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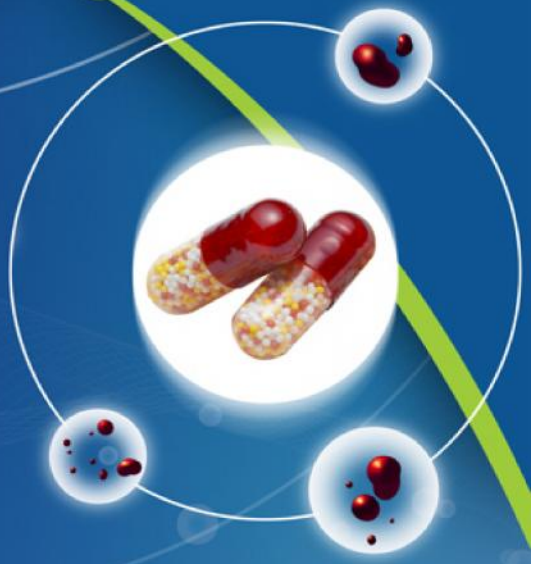

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Research Article

FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF BACLOFEN

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ABSTRACT

Transdermal drug delivery systems are becoming more popular in the field of modern pharmaceutics. The present study was carried out to develop matrix type transdermal patches containing Baclofen with different ratios of HPMC (hydroxyl propyl methyl cellulose) & EC (ethyl cellulose) by solvent casting method. Propylene glycol 3% is used as plasticizer & span 80 is used as permeation enhancer. The physicochemical compatibility of the drug and the polymers studied by infrared spectroscopy suggested absence of any incompatibility. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, folding endurance moisture. All prepared formulations indicated good physical stability. In-vitro permeation studies of formulations were performed by using Franz diffusion cells.It shown that drug release follows zero order and the mechanism of release is diffusion from the polymer. The results suggested no physicochemical incompatibility between the drug and the polymers. Blank films were prepared and evaluated characteristics like smoothness and flexible. Further drug loaded films were prepared and evaluated for thickness, percentage flatness, tensile strength, weight uniformity, drug content,moisture content, moisture uptake, swelling index, water vapourtransmission, skin irritation and invitro-drug permeation study.

KeyWords : *Transdermal Drug delivery, In-vitro permeation study, HPMC, EC, Baclofen.*

INTRODUCTION

Transdermal drug delivery system (TDDS) is topically administered medicaments in the form of patches or semisolids (gels) that deliver drugs for the systemic effects at a predetermined & controlled rate. Transdermal drug delivery system has many advantages over conventional modes of drug administration, it provides a controlled rate release of medicaments, it avoids hepatic metabolism, ease of termination and long duration of action. The benefits of using transdermal drug delivery include improved systemic bioavailability resulting from by passing the first hepatic metabolism. Variables due to oral administration, such as pH, the presence of food or enzymes, and side effects of drug can be eliminated. The aim in the development of new transdermal drug delivery devices is to obtain a controlled, predictable, and reproducible release of the drug into the blood stream of patient. To formulate transdermal patches using Hydroxy Propyl Methyl Cellulose (HPMC), evaluate the patches and study the release profile and release mechanisms from patches. Transdermal drug delivery leading edge over injectables and oral route by increasing patient compliances and avoiding first pass metabolism respectively. TDDS not only provides a controlled, constant administration of drug, but also allows continuous input of drug with short biological half life and eliminates pulsed entry into systemic circulation which often causes undesirable side

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effect. Transdermal drug delivery provides a leading edge over injectables and oral route by increasing patient compliances and avoiding first pass metabolism respectively. TDDS not only provides a controlled, constant administration of drug, but also provide short biological half life and eliminates pulsed entry into systemic circulation which often causes undesirable side effect. The objective of this research work was to develop a transdermal system which can produce a constant and prolonged release of the drug, to evaluate the effect of ethyl cellulose on the fabrication of the patch and drug release from the patch, to evaluate the effect of plasticizers on the physico-chemical properties of the patch and on drug permeation across the membrane.

Materials and Methods:

Baclofen (Novartis pharmaceuticals corp, Mumbai), Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl Cellulose (EC) (Research Lab Fine Chem Industries, Mumbai), Chloroform, Methanol and Span 20 (Finar chemicals Ltd., Ahmadabad), Propylene Glycol, Glycerol, Di butyl phthalate, KH2PO4 (Sd fine chem. Ltd., Mumbai),

Method

Preparation of transdermal patch

Transdermal patches containing Baclofen were casted on glass slide by solvent casting technique. The drug matrix was prepared by dissolving hydroxyl propyl methyl cellulose HPMC K100 and HPMC K4M in distilled water. Poly ethylene glycol (30%) was used as a plasticizer. Baclofen 30gm dissolved in 5 ml methanol and the homogenous dispersion was produced by slow stirring with a magnetic stirrer. The rate controlling membrane was incorporated into the drug reservoir.1% m/v of permeation enhancer of non ionic surfactant (span 20) ,After complete drying, patches were cut into small pieces each of 3 square centimeters and stored of wax paper in a desiccators.

TABLE 1: **Composition of transdermal patches**

Ingredient	Formulation Batches					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Baclofen(Drug)mg	40gm	40gm	40gm	40gm	40gm	40gm
HPMC K 100mg	300gm	300gm	-	350gm	400gm	
HPMC K4M mg	280gm	-	300gm	-	350gm	
Span 20	0.5gm	0.5gm	0.5gm	-	0.5gm	
Poly Ethylene Glycol	0.6gm	0.6gm	-	0.6gm	0.6gm	0.6gm
Dibutylphthalate	0.7gm	0.7gm	-	0.7gm	0.7gm	-

Calibration Curve of Baclofen drug-

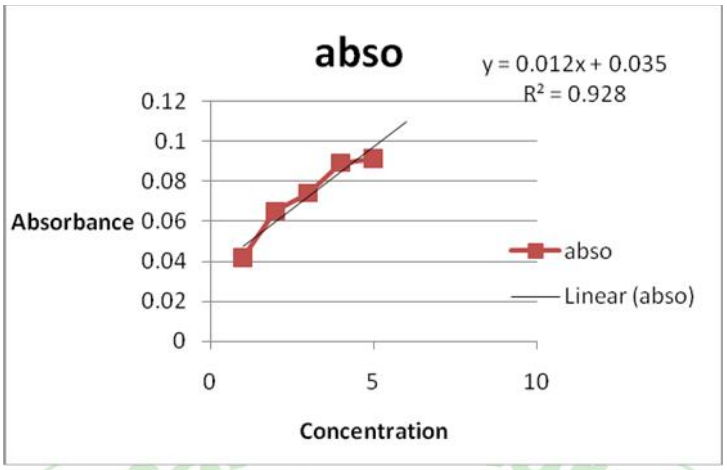
Preparation of Baclofen Standard Solution:

Baclofen is estimated by measuring the absorbance at 275nm. The standard curve of Baclofen is prepared in phosphate buffer pH 7.4 and the standardization obeyed Beers law.

Preparation of Standard Curve:

Calibration Curve of Baclofen drug-

Concentration ug/ml	Absorbance
20	0.0417
40	0.0655
60	0.0742
80	0.0894
100	0.0916



Fabrication of Transdermal Patches:

Matrix patches were casted on a glass mould by solvent casting method. First three formulations were prepared by using HPMC K 100 alone having drug and polymer ratio 1:2, 1:3, 1:4 using distilled water as a solvent and one more formulation is formulated using HPMC K4Mith permeation enhancer Span 20 (1%) having drug polymer ratio 1:4. Next two formulations were prepared by using HPMC K4M and HPMC K 100 in combination having drug and polymer in the ratio 1:(2:8),1:(1:9) using methanol and chloroform as solvent (1:1) ratio and the remaining formulation is formulated with HPMC K4M and HPMC K 100 by using permeation enhancer Span 80 (1%) in ratio of 1:(2:8). Propylene glycol (3%) used as a plasticizer.

Evaluation of Transdermal Patches-

Physico-Chemical Evaluation-

Partition coefficient determination

The partition coefficient (log D) is a measurement of lipophilicity of molecules, which can be used to predict its capability to cross biological membrane. The Partition coefficient studies were performed using n-octanol/skin as non aqueous phase and water as aqueous phase. The two
phases were mixed in equal quantities and kept for saturation with each other in separating funnel. After mixing the system remain undisturbed for half an hour.
About 10 mg of drug added to this solution and was shaken occasionally in separating funnel. After shaken the resulting solution was kept a site for 24 hour. After 24 hour two phases were separated in a separating funnel. The aqueous phase was filtered through Whatman filter paper, suitably diluted and amount of Baclofen in aqueous phase was determined by measuring absorbance at 220 nm using UV spectrophotometer (Shimadzu 160). The partition coefficient of Baclofen was calculated from the ratio between the concentration of Baclofen in organic and aqueous phases from the below mentioned formula.

$$\text{D O/PBS} = \frac{\text{Concentration of drug in non aqueous phase}}{\text{Concentration of drug in aqueous phase}}$$

Permeation study of pure drug

The in-vitro drug permeation studies were carried out by using Franz diffusion cell. The rat skin of abdominal part was cut and hair was removed and clamped between the receptor and donor compartments. The receptor compartment was filled with 15 ml of diffusion medium (Phosphate buffer pH 7.4) through sampling port taking care to remove all the air bubbles. Baclofen were stirred at 500 rpm. by externally driven, teflon coated small magnetic bead to keep them well mixed. The temperature of the system was maintained at 37 Accurately weighed 5 mg of clopidogrel bisulfate was dissolved in phosphate buffer pH 7.4 and placed in receptor compartment. At suitable time intervals, aliquots (3ml) were collected and suitable diluting the aliquot with phosphate buffer and absorbance was measuring at 220 nm using a double beam UV spectrophotometer (Shimadzu 160). The

diffusion medium of the same volume (3ml), which was pre warmed at 370C, was then replaced into the receptor compartment. Duration of the experiment was 12-24 hours. The amount of drug permeated through skin was calculated from absorbance of aliquots.

Thickness of the patch

The thickness of the drug loaded patch was measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Weight uniformity

The prepared patches were dried at 60°c for 4hrs before testing. A specified area of patch was cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weight.

Folding endurance

A strip of specific area was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

Percentage Moisture content-

The prepared films were weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

$$\text{Percentage Moisture content} = \frac{\text{Initial wight- Final Weight}}{\text{Final Weight}} \times 100$$

Percentage Moisture uptake

The weighed films were kept in a desiccators at room temperature for 24hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

$$\text{Percentage Moisture Uptack} = \frac{\text{Final Weight - Initial Weight}}{\text{Initial Weight}} \times 100$$

Water Vapour permeability

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1gm of fused Calcium chloride was taken in the vials & the polymer films were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber at 85 % RH condition for a period of 24 hours. The vials were removed and weighed at various time intervals like 3, 6, 12, 18 and 24hrs to note down the weight gain

Drug content

A specified area of patch was dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique).

Percentage Elongation break test

The percentage elongation break was determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned

$$\text{Elongation Percentage} = \frac{L1 - L2}{L1} \times 100$$

Where, L1is the final length of each strip and L2 is the initial length of each strip

In vitro drug diffusion studies

The in vitro diffusion study was carried out Franz diffusion cell. The cylinder consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at 37 and receptor compartment was provided with sampling port. The diffusion medium used was phosphate buffer (pH 7.4).The diffusion studies were done to get an idea of permeation of drug through barrier from the transdermal system. In vitro studies are also done for TDDS development. Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of horizontal type of cells. In this work, K-C type of diffusion cell was used. Diffusion cells generally comprise two compartments,the active component (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier .The cell consisted of sampling port and temperature maintaining jacket. The outlet and inlet was connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. The stainless steel pin was used

to stir the receptor solution using magnetic stirrer. The mice abdominal skin was placed on receptor compartment and both compartments held tight by clamps. Phosphate buffer pH 7.4 was used as receptor solution. The volume of diffusion cell was 15 ml and stirred with bent stainless steel pin. The temperature was maintained at 37 ± 2°C with the help of magnetic stirrer. The diffusion was carried out for 24 hours and 1 ml sample was withdrawn at an interval of 1, 2, 3, 4, 5, 6, 7, 8,10, 12 and 24 hour. The same volume of phosphate buffer pH7.4was added to receptor compartment to maintain sink conditions and the samples were analyzed at 220nm in UV spectrophotometer.

Skin irritation test:

The skin irritation test was done on a healthy rabbit weighing between 2 to 3 kg. Drug loaded polymeric film of 3.14 sq cms was placed on the left dorsal surface of the rabbit. The patch was removed after 24 hours with the help of alcohol swab. The skin was examined for erythema/oedema.

Stability studies:

All the films were exposed to two selected temperatures of 37°C and 45°C in two different hot air ovens. Transdermal films were kept in the oven for period of 4 weeks. The films were analyzed for the drug content at the end of every week. The averages of triplicate readings were taken.

Shear Adhesion test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength 15.

Peel Adhesion test-

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulledfromthe substrate at a 180 angle, and the force required for tape removed is measured 15.

Water Vapour transmission studies (WVT)

For the determination of WVT, weigh one gram of calcium chloride and place it in previously dried empty vials having equal diameter. The polymer films are pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials are accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials are again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch. In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccators was measured by using hygrometer. The weighed vials were then placed in desiccators and procedure was repeated. WVT = W/ ST W is the increase in weight in 24 h; S is area of film exposed T is exposure time .16

Rolling ball tack test

This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch .17.

Quick Stick (peel-tack) test

In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width .17

Probe Tack test

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams. 17

In vitro drug release studies

The paddle over disc method (USP apparatus V) is employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness are to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate is then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus is equilibrated to 32± 0.5°C. The paddle is then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrometry The experiment is to be performed in triplicate and the mean value can be calculated.18

Skin Irritation study

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury 15.

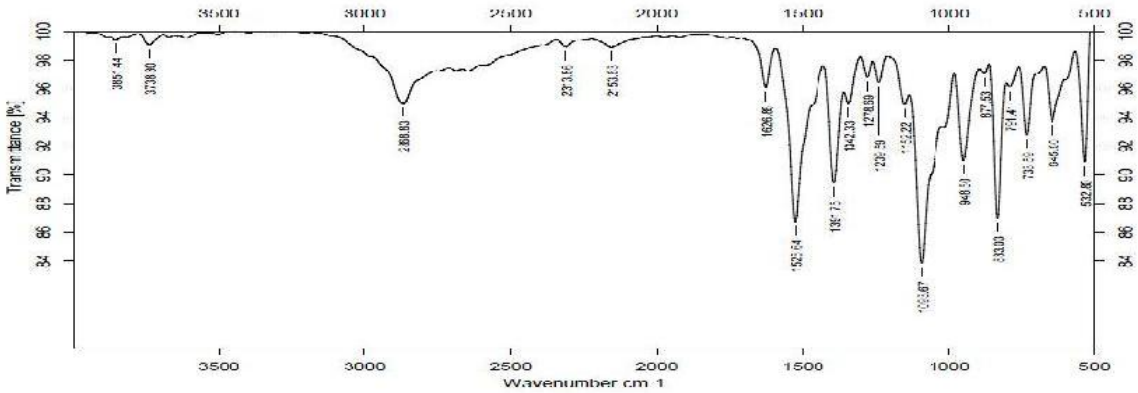
Stability studies

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40 and 75±5% RH for 6 months. The samples are withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content

Result---

FT-IR spectrum of Baclofen

Figure



FT-IR spectrum of HPMC K100

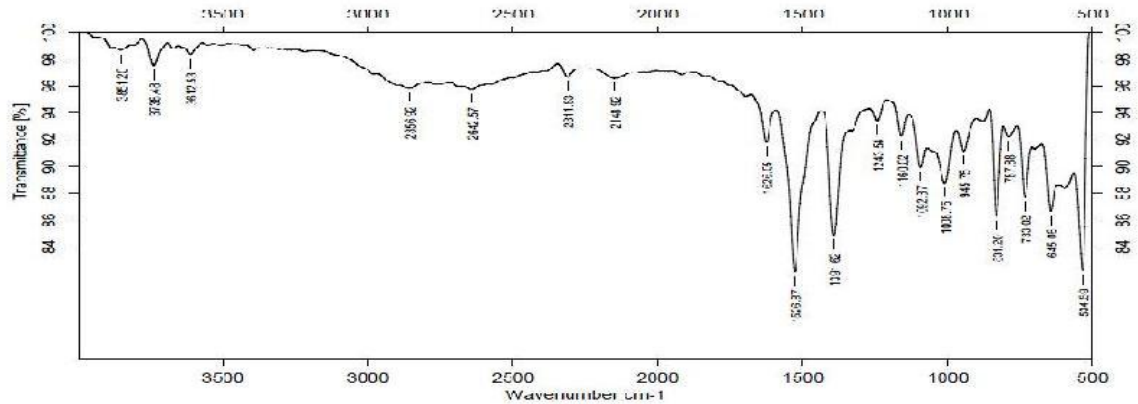


TABLE 2: Partition coefficient of drug in PBS 7.4

Partition coefficient of drug	Solvent system	Log D Values
Baclofen	Phosphate buffer: n-octanol	2.4

TABLE 3: Partition coefficient of drug in skin

Partition coefficient of drug	Solvent system	Log D Values
Baclofen	Phosphate buffer: skin	2.6

TABLE 4: Permeation study of Baclofen in phosphate buffer pH 7.4

Time (hrs.)	% Amount permeation
0	0
1	8.32
2	14.54
3	16.45
4	26.12
5	36.32
6	42.12
8	50.04
10	56.06
12	62.14
24	70.22

TABLE 5: Physico-chemical properties of prepared formulations

Formulation Code	Thickness (mm) ± S.D	Weight uniformity (mg)	Folding endurance ± S.D	Moisture content (%) ± S.D
F1	0.145	92.86	46	3.06
F2	0.164	112.42	68	2.76
F3	0.244	142.44	76	2.45
F4	0.142	154.54	40	1.30
F5	0.174	164.42	52	1.22
F6	0.284	176.66	40	1.18

TABLE 6: Physio-chemical properties of prepared formulations

Formulation code	Moisture uptake ± S.D	Percent elongation break test ± S.D	cumulative drug release (%)	Water Vapour transmission test ± S.D
F1	1.42	76.32	88.88	0.26
F2	1.78	82.70	94.64	0.46
F3	2.30	101	86.87	0.60
F4	2.84	72	80.56	0.38
F5	3.65	84	72.12	0.68
F6	3.80	120	84.08	0.78

TABLE 7: Drug content of prepared formulations

Formulation code	Drug content(%)
F1	92%
F2	94%
F3	82%
F4	84%
F5	81%
F6	96%

TABLE 8: Curve fitting data for the release rate profile of formulation F2

Model	r 2 value
Krosmeyers – peppas	0.967
Zero order	0.855
First order	0.146
Higuchi matrix	0.648
Hixson Crowel	-0.9548

Fig 2. Thickness

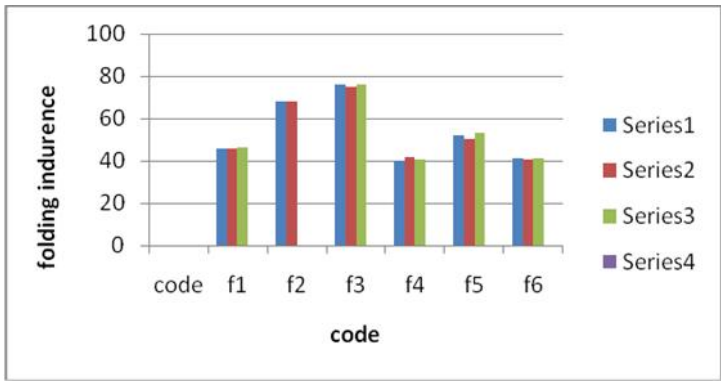


Fig 3. Folding endurance of various batches.

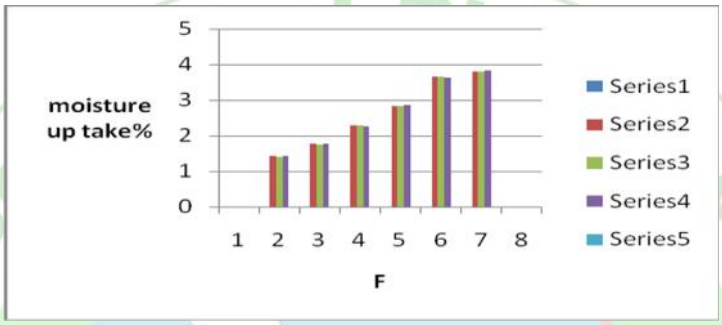


Fig. 4 Moisture Uptake study of various batches.

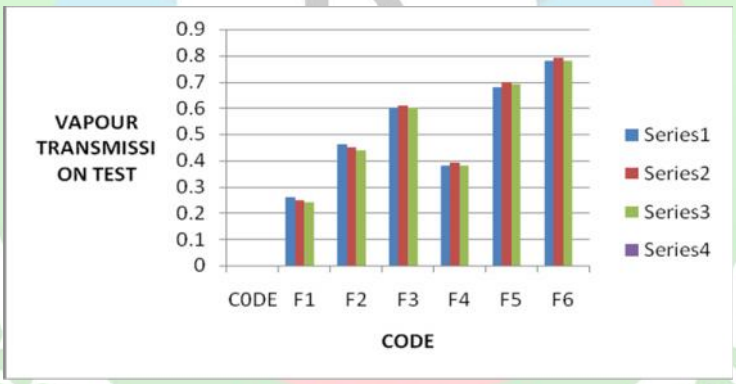


Fig. 5: Water vapour transmission study of formulated batches.

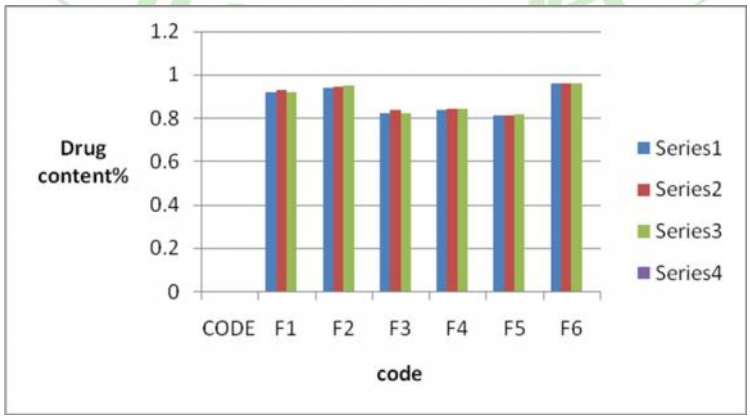


Fig. 6 Drug Content study of formulated batches.

DISCUSSION-

The calibration curve of pure Baclofen was plotted with phosphate buffer pH7.4. The compatibility between Drug and polymer was studied by using FTIR absorption spectra showing in fig no. 2, 3, and 4.The preliminary study conducted On compatibility between Baclofen with HPMC and EC revealed that there is no interaction between the drug and polymer as from FTIR
spectra.The polymers are the backbone for Transdermal delivery. The widely used polymers for the fabrication of Transdermal patches are Cross-linked polyethylene glycol(PEG) networks, Acrylic-acid matrices, Ethyl Among these formulations HF4 and HE3 showed good permeations in 24hrs. So these HF4 and HE3 were selected as best formulations. All the patches showed Zero order release with diffusion, as the possible mechanisms of drug release. This study suggesting that the patches can meet the sustained release characteristics.

CONCLUSION-

Transdermal patch showed good controlled release properties. The results of the present study demonstrated that Baclofen can be considered for Transdermal patch containing HPMC & EC as polymers & Span 80 as permeation enhancer for controlled release of the drug over a period of 24 hrs for the management of hypertension. The Transdermal drug delivery system holds a promising future in effective Transdermal delivery of bioactive agents and opportunities for clinicians to experiment with various drugs to study their systemic and local effects

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