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Formulation And Characterization Of Ethylcellulose Based Transdermal Patches Of Atenolol For Improved Invitro Skin Permeation

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ABSTRACT

The skin can be used as the site for drug administration for continuous transdermal drug infusion into the systemic circulation. For the continuous diffusion penetration of the drugs through the intact skin surface membrane-moderated systems, matrix dispersion type systems, adhesive diffusion controlled systems and micro reservoir systems have been developed. Various penetration enhancers are used for the drug diffusion through skin. In matrix dispersion type systems, the drug is dispersed in the solvent along with the polymers and solvent allowed to evaporate forming a homogeneous drug-polymer matrix. Matrix type systems were developed in the present study. In the present work, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising of Atenolol with different concentration of various polymers alone using solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. F1formulation has been selected as the best formulation among all the other formulations. The *in vitro* drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory.The data obtained from the *in vitro* release studies were fitted to various kinetic models like zero order, first order, Higuchi model and peppas model. From the kinetic data it was found that drug release follows peppasmodelrelease by diffusion technique from the polymer.

Keywords*:* Transdermal drug delivery, hydrophobic polymers and Atenolol.

INTRODUCTION

Controlled drug delivery

Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release.

The term controlled release has a meaning that goes beyond scope of sustained release. The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically, but also reproducible from one unit to other[1].

The classification of controlled drug delivery can be given as follows.

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Out of these classes first class contains new drug delivery systems as transdermal delivery, intra uterine delivery, ocular inserts, and sub dermal implants. The transdermal drug delivery has advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time.

Transdermal drug delivery: An Introduction

The idea of delivering drugs through skin is old, as the use is reported back in 16th century B.C. Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation.

Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin typically cardiac drugs such as nitroglycerin and hormones such as estrogen.

Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation.

The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a one-day period.

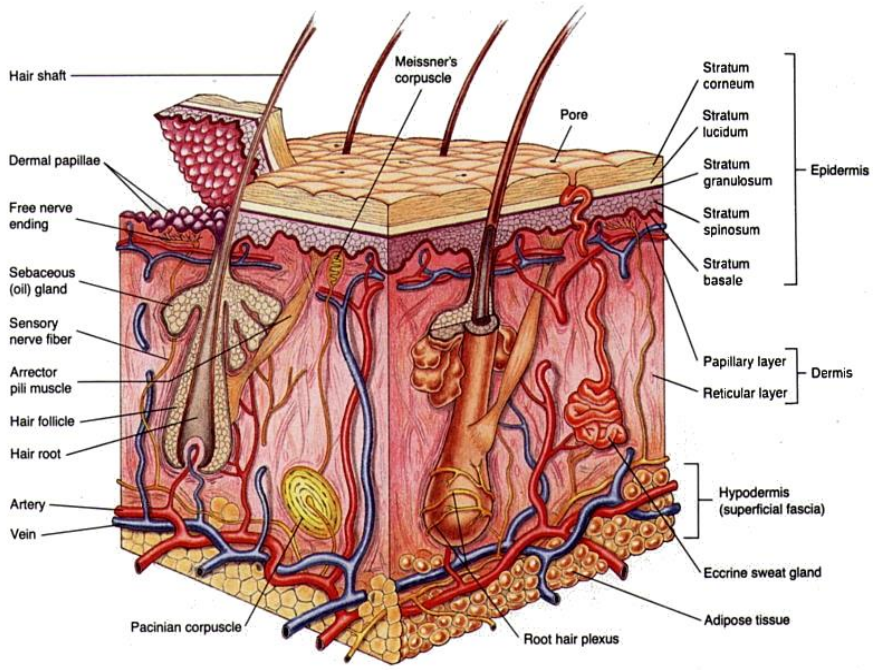
Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories — therapeutic and cosmetic), aroma patches, and weight loss patches, and patches that measure sunlight exposure. Transdermal drug delivery has many advantages over conventional drug delivery and can be discussed as follows.

Advantages[2, 3, 4, 5]

- They canavoid gastrointestinaldrug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
- They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea.
- They avoid the first-pass effect, that is, the initial pass of s drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
- They are noninvasive, avoiding the inconvenience of parenteral therapy.
- They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
- The activity of a drugs having s short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
- They are easily and rapidly identified in emergencies (e.g., unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.
- They are used for drugs with narrow therapeutic window. At the same time transdermal drug delivery has few disadvantages that are limiting the use of transdermal delivery.

Disadvantages[3, 4, 6]

- Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- The delivery system cannot be used for drugs requiring high blood levels.
- The use of transdermal delivery may be uneconomic. For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.



The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers.[6,9,10.]

- **The epidermis** – thin protective outer layer.
- **The dermis** – the tough elastic second layer.
- **The hypodermis** – layer of fatty and connective tissue.

The Epidermis

The outer (epidermal) layer of the skin is composed of stratified squamus epithelial cells. The multilayered envelope of the epidermis varies in thickness, depending on cell size and then number of cells and then number of cell layers, ranging from about 0.8mm on the palms and the soles down to 0.66mm on the eyelids. Cells which provide epithelial tissue differ from those of all other organs provide epithelial tissue differ from those of all other organs in that as they change in an ordered fashion from metabolically active and dividing cells to dense, dead, keratinized protein.

Stratum germinativum (basal layer)

The basal cells are nucleated, columnar, and about 6 microns wide, with their long axis at right angles to the dermoepidermal junction; they connect by cytoplasmic intercellular bridges. Mitosis of the basal cells constantly renews the epidermis and this proliferation in healthy skin balances the loss of dead horny cells from the skin surface. The epidermis thus remains constant in thickness. Below the basal cell layer lies the complex dermoepidermal junction, which constitutes an anatomic functional unit. The junction serves three functions of dermal-epidermal adherence, mechanical support for the epidermis, and control of the passage of cells and some large molecules across the junction.

Stratum spinosum (prickle cell layer)

As the cells produced by the basal layer move outward, they alter morphologically and histochemically. The cells flatten and their nuclei shrink. These polygonal cells are called as prickle cells because they interconnect by fine prickles.

Stratum granulosum (granular layer)

As the Keratinocytes approach the surface, they manufacture basic staining particles, the keratohyalin granules. It was suggested that these granules represent an early form of keratin 3, 4. The term transitional zone is convenient region between living cells and dead keratin.

Stratum lucidum

In the palms and the soles an anatomically distinct, poorly staining hyaline zone forms a thin, translucent layer immediately above layer immediately above the granular layer. This region is the stratum lucidum.

Stratum corneum (horny layer)

As the final stage of differentiation, epidermal cells construct the most the superficial layer of the epidermis, the stratum corneum. On general body areas the membrane provides 10-15 layers of much flattened, keratinized dead cells (corneocytes). Ultimately these cells are sloughed off through desquamation.
The barrier nature of stratum corneum depends critically on its unique constituents; 75-80% is protein, 5-15% is lipid with 5-10% unidentified on a dry weight basis. The protein is located primarily within the keratinocytes and is predominantly alpha-keratin (around 70%) with some beta-keratin (approximately 10%) and a proteinaceous cell enveloping (around 5%). Enzymes and other proteins account for approximately 15% of the protein component. The cell envelop protein is highly

insoluble and is very resistant to chemical attack.

MATERIALS

AtenololProcured from Sanofi Aventis Pharma, Ltd, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad, Ethyl Cellulose (Merck SpecialitiesPvt Ltd), HPMC, MerckSpecialitiesPvt Ltd, Eudragit RSPOMerck SpecialitiesPvt Ltd, PEG-400 (ml) Merck, SpecialitiesPvt LtdChloroformMerck SpecialitiesPvt Ltd, DimethylsulphoxideMerck SpecialitiesPvt Ltd, Dibutyl phthalateMerck SpecialitiesPvt Ltd.

METHODOLOGY

Analytical method development

UV scan

A 100mg of Atenolol was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH- 7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10µg/ml. 10µg/ml solution was scanned from 200-400nm.

Construction of calibration curve

A 100mg of Atenolol was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH-7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). It was further diluted with phosphate buffer pH – 7.4 to get solutions in concentration range of 5,10,15,20 and 25µg /ml. The absorbances of these solutions were determined spectrophotometrically at 270 nm.

Preformulation study

Colour, Odour, Taste and Appearance

The drug sample was evaluated for its Colour, odour and appearance.

Melting point determination

Melting point of the drug sample was determined by capillary method by using melting point apparatus.

Determination of solubility

The solubility of Atenolol was determined by adding excess amount of drug in the solvent.

The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows.

Saturated solution of Atenolol prepared using 10 ml. of distilled water/ phosphate buffer pH 7.4 in 25 ml volumetric flasks in triplicate. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flasks were shaken for 48 hours. The sample withdrawn (1 ml after filtration) was diluted with appropriate medium and analyzed by using UV spectrophotometer at 270 nm and 273 nm for phosphate buffer and distilled water respectively.

Formulation of transdermal patches

Preparation of blank patches

Polymers of single or in combination were accurately weighed and dissolved in respective solvent and then casted in a Petri-dish with mercury as the plain surface. The films were allowed to dry overnight at room temperature.

Formulation of drug incorporated transdermal patches

The matrix-type transdermal patches containing Atenolol were prepared using different concentrations of Ethyl Cellulose,HPMC and Eudragit RSPO polymers. The polymers in different concentrations were dissolved in the respective solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Dibutyl phthalatewas used as plasticizers. Then the solution was poured on the Petri dish having surface area of 78 cm2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch.

Table 1: Formulation of Atenolol patches

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	25	25	25	25	25	25	25	25	25
Ethyl Cellulose	25	50	100	-	-	-	-	-	-
HPMC	-	-	-	25	50	100	-	-	-
Eudragit RSPO	-	-	-	-	-	-	25	50	100
PEG-400 (ml)	10	10	10	10	10	10	10	10	10
Chloroform	15	15	15	15	15	15	15	15	15
Dimethylsulphoxide(ml)	2	2	2	2	2	2	2	2	2
Dibutyl phthalate* (ml)	7	7	7	7	7	7	7	7	7

RESULTS AND DISCUSSION

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

Analysis of drug

UV scan

The lambda max of Atenolol was found to be 270 nm.

Construction of calibration curve

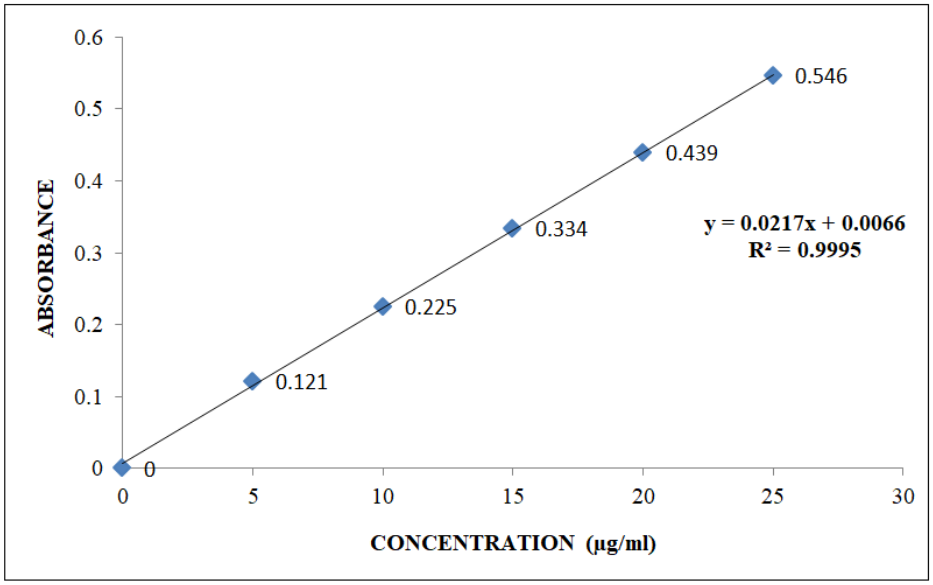


Fig 1: Standard calibration curve of Atenolol

Table 2: Evaluation of patches

Formulation Code	Average weight (mg)	Thickness (mm)	Folding endurance	Flatness (%)	Appearance	% Drug Content
F1	75±1.05	0.046 ± 0.003	81 ± 0.15	100	Transparent	97.1 ± 2.10
F2	78 ±5.36	0.049±0.008	86 ± 1.39	99	Transparent	98.28 ± 0.45
F3	71 ±2.84	0.051±0.004	85 ± 2.26	100	Transparent	97.69 ± 2.21
F4	75 ±5.41	0.041±0.009	80 ± 1.84	100	Transparent	95.1 ± 2.61
F5	77 ±9.18	0.049±0.004	82 ± 3.10	99	Transparent	99.2 ± 3.87
F6	79 ±4.69	0.041±0.007	89 ± 2.15	100	Transparent	98.35 ± 0.59
F7	70 ±9.58	0.047±0.001	84 ± 2.36	99	Transparent	99.11 ± 2.34
F8	76 ±3.86	0.045±0.009	87 ± 2.04	100	Transparent	99.74 ± 1.57
F9	74 ±7.29	0.048±0.006	82 ± 2.96	100	Transparent	98.48 ± 0.44

Table 3: *In vitro* drug permeation of Atenolol

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	4.22	7.04	2.81	3.68	4.56	2.17	5.14	7.29	4.98
2	13.57	14.07	10.37	7.29	10.32	9.74	8.66	11.63	9.35
3	16.78	22.00	15.20	13.04	16.44	16.54	12.73	16.13	12.70
4	20.09	28.75	23.03	20.61	21.80	22.20	17.65	23.80	17.74
5	28.77	30.42	30.43	24.68	29.08	29.44	23.22	29.10	22.88
6	36.28	39.25	38.17	29.30	35.44	35.87	30.49	35.54	29.18
7	54.93	48.77	43.39	36.94	51.36	42.76	36.73	40.81	33.99

8	66.75	56.42	46.45	45.22	67.97	50.62	44.30	48.21	41.40
9	73.37	60.38	54.91	57.35	76.35	58.26	53.10	67.06	47.78
10	79.12	76.86	60.38	74.73	82.15	62.79	66.08	78.10	54.20
11	83.69	86.19	64.99	89.11	95.64	72.08	79.99	82.64	60.21
12	98.29		69.51			81.32		86.78	65.52

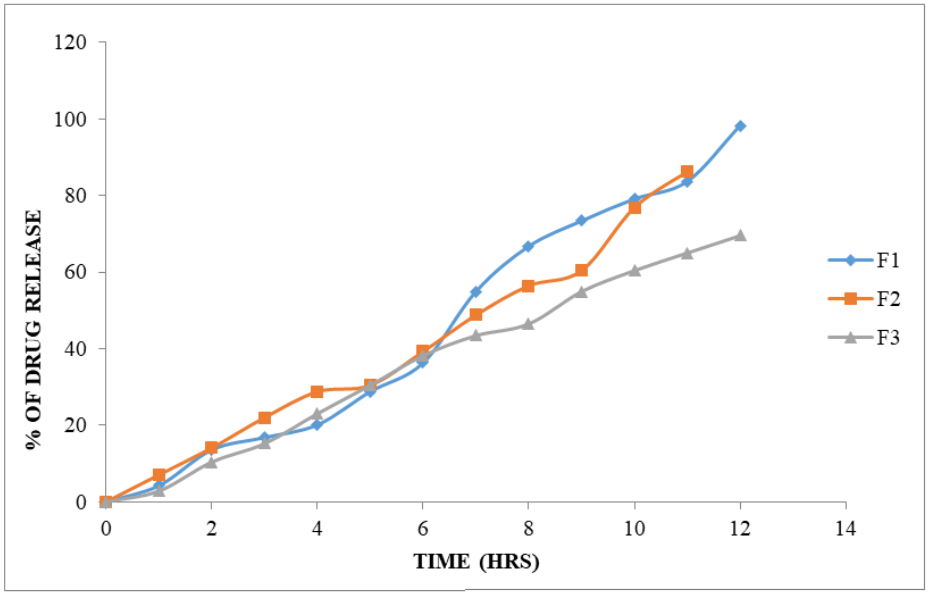


Fig 2: Cumulative % drug permeation of Atenolol patch (F1, F2 and F3)

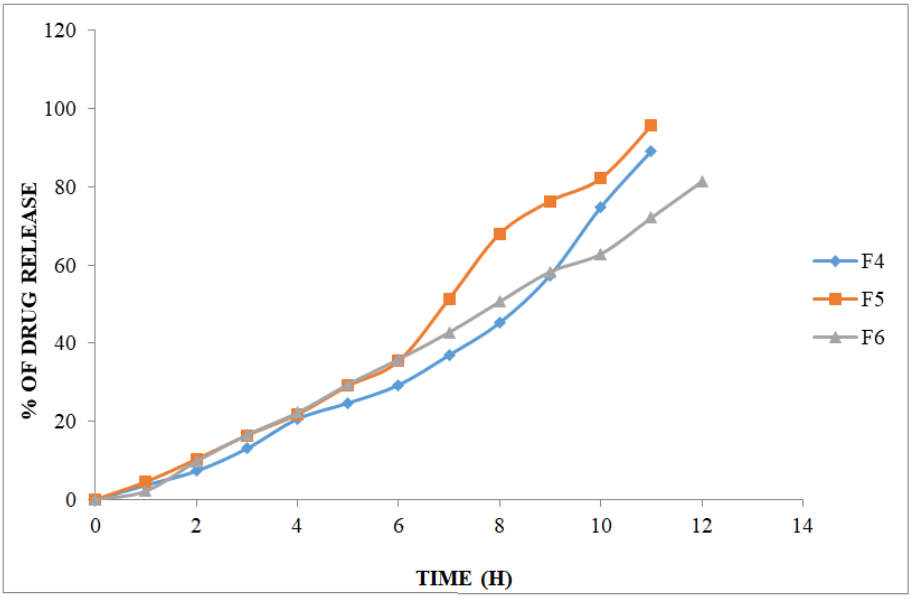


Fig 3:Cumulative % drug permeation of Atenolol patch (F4, F5 and F6)

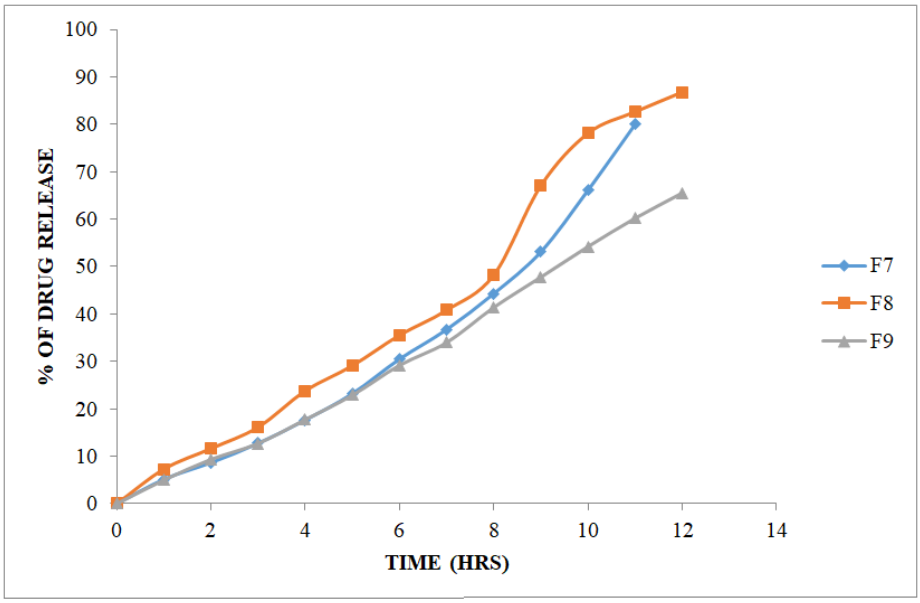


Fig4: Cumulative % drug permeation of Atenolol patch (F7, F8 and F9)

Table 4: Kinetics data of F1Atenolol patch

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0	0	0	2.000	0	0	0	100	4.642	4.642	0.000
4.22	1	1.000	0.625	0.000	1.981	4.220	0.2370	-1.375	95.78	4.642	4.575	0.066
13.57	2	1.414	1.133	0.301	1.937	6.785	0.0737	-0.867	86.43	4.642	4.421	0.220
16.78	3	1.732	1.225	0.477	1.920	5.593	0.0596	-0.775	83.22	4.642	4.366	0.276
20.09	4	2.000	1.303	0.602	1.903	5.023	0.0498	-0.697	79.91	4.642	4.307	0.334
28.77	5	2.236	1.459	0.699	1.853	5.754	0.0348	-0.541	71.23	4.642	4.145	0.496
36.28	6	2.449	1.560	0.778	1.804	6.047	0.0276	-0.440	63.72	4.642	3.994	0.647
54.93	7	2.646	1.740	0.845	1.654	7.847	0.0182	-0.260	45.07	4.642	3.559	1.083
66.75	8	2.828	1.824	0.903	1.522	8.344	0.0150	-0.176	33.25	4.642	3.216	1.426
73.37	9	3.000	1.866	0.954	1.425	8.152	0.0136	-0.134	26.63	4.642	2.986	1.655
79.12	10	3.162	1.898	1.000	1.320	7.912	0.0126	-0.102	20.88	4.642	2.754	1.888
83.69	11	3.317	1.923	1.041	1.212	7.608	0.0119	-0.077	16.31	4.642	2.536	2.106
98.29	12	3.464	1.993	1.079	0.233	8.191	0.0102	-0.007	1.71	4.642	1.196	3.446

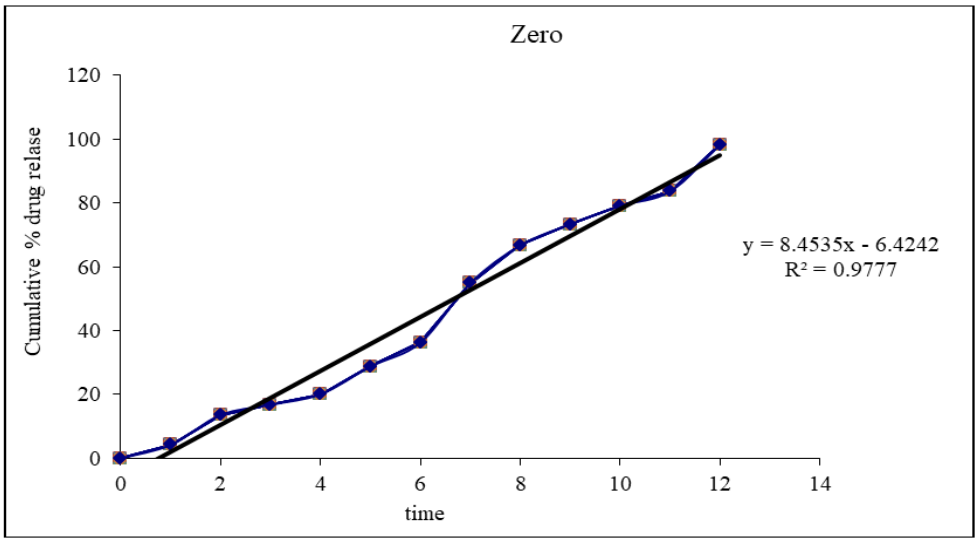


Fig 5:Zero order release kinetics graph

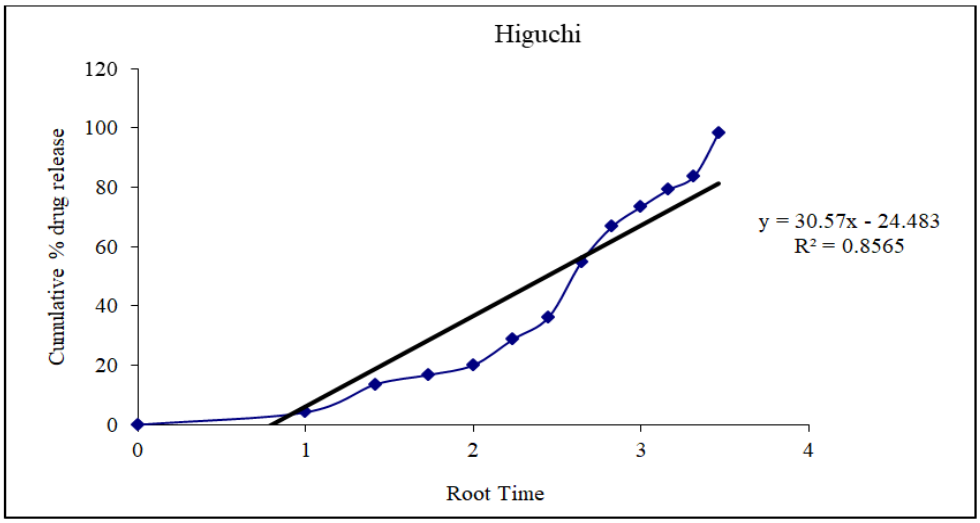


Fig 6:Higuchi release kinetics graph

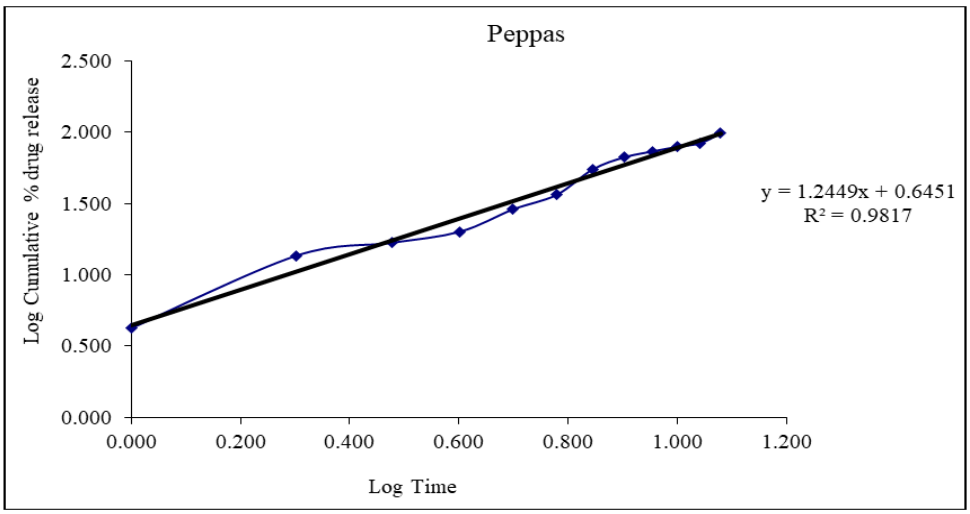


Fig 7:Peppas release kinetics graph

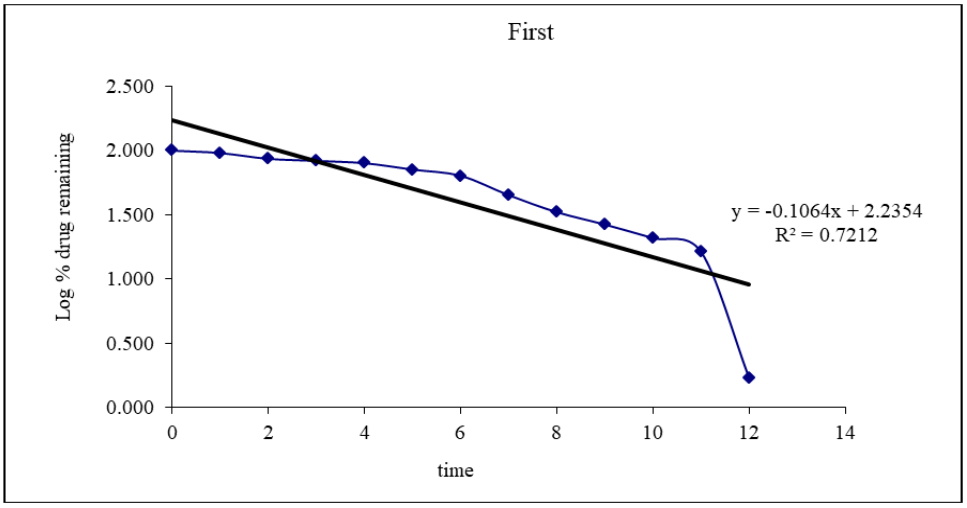


Fig 8:First order release kinetics graph

Drug – Excipient compatibility studies

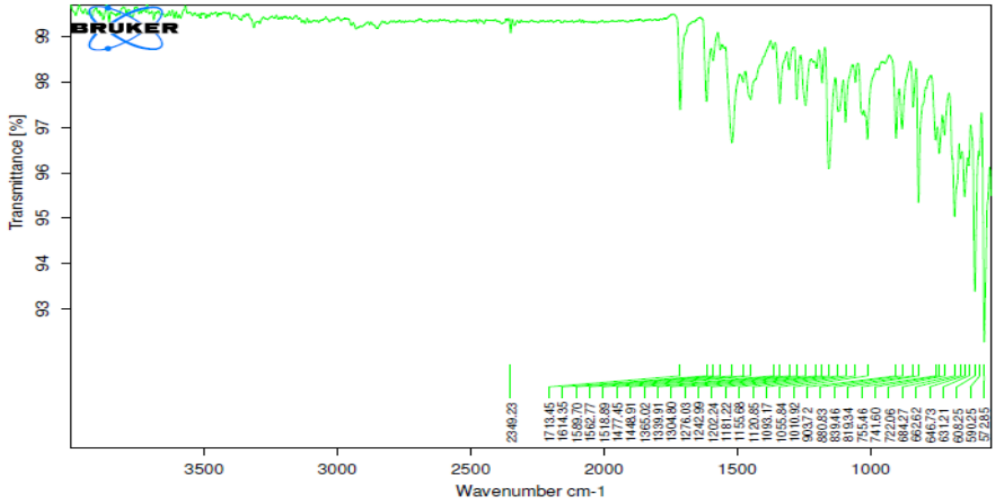


Fig 9: FTIR Spectrum of pure Atenolol drug

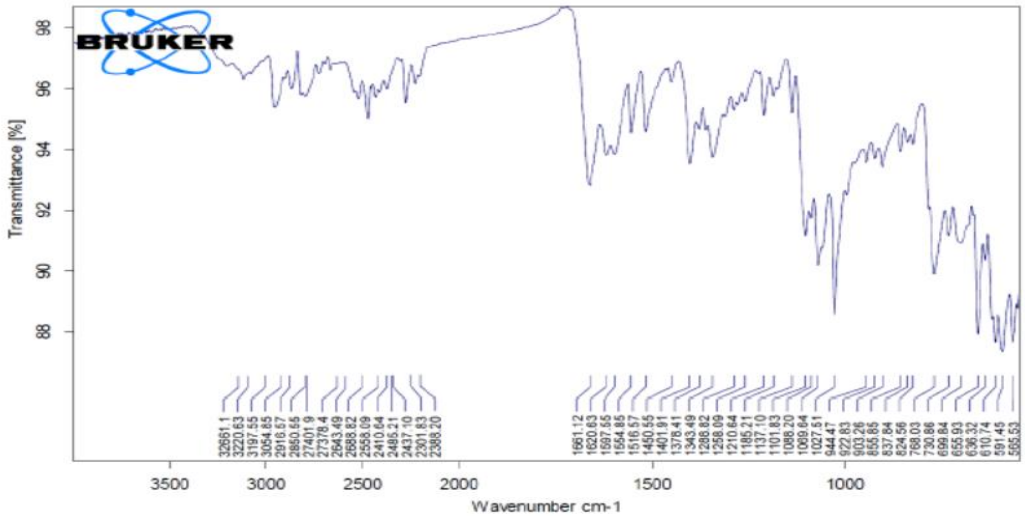


Fig10: FTIR of Optimized formulation

CONCLUSION

In the present investigation an attempt has been made to design and develop the formulation of Atenolol patches using different types of polymers by solvent evaporation technique and mercury substrate method. The drug used isthe best studied for therapy in treating high blood pressure.Atenolol was successfully formulated as controlled release transdermal patches, which prevents the frequency of administration and gives good patient compliance.From the experimental results obtained, F1formulation has been selected as the best formulation among all the other formulations. The *invitro* drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory.The data obtained from the *invitro* release studies were fitted to various kinetic models like zero order, first order, Higuchi model and Pappas model. From the kinetic data it was found that drug release follows peppas model release by diffusion technique from the polymer.Based on the observations, it can be concluded that the attempt of formulation and evaluation of theAtenolol patches was found to be successful in the release of the drug for an extended period of 12hrs.

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