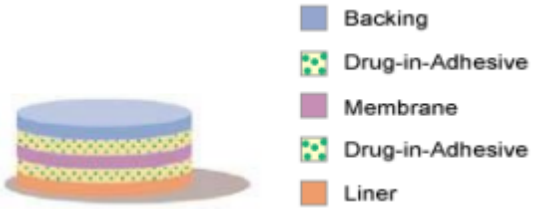
1. Single-layer Drug-in-Adhesive

In this system, drug is placed in between the two layers of adhesives and both drug and adhesive forms a single layer. This single layer drug-in-adhesive is placed between layers of backing and liner.

Adhesive plays a dual role of adhering to the skin along with being the formulation foundation containg all the excipients and drug in single layer. Simple diffusion controls the rate of drug release.

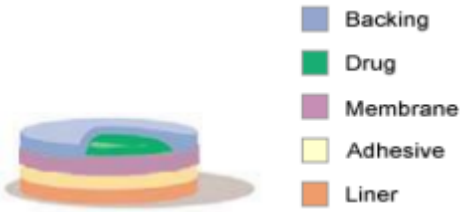
2. Multi-layer Drug-in-Adhesive

It is similar to the single layer drug-in-adhesive but it contains more than one layer of drug-in-adhesive. Layers of drug-in-adhesive are separated by membrane or backing film.



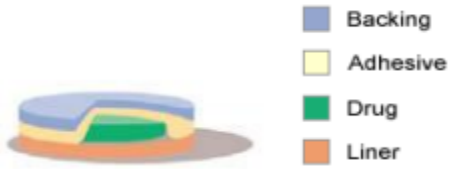
3. Drug Reservoir-in-Adhesive

In this system, drug is not connected to the adhesive and is seperated by a layer of semi permeable membrane. Reservoir is placed in between the adhesive. Drug is situated in the form of solution or suspension. Backing and liner forms the outer layer of this system.



4. Drug Matrix-in-Adhesive

In this system, a semisolid matrix containing drug in solution or suspension form is incorporated in contact with liner. Adhesive is placed over the matrix which in turn in contact with backing.



MATERIALS AND METHODS

Materials:

Atenolol powder was obtained as a gift from Ranbaxy Laboratories Limited (Paonta sahib) , Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl Cellulose (EC), Chloroform, Methanol and Span 80 , Propylene Glycol, Glycerol, KH_2PO_4, NaOH, Magnetic Stirrer, UV Spectrophotometer , pH Meter from Siddhartha Institute of Pharmacy Laboratory unless and untill specific all the chemicals were of analytical grade

DRUG PROFILE

ATENOLOL

Atenolol is a selective β_1 receptor antagonist, a drug belonging to the group of β-blockers, a class of drug used primarily in cardiovascular diseases. Introduced in 1976, atenolol was developed as a replacement for propranolol in the treatment of hypertension. The chemical works by slowing down the heart and reducing its workload. Unlike propranolol, atenolol does not pass through the blood brain barrier thus avoiding various central nervous system side effects.

Atenolol is one of the most widely used β-blockers in the United Kingdom and was used once the first-line treatment for hypertension. The role β-blockers in hypertension was downgraded in june 2006 in the United Kingdom to fourth-line, as they perform less appropriately or effectively than newer drugs, particularly in the elderly.

Table 3: Marketed Products of Transdermal Drug Delivery System [25,26,27]

S.No.	Prodrug	Active Drug	Type of transdermal patch	Purpose
1	Alora	Estradiol	Matix	Postmenstrual syndrome
2	Androderm	Testosterone	Membrane	Hypogonadism in males
3	Captopress TTS	Clonidine	Membrane	Hypertension
4	Climaderm	Estradiol	Matrix	Postmenstrual syndrome
5	Climara	Estradiol	Matrix	Postmenstrual syndrome
6	Combipatch	Estradiol	Matrix	Postmenstrual syndrome
7	Deponit	Nitroglycerine	Drug in adhesive	Angina pectoris
8	Duragesic	Fenatnyl	Reservoir	Pain relief patch
9	Esclim	Estradiol	Matrix	Hormone replacement therapy
10	Estr aderm	Estradiol	Membrane	Postmenstrual syndrome
11	Fematrix	Estrogen	Matrix	Postmenstrual syndrome
12	Flempatch	Estradiol	Matrix	Postmenstrual syndrome
13	Habitraol	Nicotine	Drug in adhesive	Smoking cessation
14	Lidoderm	Lidocaine	Drug in adhesive	Local Anesthetic
15	Matrifen	Fentanyl	Reservoir	Pain relief patch
16	Minitran	Nitroglycerine	Drug in adhesive	Angina pectoris
17	Nicoderm CQ	Nicotine	Drug in adhesive	Smoking cessation
15	Nicotrol	Nicotine	Drug in adhesive	Smoking cessation
19	Nitrodisc	Nitroglycerine	Micro reservoir	Angina pectoris
20	Nitrodur	Nitroglycerine	Matrix	Angina pectoris
21	Nupatch 100	Diclofenac dimethylamine	Drug in adhesive	Anti-inflammatory
22	Nuvelle TS	Estradiol	Drug in adhesive	Harmone replacement therapy
23	Ortho evra	Estradiol	Drug in adhesive	Postmenstrual syndrome
24	Oxytrol	Oxybutynin	Matrix	Overactive bladder
25	Prostep	Nicotine	Reservoir	Smoking cessation
26	Testoderm TTS	Testosterone	Reservoir	Hypogonadism in male
27	Transdermal – scop	(scopolamine)		Motion sickness
28	TransdermNitro	Nitroglycerine	Reservoir	Angina pectoris
29	Vivelle	Estradiol	Reservoir	Postmenstrual syndrome
30	Vivelle-dot	Estradiol	Reservoir	Postmenstrual syndrome

Methods

Fabrication of Transdermal Patches:

Matrix patches were casted on a glass mould by solvent casting method. Five types of polymer patches were prepared. First two formulations were prepared by using HPMC alone having drug and polymer ratio 1:2, 1:3 using distilled water as a solvent and one more formulation is formulated using HPMC with permeation enhancer Span 80 (1%) having drug polymer ratio 1:4. Next two formulations were prepared by using HPMC and EC in combination having drug and polymer in the ratio 1:(4:8),1:(1:9) using methanol and chloroform as solvent (1:1) ratio and the remaining formulation is formulated with HPMC and EC by using permeation enhancer Span 80 (1%) in ratio of 1:(2:8). Propylene glycol (3%) used as a plasticizer.

FORMULATION (at room temperature 25ºC)

Drug loaded matrix type transdermal patches prepared by using solvent casting method. A petri dish with a total area of 44.15cm^2 is used. Polymers are accurately weighed and dissolved in water, methanol (1:1) solution and kept aside to form clear solution. Drug was dissolved and mixed until clear solution obtained. Polyethylene glycol 400 used as plasticizer and propylene glycol used as permeation enhancer. Mix the above solution and the resulted uniform solution is poured on the petri dish, which was lubricated with glycerine and dried at room temperature for 24hrs. An inverted funnel is placed over the petri dish to prevent fast evaporation of the solvent. After 24hrs, the dried patches is taken out and stored in a desiccators for further studies (evaluation).

Reagents Preparation:

Table No. 4: Fabrication of matrix transdermal patches 3.14 sq.cm

INGREDIENTS	F1	F2	F3	F4	F5
Drug (Atenolol)	50mg	50mg	50mg	50mg	50mg
HPMC	100mg	150mg	200mg	50mg	100mg
EC	------	------	400mg	450mg	400mg
Span 80 (%)	5	------	5	------	5
Propylene Glycol (%)	15	15	15	15	15

Phosphate buffer pH 7.4:

Place 50ml 0.2M KH_2PO_4 in 200ml volumetric flask add 39.1 ml of 0.2M NaOH and then add distilled water to make up the volume.

Preparation of Standard Curve of Atenolol:

Standard graph of Atenolol was prepared by suitably diluting the stock solution of the drug using methanol. Using the stock solution of drug (100 µg/ml in methanol) suitably calculated volume of alliquotes were withdrawn & diluted with plain methanol to get various concentration of Atenolol. Final solution was filtered through 0.45 micron filter & was analyzed by UV Spectroscopy at λmax of 275 nm.

After calculation of λmax graph was plotted between concentration (µg/ml) at X – axis & absorbance (nm) at Y – axis. A linear line was obtained from the graph & R^2 value & value of slope of the graph was calculated. Standard curve with Atenolol was also prepared using the above method and using pH 7.4 at place of methanol. Dilutions prepared was in range of 1-10 µg/ml and was analyzed by UV spectroscopy at λmax of 275 nm.

EVALUATION OF TRANSDERMAL PATCHES[28,29]

Evaluation studies for the transdermal dosage forms can be classified into following types:-

(1) Physicochemical evaluation

(2) In vitro evaluation

(1) Physicochemical Evaluation:

(a) Uniformity of weight:

Weight variation is studied through individually weighing 5 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

(b) Flatness:

For flatness determination, one narrow piece is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

(c) Tensile Strength:

To determine tensile strength of the transdermal patches. The polymeric films in the transdermal patch are sandwiched individually by. One end of the films is kept fixed and other end is connected to a freely movable thread . The weights are added gradually to the pan close with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

Tensile strength= F/a. b (1+L/l)

Where,

F is the force required to break,
a is width of film,
b is thickness of film,
L is length of film,
l is elongation of film at break point.

(d) Moisture content:

The prepared films are weighed individually and put in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

$$\%\text{Moisture content} = \frac{\text{(Initial weight –Final weight) X 100}}{\text{Final weight}}$$

(e) Drug content determination:

Accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

(f) Content uniformity test:

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

(g) Moisture uptake

Weighed films are put in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.

$$\%\text{ moisture uptake} = \frac{\text{(Final weight – Initial weight)}}{\text{Initial weight}} \text{ X 100}$$

(h) Folding Endurance:

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

(i)Adhesive studies:

The adhesive studies are used to determine the adhesive properties of TDDS. The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin.

The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors.

Peel Adhesion properties: It is the force necessary to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° angle. The test is passed if there is no residue on the substrate.

(2) In vitro evaluation:

(a) In vitro release studies:

In vitro release studies performed outside the body. This is used to determine the drug release mechanism and kinetics are two characteristics of the dosage forms which play an important role in describing the drug

dissolution profile from a controlled release dosage forms. The dissolution data explain the release mechanism of the drug.

(b) In vitro permeation studies:

It is used to determine the permeation of the drug from the transdermal dosage form. The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages. Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment.

Table No.5: Physico-chemical evaluation data of Atenolol Transdermal patches

Formulation code	*Folding Endurance	*Moisture Absorbed (%)	*Moisture Lost (%)	*Thickness (mm)
F1	25	2.20	1.20	0.156
F2	28	2.27	1.45	0.175
F3	35	1.57	1.50	0.196
F4	51	2.95	1.38	0.281
F5	47	2.25	1.27	0.248

*indicates average of 3 values

Table No. 6: Drug Content Uniformity

Formula code	% of drug in 3.14 sq.cm			
	1	**2**	**3**	**Mean**
F1	87.12%	86.45%	89.12%	87.56
F2	92.21%	93.01%	92.67%	92.59
F3	95.36%	96.14%	97.42%	96.30
F4	98.18%	98.65%	98.99%	98.60
F5	96.45%	96.12%	96.06%	96.12

Table No. 7: In-vitro diffusion studies of various formulation

Time(hrs)	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.25	0.98	3.934	1.85	3.932	2.95
0.5	1.98	8.918	3.78	7.456	7.918
0.75	3	11.032	6.01	10.082	13.95
1	4.03	17.114	9	17.115	19
2	6.06	21.327	12.01	21.522	23.234
4	10.09	27.573	14.11	26.455	28.979
6	15.18	33.918	17.46	30.767	34
8	18.37	39.377	21.56	35.232	40.416
10	22.6	43.934	27.67	39.878	45.676
12	29.29	50.524	33.31	42	50.132
14	31.72	58.196	38.78	48.091	55.091
16	35.16	63.032	44.3	53.196	63.131
18	37.67	67.937	49.91	58.676	69.182
20	40.21	73.878	54.63	61.001	72.343
22	40.12	75.112	58.21	67.212	76.873
24	44.75	79.001	63.12	82.131	73.156

Table No 8. Standard curve of Atenolol in phosphate buffer pH 7.4

Concentration (µg/ml)	Absorbance
0	0
10	0.055
20	0.091
30	0.142
40	0.201
50	0.291
60	0.357
70	0.412
80	0.497
90	0.565
100	0.601

RESULT AND DISCUSSIONRESULT & DISCUSSION

The physicochemical parameters were performed and the data was reported. F4 have shown tha best formulation whose Thickness(0.281), Folding endurance(51), Moisture absorbed (2.95), Moisture lost (1.38), Drug content uniformity (98.96).

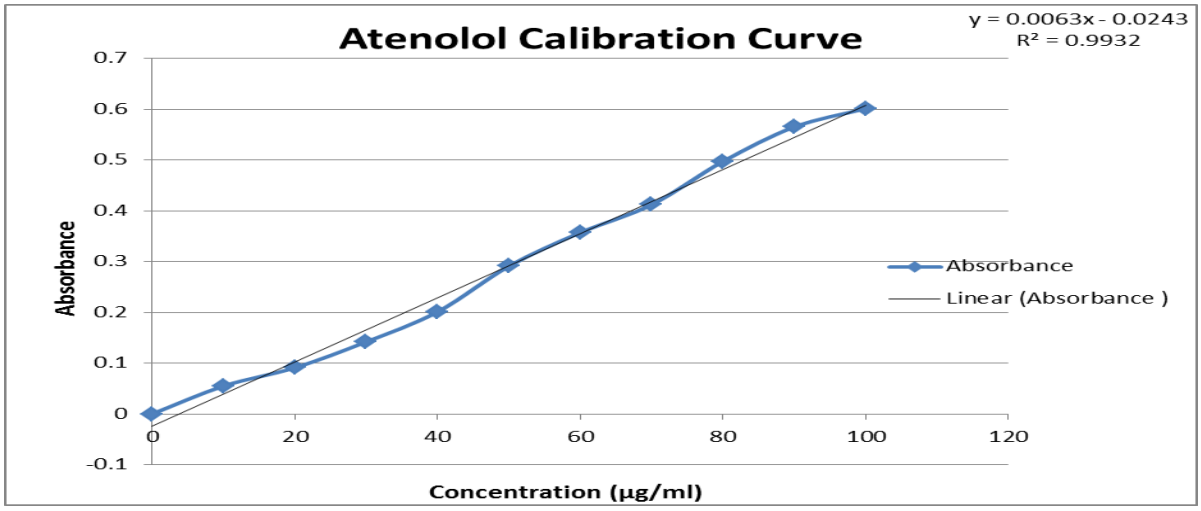


Fig 1 Slope= 0.0061 Regression=0.993

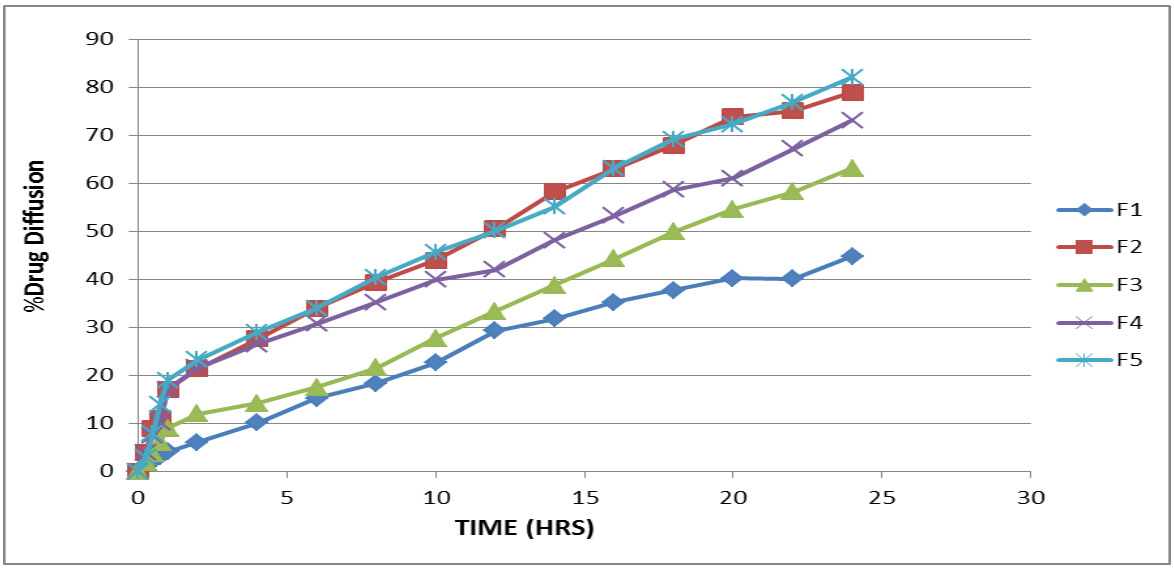


Fig 2: In vitro drug release

SUMMARY AND CONCLUSION

Transdermal patch showed good controlled release properties. The results of the present study demonstrated that Atenolol can be considered for Transdermal patch containing HPMC & EC as polymers & Span 80 as permeation enhancer for controlled release of the drug over a period of 24 hrs for the management of hypertension. The Transdermal drug delivery system holds a promising future in effective Transdermal delivery of bioactive agents and opportunities for clinicians to experiment with various drugs to study their systemic and local effects.

We concluded that the formulation F1, F2, F3, F4 and F5 is considered that the thickness is found to be 0.156mm, 0.175mm, 0.196mm, 0.281mm and 0.248mm respectively, Folding endurance found to be 25, 28, 35, 51, 47 respectively, moisture absorbed 2.20%, 2.27%, 1.57%, 2.95%, 2.25 respectively, moisture lost was found to be 1.20%. 1.45%, 1.50%, 1.38% and 1.27% respectively ,drug content was found to be 87.56%, 92.59%, 96.30%, 98.60% and 96.12% respectively and diffusion of the drug in 24 hours was 44.75%, 79.001%, 63.12% , 82.131% and 73.156% respectively.

The best formulation was found to be F4 with drug diffusion in 24 hours 82.131%, thickness (0.281) folding endurance (51), moisture absorbed (2.95%) moisture lost (1.57%) and drug content (98.60%)

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