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Transdermal Drug Delivery System of Phytopharmaceuticals

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Abstract

Curcumin is used as a model drug to assess its suitability as a transdermal drug delivery system. Due to its poor aqueous solubility and permeability, curcumin is classified as a biopharmaceutical classification system (BCS) class IV molecule. Curcumin has antioxidant, anti-inflammatory, antiviral, and antifungal properties. Turmeric has been shown to help with post-surgical inflammation. Curcumin, the active ingredient of Curcuma longa, has been shown to have anti-inflammatory properties.The main objective of this study was to prepare and characterize transdermal patch of Curcumin. Patch were prepared using HPMC and Ethyl Cellulose, as Hydrophillic and Hydrophobic Polymer using solvent casting evaporation method. Patch were evaluated for appearance, Folding endurance, and their performance in vitro using Franz diffusion cell. According to the findings of this research, Curcumin could be considered as a transdermal delivery system for treatment of post-surgical inflammation pain relief without the risk of unwanted drowsiness and kill microorganisms.

Kerwords: Curcumin, antiiflammatory, transdermal drug delivery.

I. Introduction

Curcumin

Curcumin is the main curcuminoid in turmeric, a renowned Indian spice that belongs to the ginger family (Zingiberaceae). Desmethoxycurcumin and bis-desmethoxycurcumin are the other two curcuminoids. Turmeric's yellow hue is attributed to curcuminoids, which are polyphenols.[(1)] Curcumin is not hazardous to humans, according to research. Curcumin works as an anti-inflammatory agent by inhibiting a variety of distinct compounds involved in inflammation.

Curcumin has a wide range of biological and pharmacological action, however its therapeutic potential is limited due to its low water solubility and quick elimination rate.Turmeric is a spice that has captured the interest of both the medical and scientific worlds, as well as the culinary world. Turmeric is a rhizomatous herbaceous perennial plant in the ginger family (Curcuma longa). The therapeutic benefits of turmeric, the source of curcumin, have been known for thousands of years, but only lately has it been possible to pinpoint the exact mechanism(s) of action and identify the bioactive components. Curcumin (1,7-bis(4-hydroxy3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also known as diferuloylmethane, is the major natural polyphenol found in Curcuma longa (turmeric) rhizomes and other Curcuma spp. Because of its antioxidant, anti-inflammatory, antimutagenic, antibacterial, and anticancer characteristics, Curcuma longa has been utilised as a medical plant in Asian countries for centuries. Curcumin, a polyphenol, has been demonstrated to target several signalling molecules while also displaying cellular activity, supporting its multiple health advantages. Inflammatory disorders, metabolic syndrome, pain, and the management of inflammatory and degenerative eye conditions have all been proven to benefit from it. It has also been demonstrated to be beneficial to the kidneys.[(2)]Curcumin, also known as diferuloylmethane, is a yellow pigment that constitutes up 60 to 70% of crude turmeric extracts and is the main curcuminoid studied for health benefits..[(3)]

Pharmacokinetic (1),(5),(6)

In animal pharmacokinetic studies, 40-85% of an oral dose of curcumin passes through the gastrointestinal tract intact, with the majority of the absorbed flavonoid being metabolised in the intestinal mucosa and liver. Curcumin is frequently used with bromelain to boost absorption and enhance anti-inflammatory effects due to its low absorption rate.[(1)]

Curcumin pharmacokinetics and pharmacodynamics Curcumin's low solubility and poor absorption have been noted in studies as a barrier to attaining optimal therapeutic doses. Curcumin is thought to be biotransformed into dihydrocurcumin and tetrahydrocurcumin before being converted to monoglucuronide conjugates, according to studies. Curcumin's limited bioavailability led to the development of Theracurmin, a synthetically produced nanoparticle version of curcumin with a greater bioavailability.[(5)]

Curcumin levels in the bloodstream of animals and humans following oral consumption have been studied using pharmacokinetic investigations. Curcumin is rarely found in complete form in the bloodstream. According to these research, just a limited percentage of ingested curcumin reaches the systemic circulation in humans, potentially limiting its biological activity.[(6)]

Curcumin has a low absorption rate from the GI tract since it is quickly digested. Curcumin is used for its therapeutic efficacy, ease of availability, and lack of documented negative effects. Unlike the challenges with curcumin absorption in the gut, topical preparation of the hydrophobic curcumin through the skin. Because of inflammation and loss of normal skin barrier function, topical curcumin penetration may be exacerbated in dermatologic diseases.

Curcumin has a low water solubility. It's a natural component of turmeric's (Curcuma longa) rhizome, and it has biological properties ranging from antioxidant to anti-inflammatory. Curcumin has a wide range of biological and pharmacological action, however its therapeutic potential is limited due to its low water solubility and quick elimination rate. Curcumin is a spice that is used in transdermal treatments to kill

microorganisms and reduce acne. Transdermal drug delivery route for antiinflammatory herbs is needed, and curcumin's low oral bioavailability encourages to investigate topical preparations.

II.MATERIALS AND METHODS

2.1Drug and Chemicals

Curcumin which used for the work was gifted by Sunpure Extract Private Limited Dehli. HPMC, Ethyl Cellulose, PEG400 was obtained from loba chemie Pvt.Ltd, Mumbai ,India.

2.2Experimental Design

Preparation Of Transdermal Patches:

Following method done:-

Solvent casting technique The Transdermal patches prepared are of matrix diffusion controlled systems.

- Initially the placebo was prepared by taking **HPMC , Ethyl Cellulose** as film forming polymers. Both polymers were used in different concentration.
- Accurately weighed polymer was dissolved in their solvent Distilled water and Ethanol respectively.
- Plasticizer was then added in different beakers followed by the addition of drug solution to make up volume up to 10 ml and then sonicated at room temperature to ensure bubble free, gels.
- They were casted into film former and allowed to dry at room temperature till a flexible patch was formed.

All patch excipients, including the medicine, are co-dispersed in an organic solvent and coated onto a release liner sheet in this process. After the solvent has evaporated, a thin layer of protective backing material is laminated to the coated release liner sheet, resulting in a laminate that can be die-cut into patches of the specified size and geometry. On trial and error basis formulation was prepared for several time and checked for physical appearance, transparency, uniformity and visible coalescence all the formulation.

Preparation of Patches: -

By Solvent Casting Method.

- Take 2mg of drug solution; pour it into 5 ml ethanol containing beaker. Mix it properly and sonicate it on bath solicitor.
- Mix all polymer solution as per formula given in the Formulation Table
- Add 2mg of drug solution in polymer containing beaker. Mix it properly and sonicate it on bath solicitor.
- Remove the patch after drying , And cut patch with help of knife containing 4mg of curcumin. i.e. 2cm × 2cm.

Plasticizer plays an important role in formulation of patch as it affects many physical parameters like folding endurance, tensile strength and percent elongation. Mechanical properties such as folding endurance and tensile strength play a crucial role on the physical integrity of the dosage form. Flexibility of patches increase with increase in concentration of plasticizer to certain limit, above that critical point further increase in plasticizer results in leaking of contents from patch.

Formulation table Formulation Table No.2.1

Formulation Code	Drug (mg)	HPMC	Ethyl Cellulose	PEG400	Glycerol
F1	10	10%	10%	0.2	0.1
F2	10	10%	5%	0.2	0.1
F3	10	5%	10%	0.2	0.1
F4	10	10%	10%	0.2	0.2
F5	10	10%	5%	0.2	0.2
F6	10	5%	10%	0.2	0.2
F7	10	10%	10%	0.2	0.3
F8	10	10%	5%	0.2	0.3
F9	10	5%	10%	0.2	0.3

2.3Evaluation Of Patch[8],[9],[10]

Transdermal patch evaluation: The following parameters can be used to categorize transdermal patches.

- Physicochemical evaluation
- In vitro evaluation

Physicochemical evaluation: These factors can be used to evaluate transdermal patches physicochemically:

Thickness:Transdermal film thickness is measured using a travelling microscope, dial gauge, screw gauge, or micrometre at various places on the film.

Uniformity of weight: Weight uniformity is investigated by weighing 10 randomly selected patches individually and finding the average weight. The average weight should not be significantly different from the individual's weight.

Drug content determination: Drug content is determined by dissolving an accurately weighed portion of film (approximately 100 mg) in 100 mL of a suitable solvent in which the drug is soluble and shaking the solution continuously in a shaker incubator for 24 hours. The entire solution is then sonicated. Drug concentration in solution is determined spectrophotometrically after sonication and subsequent filtration.

Content uniformity test: Content uniformity test: 10 patches are chosen, and the content of each patch is determined. Transdermal patches pass the content uniformity test if 9 out of 10 patches have content between 85 and 115 percent of the required value, and one patch has content between 75 and 125 percent of the stated value. If the composition of three patches is between 75 and 125 percent, an additional 20 patches are tested for drug content. If the results of these 20 patches range from 85 to 115 percent, the transdermal patches pass the test.

Moisture content: The produced films are weighed separately and maintained at room temperature for 24 hours in desiccators containing calcium chloride. After a given interval, the films are weighed again until they exhibit a steady weight. The following formula is used to compute the percent moisture content.

% Moisture content = Initial weight – Final weight / Final Weight X 100

Moisture Uptake: Weighed films are maintained for 24 hours in a desiccator at room temperature. These are then removed and exposed to an 84 percent relative humidity in a desiccator using a saturated potassium chloride solution until a consistent weight is attained. The percentage moisture uptake is computed as follows:

% moisture uptake = Final weight – Initial weight / Initial weight X 100

Flatness: The surface of a transdermal patch should be smooth and not constrict over time. This can be proved through a study of flatness. One strip is cut from the centre and two from each side of patches to determine flatness. Each strip's length is measured, and the variance in length is calculated using the percent constriction method. 100 percent flatness is the same as zero percent restriction.

% constriction = I1 – I2 X 100

I2 = Final length of each strip

I1 = Initial length of each strip

Folding Endurance: Folding endurance testing entails assessing the folding ability of films that have been subjected to repeated harsh folding circumstances. Folding endurance is measured by folding the film in the same spot over and over until it breaks. Folding endurance value is the number of times a film can be folded in the same spot without breaking.

Tensile Strength: Polymeric sheets are placed between corked linear iron plates to evaluate tensile strength. An iron screen holds one end of the films in place, while the other is attached to a freely moveable thread passing through a pulley. The weights are gradually put to the pan, which is held in place by the thread's dangling end. The elongation of the film is measured using a pointer on the thread. It is stated that the weight is just enough to break the film.

In vitro release studies: The Franz diffusion cell, which is made up of two compartments: donor and receptor, can be used to analyse transdermal patches in vitro. The receptor compartment is 5-12 mL in volume and 1-5 cm2 in effective surface area. A magnetic bar continuously stirs the diffusion buffer at 600rpm. The bulk of the solution is kept at a constant temperature by circulating thermostated water via a water jacket that surrounds the receptor chamber. The drug content is determined using the appropriate procedure, and the sink must be kept in good working order.

III.RESULTS AND DISCUSSIONS

Preformulation Study:-Preformulation testing is an investigation of physical and chemical properties of drug or drug substances alone and when combined with excipients. It is the first step in the rational development. The use of Preformulation parameters maximizes the chances of formulating an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimization of the drug product quality.

AUTHENTICATION OF DRUG CURCUMIN Organoleptic properties

1. **Physical Appearance**: The sample of curcumin was studied for its organoleptic characters such as Color, Odour and Appearance. The results are presented in table No.3.1

2. **Melting point**:-

Melting point is one of the important parameter to identify the purity of drug along with it helps to identity the crystalline nature of compound. Variation in melting point gives idea about purity of drug. Melting point of curcumin is determined by capillary tube method, and it is mentioned in table no.3.1

Table No.3.1 Organoleptic properties of Curcumin

Parameters	Reported	Observed
Apperance	Crystalline powder	Crystalline powder
Odour	Odorless	Odorless
Colour	Orange yellow	Yellow
Melting Point	180c –191c	184c

3. Drug solubility

Solubility of curcumin was determined in water, ethanol,DMSO

Table No.3.2 Solubility Of Curcumin

Sr.No.	Solvent	Observed Solubility in conc.(mg/ml)
1.	water	0.1mg
2.	Ethanol	10
3	Dmso	25

Fourier Transform Infra-red (FTIR) analysis

INTERPERETATION oF IR OF CURCUMIN

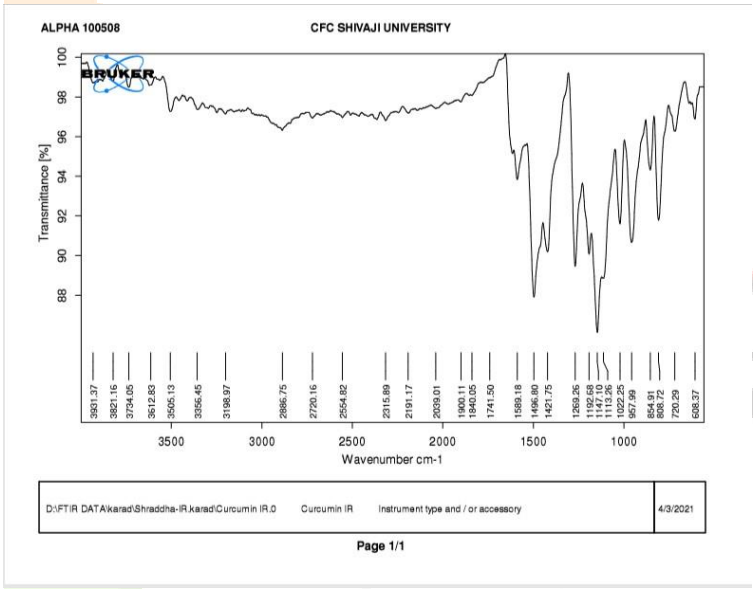


Figure No.3.1 IR Spectrum of Curcumin

Table 3.3 IR Spectrum Interpretation of Curcumin

Bonds	Type of compound	Observed frequency	Standard frequency
C=o strectching	BETA DIKETONE	1625.90	1640-1580
c-o strectching	SECONDARY	1273.93	1350-1260
	ALCOHOL		
c-o strectching	ETHER	1272.93	1270-1200

Discussion

The sample drug under study exhibits characteristic peaks at 1625.92cm (C-O stretch), 1272.93 cm (C-O strech), 1272.93(C-O strech), which represents beta diketone, secondary alcohol, and ether groups respectively, The peaks observed are under the standard limit of frequency which confirm the purity of drug.

Assessment of curcumin by analytical method

UV spectroscopy (determination of lambda max)

The UV spectrum of curcumin in methanol was scanned and lambda max of curcumin was found to be 401 nm using UV spectrophotometer. The lambda max of standard drug as per the literature review is found to be 401 nm. Hence the drug sample found to be pure and suitable for further work.

Table No.3.4 C.C. of curcumin in ethanol

Sr.no.	Concentration	Absorbance
1.	0	0
2.	10	0.252
3.	20	0.412
4.	30	0.642
5.	40	0.811
6.	50	0.975
7.	60	1.1

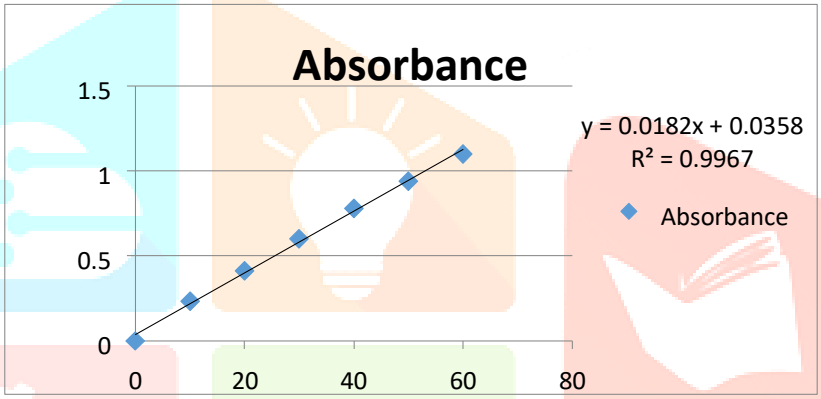


Figure No.3.2 C.C. of curcumin in ethanol

Discussion From the calibration curve we can say that line passes through points which Shows linear relationship so the slope y = 0.018x + 0.035 , R^2 = 0.996 approaching near 1 indicates best fit line. approaching near 1 indicates best fit line.

Lambda max of curcumin in Phosphate buffer pH 7.4

From the experimental work, lambda max of curcumin in Phosphate Buffer pH 7.4 was found to be at 525nm. This wavelength was selected for preparation of calibration of calibration curve

Table No.3.5 C.C. of Curcumin in Phosphate Buffer 7.4

Sr.No.	Concentration	Absorbance
1	0	0
2	10	0.176
3	20	0.304
4	30	0.41
5	40	0.521
6	50	0.655
7	60	0.789

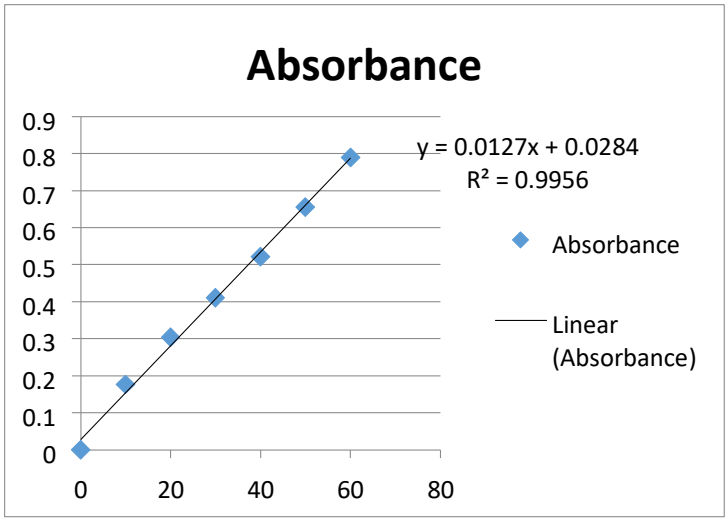


Figure No.3.3 C.C. of Curcumin in Phosphate Buffer 7.4

Discussion From the calibration curve we can say that line passes through points which Shows linear relationship so the slope y = 0.012x + 0.028 , R^2 = 0.995 approaching near 1 indicates best fit line.

B) AUTHENTICATION OF POLYMERS

1. Organoleptic properties:

The polymers were studied for organoleptic properties such as color, odor and appearance.

2 Melting point:

The melting points of polymers were determined by melting point apparatus using capillary method. Observed value was compared with the reported value. The organoleptic properties of polymers are mentioned in table No. 3.6

Table No.3.6 Organoleptic properties of Polymer

Sr no.	**Test**	**HPMC**		**Ethyl Cellulose**	
		Observed	**Reported**	Observed	**Reported**
1.	Colour	White	White	White	White
2.	Odour	Odourless	Odourless	Odourless	Odourless
3.	Melting Point	192^0C	190^0- 200^0C	198^0C	160^0C-210^0C
4.	Solubility	Soluble in cold water, forming viscous colloidal Solution.	Soluble in cold water, forming Viscous colloidal Solution	Soluble in water, ethanol, chloroform	Soluble in water, ethanol, chloroform

The result shows that the polymer sample HPMC and Ethyl Cellulose used for the ongoing research work was pure.

Interpretation of HPMC FTIR spectra

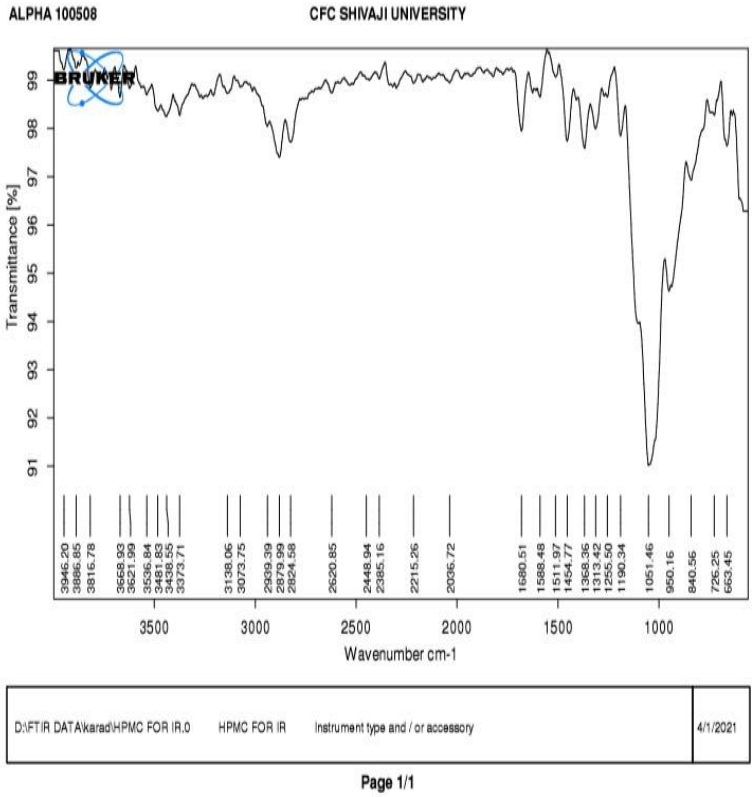


Figure No.3.4 IR Spectrum Of HPMC

Table No.3.7 IR Spectrum Interpretation Of HPMC

Functional Group	Peak observed cm-1	Peak reported cm-1
C-O	1051.46	1050-1150
C-H	2879.99	2850-3000

Discussion Spectrum shows 1046.99 cm−1 corresponds to stretching vibrations of C = O and The band around 2888.64cm−1 corresponds to C-H stretching vibrations.

Interpretation of Ethyl Cellulose FTIR spectra

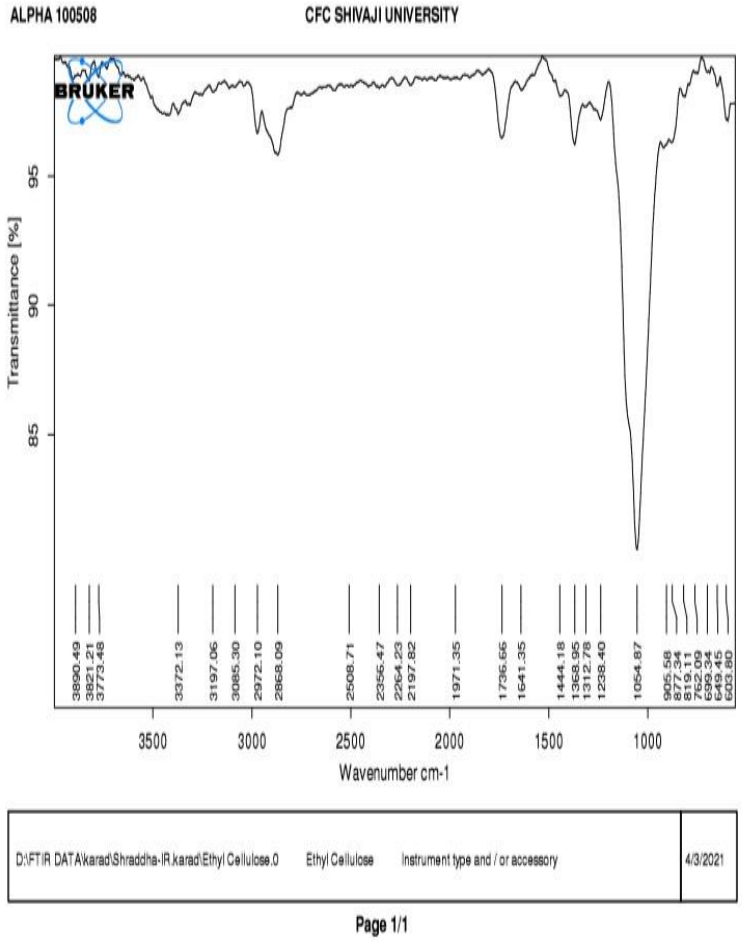


Figure No.3.5 IR Spectrum Of Ethyl Cellulose

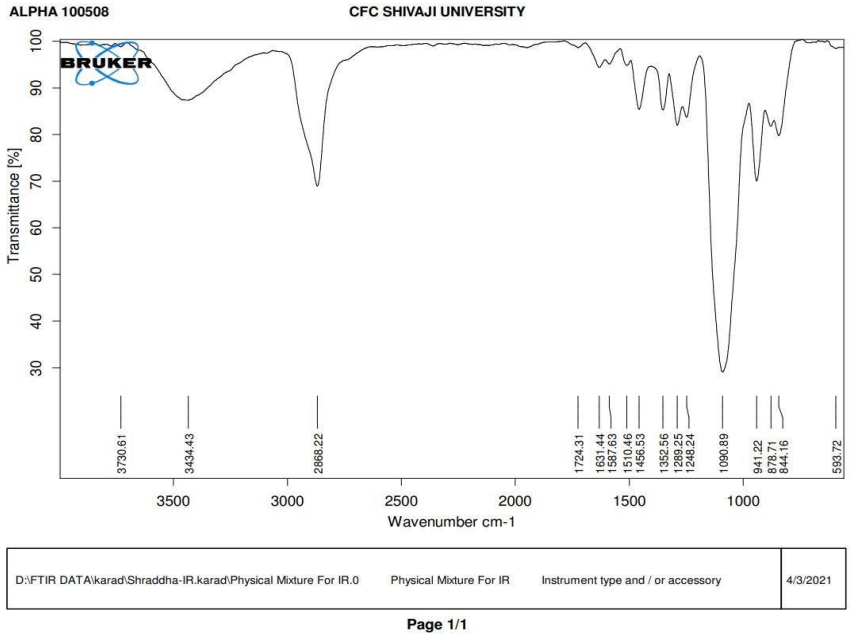
Table No.3.7 IR Spectrum Interpretation Of Ethyl Cellulose

Sr.no	Functional group	Reported range	Observed Peak
1	C-H stretching	2850-3000	2888.25
2	C-H Bending	1350-1480	1373.75
3	C-O Stretching	1050-1150	1054.87
4	C-H stretching	675-1000	917.47

Discussion Spectrum shows 1051.22cm−1 corresponds to stretching vibrations of C = O and around 2888.25cm−1 corresponds to C-H stretching vibrations, 1373.75 cm−1 was C-H Bending and 917.47 corresponds C-H stretching.

Interpretation of Polymer and Drug Curcumin FTIR spectra

Figure No.3.6 IR Spectrum Mixture



IR Spectrum Interpretation Of Mixture C-O Strectching secondary alcohol at 1273.93 cm-1 , c-o strectching 1272.93 cm-1 , C=o strectching1625.90 cm-1 from this coclude that curcumin is pure drug and due to interaction with the polymer that we have used in this formulation there no major interaction and no change in the peak occur in the main peak that are present.

EVALUATION OF TRANSEDRMAL PATCHES A.

PHYSICAL PROPERTIES:

Physical appearance: All the patches were even and smooth in texture.

Weight uniformity

Table No. 3.8 Weight uniformity

Formulation code	Average Weight (g)
F1	2.2
F2	2.3
F3	2.2
F4	2.1
F5	2.3
F6	2.4
F7	2.2
F8	2.4
F9	2.5

Discussion

Physical evaluation of patches containing HPMC and Ethyl cellulose in different concentrations was evaluated and they were found to of uniform weight .The weights are in the range of 2.1 g to 2.5 g. Among which formulation F4 contains the lowest weight and F9 formulation contains the highest weight.

Thickness uniformity:

To determine the uniformity of thickness all over the patch and the batches of patches thickness uniformity test is performed.

Table No. 3.9 Thickness Uniformity

Formulation code	Mean Thickness (Mean) in mm
F1	0.25
F2	0.26
F3	0.26
F4	0.25
F5	0.26
F6	0.28
F7	0.26
F8	0.27
F9	0.29

Discussion

Physical evaluation of patches containing HPMC and Ethyl Cellulose in different concentrations was evaluated and they were found to of uniform thickness in the range of

0.25 mm to 0.29 mm. Among which F1 and F4 formulation is thinnest and F9 formulation is thickest.

Folding endurance: To determine the folding endurance of all the patch and the batches of patch fold at same point and test was performed.

Table No. 3.10 Folding endurance.

Formulation code	Folding Endurance
F1	115
F2	122
F3	113
F4	135
F5	129
F6	122
F7	136
F8	128
F9	129

Discussion

In the above table the folding endurance of all formulation was found to be in the range of 113 to 136 which is optimum ensures that patches exhibited good physical and mechanical properties.

Surface pH

The test is done to confirm that the pH of the formulation and skin are compatible with each other

Table No. 3.11 Surface pH

Formulation code	PH study
F1	5.2
F2	5.4
F3	5.4
F4	5.5
F5	5.4
F6	5.5
F7	5.2
F8	5.5
F9	5.4

Discussion

The surface pH of all patches was found to be in the range of 5.2 – 5.5. Range is 4.7-5.75. From that it is concluded that all formulations was uniform in pH.

Percentage Moisture content

The particular test is done to study the %of moisture given films carries so as to understand its stability

Table No. 3.12 Percentage Moisture content

Formulation code	**Percentage Moisture content**
F1	9.56
F2	8.12
F3	7
F4	**9.5**
F5	10
F6	8
F7	7.1
F8	6.01
F9	5

Discussion

The total moisture content of the patches was found . Above values suggest that, the prepared patches have moisture content capacity in same range.

Percentage Moisture Uptake Table No. 3.13 Percentage Moisture Uptake

Formulation code	Percentage Moisture Uptake
F1	**2.9**
F2	**2.8**
F3	**2.5**
F4	**3.07**
F5	**2.8**
F6	**2.8**
F7	**2.8**
F8	**2.7**
F9	**2.5**

Discussion The total moisture uptake of the patches was found . Above values suggest that, the prepared patches have moisture content uptake in range.

B. PERFORMANCE PROPERTIES:

Content Uniformity:

The Content Uniformity (%) in all formulations varied between the ranges of 96 to 99.93.This indicates that the drug dispersed uniformly throughout the transdermal patch and the prepared patches were uniform in drug content.

Table No.3.14 Content Uniformity

Formulation code	Content Uniformity
F1	99.12
F2	98.11
F3	96.35
F4	99.93
F5	98.33
F6	96
F7	99.67
F8	97.20
F9	96.11

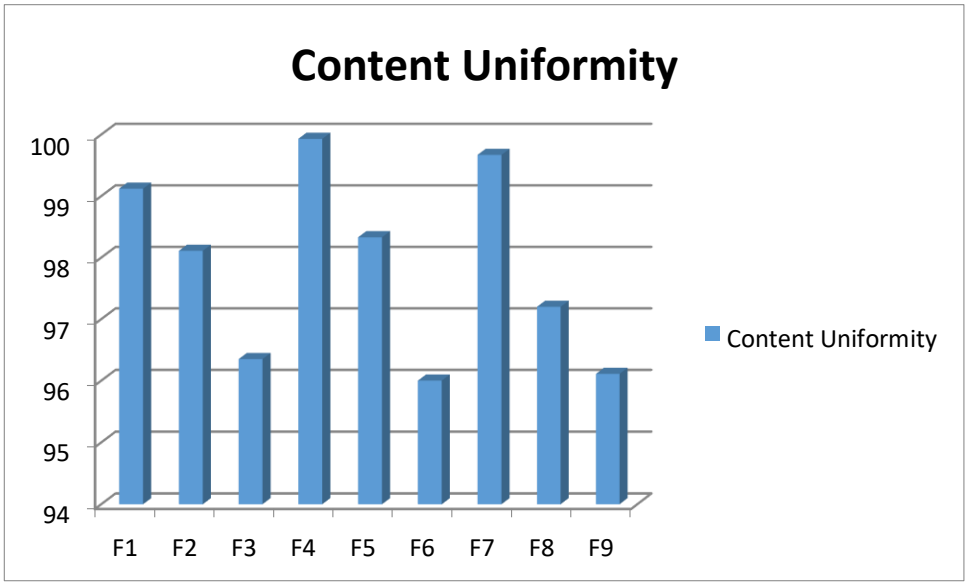


Figure No.3.7Content Uniformity In vitro drug release

Each 9 formulation Trasdermal patch of 2 × 2 cm2 (containing 4 mg of drug) cut and placed directly over the diffusion apparatus (Dolphin-diffusion cell apparatus) containing phosphate buffer 7.4 without starring. Periodically samples were withdrawn, diluted with same solvent and assayed for drug content by spectrophotometrically at 525 nm. Show in table no 3.15

Table No.3.15 In vitro drug release studies

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	1.417	1.521	1.729	1.938	1.979	2.188	2.229	2.271	2.479
10	9.890	9.811	10.486	10.661	11.496	12.338	12.498	13.341	14.183
30	10.238	10.575	10.757	11.600	12.443	13.293	13.630	14.140	16.657
60	12.334	12.596	13.446	22.090	13.483	13.758	19.264	19.446	21.988
120	18.960	19.386	21.244	44.557	22.948	23.642	22.453	30.803	32.537
180	38.146	40.409	30.15	61.663	45.589	46.457	47.256	47.356	57.689
240	56.105	60.308	44.203	79.935	70.038	70.914	71.804	72.071	73.923
300	74.240	78.484	60.888	88.968	81.644	81.695	81.177	81.778	86.987
360	87.753	86.801	79.070	92.743	88.95	86	89.99	88.24	87.11

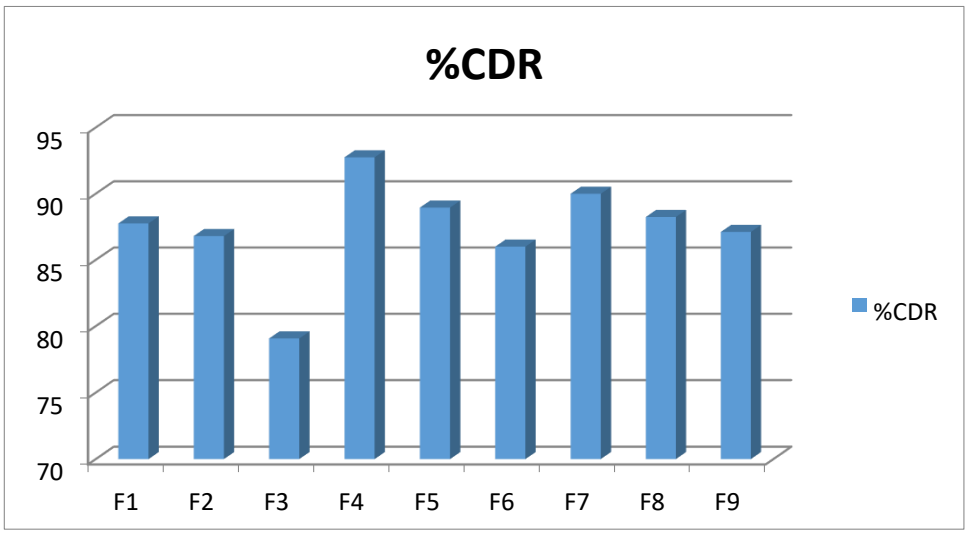


Figure No.3.8 % CDR

Discussion

Among all the formulation F4 containing 4ml of 10% HPMC solution, 1 ml of 10% Ethyl Cellulose solution,0.2 ml PEG 400 and 0.2 ml of Glycerin shows highest drug release rate at the end of 6 hours which is about 92.743%. It was concluded to be the best formulation in terms of cumulative drug release.

Higher amount of Hydroxy Propyl Methyl Cellulose Solution and Lower amount of ethyl cellulose in the patches have greater dissolution. And also the percentage drug release is based on various factors like solubility of the drug in the polymer and solubility of drug in other excipients.

CONCLUSION

From the IR spectroscopic study, it is concluded that the Curcumin drug sample was of purest form and good quality. The Higher Proportion of Ethyl Cellulose is responsible for the controlling the drug release and suitable for a prolonged regimen of drug delivery through transdermal route. The drug release kinetics studies showed that the all the formulations were governed by zero order release kinetics. The evaluation of formulation was done for thickness, drug content, folding endurance, weight variation, surface pH, in vitro drug release study.From all the studies of patches it is concluded that the release rate of the drug increase when the concentration of Hydroxy Propyl Methyl Cellulose and with same concentration of Ethyl cellulose Solution. Hence the formulation batch F4 shows better result.

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