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A DETAILED RESEARCH ARTICLE ON THE TRANSDERMAL PATCHES OF ATENOLOL USED FOR TREATING HYPERTENSION

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Abstract: Atenolol is a beta-adrenoreceptor antagonist, or a more commonly known as a beta blocker. Hypertension (higher BP) might be dealt with these drugs since of their capability to surge the width of blood veins thus allowing blood to flow under less pressure.Transdermal drug delivery systems are designed to deliver biologically active agents (drugs or cosmeceuticals) through the skin, principally by diffusion, for local internal if not systemic effects. Transdermal API delivery represents an alternative to other forms and routes of drug delivery.Development of chemical and physical enhancers of transdermal delivery systems (e.g., ethanol-enhancing skin flux, iontophoresis, microneedling, ultrasound, etc.) enables delivery of molecules with hydrophilic properties, such as peptides, proteins, and vaccines. A detailed review for the results which gives accurate and better for the treatment of hypertension using Atenolol as a curing agent is suggested further.

Keywords: Atenolol, Blood Pressure (BP), Hypertension (HTN),Moisture Content, Transdermal Drug Delivery System.

INTRODUCTION

Hypertension is an increasing worldwide issue that is related with various underlying pathophysiological circumstances. These comprise ventricular hypertrophy, along with endothelial dysfunction, as well as metabolic syndrome, with a procoagulant state, oxidative tension, irritation and a genetic predisposition to cardiovascular events. The higher prevalence of hypertension is a particular concern in developing countries as it contributes to the present and anticipated pandemic of cardiovascular disease (CVD). CVD was beforehand graded as another highest source-of-death group within South Africa, resultant in main cost inferences for developing nations.

The resistor of hypertension besides trying to control the danger features, like smoking, dyslipidaemia as well as diabetes mellitus, are among main challenge. This shows that there remains an excessive requirement for antihypertensive chemical that attain larger than the simple sinking of BP, along which provide advantages in the prevention and management of CVD[1], [2].

BP can be terms as per to definite BP and additional co-morbid circumstances. Table 1.1 gives an impression of BP groups[3], [4].

Table 1.1. Blood Pressure Stages.

Category	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Normal	< 120	< 80
Prehypertension	120-139	80-89
Hypertension (stage 1)	140-159	90-99
Hypertension (stage 2)	≥ 160	≥ 100
Hypertension (stage 3)	> 180	> 110

The following are the new optimal BP levels within patients aging 60 or greater, with or deprived of co-morbidities, as per to JNC 8:

- The BP target is < 150/90 mmHg within patients aging 60 years or greater, and who don't have diabetes or chronic kidney disease.
- The new BP target is < 140/90 mmHg within patients aging 60 years and older who have diabetes, chronic kidney disease or both.
- Optimal BP is < 140/90 mmHg within patients aged 18-59 years of age, without any co-morbidities.

A healthy lifestyle remains the foundation of managing hypertension, regardless of BP level. In addition to decreasing BP, it enhances antihypertensive drug efficaciousness and decreases total CV risk. Thus, the following measures assist the patient to ensure a better, healthier life:

- **Achieving and maintaining an ideal body we*ight:*** The ideal body weight is a body mass index of 18.5-24.9 kg/m^2.
- **Limiting total sodium intake***:* Sodium intake must be restricted to < 2 400 mg/day or < 1 teaspoon of salt.
- **Limiting alcohol *intake:*** Alcohol must be restricted to two standard drinks every day for men, and one standard drink every day aimed at women and men of a lesser stature.
- **Following the nutrition guidelines published by the World Health Organisation *(WHO)*:** The WHO guideline accentuates a diet that is low in total fat, with a high intake of fruit and vegetables

(five portions per day), regular lower-fat dairy items, fish rather than red meat, products that are low in saturated fat, a high intake of high-fibre wholegrain foods, low salt and the sparing use of sugar and sugar-containing foods.

- **Partaking in regular, moderate-intensity exercise***:* It is important to exercise for at smallest 30 minutes on most or preferably all days of the week, e.g. brisk walking.
- **Avoiding the use of all tobacco goods:** Entirely tobacco items should be avoided, including snuff.

Possible Treatment

The following factors should be considered when selecting an antihypertensive:

- The cost of the drug
- Patient-related factors, such as the presence of major risk factors, conditions favouring use and contraindications.
- Associated clinical conditions and target organ damage.

Calcium Channel Blockers

CCBs are first-line treatment for primary hypertension in patients over the age of 55 and black patients of African or Caribbean family origin. Rate-controlling CCBs (diltiazem, verapamil) are also used to manage tachyarrhythmias and angina, where their negative inotropic and chronotropic effects improve the myocardial oxygen stock: need ratio. Some CCBs have specific non-cardiac indications, for example, nimodipine in neurosurgery to reduce cerebral vasospasm in patients after spontaneous subarachnoid haemorrhage, and verapamil in neurology to treat cluster headache.

There is slight indication that beginning or ongoing the usage of CCBs perioperatively decreases the danger of myocardial infarction or demise. Whereas there is evidence that continued use of CCBs in the presence of β-blockers may lead to increased incidence of hypotension under anaesthesia, it is not generally recommended that CCBs be withheld before surgery[5].

Beta-lockers.

β-Blockers are not used as first-line antihypertensives unless there are other indications, for example, after myocardial infarction, or in tachyarrhythmias such as atrial fibrillation. Their diverse indications include stable heart failure, thyrotoxicosis, oesophageal varices, anxiety, and glaucoma. Labetalol is a β-blocker which also has α-blocking activity[6], [7].

Alpha-Blockers.

α-Blockers are utilized to deal hypertension in patients resistant to, or intolerant of, other treatments. Specific indications for their use in secondary hypertension include labetalol for pre-eclampsia and phentolamine in the perioperative management of phaeochromocytoma[8].

Conventional Dosage Forms for Drug Delivery

The administration of conventional oral dosage forms like tablets, capsules, liquids orals of drugs suffer a setback owing to issue of gastro abdominal tract engagement, local annoyance, thinning of drug asset, Liver initial pass metabolism, filth of drug through gastro abdominal tract enzymes, the protein binding of drug at an absorption surface and local toxicity. The bioavailability as well as duration of action is reduced which requires frequent administration, which in turn is associated with the problem of patient's compliance to therapy and the economy of the treatment.

Controlled Release Dosage Forms

On the basis of technical sophistication, precise drug delivery scheme can be considered into 3 major classes[9].

A. Rate Programmed Precise Drug Delivery Scheme

Such drug delivery scheme is from the drug issue which has been planned at precise rate outlines. They are additional subdivided into subsequent subclasses.

1. Dissolution Precise Drug Delivery Scheme

Slow dissolution degree of drug

Slow dissolution degree of the pool membrane or else matrix

2. Diffusion Precise Drug Delivery Scheme

Porous matrix-managed system

Porous membrane managed systems

3. Erosion Controlled Drug Delivery Scheme

Surface erosion

Bulk erosion

TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal drug delivery systems are designed to deliver biologically active agents (drugs or cosmeceuticals) through the skin, principally by diffusion, for local internal if not systemic effects. Transdermal API delivery represents an alternative to other forms and routes of drug delivery. However, there is only a limited number of drugs that are suitable for administration by this route[10]. Overall, skin properties allow the transport of a limited number of agents through passive transdermal delivery; for example, small lipophilic APIs, when dosage and consistency of release are not critical, are poised for transcutaneous delivery. Development of chemical and physical enhancers of transdermal delivery systems (e.g., ethanol-enhancing skin flux, iontophoresis, microneedling, ultrasound, etc.) enables delivery of molecules with hydrophilic properties, such as peptides, proteins, and vaccines[11].

Transdermal drug delivery offers the following potential advantages

1. Avoids first-pass hepatic metabolism.
2. Less chances of over or under dosing as the result of prolonged preprogrammed delivery of drug at the required therapeutic rate.
3. Decrease gastrointestinal side effects.

4. Elimination drug food interactions.
5. Increased patient compliance in following manner
6. Chance of toxicity due to additives e.g. preservatives, stabilizing agent antioxidants etc. are less as compared to other dosage forms.

MATERIAL & METHOD

The following materials are used in the present study.

Materials	Suppliers
Atenolol	Sun Pharmaceutical Ind. Ltd., India
Eudragit RL 100	Signet Chemical Corporation, India
Eudragit RS 100	
Ethyl cellulose 22 CPS USP/EP	
Ethylene Vinyl Acetate Copolymer	Aldrich Chemicals, U.K.
Polyvinyl Pyrrolidone	Loba Chemical Pvt. Ltd., Mumbai, India
Triethanol amine	
Propylene glycol	
Hydroxy propyl methyl cellulose 400	Signet Chemical Corporation, India
Carbopol 934	Corel Pharma Chem., Ahmedabad, India
Ethanol	Baroda Chemical Industries Ltd., Vadodara, India
Di-n-butyl phthalate (DBP)	S D Fine Chem. Ltd., Mumbai, India

Equipment'sor InstrumentsUsed in Present Investigation

Instruments	Manufacturer
Sartorius electronic balance	Shimadzu, Kyoto, Japan
Digital pH meter	Systronic, Ahmedabad, India
UV/VIS Double beam spectrophotometer 2204	Shimadzu, UV-1700, Kyoto, Japan
Differential scanning calorimeter	DSC – Shimadzu 60 with TDA trend line software, Shimadzu, Tokyo, Japan
FTIR Spectrophotometer 8400	Shimadzu Corporation, Japan
Magnetic Stirrer	Remi equipment, Mumbai, India
Mechanical water bath shaker NSW-133	
Centrifuger REMI R-23	
Micrometer (0.001mm)	Mitutoyo, Japan

RESULTS

The present investigation deals with the development of Atenolol loaded polymericmatrix using different polymers. The preliminary screening was approved out for choice of best polymer. A diffusion mediated matrix controlled transdermal drugdistribution system for Atenolol was successfully set using diverse polymersusing mercury subtract method and all matrices were evaluated using differentphysiochemical parameters.

Thickness

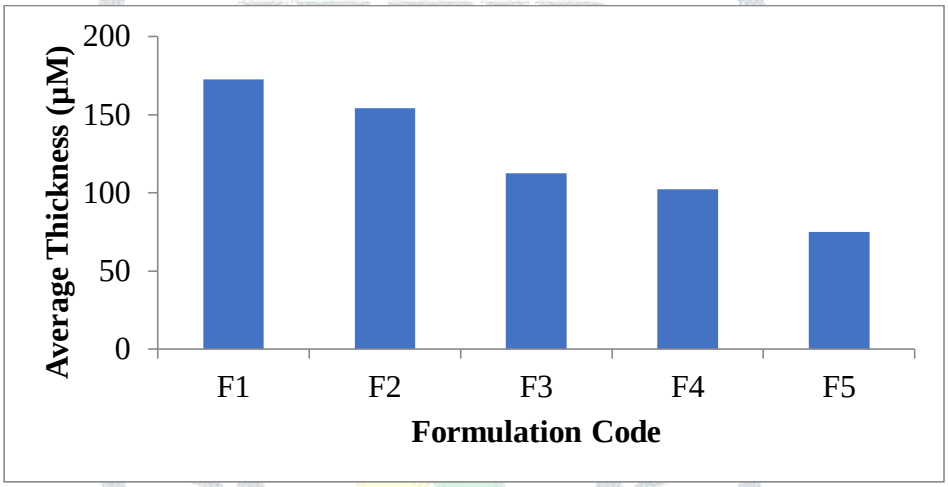
With the help of micrometre (0.001mm), Mitutoyo, Japan, the thickness of film was measured at six different points and the average thickness was noted. The results of thickness measurements are given in Table 1.2. The results indicate that there wasno much difference in the thickness with in the formulations. Thickness in thedifferent formulations was in the range of **172.5 ± 1.5 µm**to **75.0 ± 1.5 µm**.Maximum thickness was found in formulation F1, while minimum found in formulation F4. These results revealed that thickness was initiate to upsurge as hydrophobic portion of polymer increases. The results of thickness measurements alsoindicate

uniform distribution of the drug and polymer over the mercury surface. Therank order of thickness of Atenolol loaded polymeric matrices was EVA (40% VA) copolymer > ERS 100 > ERL100:ERS100 (1:1)> EC: PVP (2:3) >ERL 100: HPMC (2:3)

S.No	Formulation Code	Average Thickness (µM)
1	F1	172.50 ± 1.500
2	F2	154.16 ± 0.443
3	F3	112.50 ± 1.500
4	F4	102.50± 0.443
5	F5	75.00 ± 1.500

***Standard deviation, n=3**

Table 1.2 Results of Thickness Uniformity of F1 to F5 Film Formulations.



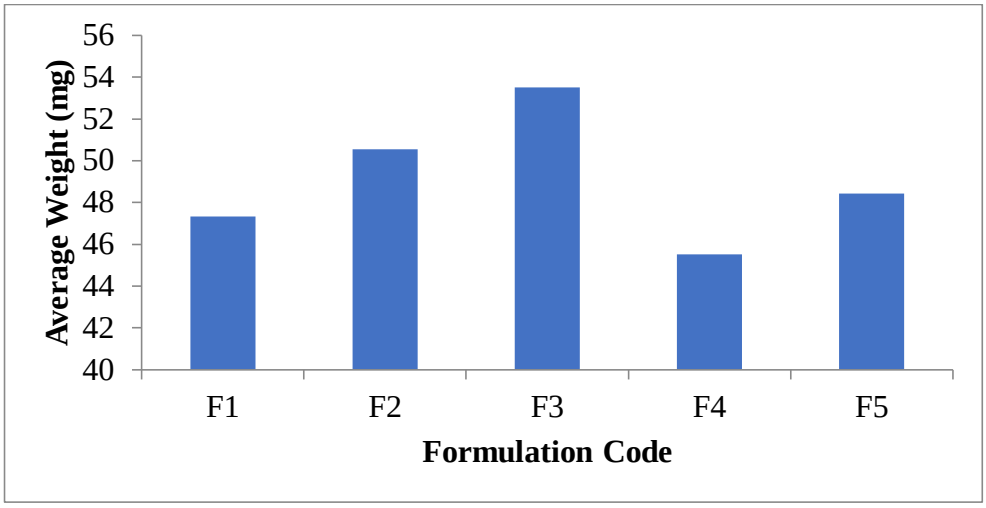
Weight Variation

Drug loaded films (3.14cm^2) were weighed using Sartorius electronic balance (ModelCP-224 S), Shimadzu, Japan and the results of weight variation are given in Table 1.3.

S.No	Formulation Code	Average Thickness (mg)
1	F1	47.33 ± 0.208
2	F2	50.56 ± 0.251
3	F3	53.50 ± 0.200
4	F4	45.53 ± 0.404
5	F5	48.43 ± 0.305

***Standard deviation, n=3**

Table 1.3 Results of Weight Variations of F1 to F5 Film Formulations



The weight of 3.14 cm^2 film ranged from **45.30 ± 0.100 mg** to **53 ± 0.500 mg.**The weight of the patches was found to be uniform among different batches.

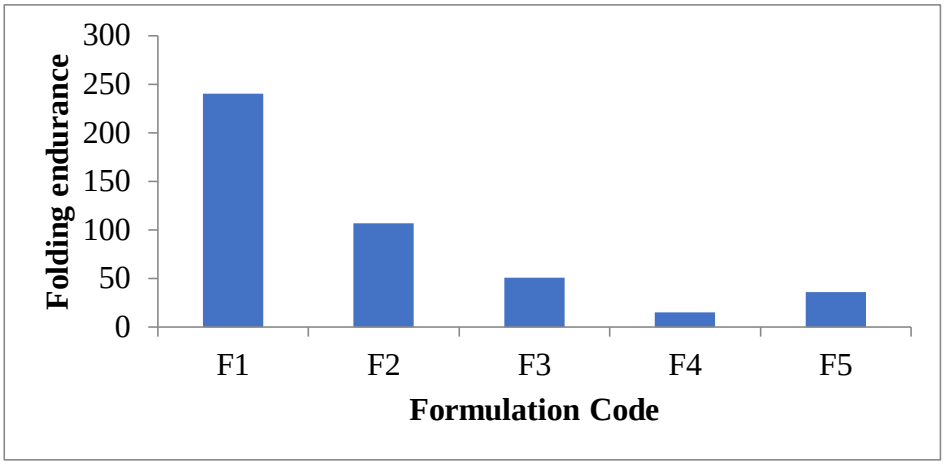
In a weight variation test, the pharmacopeial limit for the percentage deviation of allthe films of less than mg is ± 10%. The regular percentage unconventionality of all preparations was created to be inside the bound, and henceforth all the formulation agreedthe examination for weight variation as per authorized supplies. All the designs presentedsatisfactory pharmaco-technical possessions. From the outcomes found, it was vibrant thatthere was correct delivery of Atenolol within the film formulations. Hence it wasconcluded that drug was uniformly distributed in all the formulation, with smalldeviation.

Folding Resolution

Folding resolution was determined manually for drug loaded polymeric matrices. Thefolding resolution of the flicks was resolute by frequently folding a strip measuring2x2 cm size at same room till it disrupts. The sum of periods the flick could be pleatedat the similar place without flouting gave the worth of folding resolution. The results offolding endurance are given in Table 1.4.

S.No	Formulation Code	Folding endurance
1	F1	240.33 ± 1.527
2	F2	107.00 ± 2.000
3	F3	51.00 ± 1.000
4	F4	15.00 ± 1.000
5	F5	36.33 ± 5.131

Table 1.4 Results of Folding Resolution of F1 To F5 Film Formulations.



Here formulation F1, F2 and F3 shows good folding endurance as compare toformulation F4 and F5.

Moisture Content (Loss on Drying)

The wetness content was determined by keeping the drug loaded polymeric matrices patches in desiccator containing activated silica for 24h. The percentage moisturecontent was calculated from the weight differences relative to the final weight. The moisture content in all the formulations was found to be low and ranged from**0.571 ± 0.013** to **4.103 ± 0.210 %.** The result exposed that the wetness content wasoriginate to upsurge with increasing concentration of hydrophilic polymers. The smallmoisture content in the formulations helps them to maintain texture.The rank order of % moisture content of Atenolol loaded polymeric matrices was**EVA (VA 40%) copolymer < ERS 100 < ERL100:ERS100 (1:1) < EC: PVP(2:3)>ERL 100: HPMC (2:3).**

Moisture absorption

% Moisture absorption was determined by keeping the drug matrices in a desiccatorcontaining 200 ml saturated solution of Sodium chloride (Relative humidity of 75%) at normal room temperature for 72hr. The final weight was noted when there was nofurther change in the weight of individual patch. The percentage moisture absorptionwas calculated as a difference between final and initial weight with respect to initialweight.

The moisture absorption within all the preparations was initiate to be lower and ranged from**0.7400 ± 0.0360 to 5.8734 ± 0.1706.** The results exposed the moisture absorptionwas originate to upsurge with growing concentration of hydrophilic polymers. Therank order of % moisture absorption for Atenolol loaded matrices was**EVA (VA 40%) copolymer < ERS 100 < ERL100:ERS100 (1:1) < EC: PVP (2:3)<ERL100: HPMC (2:3)**

In Vitro Diffusion Experiment of Atenolol Loaded MatrixDiffusional Films

The release rate determination is one of the most important studies to be conducted for all controlled release delivery systems. The diffusion study of patches is veryvital, because one requirement to uphold the drug attention on the exterior ofstratum corneum reliably and substantially greater than the drug concentration inthe body to achieve a constant rate of drug permeation.

Experimental Results

An *in vitro* diffusion study of Atenolol from various polymeric matrices was studied using modified Keshary-Chien diffusion cell. The effective infusion area of thediffusion cell and receptor cell volume was 3.14cm^2 and 40 ml, respectively. Thetemperature was maintained at 37 ±0.5ºC. The receptor compartment contained 40 mlof 0.01N HCl stirred by magnetic stirrer.Samples (2 ml) were withdrawn and replaced with the same volume of fresh receptorsolution, through the sampling port of the diffusion cell at different time intervals. The absorbance of the withdrawn samples was measured using UV VISspectrophotometer at 237.5 nm using 0.01N HCl as a blank. The experiments weredone in triplicate. Amount of drug released per square centimetre of patch wereplotted against function of square root of time for different formulations. The releaserate Q/√T was determined by simple regression analysis of steady state data.

Diffusion studies are important for ensuring the sustained release performance and the reproducibility of rate and duration of drug release.*In vitro* release profile is an important tool that predicts in advance, the extent of concentration builds up *in vivo*.The results of *in vitro* drug diffusion studies from transdermal patches are depicted inTable1.5 and Figure 1.

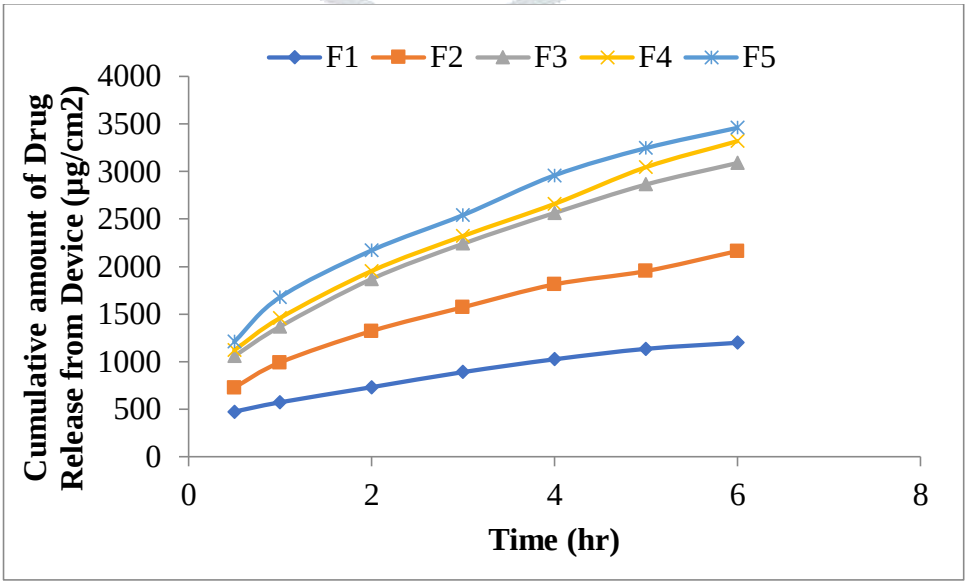
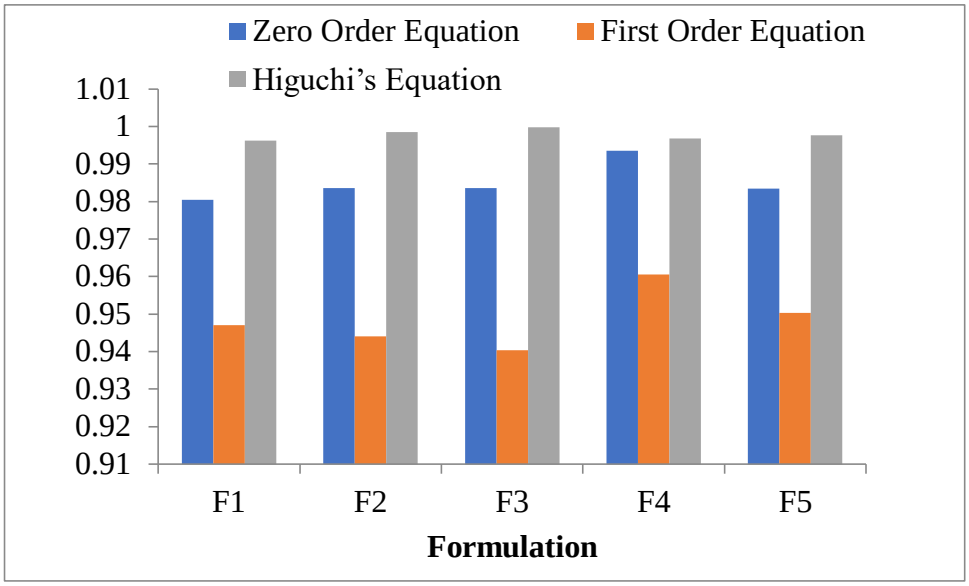


Figure1 *In vitro*Diffusion Release Profiles of Atenolol fromDifferent Matrix.

Time (hr)	Cumulative amount of Drug Release from Device (µg/cm^2)				
	F1	F2	F3	F4	F5
0.5	473.34 ± 25.67	726.48 ± 29.40	1060.46 ± 35.78	1120.23 ± 39.56	1210.39 ± 42.56
1	571.56 ± 25.46	990.49 ± 35.78	1370.89 ± 55.39	1459.23 ± 55.29	1678.34 ± 60.43
2	731.22 ± 31.56	1320.40 ± 51.34	1870.45 ± 60.99	1953.34 ± 61.64	2169.90 ± 71.34
3	890.56 ± 35.67	1570.30 ± 55.78	2241.36 ± 71.64	2321.90 ± 71.56	2541.20 ± 80.43
4	1025.89± 40.79	1810.37 ± 59.88	2564.90 ± 79.45	2659.86 ± 79.40	2958.68± 100.5
5	1136.30± 64.99	1950.34 ± 64.99	2863.94 ± 90.57	3045.75 ± 80.38	3245.46± 106.3
6	1200.13 ± 51.34	2160.80 ± 70.01	3090.34± 101.4	3320.00 ± 48.67	3458.95 ± 78.46
Q/√T	434.45	810.72	1220.90	1265.00	1337.80

Table 1.5 Cumulative Amount of Drug Release.

The results of diffusion study of Atenolol released from polymeric matrix, formulatedusing various polymers. The release rate Q/√T **(**µg/cm^2 √hr) was determined by simple regressionanalysis of steady state data. The release of Atenolol from all the matrices followedsquare root law. The rank order of release was **EVA (VA 40%)copolymer < ERS100 < ERL100:ERS100 (1:1) < EC: PVP (2:3) < ERL100: HPMC (2:3).** The *in vitro* permeation experiment indicated that when the hydrophilic polymerconcentration increased, the amount of drug permeation increased. As described initial rapid dissolution of the hydrophilic polymers occurs when thepatch is in contact with the hydrated skin, resulting in the accumulation of highamount of drug on the skin surface and thus leading to the saturation of the skin withdrug molecule at all the time.Formulation **F1 EVA (VA 40%) copolymer** exhibited minimum Q/√T release rate **(434.45 µg/cm^2√h)** while Formulation **F5** exhibited maximum Q/√T release rate(**1337.80 µg/cm^2 √h**). The physiochemical property of polymer plays important rolein drug release characteristics, from the polymeric matrix. EVA (VA 40%) copolymer is more hydrophobic as compare to other polymers and exhibited reduced permeationfrom the matrix. It was observed that as the concentration of hydrophilic polymerincreased in the formulation the rate of diffusion increased subsequently. “Bursteffect” was observed in the formulation F4 and F5 and this may be due to sufficientsolubility of drug in the polymer.

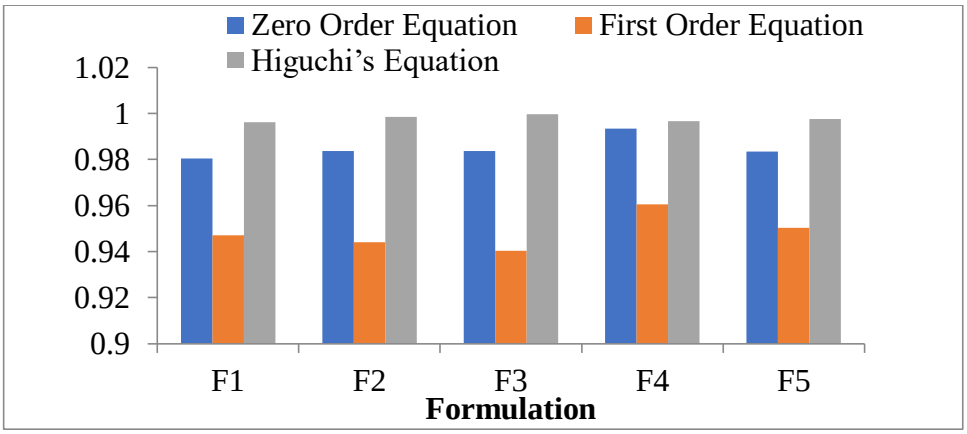


***In vitro* release kinetic**

The release data was fitted into various mathematical models using software to know which mathematical model will best fit to obtained release profiles. The obtained Rvalues for various models are given in Table 1.6.The process of drug release in most controlled release devices including transdermalpatches is governed by diffusion and the polymer matrix has a strong influence on thediffusivity as the motion of a small molecule is restricted by the three-dimensionalnetwork of polymers chain. The in vitro release profile could be best expressed byHiguchi's equation for the permeation of drug from the matrix.

Formulation	Zero Order Equation	First Order Equation	Higuchi's Equation
F1	0.9804	0.9470	0.9962
F2	0.9836	0.9440	0.9985
F3	0.9836	0.9404	0.9998
F4	0.9935	0.9606	0.9968
F5	0.9835	0.9503	0.9977

Table 9.5 Data of Various Parameters of Model Fitting of Formulations.



The importance of polymer dissolution on drug release from matrices has been knownfor ensuring the controlled release performance and the reproducibility of rate andduration of drug release. Initial "burst release" was observed in patches F4 and F5.This may be because of the much higher % of hydrophilic polymer. These hydrophilic components allow faster release of drug exhibiting small "time lag" to establish aconcentration profile in the patches resulting in a "burst effect" in diffusionstudies. When burst release as well as higher release rate was considered,formulation F4 and F5 may be avoided from the preparation of a physiochemicallystable and controlled release patch type formulation. Formulation F1 and F2 gave theslowest release. Thus, it can be reasonably be suggested that the formulation **F3** is bestsuited for further *in vitro* permeability study through human live skin.

***In Vitro* Permeation Study Through Human Live Skin**

Diffusion study of Atenolol from selected matrix device across human live skin wasperformed using modified Keshary-Chien diffusion cell. A section of skin was cut and placed on the brim of diffusion cell in such a way that the dermal side of the skinfaced donor compartment. The patch of Atenolol was affixed on the skin in such away that backing membrane was facing upward. The experiments were done in triplicate. Amount of drugreleased per square centimetre of patch were plotted against function of time. Therelease rate was determined by simple regression analysis of steady state data.

In vitro permeation studied is predictive of in vivo performance of a drug. The resultsof in vitro skin permeation of Atenolol from formulation **F3**are shown in figure 2.

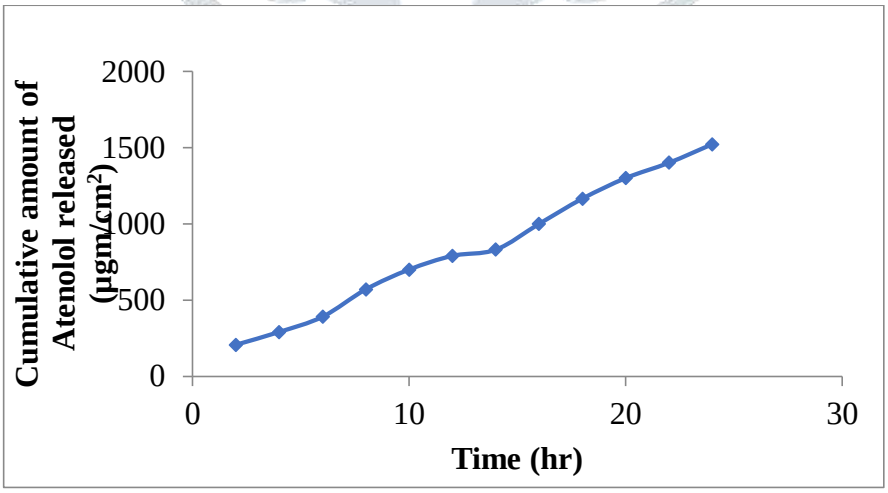


Figure 2 *In Vitro* Skin Permeation Profile of Atenolol from Matrix Patch Through Human Live Skin.

Figure represent prolong release of atenolol from matrix patch.

CONCLUSION

ERL100:ERS100 matrix moderated transdermal drug delivery system of Atenolol hasbeen prepared successfully. Among different polymers evaluated ERL100:ERS100 inratio of 1:1 containing Atenolol provided a medicated matrix, whichwas stable, non-irritant and non-sensitizing to skin and was safe. It complied withofficial and non-official pharmaceutical specification. The matrix device evaluated for Atenolol release in vitro into infinite sink and across human live skin, enabled to provide adequate rate of Atenolol, meeting requisite pharmacokinetic requirement of steady state plasma concentration for 24 hours, giving once a day drug delivery system.

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