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FORMULATION AND *IN VITRO* EVALUATION OF ALMOTRIPTAN TRANSDERMAL PATCHES

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ABSTRACT

The present study was designed to develop suitable matrix type Transdermal drug delivery systems of Almotriptan using two different polymeric combinations, E RL100 with HPMC E 15; Ethyl cellulose with HPMC E 15, E RL100 and Ethyl cellulose are acrylic acid matrices which have been used to make drug-polymer matrix patches for Transdermal delivery systems which are reported to be compatible with many drugs. Different polymeric Patches containing Almotriptan were prepared and evaluated for physicochemical, in vitro drug release and Kinetic studies. The IR spectral analysis of Almotriptan showed that the principal peaks and for the mixture of Almotriptan with different polymers additional to the principal peaks, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. Penetration enhancers that alter the partitioning can be useful to enhance the drug permeation. In this study various penetration enhancers D-Limonene, Oleic acid and were used in different concentrations to determine their effect on permeation of drug. The presence of all the characteristic bands due to functional groups in polymer mixtures suggests that there is no interaction between the drug and polymers used in the present study. Analysis of drug release mechanism showed that the drug release from the formulations followed zero order kinetics with higuchis model of drug release. Based on the results of evaluation tests formulation coded F_9 was concluded as best formulation.

KEYWORDS

Almotriptan, E RL 100, HPMC E 15, Ethyl cellulose, Penetration enhancers, D-Limonene and Oleic acid.

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INTRODUCTION

Controlled drug delivery systems are developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue[1].

Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1. Delayed release
2. Sustained release

3. Site-specific targeting
4. Receptor targeting
   More precisely, Controlled delivery can be defined as[2].
5. Sustained drug action at pre-determined rate by maintaining a relatively constant and effective drug level in body with minimization of undesirable side effects.
6. Localized drug action by spatial placing of a controlled release system adjacent to or in the diseased tissue.
7. Provide a physiologically and therapeutically based drug release system. The amount and the rate of drug release are determined by the physiological and therapeutic needs of the body.
8. One of the methods often utilized is Transdermal delivery which involve transport of therapeutic substances through the skin for systemic effect[3].

TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal drug delivery systems are topically administered drugs in the form of patches that deliver drugs for systemic effects at a predetermined controlled rate[4].

A Transdermal drug delivery which can be of an active or a passive design, which provides an alternative route for administering medication. These are used as a devices allow for pharmaceuticals to be delivered across the skin barrier[5]. A drug applied is relatively high dosage to the inside of a patch that is worn on skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin[6].

Advantages

1. Avoidance of first pass metabolism[7.]
2. Avoidance of gastro intestinal incompatibility.
3. Provides utilization of drugs with short biological half lives
4. Improving physiological and pharmacological response [8.]
5. Termination of therapy is easy at any point of time.

Limitations

1. The drug that requires high blood levels cannot be administered.
2. TDDS cannot deliver ionic drugs
3. TDDS cannot deliver drugs in a pulsatile fashion.
4. Cannot develop TDDS, if drug or formulation causes irritation to skin.
5. Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product [9.]

METHODOLOGY

Preformulation Studies

Preformulation is described as a phase of the research and developmental process where the formulation characterizes the physical, chemical and mechanical properties of the new drug substance, to check for its stability, safety and effective dosage form. Ideally, the Preformulation phase begins early in the discovery process such as the appropriate physical and chemical data is available to aid the selection of new chemical entities that enters the development process during this evaluation possible interaction with various inert ingredients intended for use in final dosage form are also considered in the present study[10-12].

Organoleptic properties

The color, odor and taste of the drug were recorded using descriptive terminology.

Solubility

The solubility of the drug sample was carried out in different solvents (aqueous and organic) according to I.P. The results are then compared with those mentioned in the official books and Indian Pharmacopoeia.

Melting point

The melting point of Almotriptan was determined by capillary method using digital melting point apparatus.

ANALYTICAL METHODS

STANDARD CURVE

Preparation of standard solution

Stock solution-I

100mg of Almotriptan was accurately weighed into 100ml volumetric flask and dissolved in small quantity of buffer. The volume was made with 0.1 Hcl to get a concentration of 1000µg/ml (SS-I)[13].

UV Absorption Maxima (λ_{max}) of Almotriptan sample in 7.4 phosphate buffer

Stock solution II

100 mg of Almotriptan was accurately weighed into 100ml volumetric flask and dissolved in small quantity of buffer. The volume was made up with 7.4 pH Phosphate buffer to get a concentration of 1000µg/ml (SS-I)[14].

Preparation of working standard solutions

Further, from (SS-II) aliquots of serial dilutions were pipetted into 10ml volumetric flasks. The volume was made up with pH7.4 Phosphate buffer to get the final concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20µg/ml respectively. The absorbance of each concentration was measured at 234 nm[15].

Compatibities studies

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish any possible interaction of Almotriptan with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug. The results indicated that the characteristic absorption peaks due to pure Amlotriptan have appeared in the formulated Transdermal patches[16].

Preparation of Almotriptan Transdermal Patches

Matrix type transdermal patches containing Almotriptan were prepared by solvent evaporation technique, using different ratios of HPMC E 15, ERL100 (F1 to F5) and HPMC E 15, Ethyl cellulose (F6 to F10). The polymers were weighed in requisite ratios and allowed for swelling for about 6 hrs in solvent mixture (1:1 ratio of di- chloromethane, methanol). 15%v/w propylene glycol was incorporated as plasticizer. Then the drug solution was added to the polymeric solution, casted on to anumbra petriplate of surface area about 69.42sq.cm, allowed for air drying overnight followed by vacuum drying for 8-10 hr. The entire sheet was cut into small patches with an area of 6.9cm^2 i.e. with a diameter of 2.9cm. About 7 patches were obtained from each sheet. All formulations carried 15% v/w polyethylene glycol as plasticizer and 12% DMSO as penetration enhancer, 15% v/w propylene glycol was used as plasticizer, 12%v/w DMSO was used as penetration enhancer each patch (6.9 cm^2) contains 6.25mg of Almotriptan[17-19].

RESULTS AND DISCUSSION

Calibration curve for the estimation of Amlotriptan

Calibration curve of Amlotriptan was estimated in 7.4 phosphate buffer.

PREFORMULATION STUDIES

SPECTROSCOPIC STUDIES

Determination of λ max

A solution of 10µg/ml of Amlotriptan was scanned in the range of 200 to 400nm. The drug exhibited a λmax at nm in simulated gastric fluid pH 1.2 and hadgoodreproducibility.Correlation between the con centration and absorbance was found to be near to 0.999, with a slope of 0.047 and intercept of 0.0097[20].

Standard calibration curve

FTIR of Almotriptan[21]

Characterization of Almotriptan Transdermal Patches[22-23]

Physicochemical properties

The Patches prepared by general procedure were evaluated for the following properties

Thickness

The thickness of the film was measured at ten different points on one film using vernier calipers. For each formulation three selected Patches were used and average thickness was recorded [24].

Weight variation

Six Patches from each batch of an area of 6 cm^2

were weighed individually and the average weight was calculated.

Folding endurance

Folding endurance of the patch was determined manually by repeatedly folding a small strip of the medicated patch at the same place until broke. The number of times the strip could be folded at the same place without breaking gave the folding endurance number[25].

Drug Content Estimation in Patches

Patches from each formulation has been taken, cut into small pieces and it was allowed to dissolve in a 100 ml solution containing 50 ml of methanol and 50 ml of dichloromethane. The solution was diluted suitably and the absorbance of the solution was measured using UV-Vis spectrophotometer at a wavelength of 234nm against methanol dichloromethane mixture (1:1) as blank[26].

Moisture Content Determination

The patches were weighed accurately and placed in a desicator containing calcium chloride at 40ºC for 24hr. The final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture loss was determined by the given formula.

$$\% \text{ Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

***In -vitro* drug release kinetics**

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the *vitro* drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer- Peppas model. The values are compiled in below table. The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the formulations reached higher coefficient of determination with the Zero order (R^2 = 0.985). From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion[27-30].

***In vitro* Release Studies**

***In vitro* Drug Release Studies from Transdermal Patches**

The cumulative amount of drug released from A and B series patches are shown in the **Table**. The results indicate that there was increase in the amount of drug release with an increase in HPMCE 15.

Formulations F9 exhibited greatest (97.9%) percentage of drug release values when compared with the other formulations. In the study it was observed that as the concentrations of hydrophilic polymer (HPMC) has increased in the formulations, the drug release rate also increased substantially[30].

KINETIC STUDIES FOR OPTIMIZED FORMULATION F9[31-35]

Zero Order Kinetics

Drug dissolution from pharmaceutical dosage forms do not disaggregate and release the drug slowly, assuming that the area does not change as well as no equilibrium conditions are obtained can be represented by the following equation,

$$Q\,t = Q\,o + K\,o\,t$$

Where $Q\,t$ = *amount of drug dissolved in time t.*

$Q\,o$ = *initial amount of the drug in the solution an*

$K\,o$ = *zero order release constant.*

FIRST ORDER KINETICS

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$Log\ Qt = log\ Qo + K1t/2.303$$

Where Q_t=amount of drug released at time t, Q_o = initial amount of drug and K_1=first order release constant First order remains constant.

HIGUCHI MODEL

This model is used to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical

expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$$Qt = KH \cdot t1/2$$

Where Qt = *amount of drug released in time* t,

KH = *Higuchi dissolution constant*

KORSMEYER AND PEPPAS RELEASE MODEL

To study this model the release rate data are fitted to the following equation,

$$Mt / M\infty = K \cdot t^{n}$$

Where Mt / M is the fraction of drug release, K is the release constant, t is the release time and n is the diffusional coefficient for the drug release that is dependent on the shape of the matrix dosage.

Table No.1: Terbutaline sulphate

S.No	parameters	Terbutaline sulphate
1	Wavelength(nm)	234
2	Beer's Law limit(ppm)	2-20
3	Regression equation(7.4 pH buffer)	Y=0.047x+0.0033
4	R2 value	0.999

Table No.2: Composition of Almotriptan Transdermal patches

S.No	Formulation code	Drug (mg)	HPMC E15 (mg)	ERL 100 (mg)	Ethyl cellulose (mg)
1	F1	62.5	180	180	-
2	F2	62.5	240	120	-
3	F3	62.5	120	240	-
4	F4	62.5	300	60	-
5	F5	62.5	60	300	-
6	F6	62.5	180	-	180
7	F7	62.5	240	-	120
8	F8	62.5	120	-	240
9	F9	62.5	300	-	60
10	F10	62.5	60	-	300

Calibration Curve of Almotriptan in Phosphate Buffer pH7.4

S.No	Conc (µg/ml)	Absorbance
1	0	0
2	2	0.101
3	4	0.184
4	6	0.234
5	8	0.370
6	10	0.460
7	12	0.567
8	14	0.655
9	16	0.760
10	18	0.843
11	20	0.952

Table No.3: Weight, thickness and folding endurance of Almotriptan Transdermal patches

S.No	Formulation	Weight (mg)	Thickness (mm)	Folding endurance
1	F1	431	0.27	91
2	F2	428	0.31	93
3	F3	435	0.30	89
4	F4	426	0.30	100
5	F5	428	0.29	88
6	F6	433	0.29	86
7	F7	429	0.31	92
8	F8	436	0.27	95
9	F9	435	0.24	102
10	F10	428	0.27	82

Table No.4: Drug content and % Moisture content of Almotriptan Transdermal patches

S.No	Formulation	Drug content (mg)	% Moisture content
1	F1	69.2	3.0
2	F2	67.5	3.7
3	F3	69.8	3.9
4	F4	70.2	4.9
5	F5	68.5	3.8
6	F6	69.8	4.2
7	F7	70.1	3.1
8	F8	70.3	4.2
9	F9	68.4	5.4
10	F10	69.7	3.8

Table No.5: Cumulative percent release of Almotriptan from Transdermal patches

S.No	TIME (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	0	0	0	0	0	0	0	0	0	0	0
2	1	10.2	9.5	6.3	24.8	17.4	17.8	8.2	25.3	14.7	17
3	2	38.4	15.6	24.1	37.4	32.6	34.2	15.5	38.2	27.9	22.4
4	3	54.3	25.7	35.4	46.8	37.8	45.9	25	52.9	42.6	29.3
5	5	66.9	37.4	46.2	59.0	47.2	54.8	40.2	80.6	50	40.2
6	8	83.4	54.2	75.3	72.1	58.4	77.3	46.2	93.1	54.8	45.2
7	10	96.4	74.8	94.8	94.6	61.7	92.8	52.5		77.2	53.8
8	12		87.5			68.8		65.8		97.9	59.6

Table No.6: Release kinetics for optimized formulation

S.No		ZERO	FIRST	HIGUCHI	PEPPAS
1		% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
2	Slope	7.030958904	-0.105041523	26.45477458	1.201500711
3	Intercept	9.603835616	2.111095151	-6.73349194	0.775064806
4	Correlation	0.969800473	-0.85632620	0.968793896	0.812756379
5	R 2	0.940512957	0.733294563	0.938561613	0.660572931

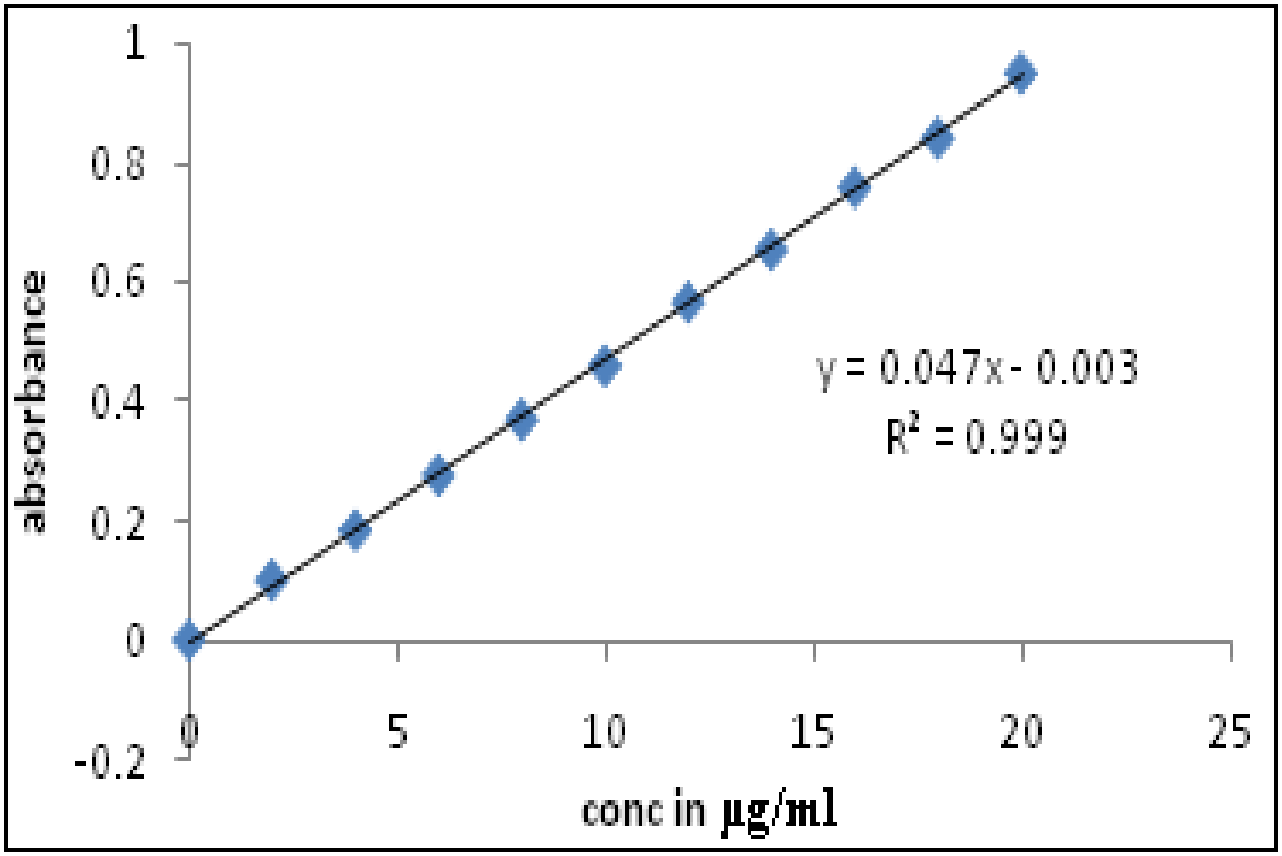

Figure No.1: Standard Graph of Almotriptan in Phosphate Buffer pH 7.4

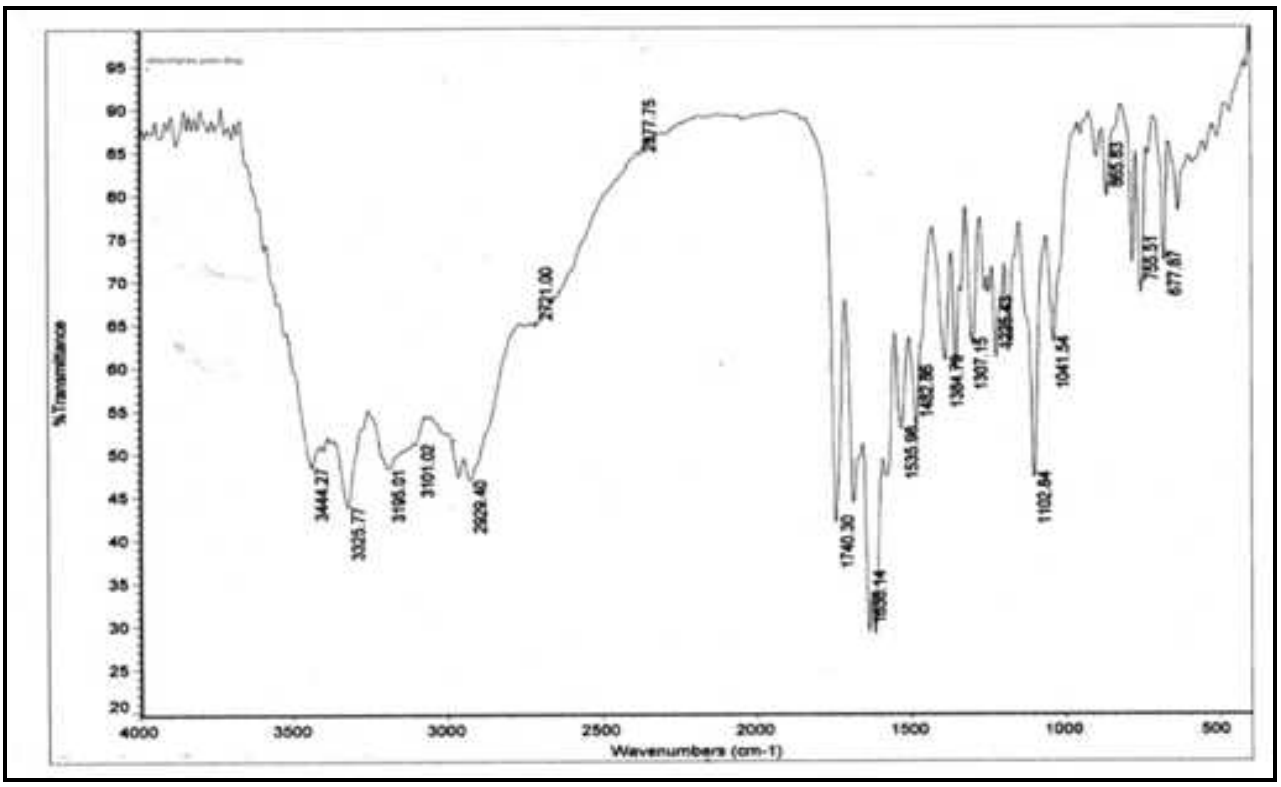

Figure No.2: Ftir Spectrum of Amlotriptan Pure Drug

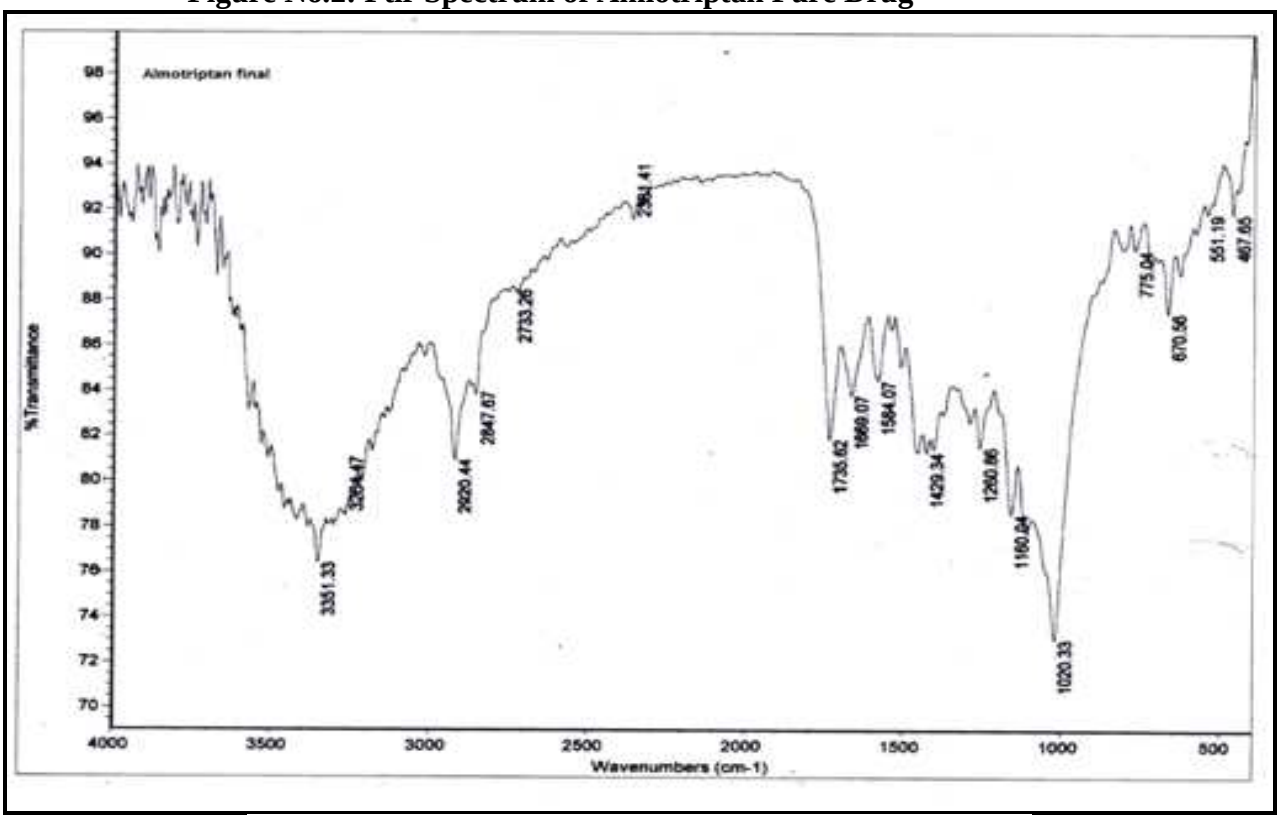

Figure No.3: FTIR of Amlotriptan optimized formulation

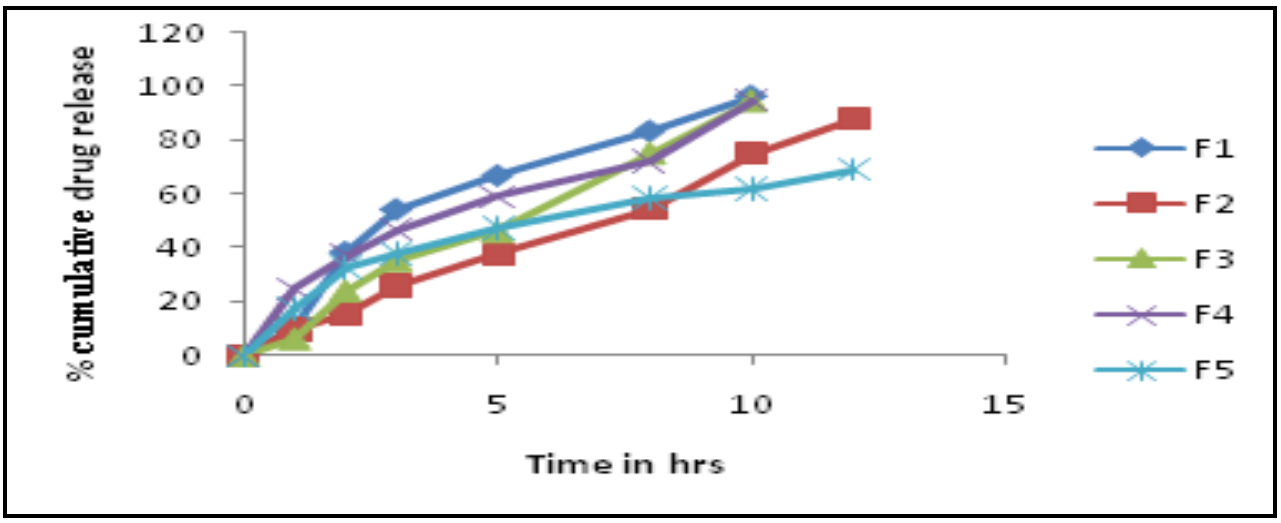

Figure No.4: Cumulative percent release of Almotriptan from transdermal patches F1-F5

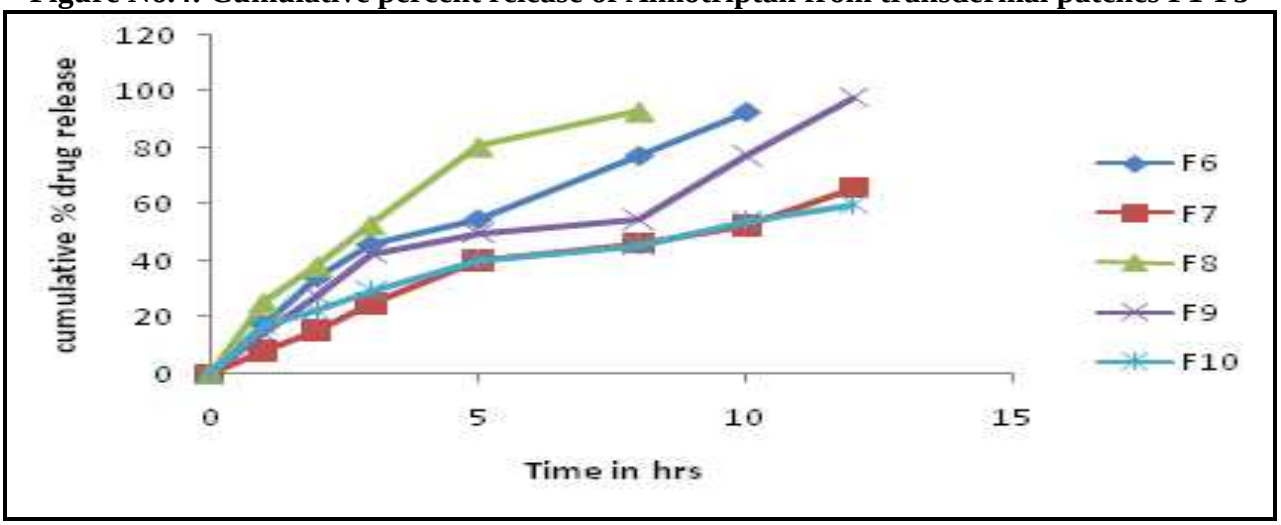

Figure No.5: Cumulative percent release of Almotriptan from transdermal patches F6-F10

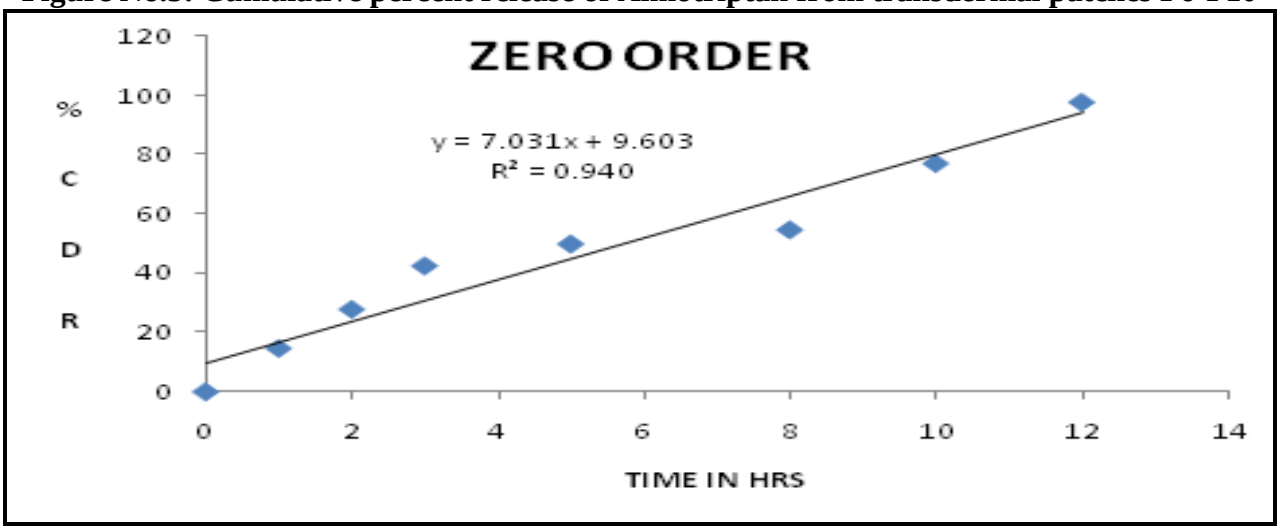

Figure No.6: Zero order plot for optimized formulation

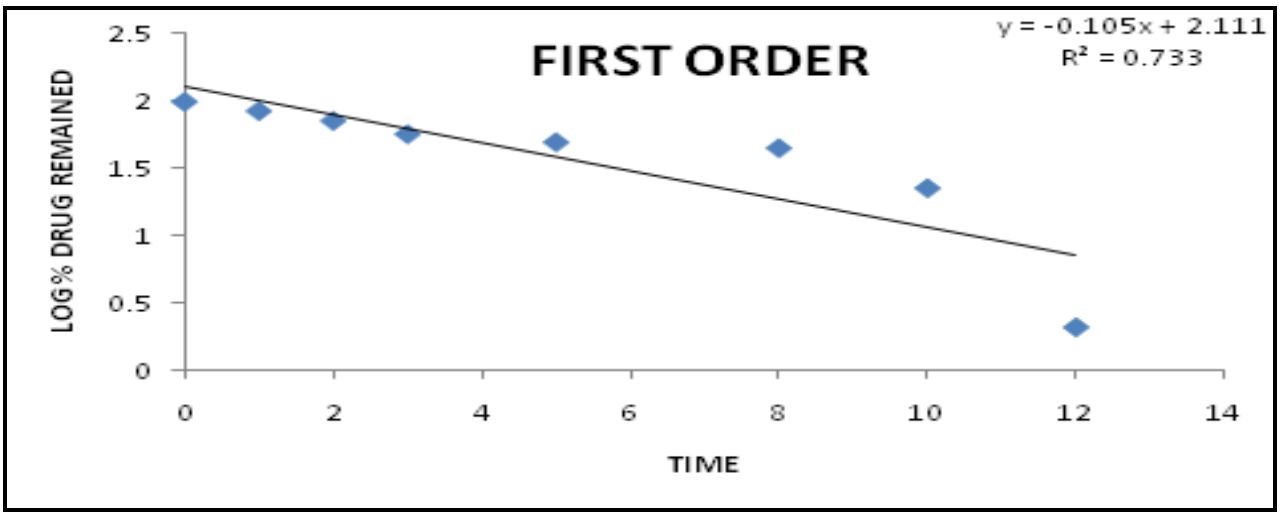

Figure No.7: First order plot for optimized formulation

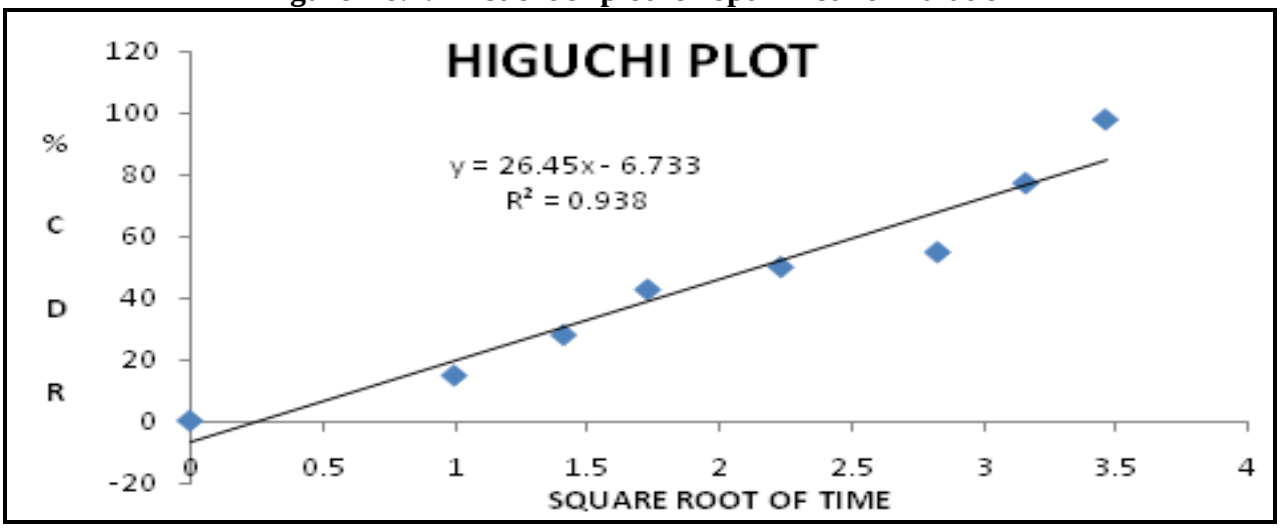

Figure No.8: Higuchi plot for optimized formulation

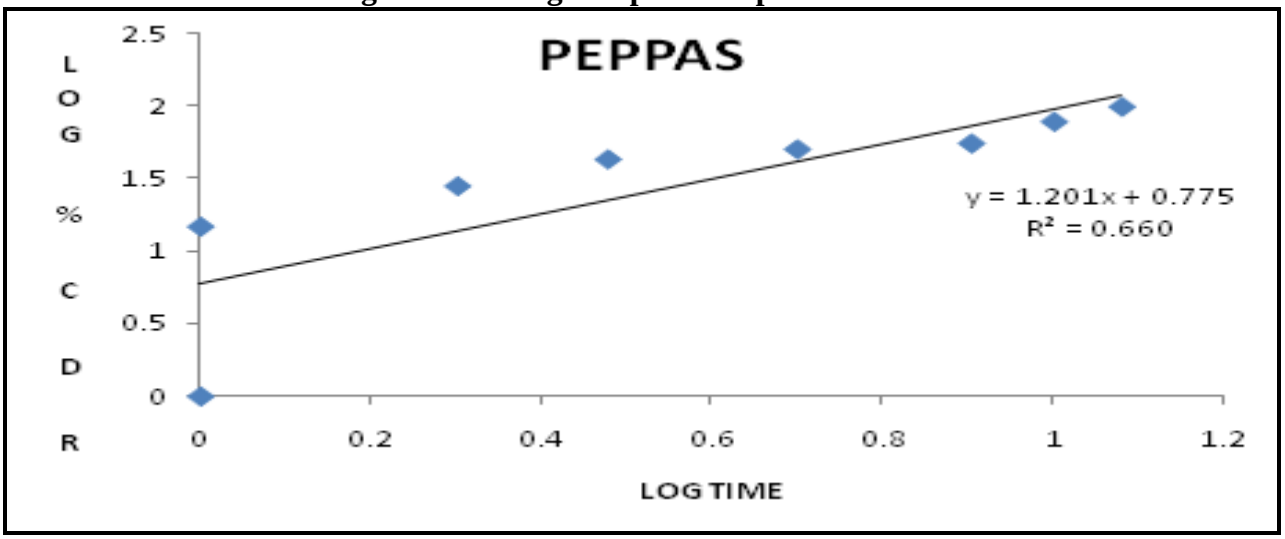

Figure No.9: Peppas plot for optimized formulation

CONCLUSION

Different polymeric Patches containing Almotriptan were prepared and evaluated for physicochemical, in vitro drug release and Kinetic studies.

The IR spectral analysis of Almotriptan showed that the principal peaks and for the mixture of Almotriptan with different polymers additional to the principal peaks, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. The presence of all the characteristic bands due to functional groups in polymer mixtures suggests that there is no interaction between the drug and polymers used in the present study.

The prepared Transdermal patches were evaluated for their physiochemical characteristics such as physical appearance, weight uniformity, thickness, folding endurance; moisture content, drug content were suitable.

Transdermal patches with Ethyl cellulose and HPMC E15 showed better release than patches with ERL 100 and HPMC E15. The release rate was increased with an increase in HPMC E15 content

The release kinetics of the optimized formulations followed zero order and release mechanism was Non-fickian diffusion rate controlled mechanism.

The research work gives a rational guideline for formulating a controlled release Transdermal delivery system F9 for effective therapy.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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