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Formulation And Evaluation of Herbal Transdermal Patches for Rheumatoid Arthritis

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Abstract

The allopathic healthcare system provides two conventional ways of treatment for rheumatoid arthritis, both of which have side effects. As a result, turning to Ayurvedic herbal treatment formulation that is safe, effective, and proven would be a better choice.Rheumatoid arthritis is an autoimmune disease that is chronic and progressive ,distinguished by chronic inflammation affecting the peripheral joints.Transdermal films containing herbal medicinal plants such as *Cardiospermum helicacabum* and *Aloe barbadensis* were designed in this study to treat rheumatoid arthritis . The solvent casting method was used to develop transdermal patches using plant extracts. The patches were evaluated based on physicochemical parameters such as thickness, folding endurance, physical appearance, weight uniformity, moisture content, drug content, flatness, moisture uptake, pH, and invitro drug release and stability study. The plots for average absorbance release vs time through transdermal film shows that drug release occurred at a steady rate. The skin irritation study on human volunteer's skin revealed that the formulation does not cause skin irritation.Overall, the present research provides a novel approach to the implementation of transdermal drug delivery techniques in the design of herbal remedies.

Keywords: Herbal transdermal patch, Antiarthritic patch, Antiinflammatory patch, Painless drug delivery, Rheumatoid arthritis patch.

INTRODUCTION:

Transdermal drug delivery is one of the most prevalent and widely utilized drug delivery methods. When compared to other routes of distribution, the transdermal route has attracted more attention in medication delivery due to its flexibility in palatability and convenience[1]. The transdermal route is one of the most appropriate, older, easy, safe, and cost-effective medication delivery methods. The main objectives of a transdermal medication delivery system are to target a specific region of action and to manage the rate of delivery. Transdermal drug delivery devices are self-contained, discrete dosage forms that, when applied to undamaged skin, release medications into the systemic circulation at a controlled rate[2].

A transdermal patch, also known as a skin patch, is a medicated adhesive patch that is applied to the skin and allows a particular dose of medication to be delivered via the skin and into the bloodstream. Transdermal drug delivery systems (TDDS patches) are self-contained discrete dose forms designed to

distribute the drug via the skin at a controlled pace of systemic circulation when placed to intact skin. The purpose of dosage design for transdermal medications is to increase drug flux through the skin into systemic circulation while minimizing drug retention and metabolism in the skin. The transdermal method of administration is regarded as a potential mechanism for local and systemic medication delivery.

The TDDS provides several advantages such as non-invasive, painless method of delivering drugs directly into the body, more effective approach to administer drugs that are broken down by stomach acids, provide controlled, consistent drugs distribution over long periods of time, fewer negative effects than oral drugs or supplements, easier to apply and remember, alternative for persons who are unable or prefer not to take drugs or vitamins orally, cost-effective[3].

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune illness whose etiology is unknown. It is distinguished by chronic inflammation that mostly affects the peripheral joints. The allopathic medical system has two standard methods of treatment for rheumatoid arthritis, both of which have definite negative effects. As a result, resorting to Ayurvedic herbal treatment composition that is safe, effective, and time-tested would be a better option. Apart from the standard treatment techniques of nonsteroidal anti-inflammatory medications, disease-modifying antirheumatic medicines, and glucocorticoids, newer and safer drugs are constantly being sought, as long-term use of these drugs has resulted in harmful effects. Alternative medicine offers another therapy option for RA, and a number of medicinal plants are now being studied in order to generate a new drug[4].

Aim: The aim of the study is to prepare and evaluate the Herbal Transdermal patches for the efficient treatment of Rheumatoid arthritis by using leaves extract of *Cardiospermum halicacabum* and *aloe barbadensis.*

Objectives: Develop and Authenticate Herbal Transdermal patches using leaves extracts of *Cardiospermum halicacabum* and *aloe barbadensis* for the treatment of Rheumatoid Arthritis. Conduct *invitro* screening of its efficiency towards Anti rheumatoid arthritis.

MATERIALS AND METHODS:

1. Collection of plant material

The leaves of *Cardiospermum halicacabum* were collected from Cheyyar, Thiruvannamalai district and the leaves of *aloe barbadensis* were collected from Pillaiyarpalayam, kanchipuram district in Tamil Nadu in the month of October 2023.

2. Identification and authentication of plant material

The collected specimens were botanically identified and authenticated by Dr.N.K. Sunil Kumar, Research officer, Department of Pharmacognosy, Siddha Central Reasearch institute, Chennai - 600106. The Samples were identified as *Cardiospermum halicacabum* belongs to the family Sapindaceae and *Aloe Barbadensis* belongs to the family Liliaceae.

3. Plant profile

Cardiospermum halicacabum

VERNACULAR NAMES[5]

Table 1: Vernacular names of *Cardiospermum halicacabum*

English	Balloon vine
Tamil	Moedakottan
Malayalam	Jyotishmati
Telugu	Buddakaakaraeega
Bengali	Lataphatkar
Hindi	Kanphuti
Sanskrit	Jyotishmati
Assam	Kopalphuta

TAXONOMICAL CLASSIFICATION[6]

Table 2: Taxonomical Classification of *Cardiospermum halicacabum*

Kingdom	Plantae
Phylum	Tracheophytes
Subphylum	Angiosperms
Class	Eudicots
Order	Sapindales
Family	Sapindaceae
Genus	Cardiospermum
Species	Halicacabum

Figure 1 : Leaves of *Cardiospermum halicacabum*

Aloe barbadensis

VERNACULAR NAMES[7]

Table 3: Vernacular Names of *Aloe Barbadensis*

English	Burn plant
Tamil	Katralai
Malayalam	Kattar vazha
Telugu	Kalabanda
Bengali	Greeto Kumari
Hindi	Matlab

Sanskrit	Aphala
Assam	Chaal kunwari

TAXONOMICAL CLASSIFICATION[8]

Table 4 : Taxonomical Classification of *Aloe barbadensis*

Kingdom	Plantae
Phylum	Tracheophytes
Subphylum	Angiosperms
Class	Liliidae
Order	Tracheobionta
Family	Xanthorrhoeaceae
Genus	Aloe
Species	Aloe vera

Figure 2 : Leaves of *Aloe barbadensis*

4. Extraction of plant material[9]

The leaves of plants were washed three times with tap water and then once with deionized water to remove dirt. The washed leaves were dried in the shade at room temperature. Using a blending machine, a coarse powder of the dried leaves was made to be used for solvent extraction. C.halicacabum coarse leaf powder (50g) was macerated for 3 days in 500ml of ethanol by using cold maceration extraction method. Evaporation was used to concentrate the extracts, which were then stored in an airtight container at a cool temperature for future use.

Figure 3 : Maceration of *Cardiospermum halicacabum* and *Aloe barbadensis*

Figure 4 : Filtered Extracts of *Cardiospermum halicacabum* and *Aloe barbadensis*

5. Phytochemical Screening[10-13]

Table 5 : Phytochemical Screening of plant extracts

S.No.	Identification test	Observation	Inference
1.	**Alkaloids** **a. Mayer's Test** Test extract + Mayer's reagent **b. Tannic acid Test** Test extract + Tannic acid solution	 Cream coloured precipitate Buff coloured precipitate	 Presence of alkaloids Presence of alkaloids
2.	**Glycosides** **a.** Extract +5ml dil.H_2SO_4 ,heat on water bath, neutralize with 5% NaOH solution,0.1ml Fehling's A and B until it becomes alkaline, heat on water bath for 2 minutes. **b.** Extract +5ml water , heat on water bath, 5% NaOH solution,0.1ml Fehling's A and B until it becomes alkaline, heat on water bath for 2 minutes.	 Red precipitate Red precipitate	 Presence of Glycosides Presence of Glycosides
3.	**Tannins** **a. Gelatin Test** Test solution + Gelatin solution containing 10%NaCl **b. Lead acetate Test** Alcoholic extract + Lead acetate solution	 Precipitate is formed White precipitate	 Presence of Tannins Presence of Tannins
4.	**Carbohydrates** **a. Molisch's Test**		

	Extract + Molisch's reagent,shake and add Conc.$H_2SO_4$from sides of test tube. **b. Fehling's Test** Extract + Fehling's Solution A and B reagents	Formation of Violet colour ring at junction of 2 liquids. Brick red precipitate	Presence of Carbohydrates Presence of Carbohydrates
5.	**Flavonoids** **a. NaOH test** Extract + NaOH Solution **b. Lead acetate Test** Extract + Lead acetate solution	 Coloured precipitate Yellow coloured precipitate	 Presence of Flavonoids Presence of Flavonoids
6.	**Amino acids** **a. Ninhydrin Test** Extract + Ninhydrin Solution and boil. **b. Millon's test** Extract + Millon's reagent	 Purple colour White precipitate	 Presence of Amino acids Presence of Amino acids
7.	**Proteins** **a. Coagulation Test** Heat the Test solution in a water bath **b. Lead acetate Test** Test solution + 40%NaOH + 10%lead acetate Solution.	 Coagulation occurs Brown precipitate	 Presence of Proteins Presence of Proteins
8.	**Phytosterols and Triterpenoids** **a. Salkowski Test** Extract + Chloroform + Conc.H_2SO_4,Shake well. **b. Sulphur Test** Test solution + sulphur powder	 Red coloured $CHCl_3$layer Yellow coloured $CHCl_3$layer Sinks at the bottom	 Presence of Steroids Presence of Treiterpenoids Presence of Treiterpenoids
9.	**Terpenoids** **Test for Volatile Oils** **a.** Extract placed on filter paper	 Filter paper is	 Presence of Volatile

	b. Extract + Alcohol **Test for Resins** **a.** Heat the extract **b.** Burn the extract	permanently stained. Soluble Softens and melts Smoky flame is produced	Oils Presence of Volatile Oils Presence of Resins Presence of Resins
10.	**Fixed oils and Fats** **a.** Extract pressed between two filter papers **b.** Extract + Alcohol	 Filter paper is permanently stained. Insoluble	 Presence of Fixed oils Presence of Fixed oils
11.	**Gums and Mucilage** **a.** Test solution + Ruthenium red solution **b.** Powdered drug + water	 Pink colour Particles swell	 Presence of Gums and Mucilage Presence of Gums and Mucilage

6. Finding the absorption maxima (λ max)[14-15]

The absorption maxima have been established for identification of drugs. In order to obtain detailed information on the chromophoric portion of the molecules, ultraviolet visible spectrophotometry was employed. When exposed to light in the Visible/Ultraviolet portion of the spectrum, organic molecules in solutions absorb light of a certain wavelength based upon the particular type of electronic transition related with the absorption. The extract solution (5, 10, 15, 20, 25 µg/ml) in distilled water was placed in a standard cuvette and measured in a UV spectrophotometer within the range of 200-800 nm.

7. Chromatographic evaluation[16]

Thin layer Chromatography

The plant extract was put on a pre-coated TLC plate by utilizing capillary tubes. Drawing sharp lines and dots on the plate to identify the location of each extract put to the plate. The TLC plate was air dried and examined under ultra violet light after mobile phase of Chloroform : Glacial acetic acid :methanol (4:5:1) was used. They were then sprayed with iodine vapour to develop the separated bands, and the movement was represented by its retention factor (R_f) values, which were determined for each sample.

$$\mathbf{R_f} = \frac{\boldsymbol{Distance\ travelled\ by\ solute}}{\boldsymbol{Distance\ travelled\ by\ solvent}} \times \mathbf{100}$$

Stationary phase : Silica gel G
Mobile phase : Chloroform : Glacial acetic acid : Methanol (4:5:1)
Detecting agent : Dragendorff reagent

8. Formulation development[17]

Transdermal patches were developed by using ethanolic extract of *Cardiospermum halicacabum* and *Aloe barbadensis* leaves in various ratios (100:100, 60:40, 40:60, 50:50) and polymer. A weighed amount of polymer was mixed in a calculated quantity of chloroform and ethanol and then heated on

hot plate . The calculated amount of extract was added to the polymer solution and thoroughly mixed until the mixture became homogeneous. After the permeation enhancer and glycerin were then added in the calculated amounts. The resulting solution was put into a Petridish and air dried for 24 hours at room temperature. The patches from the petridish were then removed with a knife and then stored in a desiccator.

Table 6 Formulation of Herbal transdermal patches

Ingredients	Formulation Code			
	F1	F2	F3	F4
CH + AB Extract	100:100	60:40	40:60	50:50
HPMC	0.5	0.5	0.5	0.5
Chloroform	6.25	6.25	6.25	6.25
Ethanol	6.25	6.25	6.25	6.25
Tween 80	1.5	1.5	1.5	1.5
Glycerine	0.3	O.3	0.3	0.3

Figure 5 : Preparation Of Casting Solution In Magnetic Stirrer

Figure 6 : Casting Solution Is Poured In A Petridish Containing Aluminium Foil

9. Anti-inflammatory activity - Inhibition of albumin denaturation[18-19]

Materials required

Chemical and Reagents are Egg albumin solution ,Phosphate buffered saline , Distilled water. Equipments are Clean pipettes , test tubes ,Incubator , Spectrophotometer ,Water bath.

Procedure

The efficacy of plant extracts to suppress albumin denaturation was examined using the Mizushima and Kobayashi (4) method, as described by Sakat (20), with slight modifications. The extracts were prepared in varying concentrations (50 g-300 g), and the quantities were made up to 2.5 ml with 0.85% NaCl. After that, 0.5 ml albumin (1.5 mg/ml) was added. The mixture was left to incubate at 37 ℃ for 20 minutes, followed by 20 minutes at 57 ℃. After cooling the tubes, 2.5 ml of 0.5 M sodium phosphate buffer (pH 6.3) were added. At 660 nm, turbidity was observed spectrophotometrically. The experiment was repeated three times, and aspirin was used instead of the extract. The percentage inhibition of protein denaturation was calculated using the following formula.

$$Percentage\ inhibition = \frac{Absorbance\ of\ control - Absorbance\ of\ test\ sample}{Absorbance\ of control} \times 100$$

10. Evaluation of Herbal Transdermal patches[20-22]

I. Organoleptic Characteristics

The physical appearance of developed patch was evaluated by using a naked-eye examination for its appearance, colour, clarity, flexibility, and smoothness.

II. Physico-Chemical Evaluation

A. Thickness of Patch

A Vernier caliper was used to measure patch thickness uniformity at six different places. The mean thickness of all six places was then determined.

B. Determination of Surface pH

The pH of the patch is evaluated by swelling it with 1 ml of distilled water for two hours at room temperature before use. Then,place the pH electrode on the patch's surface to record the pH value and make them to adjust itself for 1 minute.

C. Percent moisture content

The percent moisture content of the patches was determined by weighing the patches after placing them inside a desiccator for 24 hours. The percent moisture content can be calculated using the following formula:

$$Percentage\ Moisture\ content = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

D. Percentage drug content

Small fragments of patches were cutted and then immersed in a phosphate buffer (PH 7.4) solution for 24 hours. The entire solution was then ultrasonicated for 15 minutes. Following filtering, the drug content was measured spectrophotometrically at λmax 429nm.

$$Percentage\ Drug\ content = \frac{Absorbance\ of\ test}{Absorbance\ of\ standard} \times 100$$

E. Folding endurance

Folding endurance was evaluated by folding the patches repeatedly in the same area even after it broke. Folding endurance is the number of times the patches can be folded in the same area without breaking.

F. Uniformity of weight

Each of the three patches were weighted for each batch, and the mean weight were determined.

G. Moisture Uptake

At room temperature the previously Weighed patches were placed in desiccators for 24 hours in a saturated potassium chloride solution in order to keep 84% RH. After 24 hours, the patches were reweighed and the % moisture uptake was calculated using the following formula .

$$Percentage\ Moisture\ uptake = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100$$

J. Percent Elongation test

When external Stress is applied to patches, it stretches to produce strain and elongation increases as plasticizer concentration increases.

$$Percentage\ elongation = \frac{Increase\ in\ length\ of\ patch}{Initial\ length\ of\ patch} \times 100$$

K. Water vapour permeability test

Normal air circulation oven can be used to measure water vapour permeability. The WVP can be calculated using the formula below.

$$WVP = \frac{Amount\ of\ vapour\ permeated\ through\ the\ patch}{Surface\ area}$$

L. Flatness test

Patches were cut into three longitudinal strips, with the length of each strip was measured and the difference due to non-uniformity in flatness calculated using percentage constriction, with 0% constriction equal to 100% flatness.

$$Percentage\ Constriction = \frac{Final\ length\ of\ each\ strip}{Initial\ length\ of each\ strip} \times 100$$

11. Drug permeation study[23]

Materials required

Chemical and Reagents are Cellophane membrane, Open ended tube ,Buffer solution pH 7.4 and Distilled water. Equipments are Hot plate with magnetic stirrer and UV-visible spectrophotometer.

Procedure

The invitro diffusion rate of formulated transdermal patches was studied through an open-ended tube containing distilled water as the diffusion medium for 8 hours. The cellophane membrane was placed at the base of the tube and dipped in the receptor compartment, which contains 200ml of 7.4 buffer solution. This was stirred at a medium speed and kept at 37°C ± 2°C by using Hot plate with magnetic stirrer. At regular intervals, samples were taken out and the same volume was refilled with fresh diffusion medium. A UV-

visible spectrophotometer with a wavelength range of 260-280nm was used to evaluate the samples.

Figure 7 : Invitro Drug release in cellophane membrane

12. Skin irritation test[24]

Before applying the patch, the dorsal skin of a volunteer was washed with 70% ethanol. The patches were applied on right forearm for 24hrs. After 24 hours , the patches were removed and the forearms were cleansed with saline. The cutaneous responses were assessed by observing erythema, edema, pruritus and urticaria, skin allergy and irritation at 15 minutes, 1 hour and 24 hours after the test patch was removed.

Table 7 : Skin irritation test

Reactions	Score
No	0
Very slight	1
Well defined	2
Moderate	3
Severe	4

RESULTS AND DISCUSSION :

1. Extraction of plant material

Table 8 : Percentage yield of Plant extracts

S.No.	Extracts	Colour and Consistency	Percentage yield (w/w)
1.	Ethanolic extract of *Cardiospermum halicacabum*	Green and semisolid	5.32
2.	Ethanolic extract of *aloe barbadensis*	Brown and semisolid	4.25

Fig.8 Crude extracts of *Cardiospermum helicacabum* and *Aloe barbadensis*

2. Phytochemical screening

It has been confirmed that the leaves of *Cardiospermum halicacabum* and *Aloe barbadenesis* contain various phytochemical constituents. Therefore, it is important to establish a standard to maintain their quality. The extracts were subjected to preliminary phytochemical analysis to detect the various phytochemical constituents. The analysis revealed the presence of alkaloids, glycosides, flavonoids, tannins, and other compounds.

Preliminary phytochemical analysis of *Cardiospermum halicacabum* leaves extract

Table 9 : Phytochemical screening of plant extracts

(+) Presence (-) Absence

S. No.	Test	Ethanolic extract of *Cardiospermum halicacabum*	Ethanolic extract of *aloe barbadenesis*
1.	Alkaloids	+	+
2.	Glycosides	+	+
3.	Tannins	+	+
4.	Carbohydrates	+	+
5.	Flavonoids	+	+
6.	Amino acids	+	+
7.	Proteins	+	+
8.	Phytosterols and Triterpenoids	-	+
9.	Terpenoids	-	-
10.	Fats and oils	-	-
11.	Gums & Mucilage	-	-

3. Absorption maxima (λ max)

Absorption maxima (λmax) of *Cardiospermum halicacabum*

The extract solution (5, 10, 15, 20, 25 g/ml) was placed in a cuvette and analyzed in a UV spectrophotometer within the range of 200-800 nm. It reaches absorbtion maxima at 330 nm. Hence, all further measurements were performed at 330nm.

Table 10 : Absorbance maxima of *Cardiospermum halicacabum*

S.No	Concentration of *Cardiospermum halicacabum* extract	Absorbance at 330 nm
1	5 µg/ml	0.230
2	10 µg/ml	0.285

3	15 µg/ml	0.312
4	20 µg/ml	0.385
5	25 µg/ml	0.438

Absorption maxima (λmax) of *aloe barbadensis*

The extract solution (5, 10, 15, 20, 25 g/ml) was placed in a cuvette and analyzed in a UV spectrophotometer within the range of 200-800 nm. It reaches absorbtion maxima at 424 nm. Hence, all further measurements were performed at 424nm.

Table 11 : Absorption maxima (λmax) of *aloe barbadenesis*

S.No	Concentration of *aloe barbadenesis* extract	Absorbance at 424nm
1	5 µg/ml	0. 383
2	10 µg/ml	0.432
3	15 µg/ml	0.483
4	20 µg/ml	0.542
5	25 µg/ml	0.609

Figure 9 : UV Analysis Of Different Concentrations Of Plant Extracts

4. Chromatographic evaluation

Thin Layer Chromatography (TLC)

Thin layer chromatographic studies was performed on ethanolic extracts of *Cardiospermum halicacabum* and *aloe barbadensis* to identify the presence of various phytoconstituents in the plant extracts, using previously reported methods.

Table 12 : R_f values of ethanolic extracts of *Cardiospermum halicacabum*

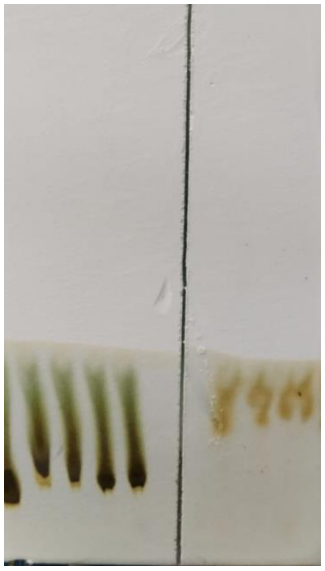
No. of spots	Distance travelled by solute	Distance travelled by solvent	R_f value
1	4.1	5.2	0.78
2	3.9	5.2	0.75
3	3.8	5.2	0.73
4	3.6	5.2	0.69

5	3.4	5.2	0.65

Table 13: R_f values of ethanolic extracts of *aloe barbadensis*

No. of spots	Distance travelled by solute	Distance travelled by solvent	R_f value
1	3.8	5.2	0.73
2	3.7	5.2	0.71
3	3.5	5.2	0.67
4	3.6	5.2	0.69
5	3.8	5.2	0.73

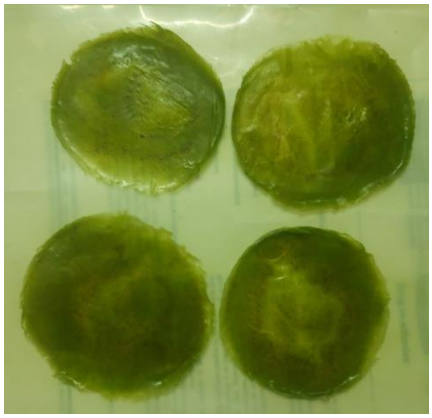
Figure 10 : TLC Analysis of plant extracts



5. Formulation Development

Transdermal patches of *Cardiospermum halicacabum* and *aloe barbadensis* were successfully developed using the solvent casting technique to improve the bioavailability of herbal drugs when combine together . The developed film was homogeneous, flexible, smooth, and clear.

Figure 10 : Formulated Herbal Transdermal patches



6. Anti-inflammatory activity - Inhibition of albumin denaturation

Anti-inflammatory activity was evaluated against denaturation of egg albumin method. The highest inhibition rate was observed in F3 (40:60) ratio of formulation.

Table 14 : Percentage of inhibition of protein denaturation

Concentration (µg\ml)	Percentage inhibition of protein denaturation(%)±SEM			
	F1	F2	F3	F4
Control	100 ± 0.0311	100 ± 0.0311	100 ± 0.0311	100 ± 0.0311
500	65 ± 0.4041	69 ± 0.0063	74 ± 0.0034	57 ± 0.0008
400	54 ± 0.0023	57 ± 0.0063	65 ±0.0015	52 ± 0.0014
300	30 ± 0.0026	48 ± 0.0046	59 ± 0.0008	47 ±0.0040
200	43 ±0.0035	37 ±0.0018	46 ± 0.0014	38 ± 0.0012
100	27 ± 0.0020	23 ± 0.0040	28 ± 0.0008	22 ± 0.0031
Standard	83±0.01	83±0.01	83±0.01	83±0.01

Values are expressed as the Means ± SEM, where (N=3).

Figure 11 : Concentration (µg\ml) Vs Percentage inhibition of protein denaturation(%)±SEM

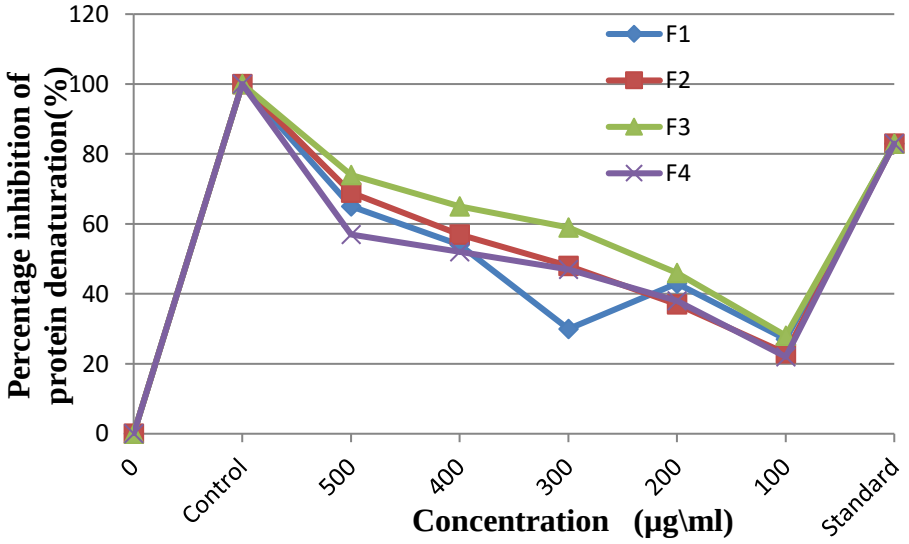


Figure 12: Protein denaturation assay of plant extracts

7. Evaluation of Herbal transdermal patches

Organoleptic Characteristics

Table 15 : Organoleptic Characteristics of Herbal Transdermal patches

S.No.	Physical Appearance	F1	F2	F3	F4
1	Appearance	Jellified Preparation	Jellified Preparation	Jellified Preparation	Jellified Preparation
2	Colour	Light green	Light green	Light green	Light green
3	Clarity	Opaque	Opaque	Opaque	Opaque
4	Flexibility	Yes	Yes	Yes	Yes
5	Smoothness	Good	Good	Good	Good

Physiochemical Evaluation

Table 16 : Physiochemical evaluation of herbal transdermal patches

S.No	Physico-Chemical Evaluation	F1	F2	F3	F4
1	Thickness of Patch	0.2 ± 0.089 g	0.3 ± 0.089 g	0.11 ± 0.040 g	0.18 ± 0.075 g
2	Determination of Surface pH	4.5 ± 0.264	4.44 ± 0.095	4.55 ± 0.229	4.61 ± 0.090
3	Percent moisture content	1.97 ± 0.711 %	0.86 ± 0.364 %	1.36 ± 0.400 %	1.06 ± 0.497 %
4	% drug content	81 ± 1.414 %	83.6 ± 2.494 %	85.6 ± 1.247 %	89 ± 1.414 %
5	Folding endurance	31.8 ±0.849	35.06 ± 0.899	37 ± 0.816	26.7 ± 1.247
6	Uniformity of weight	0.87 ± 0.0153 g	1.56 ± 0.0156 g	1.53 ± 0.0157g	1.25 ± 0.0152g
7	Percent Moisture Uptake	3.91 ± 1.361%	1.72 ± 0.386%	1.77 ± 1.013%	3.96 ± 2.132%
8	Percent Elongation	101.4 ± 0.529%	101.4 ± 0.529%	101.6 ± 0.577%	101.4 ± 0.529%
9	Water vapour permeability test	0.096 ± 1.699 g/m^2	0.142 ± 0.0005 g/m^2	0.133 ± 0.001 g/m^2	0.088 ± 0.0005 g/m^2
10	Flatness test	105.8 ± 0.776%	107.5 ± 2.663%	110 ± 5.211%	107.8 ± 3.419%

Values are expressed as the Means ± SD, where (N=3).

8. Invitro drug release

The drug release from developed patches slowed down after an hour and then increased linearly up to 8 hours. The peak was observed at 7 hours, as demonstrated by plotting drug releases in absorbance versus time.

Table 17 : Invitro drug release of Herbal transdermal patches

Time (mins)	Absorbance at 260nm			
	F1	F2	F3	F4
30	0.048	0.027	0.015	0.086
60	0.127	0.152	0.147	0.274
120	0.346	0.257	0.226	0.462
180	0.394	0.289	0.345	0.578
240	0.475	0.350	0.467	0.762
300	0.667	0.479	0.676	0.895
360	0.841	0.619	0.754	1.034

9. Skin irritation test

Repeated and single patch tests on a healthy volunteer showed no potential for irritation or sensitization.

Table 18 Skin irritation test

S. No.	Parameter	Single patch test	Repeat patch test		
			15 min	30 min	24 hr
1.	Erythema	Nil	Nil	Nil	Nil
2.	Edema	Nil	Nil	Nil	Nil
3.	Pruritus & urticaria	Nil	Nil	Nil	Nil
4.	Skin allergy	Nil	Nil	Nil	Nil
5.	Irritation	Nil	Nil	Nil	Nil

CONCLUSION:

This present study was performed to develop transdermal patches for treating Rheumatoid arthritis using two medicinal plants – Cardiospermum halicacabum and aloe barbadensis. The plants were analyzed for phytochemicals and were found to contain alkaloids, flavonoids, glycosides, saponins, and tannins. An ethanolic extract of this plant was chosen for the formulation development, and the best formulation F4 was selected based on its invitro anti-inflammatory activity. The developed formulation exhibited maximum percent moisture uptake, moisture content,drug content thickness, folding endurance and percent elongation. The safety evaluation of the developed formulation showed that it did not cause any irritation on human skin. The herbal transdermal patch developed is considered a better medicine for rheumatoid arthritis than conventional dosage forms.

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