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Formulation And Invitro Evaluation of Terbutaline Sulphate Transdermal Patches

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ABSTRACT:

In the present work, attempts were made to prepare and evaluate "Terbutaline sulphate transdermal patches". It acts as controlled and sustained release bronchodilator. Technique used to prepare these polymeric patches is solvent evaporating technique, used various ratios of ethyl cellulose, HPMC, glycol, terbutaline sulphate etc,. From T1-T5 combination with active ingredient, eudragid RL and from T6-T10 ethyl cellulose were used. Require quantity of polymer measure n taken and allow swelling for hours in solvent (which is combination of ethanol and dichloromethane equally) included plasticizer as well. Mixing of polymeric and drug solution followed by spreading on petriplate of surface area about 6.9 cm^2 kept for drying followed by vacuum drying for few hours. From the area 6.9 cm^2 cut the patches from complete sheet. About 10 patches of terbutaline sulphate were formed from single sheet. All formulations contain different ratios of ingredients. All typical bands occur due to polymer which shows the report as 'there is no interaction between polymer and drug'. Bands observed through IR spectrolysis.
The drug release rate was increased with increase in polymer concentration. The patch which contains ethyl cellulose & HPMC E15 gives better release than patches with HPMC E15 & Eudragit RL 100. The drug release kinetics of optimized formulations followed the zero (0) order kinetics and the release mechanism were found to be non-flicking controlled rate mechanism. The research work shows a rational guideline to formulate a controlled release transdermal drug delivery system T9 for efficient therapy.

INTRODUCTION:

TRANSDERMAL DRUG DELIVERY SYSTEMS

Transdermal drug delivery systems are externally applied medicaments in the form of patches that deliver drugs for systemic effects at a predestined and controlled rate.

A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides a substitute route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch

and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.

Terbutaline is a relatively selective beta2-adrenergic bronchodilator that has little or no effect on alpha-adrenergic receptors. Terbutaline appears to have a greater stimulating effect on beta-receptors of the bronchial, vascular, and uterine smooth muscles (beta2 receptors) than on the beta-receptors of the heart (beta1 receptors). This drug relaxes smooth muscle and inhibits uterine contractions, but may also cause some cardiostimulatory effects and CNS stimulation.

Pathways of transdermal drug permeation [12]

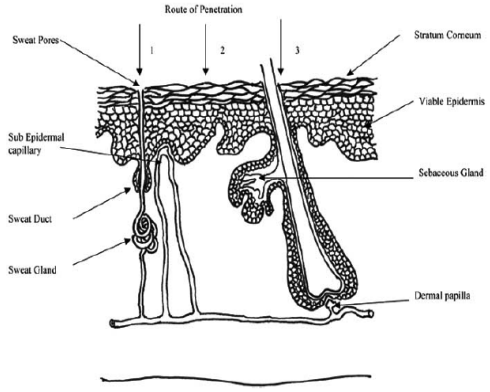


Fig 1: Simplified representation of skin showing routes of penetration; 1.Through the sweat ducts 2.Directly across the stratum corneum (intracellular) 3. Via the hair follicles

Basic components of TDDS[8]:

The components of transdermal devices include;

1. Polymer matrix
2. Drug
3. Permeation enhancers
4. Others

PERMEATION ENHANCEMENT TECHNIQUES

The method employed for modifying the barrier properties of the stratum corneum to enhance drug penetration and absorption through skin may be classified into the following categories:

1. Chemical Enhancement Techniques

2. Physical Enhancement Techniques
3. Carriers/ Vehicles
4. Vesicular Carriers
5. Miscellaneous Techniques

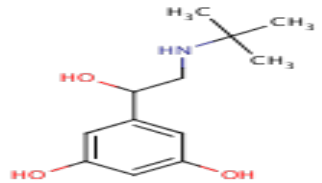
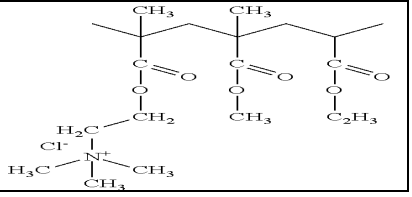
Objectives

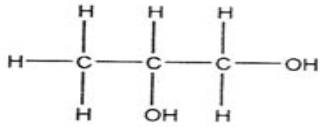
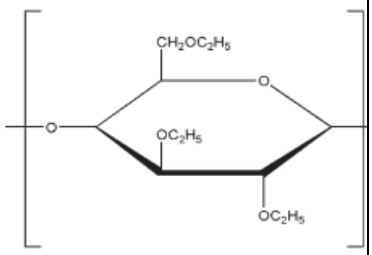
- To develop the extended release system over a period of time.
- Enhanced patient compliance by reducing the dose frequency
- To achieve this goal various trials are to be taken and evaluated with respect to the various quality parameters such as dissolution and related studies.
- To design customized pre-formulation studies to predict the formulation and process variables for preparation of Terbutaline sulphate transdermal patch.

Plan of work

- **LITERATURE SURVEY**
- **SELECTION OF DRUG,MATERIALS & FORMULATION DESIGN**
- **PREFORMULATION STUDIES**
  - Description
  - UV spectroscopy
  - Drug – Excipient Compatibility Studies
- **FORMULATION DEVELOPMENT**
- **EVALUATION STUDIES**

Table 1: Drug Profile

Drug Name	Molecular formula	Structure
Terbutaline	$C_{12}H_{19}NO_3$	
EUDRAGIT RL 100	$C_{19}H_{34}ClNO_6$	

PROPYLENE GLYCOL	$C_3H_8O_2$	
Ethyl cellulose	$C_{12}H_{23}O_6$	

LITERATURE REVIEW

R. Panner selvam et al., (2010) reported a review on transdermal drug delivery systems for antihypertensive drugs. They mentioned that transdermal delivery of antihypertensives enhancing the bioavailability as well as improoving the patient compliance. This review reported that various antihypertensives like timolol maleate, nicardapine HCL, captopril, atenlol, metoprolol, clonidine, labetolol, pinacidil, verapamil HCL, niterndipine, nifedapine, carvedilol were formulated into transdermal delivery systems[17]

Pravin. Gavali et al., (2010) reported design and development of HPMC based polymeric films of enalapril maleate. Patches were prepared using different concentrations and grades of HPMC (K4M, K15M, K100M) and evaluated for their physico chemical characterization[19].

METHODOLOGY

STANDARD CURVE

Preparation of standard solution:

Weight 100 mg of Terbutaline sulphate and transfered in 100ml volumetric flask and dissolved in 25ml of buffer. The volume was made upto mark with 7.4 pH Phosphate buffer (1000µg/ml) (SS-I).

UV Absorption Maxima (λ_{max}) of Terbutaline sulphate sample in pH 7.4 Phosphate buffer

- Stock II: pippetout 10 ml from stock – I and made up to 100 ml with pH 7.4 Phosphate buffer to get a concentration of 100µg/ml. The wavelength was determined using 100 µg/ml drug solution in the range of 200-400 nm using pH 7.4 Phosphate buffer as a blank. The maximum wavelength was found to be at 277 nm.

Preparation of working standard solutions:

Further, from (SS-II) aliquots of dilutions were pipette into 10ml volumetric flasks. The volume was made up with pH7.4 Phosphate buffer to get 2, 4,6,8,10,12,14,16,18 and 20µg/ml concentrations respectively. The absorbance of each concentration was measured at 277 nm.

Drug – Excipient Compatibility Study:

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients.

FORMULATION OF TRANSDERMAL PATCHES

Table 2: Composition of Terbutaline sulphate transdermal patches

Formulation code	Terbutaline (mg)	HPMC E15 (mg)	ERL 100 (mg)	Ethyl cellulose (mg)
T1	25	180	180	-
T2	25	240	120	-
T3	25	120	240	-
T4	25	300	60	-
T5	25	60	300	-
T6	25	180	-	180
T7	25	240	-	120
T8	25	120	-	240
T9	25	300	-	60
T10	25	60	-	300

- 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 2.5mg of Terbutaline sulphate

Characterization of Terbutaline sulphate Transdermal Patches

1. Physicochemical properties
2. Thickness
3. Weight variation
4. Folding endurance
5. Estimation of drug content in polymeric Patches
6. Moisture Content Determination
7. *In vitro* Release Studies

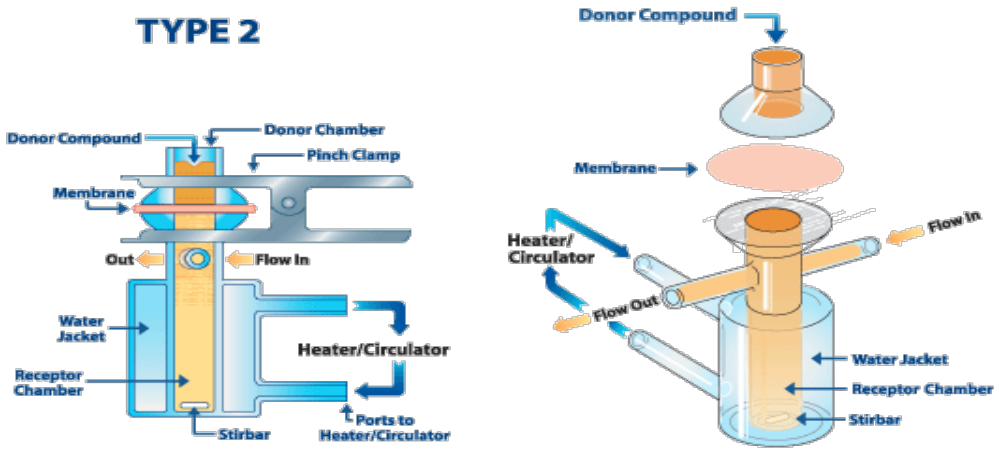


Fig. 2: Franz diffusion cell

Kinetic Analysis of Dissolution Data

The results of *in vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows,

i) ZERO ORDER KINETICS

Zero order release constant with initial amount of the drug in solution is the quantity of drug dissolved in time; it can be represented as, $Q_t = Q_0 + K_{0t}$.

Where: Q_t = quantity of drug dissolve in time t, Q_0 = initial quantity of the drug in solution and K_0 = zero order release constant.

ii) FIRST ORDER KINETICS

Apply following equation to learn the first order kinetics release rate. Log Q_t = log Q_0 = K_{1t}/2.303(constant)

Where: Q_t = quantity of drug release in time t, Q_0 = initial quantity of drug in the solution and K_1 = first order release constant.

iii) HIGUCHI MATRIX

The following equation represents the Higuchi model, $Q_t = K_H.t_{1/2}$

Where: Q_t = quantity of drug released in time t, K_H = Higuchi dissolution constant.

iv) KORSMEYER EQUATION/ PEPPAS RELEASE MODEL

The release rate data are fitted to the following equation to study this peppas model $Mt/M\infty = K.t_n$

Where: $Mt / M\infty$ = fraction of drug release, K = constant, t = time & n = diffusion coefficient for the drug release that is reliant on the profile of the matrix dosage form.

RESULTS AND DISCUSSION

1. Preformulation Study:

A. Organoleptic Properties (Color, odor, taste and appearance)

Table 3: Results of identification tests of drug

S.NO	Parameter	Drug
1	Color	White to gray-white
2	Odor	Odorless or has a faint odor of acetic acid
3	Taste	Tasteless
4	Appearance	Crystalline powder.

B. Melting point determination: Drug: Terbutaline Sulphate

Table 4: Results of Melting point determination test of drug

Reported Melting Point	Observed Melting Point
245 - 248	**247**

C. Determination of solubility:

Terbutaline sulfate, USP is soluble in water and in 0.1N hydrochloric acid, slightly soluble in methanol, and insoluble in chloroform. Its molecular weight is 548.65.

D. Standard calibration curve

In the pre-formulation study, it was found that the λmax of Terbutaline sulphate by spectrophotometric method in phosphate buffer pH 7.4 was found to be 277nm.

Table 5: Calibration Curve of Terbutaline sulphate in Phosphate Buffer pH7.4

Conc (µg/ml)	Absorbance
0	0
2	0.101
4	0.184
6	0.277
8	0.370
10	0.460
12	0.567
14	0.655
16	0.760
18	0.843
20	0.952

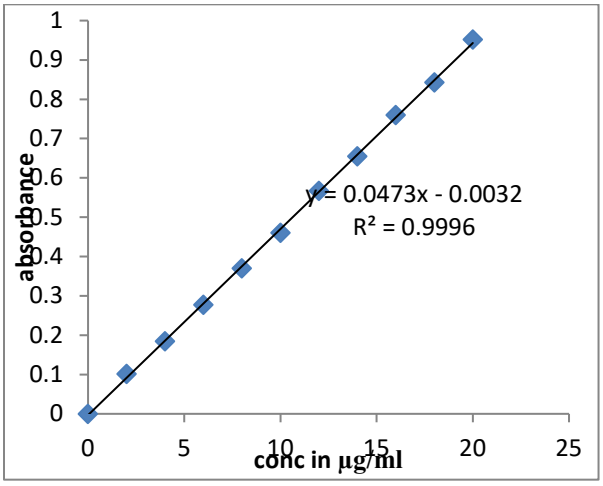


Fig 3: Standard Graph of Terbutaline sulphate in Phosphate Buffer pH 7.4.

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E. Drug excipient compatibility study

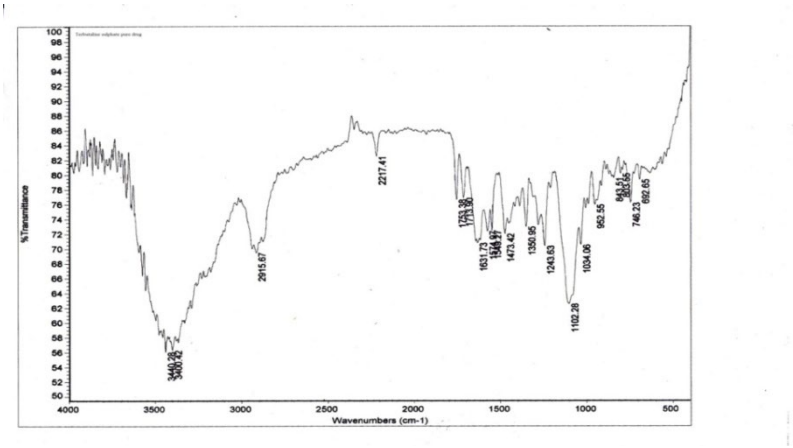

Fig 4: Terbutaline Sulphate Pure Drug FTIR.

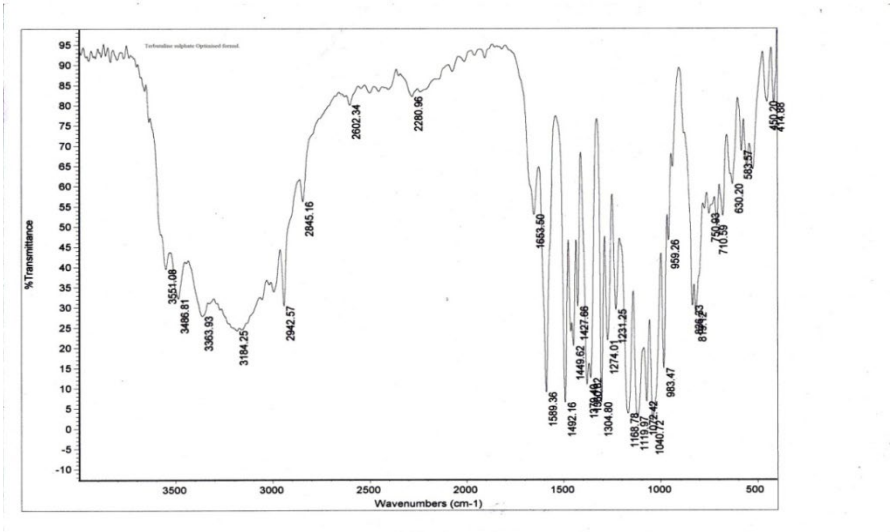

Fig 5: Terbutaline Sulphate Final Optimized FTIR

Table 6: Weight, thickness and folding endurance of Terbutaline sulphate transdermal patches.

Formulation	Weight (mg)	Thickness (mm)	Folding endurance
T1	431	0.27	91
T2	428	0.31	93
T3	435	0.30	89
T4	426	0.30	100

T5	428	0.29	88
T6	433	0.29	86
T7	429	0.31	92
T8	436	0.27	95
T9	435	0.24	102
T10	428	0.27	82

Table 7: Drug content and % Moisture content of Terbutaline sulphate transdermal patches.

Formulation	Drug content (mg)	% Moisture content
T1	69.2	3.0
T2	67.5	3.7
T3	69.8	3.9
T4	70.2	4.9
T5	68.5	3.8
T6	69.8	4.2
T7	70.1	3.1
T8	70.3	4.2
T9	68.4	5.4
T10	69.7	3.8

In vitro Release Studies

Table 8: Cumulative percent release of Terbutaline sulphate from transdermal patches.

TIME (Hrs)	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
0	0	0	0	0	0	0	0	0	0	0
1	10.2	9.5	6.3	24.8	17.4	17.8	8.2	25.3	14.7	17
2	38.4	15.6	24.1	37.4	32.6	34.2	15.5	38.2	27.9	22.4
3	54.3	25.7	35.4	46.8	37.8	45.9	25	52.9	42.6	29.3
5	66.9	37.4	46.2	59.0	47.2	54.8	40.2	80.6	50	40.2

8	83.4	54.2	75.3	72.1	58.4	77.3	46.2	93.1	54.8	45.2
10	96.4	74.8	94.8	94.6	61.7	92.8	52.5		77.2	53.8
12		87.5			68.8		65.8		97.9	59.6

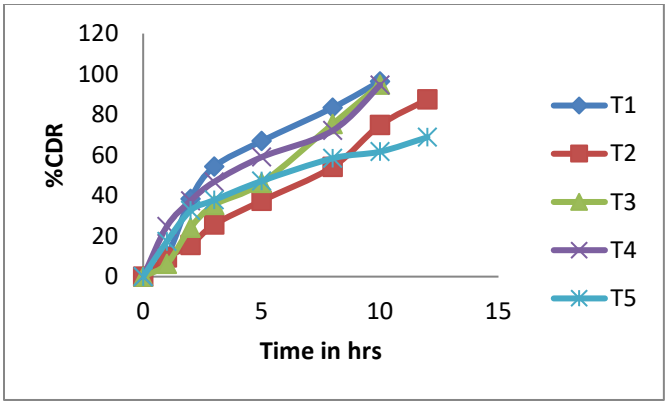

Figure 6: Cumulative % release of Terbutaline sulphate from transdermal patches T1-T5.

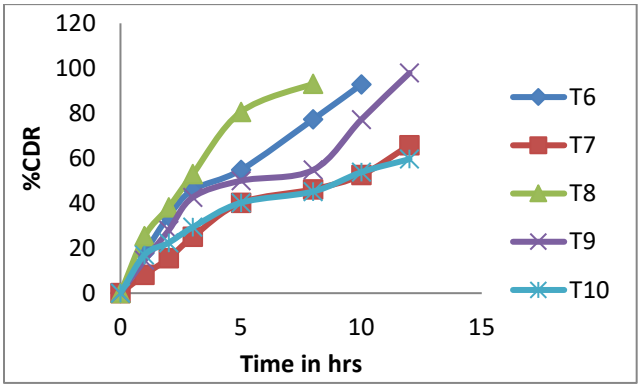

Figure 7: Cumulative percent release of Terbutaline sulphate from transdermal patches T6-T10.

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

KINETIC STUDIES FOR OPTIMIZED FORMULATION T9

Table 9: Release kinetics for optimized formulation

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T

Slope	7.030958904	-0.10504152	26.45477458	1.201500711
Intercept	9.603835616	2.111095151	-6.73349194	0.775064806
R 2	0.940512957	0.733294563	0.938561613	0.660572931

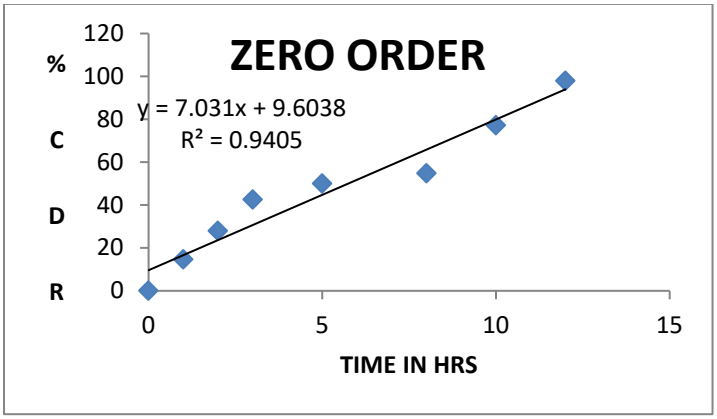

Figure 8: Zero order plot for optimized formulation T9.

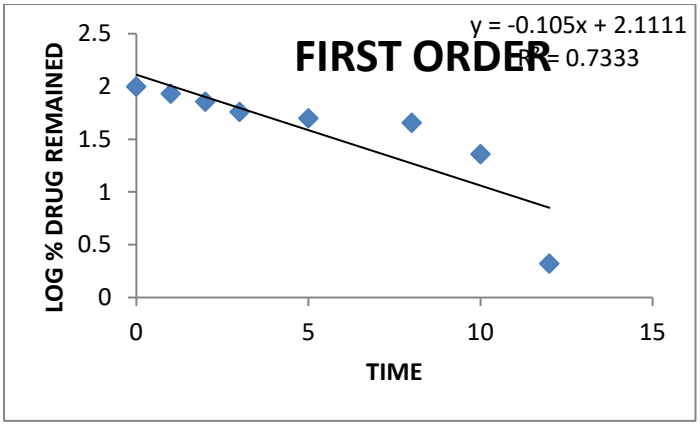

Figure 9: First order plot for optimized formulation T9.

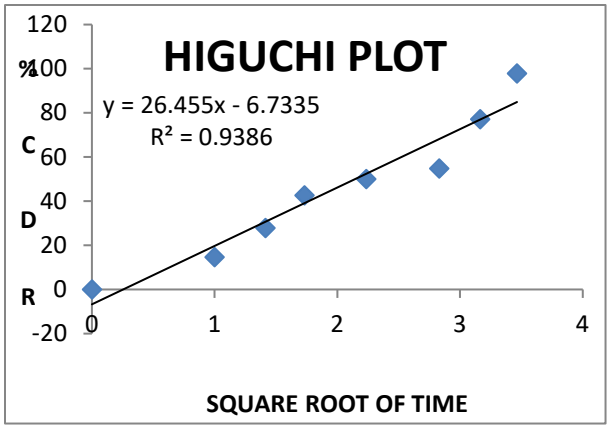

Figure 10: Higuchi plot for optimized formulation T9

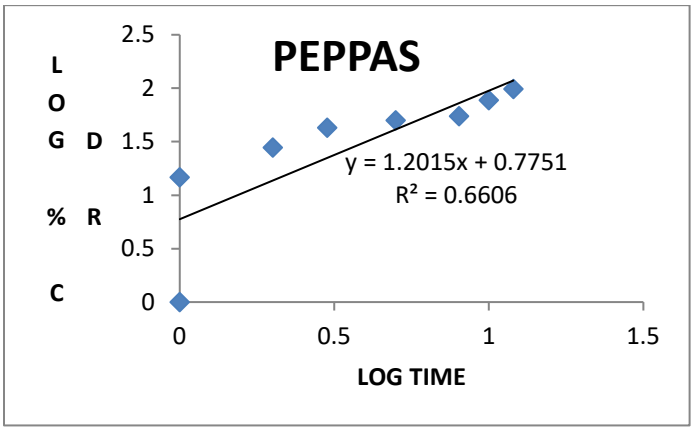

Figure 11: Peppas plot for optimized formulation T9.

CONCLUSION

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

The IR spectral analysis of Terbutaline sulphate showed that the principal peaks and for the mixture of Terbutaline sulphate 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 formulated transdermal patches were evaluated for their physiochemical characteristics such as weight uniformity, physical appearance, thickness, folding endurance; moisture content, drug content were suitable.

The optimized formulations followed zero order and *Non-flicking* release diffusion rate controlled mechanism.

The research work gives a rational guideline for formulating a controlled release transdermal delivery system T9 for effective therapy.

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