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DESIGN, OPTIMIZATION AND EVALUATION OF ACECLOFENAC TRANSDERMAL PATCH USING NATURAL POLYMER

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs commonly used to treat both the acute and chronic injuries sustained by osteoarthritis, rheumatoid arthritis and ankylosing spondylitis athletes during training and competition. Aceclofenac is well tolerated and effective in reducing pain and/or improving functional capacity in chronic (OA, AS, RA) and acute (e.g. LBP) painful musculoskeletal conditions. It appears to be more effective than other NSAIDs and has a better Gl profile.

The purpose of this research was to develop a matrix-type transdermal therapeutic system containing drug Aceclofenac with different ratios of Hydroxylpropyl methyl cellulose (HPMC) and Ethyl Cellulose and chitosan polymeric systems (F1-F9) by incorporating 25 % w/w of polyethylene glycol (plasticizer) and 0.1 ml DMSO (permeation enhancer). The physicochemical compatibility of the drug and the polymers studied by FTIR spectroscopy suggested absence of any incompatibility. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, folding endurance, percentage of moisture content and percentage moisture uptake, tensile strength and In-vitro drug release studies of formulations were performed by using Franz diffusion cells.

Keywords – Transdermal drug delivery systems, skin , chitosan, transdermal patch

Introduction

Transdermal drug technology specialists are searching for new methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with the oral route. More than 20 years ago, the first transdermal drug delivery system was introduced. In the 1980s and 1990s, the technology sparked tremendous excitement and interest among major pharmaceutical companies. Transdermal drug delivery system companies were merging into larger organisations by the mid to late 1990s. Such dosage forms have recently been developed and/or modified in order to increase the driving force of drug diffusion (thermodynamic activity) and/or increase skin permeability[1]. Penetration enhancers, supersaturated systems, hyaluronic acid, pro-drugs, liposomes, and other vesicles are examples of these approaches. The transdermal drug delivery system is one in which the active ingredients of the drug are delivered through the skin. The skin is an effective medium through which the drug is absorbed and enters the circulatory system. Transdermal patches of various types are used to introduce active ingredients into the circulatory system through the skin. The patches have proven to be effective due to significant advantages over other controlled drug delivery systems[3].

Aceclofenac is used as a model drug to assess its suitability as a transdermal drug delivery system. Aceclofenac is an anti-inflammatory and analgesic nonsteroidal anti-inflammatory drug (NSAID) that is taken orally and is used to treat osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis[6]. Aceclofenac has a strong inhibitory effect on the cyclo-oxygenase enzyme (COX), which is involved in the synthesis of prostaglandins, which are inflammatory mediators that cause pain, swelling, inflammation, and fever. Aceclofenac is classified as BCS Class II due to its low aqueous solubility. It has a high permeability to enter synovial joints, where the loss of articular cartilage causes joint pain, tenderness, stiffness, crepitus, and local inflammation in patients with osteoarthritis and related conditions[8]. NSAIDs can be purchased over-the-counter and used without any physician oversight. However, the chronic nature of overuse injuries requires NSAIDs to be taken orally for an extended period of time. As a result, they can have significant adverse effects on athletes, RA patients, namely gastrointestinal (GI), renal, and cardiovascular damage[10]. Dyspepsia and

upper Gl ulceration and bleeding are of great concern in chronic NSAID use, and as such oral NSAIDs are generally contraindicated in those with a history of peptic ulcers or irritable bowel disease. Topically applied NSAIDS are able to achieve high concentrations within the targeted site of action while simultaneously keeping plasma concentrations low, and convenience of weekly or bi-weekly application results in patient compliance, lowered pill burden. These factors make potential therapeutic value of topical NSAIDs much more promising than that found so far with oral NSAIDs[12].

Among several polysaccharides, chitosan is one of the chief commercially significant biodegradable polymer from a pharmaceutical point of view. Chitosan is a distinct cationic polysaccharide and is different from other polysaccharides in the perspective that cationic character is absent in other polysaccharides. The polycation polymer polymer contains glucosamine and N-acetyl glucosamine units linked together through B-(1-4) glycosidic bonds.Chitosan is obtained by the alkaline deacetylation of N-acetyl glucosamine polymer, chitin which is the major building constituent of shrimp and crab shell . The application of chitosan is restricted as it is insoluble in water. However it is soluble in dilute acids including formic acid, acetic acid, lactic acid etc. The presence of remarkable nitrogen content makes chitosan a commercially fascinating polymer as it can act as a chelating agent. Chitosan displays several biological activities including cholesterol lowering, antihypertension and immune response activity. The enhanced attention of chitosan especially in the biomedical field is because of its exceptional properties including non-cytotoxicity, biocompatibility, capacity to interact with certain organic compounds, biodegradability, susceptibility to enzymatic hydrolysis and non-allergenic behavior. These behaviors are mainly beneficial to several biological applications such as wound healing, tissue engineering and drug delivery. In addition to the detailed properties, the excellent film forming ability and non-skin irritatancy encouraged several research groups to explore CS in TD drug delivery system[12].

Material and method

Aceclofenac was purchased from Arati distributor Mumbai, India, Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl cellulose (EC), Poly Ethylene Glycol (PEG), Chloroform , Dimethyl Sulfoxide (DMSO) was received from Loba Chemicals Mumbai. All the other solvents and chemicals used in this project are to analytical grade. Instruments like belongs to UV-Spectrophotometer (Lab India 4000), DSC and FTIR (BRUKER Alfa) ,Franz Diffusion cell were used for evaluation processes. Design expert software for statistical and graphical representation was used.

Preparation of transdermal film

Transdermal patches containing Aceclofenac were prepared by the solvent casting method. Transdermal film containing HPMC (100 mg) , Ethyl cellulose (300 mg) , chitosan (1.5 %), PEG 400 (25%) as plasticizer, DMSO as a penetration enhancer were prepared by film casting technique. The polymers were dissolved by mixing them in suitable solvents(chloroform: Methanol 1: 1). Aceclofenac 50 mg (in 5ml solvent mixture chloroform: methanol) was added to the polymer-solvent mixture and stirred magnetic Stirrer until a homogeneous solution was obtained. The prepared solution was poured in a petridish. The rate of evaporation was controlled by placing the funnel over the petridish. After drying at room temperature for 24 hr, membrane was taken out, cut into 2 cm ×2 cm , packed in aluminium foil and stored in desiccator until further use.

Factorial design

3^2 Factorial design was used in this study and two factors were evaluated . Each at three levels experimental batches were performed at all nine possible combinations In group A the concentration of ethyl cellulose (X1) and concentration of HPMC (X2) was used as independent variables. The Tensile strength and In-vitro drug release were selected as dependent variables for both the group . The data were subjected to 3-D response surface methodology in design expert software to determine the effect of polymer on release of drug , dependent Variable.

Selection of independent variables

Level	Variable	X1 (Conc. Of ethyl cellulose)	X2 (Conc. Of HPMC)
Low	-1	100	100
Medium	0	300	300
High	+1	500	500

Experimental design 3^2

Formulation Variables	F1	F2	F3	F4	F5	F6	F7	F8	F9
X1	-1	-1	-1	0	0	0	+1	+1	+1
X2	-1	0	+1	-1	0	+1	-1	0	+1

Batch	Drug (mg)	EC (mg)	HPMC (mg)	Chitosan (%)	PEG 400 (%)	DMSO (ml)	Solvent(ml) Methanol; Chloroform
F1	50	100	100	1.5	25	0.1	1:1
F2	50	100	300	1.5	25	0.1	1:1
F3	50	100	500	1.5	25	0.1	1:1
F4	50	300	100	1.5	25	0.1	1:1
F5	50	300	300	1.5	25	0.1	1:1
F6	50	300	500	1.5	25	0.1	1:1
F7	50	500	100	1.5	25	0.1	1:1
F8	50	500	300	1.5	25	0.1	1:1
F9	50	500	500	1.5	25	0.1	1:1

Table no 1 . Formulation table

Evaluation Test For Transdermal Patch

1. **Physical Appearance and Texture**

This parameter was checked simply with visual inspection of patches and evaluation of texture by feel or touch

2. **Weight Uniformity of Patches**

Three Patches of the size 2cmx2cm were weighed individually using digital balance and the average weight were calculated.

3. **Thickness Uniformity**

The thickness of the formulated film was measured at 3 different points using a digital micrometre and average thickness was calculated.

4. **Folding Endurance**

The folding endurance was measured manually for the prepared films. A strip of film 1 cm^2 was cut 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 or cracking gives the value of folding endurance[1].

5. **Percentage Moisture Uptake**

A weighed film kept in a desiccator at room temperature for 24 h was taken out and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. Finally, average percent moisture uptake was calculated[9].

$$\% \text{ Moisture Uptake} = (wf\text{-}wi)/\ wix\ 100$$

where wf is the final patch weight, and wi is the initial patch weight.

6. **Percentage Moisture Content**

The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hours Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight[9].

$$\% \text{ Moisture Loss} = (wi - wf)/wix\ 100 \quad (3)$$

whereas wi is the initial patch weight, and wf is the final patch weigh

7. Drug Content Uniformity

A specified area of patch (2 cm*2 cm) was dissolved in 100 mL methanol and shaken continuously for 24 h. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrophotometrically at wavelength of 275 nm and determined the drug content[15].

8. Tensile Strength

The tensile strength was determined by using a tensiometer. A film of size 1 x 1 cm was held between two clamps & Weight was gradually applied so as to increase the pulling force till the patch broke. From the following equation, the total amount of force (tensile strength, kg/cm²) required to break a patch was calculated.

$$\text{Tensile Strength} = F/(a.\ b(1+L/I))$$

were,

F is the force needed to break a patch,

a is the patch width (cm) and

b is patch thickness (cm).

L is patch length (cm), and

I is patch elongation before patch breakage (cm).

9. In Vitro Drug Release

In vitro diffusion studies were performed by using modified Franz diffusion cell with a receptor compartment capacity of 15 ml. The cellophane membrane piece was mounted between two compartments of the diffusion cell. The film was placed on the membrane surface and covered with aluminium foil The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4 The whole assembly was fixed on a hot plate magnetic Stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beds and the temperature was maintained at 37+0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.[15]

Result and Discussion

Our present work comprises the formulation and evolution of Aceclofenac Transdermal patches for sustained or extended release for a prolonged period of a time. Transdermal patches were prepared by Matrix diffusion method. totally 9 formulation trial (F1 - F9) were done with aim to achieve the successful Matrix type transdermal patches. All results are shown in Table No. 6

Physicochemical properties of Aceclofenac-

1.Organoleptic Properties

The sample of Aceclofenac was studied for its organoleptic characters such as Colour, Odour and Appearance, solubility. The results are presented in Table No 2.

2. Melting point

The melting point of the drug sample range of the drug is 149 °c – 150°c .hence complies with IP standards thus indicating the purity of the drug sample .

TABLE NO 2. Organoleptic Properties of Aceclofenac

Parameters	**Observed**
Appearance	Crystalline powder
Odour	Odourless
Colour	White powder
Melting point	149°c
Solubility	Methanol, chloroform, ethanol

3. FOURIER TRANSFORM INFRA-RED (FTIR) ANALYSIS

The sample drug under study exhibits characteristic peaks at 3319.6 cm-¹(N- H stretching)(C=O stretching)at . 1718.59 cm-¹,(C- Cl stretching) at 763 Cm-¹, which represents amine group, carbonyl group, and chloride functional groups respectively. The peaks observed are under the standard limit of frequency which confirm the purity of drug.

Fig NO.1 IR Spectrum Of Aceclofenac

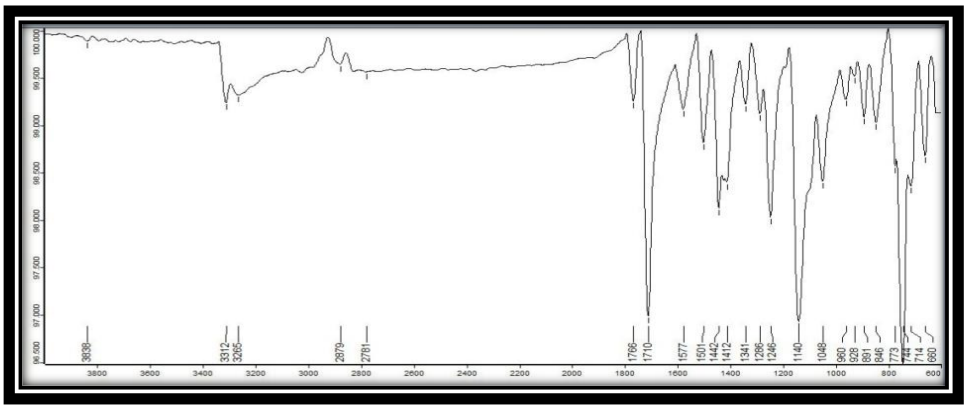


Table No .3 Spectrum interpretation of Aceclofenac

Bonds	Types Of Compounds	Observed Frequency Cm-1	Standard Frequency Cm-1
1	N- H stretching	3319.6	3200- 3400
2	O- H stretching	3319.49	3300 - 3500
3	C= O	1718.59	1700 - 1750
4	C- Cl	763	730- 550

4. Determination Of Lambda Max Of Aceclofenac

The UV spectrum of Aceclofenac in methanol was scanned and lambda max of Aceclofenac was found to be 275 nm using UV spectrophotometer. The lambda max of standard drug as per the literature review is found to be 275nm. Hence the drug sample found to be pure and suitable for further work.

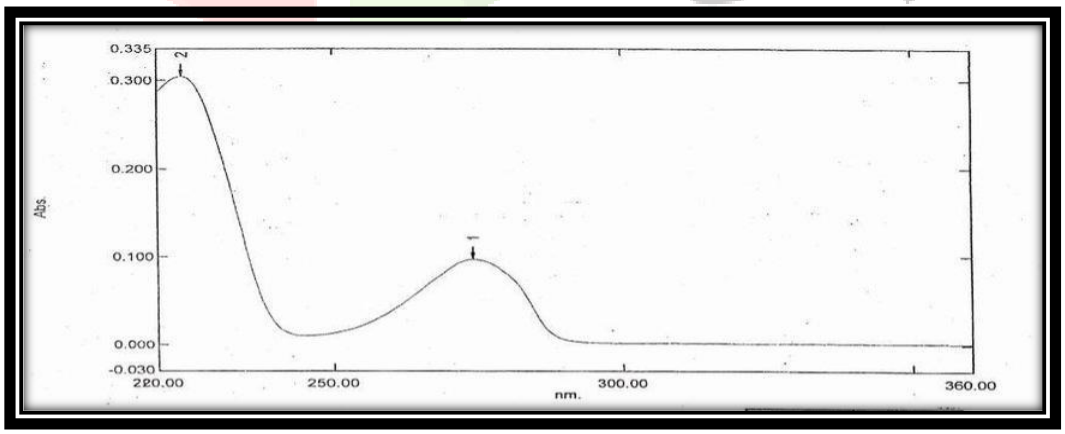
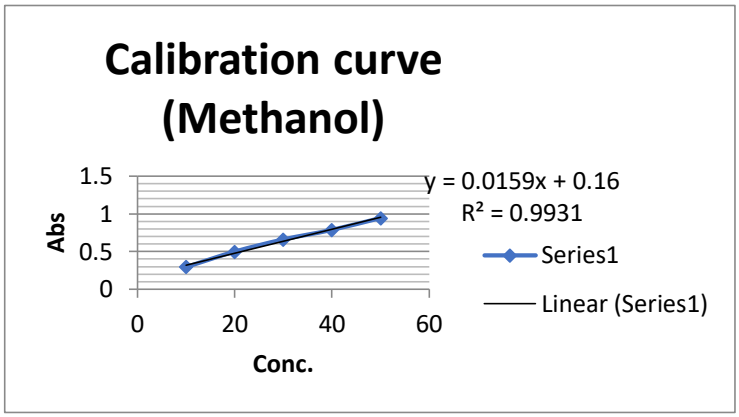


Fig NO. 2 Uv Spectroscopy of Aceclofenac in Methanol

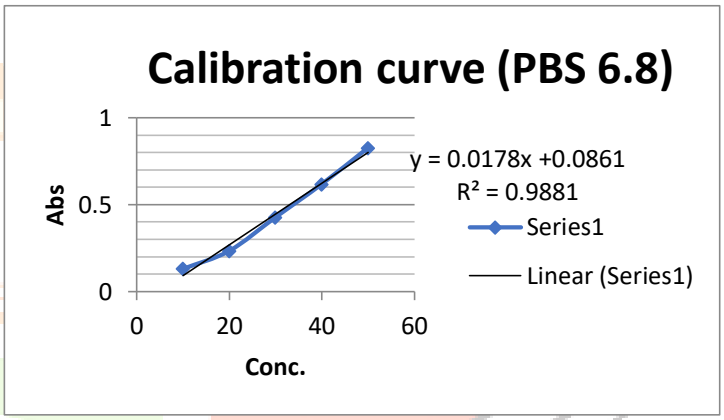
Calibration curve of Aceclofenac in Methanol

Sr. No	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	10	0.2941
3	20	0.4981
4	30	0.6600
5	40	0.7870
6	50	0.9440



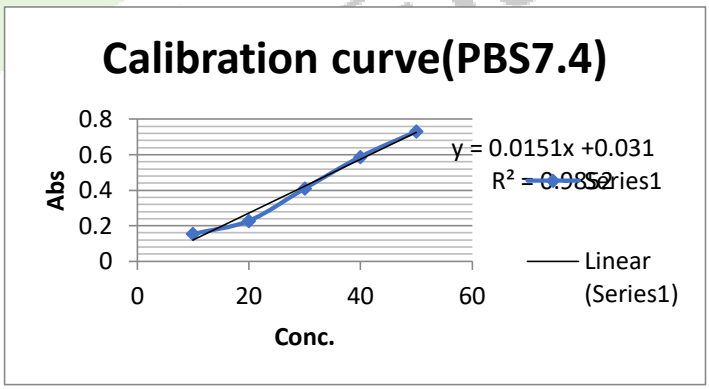
Calibration curve of Aceclofenac in phosphate buffer 6.8

Sr. No	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	10	0.1300
3	20	0.2332
4	30	0.4264
5	40	0.6170
6	50	0.8256



Calibration curve of Aceclofenac in phosphate buffer 7.4

Sr. No	Concentration (µg/m)	Absorbance (nm)
1	0	0
2	10	0.1548
3	20	0.2289
4	30	0.4098
5	40	0.5887
6	50	0.7309



DSC Of Aceclofenac

DSC was used to evaluate the thermodynamics behaviour of the drug as well as it's physical sate (amorphous or crystalline). It is discovered that drug exhibits a sharp, intense peak at 151.02 degree Celsius which corresponds to the melting point of Aceclofenac. DSC of the drug is performed and from this we get to know this drug is pure.

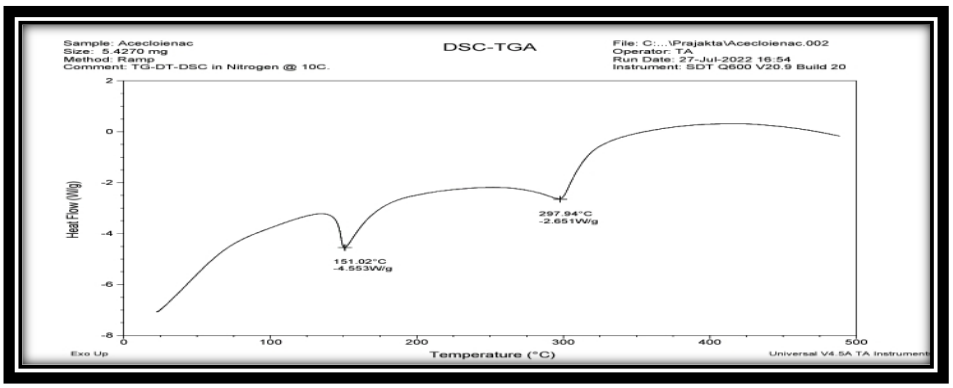


FIG NO. 3 DSC Of Aceclofenac

EVALUATION OF PATCHES -

- **Physical appearance** – All the patches were even and smooth in texture.
- **Weight uniformity** - Physical evaluation of patches was evaluated and they were found to of uniform weight .The weights are in the range of 71.57 mg to 78.67 mg. Among which formulation F1, F4 , F7 contains the lowest weight due to low Concentration of HPMC and F9 formulation contains the highest weight due to high concentrations of HPMC.
- **Thickness Uniformity**- Physical evaluation of patches was evaluated and they were found to of uniform thickness in the range 0.50 mm to 0.56 mm. Among which F2and F7 formulation is thinnest due to low Concentration of HPMC and high concentration of ethyl cellulose and F9 formulation is thickest due to high concentration of HPMC and low Concentration of ethyl cellulose
- **Folding endurance** - The folding endurance was measured and results are shown in Table No. 6
- **Percentage Moisture content** – The moisture content in the patches ranged from 6.28% to 8.88% .Among F1, F4 , F7 showed lower moisture content due to higher concentration of Ethyl cellulose whereas higher concentration of HPMC leads to increased moisture content. The lower moisture content in the formulations helps them to remain stable and become a completely dried and brittle film.

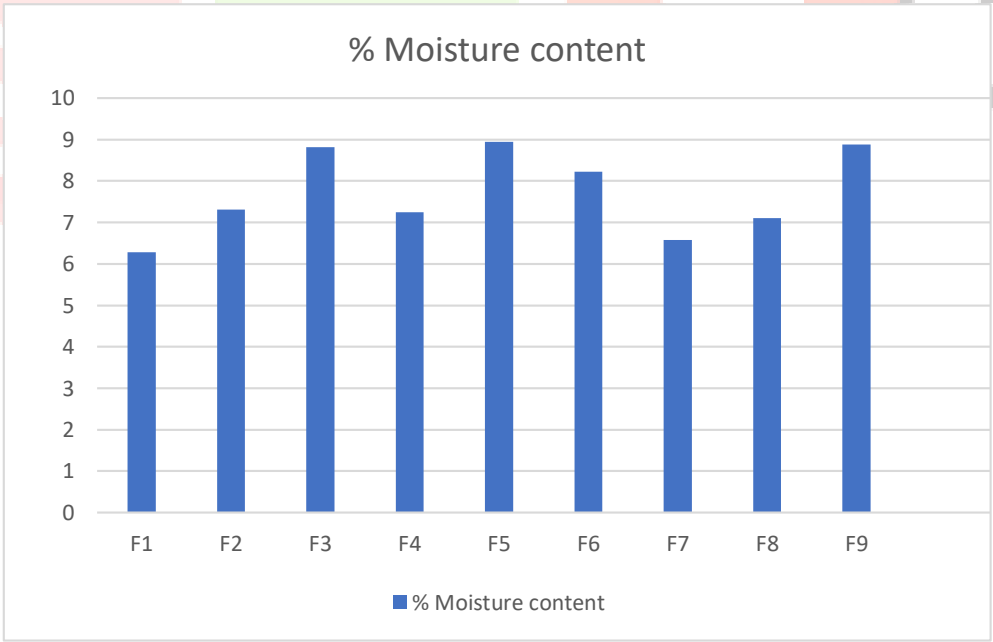


Fig No. 4 % Moisture content

- **Percentage Moisture uptake** – The percentage moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. The results of moisture uptake studies for different formulations were shown in Table and % Moisture uptake for different formulations ranges from 2.4 to 2.9 . Low moisture uptake protects the material from microbial contamination and bulkiness.

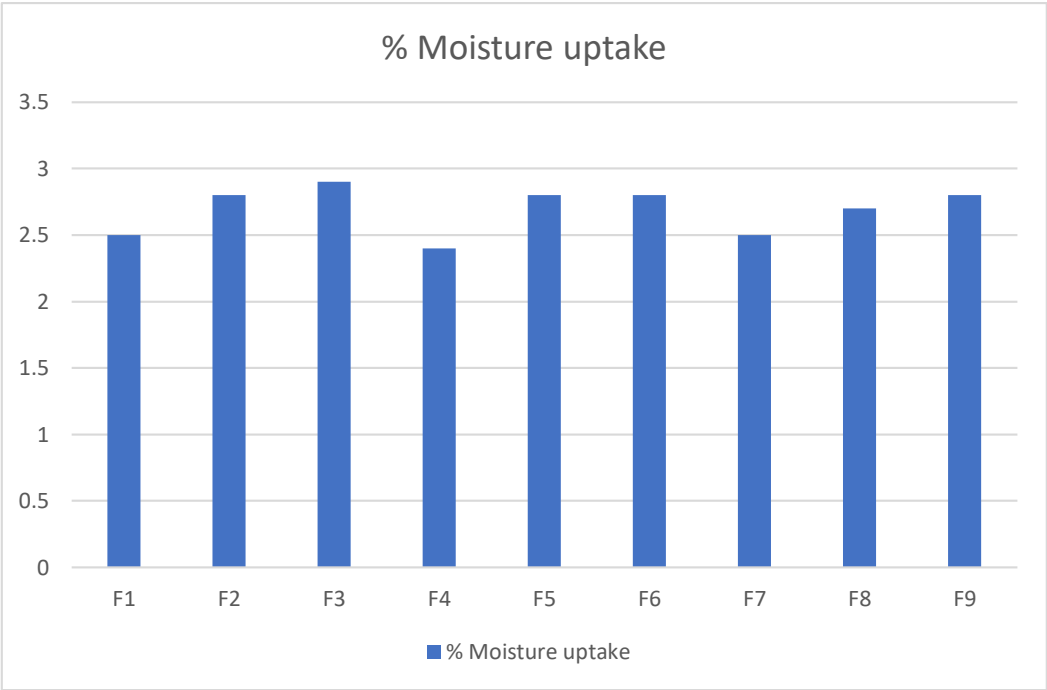


Fig No .5 % Moisture Uptake

- **Content uniformity** - The Drug content analysis The drug content analysis of different formulations was done according to the procedure . The drug content ranged between 95.45 to 99.42The percentage drug content of all formulations is shown in Table . Percentage of drug content was high for all formulations.

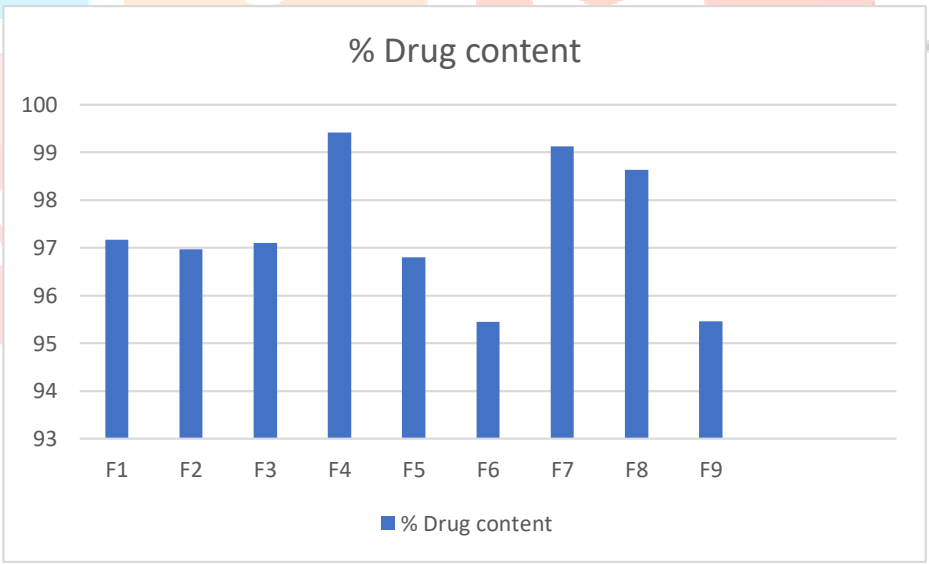


Fig No .6 % Drug content

- **Tensile strength** - The tensile strength measurement was done by using tensiometer. On applying factorial design, Linear model was suggested by software for Response 1. Factor coding is **Coded**. Sum of squares is **Type III –Partial**. The **Model F-value** of 10.33 implies the model is significant. There is only a 1.14% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicate model terms are significant.

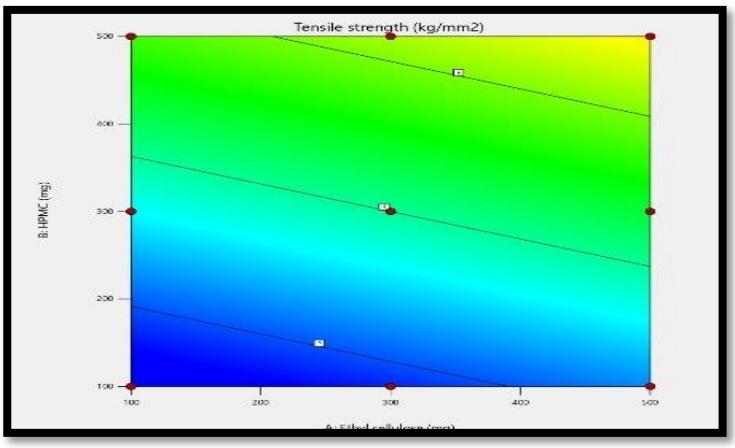


Fig NO. 7 Contour Plot of Tensile Strength

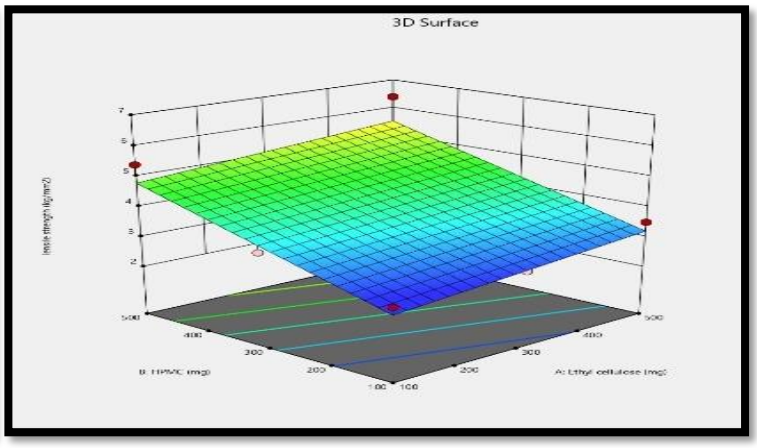


Fig NO. 8 3D Surface Graph Tensile strength

TABLE NO .4 Fit Summary Of Response 1

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	**0.0114**		**0.6999**	**0.4273**	**Suggested**
2FI	0.8951			0.6412	-0.3735
Quadratic	0.3860			0.6830	-0.1867
Cubic	0.6818			0.5579	-9.0725 **Aliased**

TABLE NO .5 ANOVA For Response 1

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	8.97	2	4.49	10.33	0.0114	significant
A-Ethyl cellulose	0.8067	1	0.8067	1.86	0.2219	
B-HPMC	8.17	1	8.17	18.80	0.0049	
Residual	2.61	6	0.4344			
Cor Total	11.58	8				

In Vitro drug release studies -

The in vitro permeation studies are predictive of in vivo performance of a drug. These studies were performed for different formulations across mice skin using phosphate buffer, pH 7.4 as an in vitro study fluid in the receptor compartment of a Franz diffusion cell. The results of these studies are given in Table No. 7 and shown in Fig.no 9 (F1-F5). Factor coding is Coded. Sum of squares is Type III-Partial. The Model F-value of 7.49 implies the model is significant. There is only a 2.34% chance that an F-value this large could occur due to noise P values less than 0.0500 indicate model terms are significant.

Formulation F4 with Ethyl cellulose: HPMC 3:1) exhibits better drug permeation 92.74%) after 10h. Nature of polymer concentration of polymer also affect the drug release. Higher concentration of HPMC (hydrophilic polymer) leads to reduced drug permeation rate. Due to best rate of drug permeation by F4, it was chosen as the optimized formulation and further study was conducted on it.

Table No. 6 Physical properties of the prepared films

Formulation	Weight uniformity (mg)	Thickness Uniformity (mm)	Folding endurance	% Moisture content (%)	% Moisture Uptake (%)	Content uniformity (%)	Tensile strength (kg/mm²)
F1	73.86	0.51	183	6.28	2.5	97.17	0.31
F2	74.37	0.50	192	7.31	2.8	96.97	0.66
F3	76.55	0.54	178	8.82	2.9	97.11	1.31
F4	72.15	0.52	186	7.25	2.4	99.42	1.58
F5	74.67	0.53	189	8.94	2.8	96.80	2.15
F6	74.75	0.55	150	8.22	2.8	95.45	0.13
F7	71.57	0.51	189	6.58	2.5	99.13	0.56
F8	73.48	0.52	152	7.10	2.7	98.64	0.83
F9	78.86	0.56	139	8.88	2.8	95.46	1.47

TABLE NO .7 In Vitro Drug Release Studies

TIME (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1.417	1.521	1.729	1.938	1.979	2.188	2.229	2.271	2.479
2	9.890	9.811	10.486	10.661	11.496	12.338	12.498	13.341	14.183
4	10.238	10.575	10.575	11.600	12.443	13.293	13.630	14.140	16.657
5	12.334	12.596	13.446	22.090	13.483	13.758	19.264	19.446	21.988
6	18.960	19.386	21.244	44.557	22.948	23.642	22.453	30.803	32.537
7	38.146	40.409	30.15	61.663	45.589	46.457	47.256	47.356	57.689
8	56.105	60.308	44.203	79.935	70.038	70.914	71.804	72.071	73.689
9	74.240	78.484	60.888	88.968	81.644	81.695	81.177	81.778	86.987
10	87.753	86.801	79.070	92.743	88.95	86	89.99	88.24	87.11

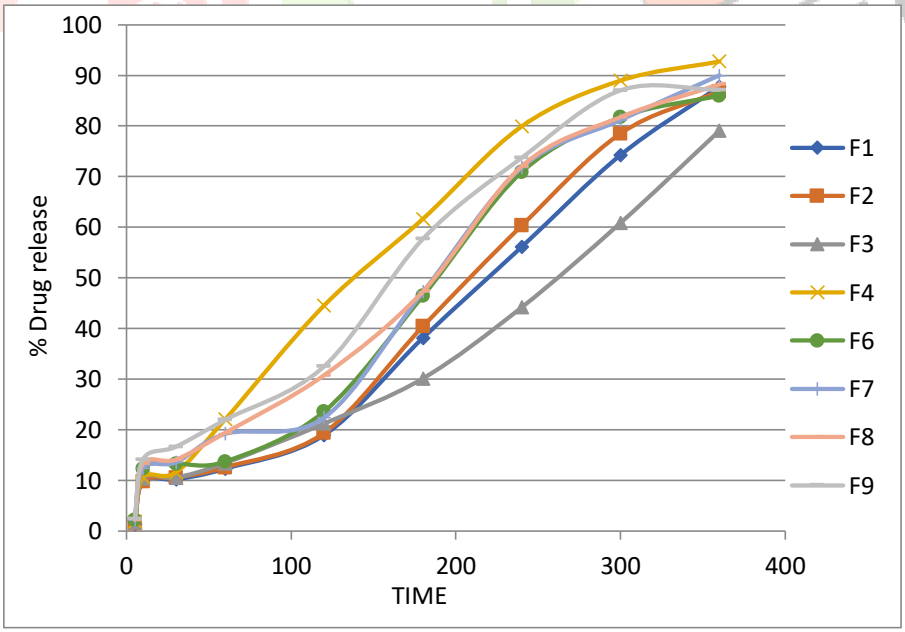


FIG NO. 9 % Cumulative Drug Release

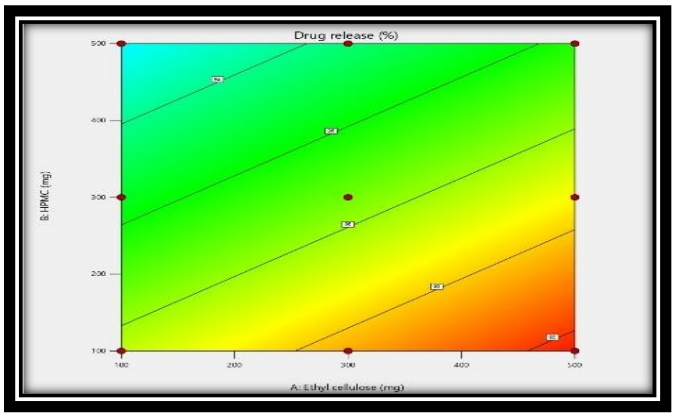


Fig No .10 Contour Plot of Drug Release

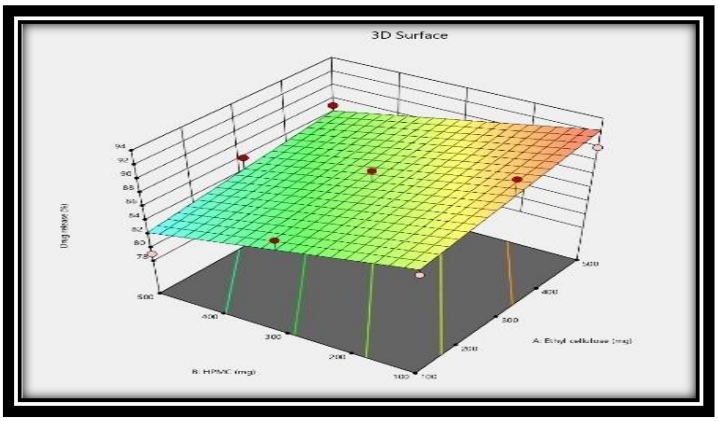


Fig NO.11 3D Surface Graph of Drug Release

TABLE NO .8 Fit Summary Of Drug Release (Response 2)

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	**0.0234**		**0.6186**	**0.2477**	**Suggested**
2FI	0.2354		0.6643	-0.1660	
Quadratic	0.1517		0.8409	0.3462	
Cubic	0.5095		0.8761	-1.8225	**Aliased**

TABLE NO .9 ANOVA For Linear Model for Drug release (Response 2)

SOURCE	SUM OF SQUARES	DF	MEAN SQUARE	F-VALUE	P-VALUE	
Model	78.71	2	39.35	7.49	0.0234	significant
A-Ethyl cellulose	22.89	1	22.89	4.36	0.0819	
B-HPMC	55.82	1	55.82	10.62	0.0173	
Residual	31.54	6	5.26			
Cor Total	110.25	8				

Release Kinetics Of Optimized Formulation F4

The diffusion profile of best optimized batch was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas to certain the kinetic modelling of drug release by using PCP Disso version 2.08 software, and this model with the highest correlation coefficient was considered to be best model. The slope and R^1 are shown in table no.10 and fig no. 12 . Optimized formulation was best fitted Zero order with $R^2 = 0.9797$. Which is higher than 1 in experiment work, hence drug transport mechanism is ficks diffusion transport mechanism.

Table No. 10 Release Kinetics of optimized batch

Order Of Release	**Correlation Coefficient R^2**
Zero order	**0.9797**
First order	**0.9695**

Higuchi model	**0.9791**
Korsmeyer- Peppas	**0.9474**

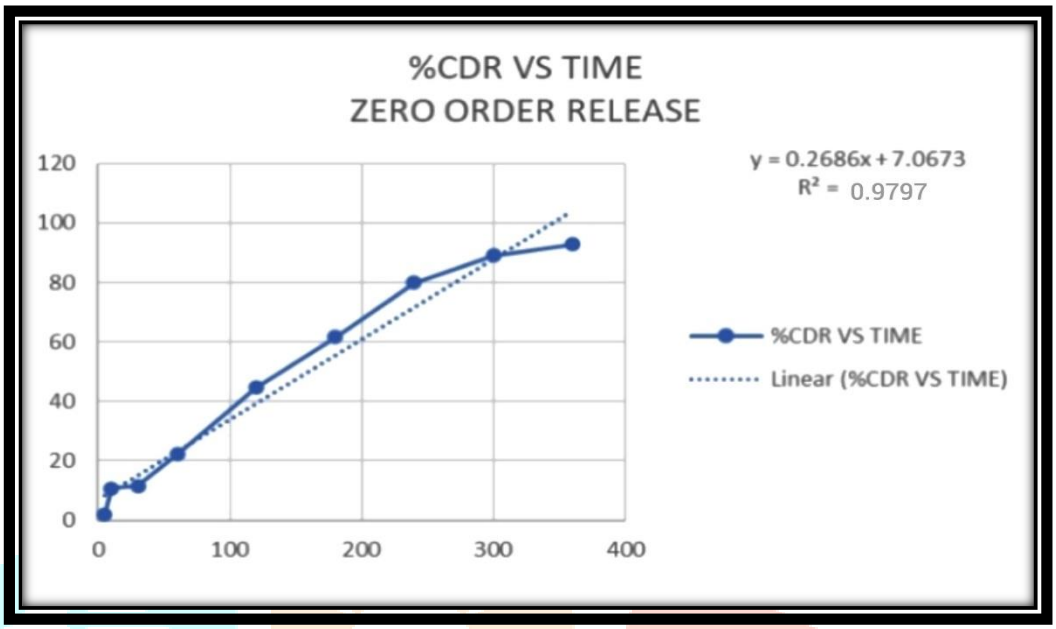


FIG No. 12 Kinetic Models of Drug Release of Optimized Batch.

Stability Study

There is no change in the selected Parameters such as Tensile strength, Surface pH, folding endurance, thickness, texture, Weight of patch, drug content and drug release. This fact results revealed that the formulation was stable after one month.

TABLE NO.11 Evaluation of Optimized Batch

Parameters	**Results (After 1 Month)**
Appearance, texture	White, smooth, flexible
Thickness	0.52 mm
Folding endurance	186
Surface pH Tensile strength	5.4 1.58 kg/ mm²
Weight of patch	72.14 mg
content Uniformity	99.42 %
Drug release	92.743 %

Conclusion

The selected transdermal patch (F4) has shown good promising result for physical appearance, Thickness, weight uniformity, folding endurance, surface pH, Tensile strength, % moisture content and uptake, Drug content. It is concluded that the HPMC, EC &Chitosan concentration of moderate level useful for preparation of sustained release matrix transdermal patch. the formulation (F4) has successfully formulated to offer cast effective and route of choice for the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis

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