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Design and evaluation of transdermal films of Atenolol

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ABSTRACT

The purpose of this research was to develop a matrix-type transdermal therapeutic system containing drug Aceclofenac with different ratios of hydrophilic (hydroxyl propyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems by the solvent evaporation technique by using 15 % w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer. Different concentrations of oleic acid and isopropyl myristate were used to enhance the transdermal permeation of Atenolol. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance, percentage of moisture content and water vapour transmission rate. All prepared formulations indicated good physical stability. In-vitro permeation studies of formulations were performed by using Franz diffusion cells. Formulation prepared with hydrophilic polymer containing permeation enhancer showed best in-vitro skin permeation through rat skin (Wistar albino rat) as compared to all other formulations. The results followed the release profile of Aceclofenac followed mixed zero-order and first-order kinetics in different formulation. However, the release profile of the optimized formulation F4 (r2 = 0.9935 for Higuchi) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. These results indicate that the formulation containing the F4 [CAP: PVP (6:1)] has shown optimum release in concentration independent manner.

Key words: Atenolol, Transdermal Film, Permeation enhancer, *In-vitro* permeation study.

INTRODUCTION

Transdermal delivery of drugs is a novel drug delivery system and this system breaks many barriers in drug therapy like need of assistance, intermediate dosing and uncomfortable administration[1]. The transdermal route of administration is recognized as one of the potential route for local and systemic delivery of drugs, it also provides a controlled release of medicament into patients [2]. Transdermal delivery has many advantages over conventional modes of drug administration, it avoids hepatic first pass metabolism, potentially decreases side effects and improves patient compliance [3]. Atenolol is a beta- adrenergic blocking agent[4-6]. Atenolol blocks the action of the sympathetic nervous system a portion of the involuntary nervous system. So the transdermal delivery systems were prepared by using cellulose acetate phthalate[7], poly vinyl pyrrolidine and poly ethylene glycol. The aims of the present study were to (1) prepare transdermal patches of Atenolol using various polymers; (2) study the *in-vitro* diffusion behavior of prepared transdermal patch formulations in the presence. The purpose was to provide the delivery of the drug at a controlled rate across intact skin.

EXPERIMENTAL SECTION

Atenolol was received as a gift samples from Lincoln Pharmaceuticals, Ahmedabad, India. Cellulose acetyl phthalate and Poly vinyl pyrrolidine, Poly ethylene Glycol were generous gift from Colorcon Asia Pvt. Ltd (Mumbai, India) and Maan Pharmaceuticals Ltd. (Ahmedabad, India), respectively. Other materials used in the analytical grade. Double-distilled water was used throughout the study.

Investigation of Physicochemical Compatibility of Drug and Polymer[8]

The physicochemical compatibility between Atenolol and polymers used in the films was studied by using differential scanning calorimetry (DSC- Shimadzu 60 with TDA trend line software, Shimadzu Co., Kyoto, Japan) and fourier transform infrared (FTIR- 8300, Shimadzu Co., Kyoto, Japan) spectroscopy. In DSC analysis, the samples were weighed (5 mg), hermetically sealed in flat bottom aluminum pans, and heated over a temperature range of 50 to 300°C at a constant increasing rate of 10°C/min in an atmosphere of nitrogen (50 mL/min). The thermo grams obtained for Atenolol, polymers, and physical mixtures of Atenolol with polymers were compared. The infrared (IR) spectra were recorded using an FTIR by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm–1. The spectra obtained for Atenolol, polymers, and physical mixtures of Atenolol with polymers were compared.

Formulation of Drug Free Patches:

Polymers of single or in combination are accurately weighed and dissolve in respective solvent and then castled on a porcelein tile with defined surface. The films were allowed to dry overnight at room temperature. Then the films are separated and noticed for film formations.

Formulation of Drug Incorporated Transdermal Patches[9-11]

Accurately weighed quantities of polymer individually and / or in combination were dissolved in required quantity of solvents namely methanol, acetone in which drug and polymer have been dissolved. The solution was mixed with magnetic stirrer to get homogeneous consistency. This

was castled on a porcelein tile with defined surface; it was covered by funnel to control evaporation of solvent and allowed to dry at room temperature over night. The films were separated and the backing membrane used was aluminum foil and the formulations were stored in desiccator. The composition of patches prepared using Atenolol was given in Table No.3.

Table-1: Composition of Transdermal Patches of Atenolol

Formulation Code	CAP (%)	PVP (%)	Permeation Enhancer
F1	1	2	Polyethylene glycol (100mg)
F2	1	4	
F3	1	6	
F4	6	1	
F5	4	1	
F6	2	1	

Drug incorporated in each film – 70 mg
Backing membrane – Aluminium foil

Physico – chemical evaluation of transdermal patches

Percent Moisture Absorption[12]:

The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions. In the present study the moisture absorption capacities of the films were determined in the following manner.

The films were placed in dessicator containing saturated solution of aluminum chloride, keeping the humidity inside the dessicator at 79.5% RH. After 3 days the films were taken and weighed the percentage moisture absorption of three films was found.

$$\text{Percent moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percent Moisture Loss [13]:

This test was also carried to check the integrity of films at dry condition. Three films of 5 square centimeter area was cut out and weighed accurately and kept in a dessicator containing fused anhydrous calcium chloride.

After 72 hours the films were removed and weighed. Average percentage moisture losses of three films were found out.

$$\text{Percent moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Thickness[14]:

Thickness of the films were measured at six different points using a screw gauge and average thickness of three films were found out.

Drug content[15] **:**
A film of 1 square centimeter area was cut and dissolved in phosphate buffer pH 7.4. After adding suitable reagent and dilution, optical density was found out at 229.2nm. Average drug content of three transdermal films were determined.

Folding Endurance [16] **:**
It was determined by repeatedly folding a small strip of films at the same place till it broke. The number of times, the films could be folded at the same place without breaking gave the value of folding endurance.

Weight Uniformity[17]**:**
Each film was weighed individually and average weight of three films was found.

***In –vitro* drug release studies**
U.V. Method
Freshly treated commercial semi permeable membrane[18] was employed in this study. The membranes used were transparent and regenerated cellulose type, which were permeable to low molecular weight substances.

The semi permeable membrane was tied on one side of the two sided open end cylinder[19]. The entire surface of the membrane was in contact with the receptor compartment containing 300ml of pH 7.4 buffer. The content of the receptor compartment was agitated by a magnetic stirrer at 50 rpm.
A transdermal patch of 5cm in diameter was placed over the membrane which in turn placed over the donor compartment. Samples of 1ml were withdrawn from receptor compartment for every hour and replaced by equal volumes of fresh receptor medium inorder to maintain the same volume of the medium. The concentration of atenolol permeated was determined spectrophotometrically at 229.2nm after suitable dilution against phosphate buffer pH 7.4 as blank.

***Ex – vivo* permeation studies in animal skin**[20]**:**
A primary skin irritation test was performed since skin is a vital organ through which drug is transported. The test was carried out on 6 healthy rabbits weighing 1.5 to 2.0 kg and age around 24 months. Formulation (Cellulose acetate phthalate: Poly vinyl pyrrolidone 6:1) was subjected to the study, the plain polymer films were used as control. The dorsal surface of the rabbit was cleared and hairs were removed by shaving. The skin was cleaned with rectified spirit. The patches were placed over skin with the help of adhesive tape. The patches were removed after 24hrs and the skin was examined for erythema and oedema.

Table-2:Draize Scoring Method

S. No	Erythema & Eschar Formation	Oedema Formation	Score Assigned
1	No erythema	No oedema	0
2	Very slight erythema	Very slight oedema	1
3	Well defined erythema	Slight oedema	2
4	Moderate to severe erythema	Moderated oedema	3
5	Severa erythema	Severe oedema	4

Table-3*: In-vivo* Skin Irritation data for F4 [CAP: PVP (6:1)]

Category	Condition	Score obtained
Control	Erythema	0
	oedema	0
Test	Erythema	0
	oedema	0

RESULTS AND DISCUSSION

In the present work efforts have been made to prepare transdermal patches of atenolol by using different polymers in different ratios such as cellulose acetate hydrogen phthalate and poly vinyl pyrrolidine. The study was targeted to prepare once a week delivery system of atenolol by using different combinations of the above-mentioned polymers and the plasticizer used was polyethylene glycol. The prepared formulations were subjected to various physicochemical characteristics such as percent moisture absorption, percent moisture loss, drug content, thickness, folding endurance and weight uniformity. The results are shown in Table no: 5. The release characteristic of the formulation was studied in in-vitro dissolution studies, ex-vivo diffusion studies by using rat skin, and guinea pig skin.

The formulation F4 (CAP**:** PVP (6:1)) has shown lowest percent moisture absorption and percent moisture loss than other formulations. This might be because of the low water permeability of cellulose acetate hydrogen phthalate polymer. It also observed that F3 (CAP: PVP (1:6)) has shown highest percent moisture absorption and percent moisture loss which might be due to high permeability of poly vinyl pyrrolidone to water.

The thickness of the films varied from 0.22 to 0.41mm. The minimum standard deviation values assumed that the process used for preparing the drug delivery system is capable of giving reproducible results. This fact is further confirmed by drug content and weight uniformity studied. In order to evaluate the flexibility the film were subjected to folding endurance studies. The values in the range of 75 to 77 were observed in all batches. This revealed that the prepared films were having capability to with stand the mechanical pressure along with good flexibility.

***In-vitro* Dissolution Studies**:
In-vitro dissolution studies were carried out in phosphate buffer pH 7.4 for 12 hours. In order to find out the order of release and the mechanism, which was predominately influences, the drug release from the membrane, the in-vitro dissolution data was subjected to 2 different modes of graphical treatment they are

1. Percentage drug release Vs Time
2. Percentage drug release Vs Square root of time

The slope value and the degree of linearity of the above graphical treatments were considered as important statistical parameters to interpret the in-vitro profile of all formulations.

Table-4. Data for Regression

Formulation Code	Regression for *In-vitro* Plot	Regression for Higuchi's Plot
F1	0.9914	0.9450
F2	0.9942	0.9343
F3	0.9954	0.9043
F4	0.9941	0.9277
F5	0.9976	0.9386
F6	0.9970	0.9091

The formulation F1 [CAP: PVP (1:2)] has shown the drug release for 12 hours to the extent of 69%. The Higuchi's plot has shown the regression value 0.9450 which indicates that the release of drug from the patch was governed by a diffusion mechanism.

The formulation F2 [CAP: PVP (1:4)] has shown the drug release for 12 hours to the extent of 73%. The Higuchi's plot has shown the regression value 0.9343 which indicates that the release of drug from the patch was governed by a diffusion mechanism.

The formulation F3 [CAP: PVP (1:6)] has shown the drug release for 12 hours to the extent of 76%. The Higuchi's plot has shown the regression value 0.9043 which indicates that the release of drug from the patch was governed by a diffusion mechanism.

The formulation F4 [CAP: PVP (6:1)] has shown the drug release for 12 hours to the extent of 57%. The Higuchi's plot has shown the regression value 0.9277 which indicates that the release of drug from the patch was governed by a diffusion mechanism.

The formulation F5 [CAP: PVP (4:1)] has shown the drug release for 12 hours to the extent of 61%. The Higuchi's plot has shown the regression value 0.9386 which indicates that the release of drug from the patch was governed by a diffusion mechanism.

The formulation F6 [CAP: PVP (2:1)] has shown the drug release for 12 hours to the extent of 63%. The Higuchi's plot has shown the regression value 0.9091 which indicates that the release of drug from the patch was governed by a diffusion mechanism.

Based on the drug release the optimized formulation selected for further study was F4 [CAP: PVP (6:1)] and the values are reported in table no: 4 and Figure no: 1,2.

***Ex-vivo* Drug Permeation Study:**

After carrying out the in-vitro diffusion studies for all the formulations, the best formulation was selected for the ex-vivo permeation studies. The study was carried out in Guinea pig skin and Rat skin in order to select the best biological system, which has good correlation with in-vitro release. When the study was carried out in rat skin, the formulation F4 [CAP: PVP (6:1)] showed drug diffusion for 12 hours up to the extent of 65%. The studies, which were carried out in guinea pig showed drug diffusion of 59% respectively.

The various among the used biological membranes could be attributed to the fat content and thickness of the membranes used. As earlier studies indicate that the human skin best correlation with the diffusion rate of guinea pig skin, the results were analyzed on this point of view. As

guinea pig skin showed good correlation with in-vitro drug release of formulation F4 and this was considered for further studies. The individual values are found in Table no: 6, 7 and Figure no: 3, 4.

***In-vivo* studies:**

Primary skin irritation test:

The skin irritation studies were also performed for the ideal patch to observe any visual skin irritation after the application of the patch to the albino rabbits. The results indicated that neither the blank patch nor the drug incorporated patch caused any noticeable irritation on the rabbit skin throughout the study. The values are reported in Figure no; 5, 6.

Table-5: Physicochemical Evaluation data of Atenolol Transdermal Patches

Formulation Code	% Moisture Absorption+SD	% Moisture Loss+SD	Thickness (mm)+SD	Weight Variation (mg)+SD	Folding Endurance+SD	% Drug Content+SD
F1	7.40+0.05	6.97+0.06	0.24+0.02	459+0.21	76+0.5	97.0+0.4
F2	8.18+0.02	10.15+0.45	0.28+0.01	660+0.13	74+1.1	98.8+0.1
F3	10.33+0.04	12.42+0.20	0.41+0.02	861+0.23	75+1.5	98.4+0.6
F4	4.64+0.02	5.10+0.18	0.39+0.01	862+0.17	76+1.2	99.0+0.4
F5	7.25+0.03	9.36+0.12	0.31+0.06	662+0.11	77+1.7	96.7+0.4
F6	6.04+0.04	8.63+0.32	0.22+0.03	463+0.19	74+1.4	96.5+0.5

Figure :1. Comparative Release profile of Atenolol formulations F1- F-6

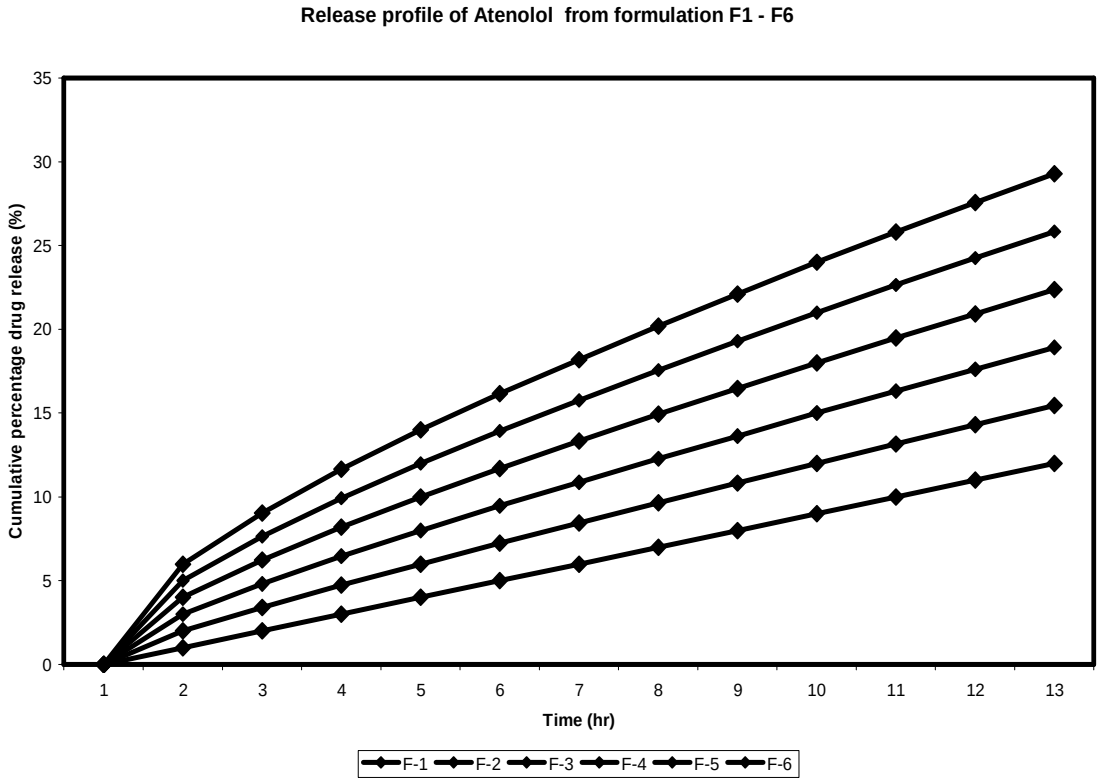


Figure: 2. Comparative Higuchi's Plot of Atenolol formulations F1- F-6

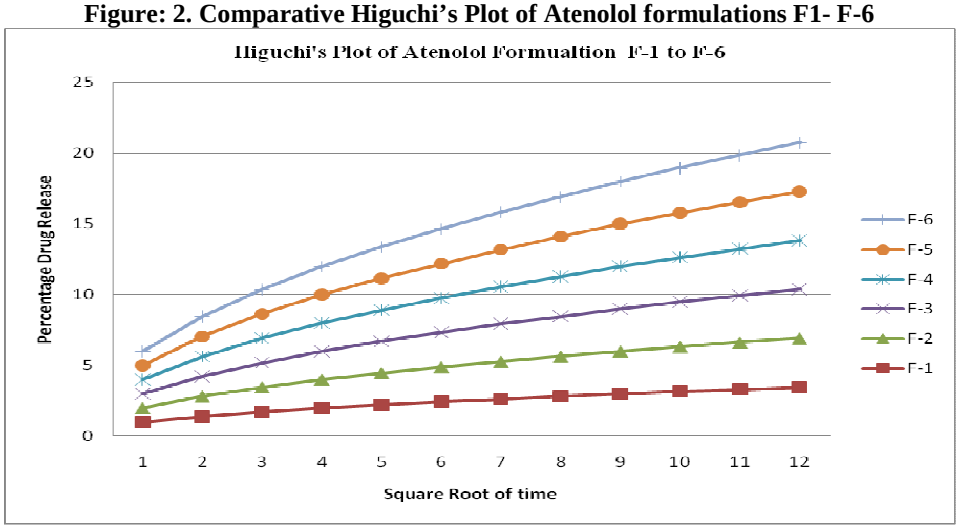


Table-6: *Ex-vivo* Permeation Studies using Rat abdominal skin with F-4[CAP: PVP-6:1]

Time (h)	Amount of Drug Release in mg	% Drug Release
1	0.4	4
2	0.7	7
3	1.5	15
4	2.0	20
5	2.6	26
6	3.0	30
7	3.3	33
8	4.1	41
9	4.7	47
10	5.2	52
11	5.9	59
12	6.5	65

Figure: 3 *Ex-vivo* Permeation Studies using Rat abdominal skin with F-4[CAP: PVP-6:1]

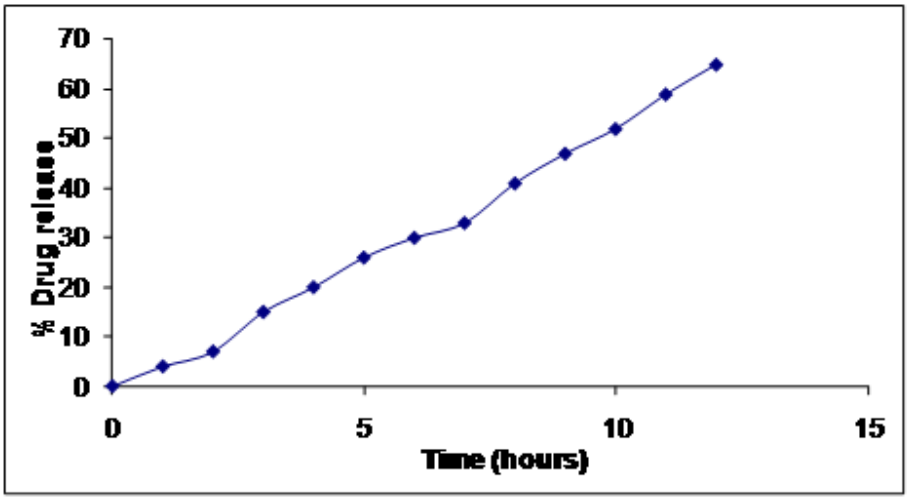


Table – 7 ; *Ex-vivo* Permeation Studies using Guinea pig skin with F4[CAP: PVP-6:1]

Time (h)	Amount of Drug Release in mg	% Drug Release
1	0.3	3
2	0.9	9
3	1.4	14
4	1.7	17
5	2.4	24
6	2.9	29
7	3.6	36
8	3.9	39
9	4.4	44
10	5.1	51
11	5.6	56
12	5.9	59

Figure: 4 *Ex-vivo* Permeation Studies using Guinea pig skin with F4[CAP: PVP-6:1]

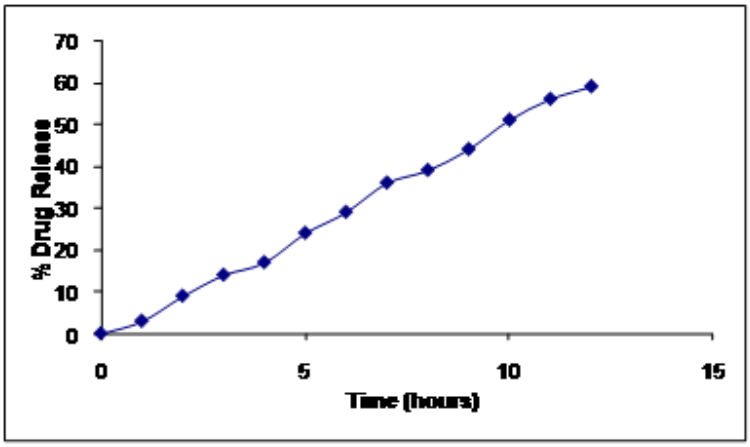


Fig.5: *Ex-Vivo* Permeation studies through various biological membranes

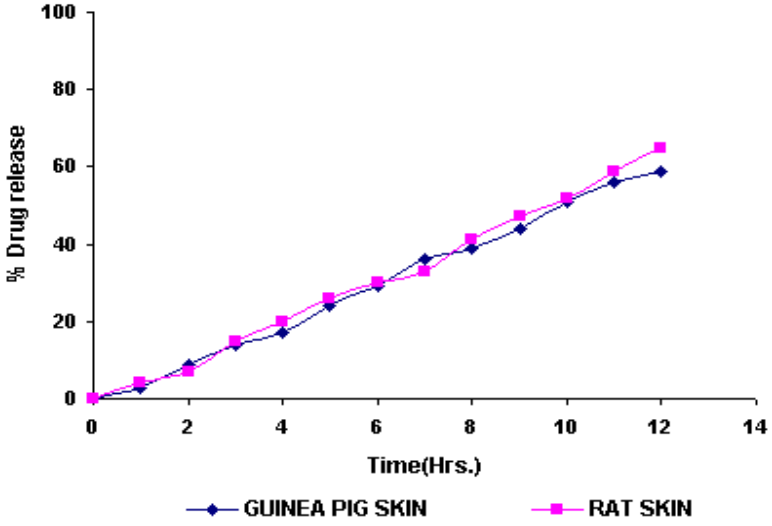
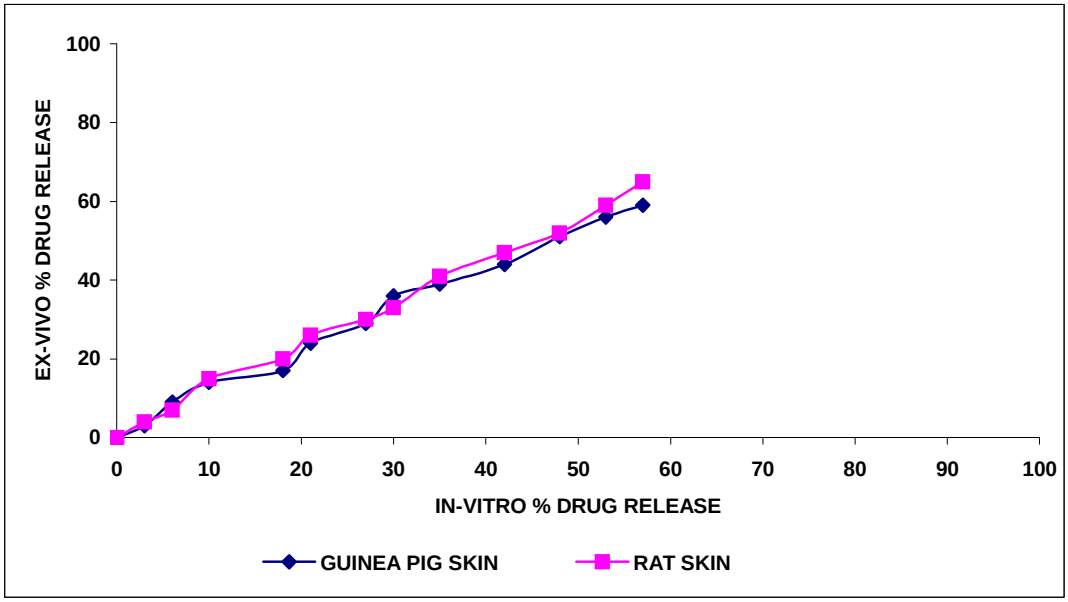


Fig.6: *In-Vitro ex-Vivo* Correlation of F-4 [CAP: PVP-6:1]



Stability studies [21, 22]

Prepared patches were kept in refrigerator, room temperature and incubator for maintaining the temperature of 4°C, 27°C and 40°C respectively. Stability testing of formulation F4 [CAP:PVP (6:1)] was conducted for 45 days at different temperature conditions like 4°C, 27°C and 40°C. At specific interval of time 0,15, 30,40th day the patches were taken out to assay their drug content, appearance and texture.

Analytical Procedure:

Patches withdrawn at particular time interval were cut in to pieces and placed in a beaker containing 50 ml of phosphate buffer pH7.4 and allowed to stir for three and half an hour, from this 1 ml of sample was taken and analyzed at 229.2 nm against blank suitable dilutions. The Results are shown in Table no.8

Table – 8 Stability studies data for F4 [CAP: PVP-6:1]

Time in days	4°C		27°C		40°C	
	R.D.C	P.A	R.D.C	P.A	R.D.C	P.A
0	70	+	70	+	70	+
15	70	+	70	+	70	+
30	69.5	+	69.5	+	69	+
45	69	+	69	+	68	_

R.D.C=Remaining Drug Content, P.A=Physical Appearance, + = Good, Translucent, - = Hard

CONCLUSION

The formulation F4 [CAP: PVP (6:1)] has shown optimum release in concentration independent manner. Higuchi's plot for the formulation revealed that the predominant mechanism of drug release is diffusion. Good correlation is observed between in-vitro and ex-vivo profile, which

reveals the ability of the formulation to reproduce the in-vitro release pattern through various biological membranes. Primary skin irritation studies revealed that the formulation F4 has no erythema and oedema.The formulation F4 has achieved the object of extended release, reduced frequency of administration and thus may improve the patient compliance. As an extension of this work pharmacokinetic studies, in-vivo studies on higher animals and controlled clinical studies on human beings can be carried out in future.

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