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"DEVELOPMENT AND EVALUATION OF ANTI-INFLAMMATORY TRANSDERMAL PATCHES OF COLOCASIA ESCULENTA PLANT EXTRACT"

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Abstract: Administration of drugs through skin received great attention through the last decade. Transdermal drug delivery systems are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. Hence this study aims to formulate an anti-inflammatory transdermal patch using different polymers such as ethyl cellulose, hydroxy propyl methylcellulose with plasticizers poly-ethyl glycol 400. Patches were prepared through solvent casting method. The backing membrane was a non-permeable aluminium foil laminated and evaluated for thickness, physical appearance, folding endurance, moisture content, moisture uptake, weight uniformity, drug content determination, skin irritation studies. Drug content uniformity effects on inflammation and in-vitro release study, patches exhibited controlled release over more than 2 hrs. It was concluded from the research that, a herbal extract of the plant with HPMC showed moderate anti-inflammatory action and controlled drug release, thus can be selected for the development of transdermal patches for effective uses. The moisture content of batch B1 was measured and found to be 3.70%. The drug content of batch B1 was measured and found to be 84.79%.

Key Words **- Transdermal Patches, Inflammation, C.** ***esculenta,*** **HPMC, Drug Content Uniformity.**

I. INTRODUCTION

Inflammation is defined as the local response of living mammalian tissues to injury due to any agent. It is a body defense reaction in order to eliminate or limit the spread of injurious agent as well as to remove the consequent necrosed cells and tissue. Inflammation is a pervasive form of defense that is broadly known as a nonspecific response to tissue malfunction and is employed byboth innate and adaptive immune systems to combat pathogenic intruders. At its basic level, it isa tissue-destroying process that involves the recruitment of blood-derived products, such as plasmaproteins, fluid, and leukocytes, into perturbed tissue. This migration is facilitated by alterations inthe local vasculature that lead to vasodilation, increased vascular permeability, and increased bloodflow[1].

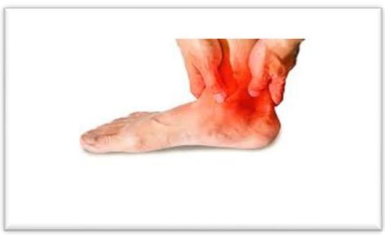


fig.1. inflammation caused by tissue damage

Types of inflammation

A. Acute inflammation

It is of short duration and represents the early body reaction and is usually followed by repair.

Its main features are:

- Accumulation of fluid and plasma at the affected site.
- Intravascular activation of platelets.
- Polymorphonuclear neutrophiles as inflammatory cells.

B. Chronic inflammation

- It is prolonged process in which tissue destruction and inflammation occurs at same time.
- It causes by three ways
  - Chronic inflammation following acute inflammation.
  - Recurrent attacks of acute inflammation.
  - Chronic inflammation of starting de nova.

Mechanism of Inflammation: Inflammatory response is the coordinate activation of signaling pathways that regulate inflammatory mediator levels in resident tissue cells and inflammatory cells recruited from the blood. Inflammation is a common pathogenesis of many chronic diseases, including cardiovascular and bowel diseases, diabetes, arthritis, and cancer. Although inflammatoryresponse processes depend on the precise nature of the initial stimulus and its location in the body, they all share a common mechanism, which can be summarized as follows:

1. Cell surface pattern receptors recognize detrimental stimuli
2. Inflammatory pathways are activated
3. Inflammatory markers are released
4. Inflammatory cells are recruited[1,2].

Transdermal drug delivery system: Transdermal drug delivery system is defined as self-contained, self-discrete dosage forms,which applied to the intact skin, and it deliver the drug at a controlled rate to the systemic circulation. A transdermal patch or skin patch is a medicated adhesive patch which are placed on the skin to deliver a specific dose of medication through the skin into the blood steam.

Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatologicaldisorders. The occurrence of systemic side-effects with some of these formulations is indicative ofabsorption through the skin. Several drugs have been applied to the skin for systemic treatment.

In a broad sense, the term transdermal delivery system includes all topically administereddrug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic system has been designed to provide control continuous delivery of drugvia the skin to the systemic circulation. Moreover, it overcomes various side effects like painful delivery of the drug and the first pass metabolism of the drug occurred by other means of drug delivery system. So, this transdermal drug delivery system has been a great field of interest in therecent time. Many drugs which can be injected directly into the blood stream via skin has been formulated[3].

Advantages

- Avoidance of significant pre-systemic metabolism (degradation in gastrointestinal tract orby the liver), and the need, therefore, for a lower daily dose.
- Drug enters the systemic circulation directly, eliminating the ‘first pass effect’ of enzymesin the gut the liver.
- They are non-invasive, avoiding the inconvenience of parenteral therapy[4].

Disadvantages

- Many hydrophilic medicines slowly penetrate the skin and offer little therapeutic effect.
- The role of skin barrier changes from a region to the next on the similar human, from patient to patient with age.
- TDDS are not able to attain maximum drug concentrations in the plasma or blood[4].

Mechanism of Action

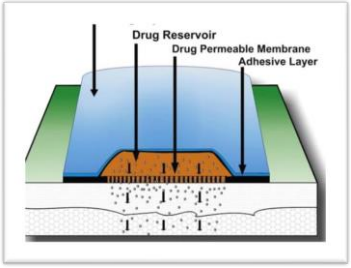


fig.2. mechanism of action

A typical transdermal patch consists of an adhesive layer which sticks on to the skin semi-solid toliquid drug is smeared between the layers between the layer of drug releasing membranes which are exclusively semi-permeable in nature. An outmost clear backing protects overall patch duringapplication. A transdermal patch when applied to skin, establishes a good connection between theskin and semi-permeable membrane. A slow sustained flow of drug occurs from drug reservoir ofthe patch to the skin via drug release membrane by simple diffusion/osmosis process trough percutaneous drug delivery system[4].

Ideal properties of drugs during preparation of TDDS

Parameters	**Properties**
Dose	Should be low (less than 20mg/day).
Half-life	Less than 10 hr.
Molecular weight	Less than 400 da.
Skin permeability coefficient	More than 0.5×10^{-3} cm/h
Skin reaction	Non-irritating, non-sensitizing
Oral bioavailability	Low

Table 1: ideal property of drug

Plant Profile

Fig.3. Colocasia esculenta

- **Biological Name:** *Colocasia esculenta*
- **Synonyms:** Taro (English), Alti Kachu (Bengali), Dhopa (Marathi), Aalavi (Gujarati).
- **Taxonomy***:*
  - Kingdom - Plantae
  - Order - Alismatales
  - Family - Araceae
  - Sub-family - Aroideae
  - Tribe - Colocasieae
  - Genus - Colocasia
  - Species - C. esculenta

PLANT PART	CHEMICAL CONSTITUENT
1) Leaves	Calcium oxalate, minerals like calcium phosphorous,fibers, starch, vitamin A, B, C.
	Apigenin
	Luteolin
	Anthocyanin
	Flavonoids (orientin, Iso-orientin, Iso-vitexin, Vicenin,orientin 7-O-glucoside, Iso-vitexin 3'-O-glucoside, Vitexin X''-O-glucoside, Luteolin 7-O-glucoside.)
2) Tubers	Starch (73-76%)
	Natural polysaccharides (56% natural sugar and 40%anionic components)
	Oxalates (soluble 19-87 mg/100g, insoluble 33-156mg/100g)
	Amino acid (13 to 23%)
	Nitrogen content
	Lipids, Enzyme (lipoxygenase, lipid hydro peroxide-converting enzyme)
	Phosphate monoester derivatives
	Dihydroxy sterols.
	B-sitosterol, Stigmasterol's, cyaniding 3-glucoside.Octadecenoic acid.
	Aliphatic compounds (Tetracos-20-en-1,18-diol, 25-methyl triacont-10-one, Octacos-10-en-1,12-ol, 25- methyl-triacont-2-en-1,9,11-triol.)
3) Petiole	Anthracyanins (3.29%)

Table 2. Chemical Constituents of Colocasia esculenta[5,6]

Pharmacological activity of Plant:

Anti-inflammatory activity: The Anti-inflammatory activity of C. esculenta leaf extract was demonstrated on the carrageenan-induced acute paw edema model and the cotton pellet granuloma method.it shows significant inhibition of carrageenan-induce edema and showed an inhibitory effecton leukocyte migration and a reduction of pleural exudates[5].

Anti-microbial activity: The in-vitro antimicrobial activity in aqueous extract of C. esculenta leaves was studied against gram-positive bacterial strains i.e.streptococcus mutans and showed maximum activity at low concentration against streptococcus mutans[6].

Anti-fungal activity: The in vitro antifungal activity of C. esculenta was assayed by the food poisoning techniquemethod against two fungal species. The alcoholic leaf extract showed good antifungal activity than the aqueous extract of Colocasia esculenta. Alcoholic extract of Colocasia esculenta showed 100% antifungal action against Alternaria solani and Alternaria ricini at the 25% concentration. Aqueous leaf extract reduced the growth of fungal pathogen at highconcentrations only[7].

Uses: Colocasia esculenta has been reported that it leaves is applied to the inflamed area in which its shows anti-inflammatory activity, and reduce inflammation. It's also useful in the conditionof inflammation caused by microorganisms due to the presence of anti-microbial activity of plant. Plant possessed anti-oxidant, anti-helminthic, hepatoprotective and anti-diabetic properties[7].

Material and Methods

1. HPMC: used as polymer.
2. Ethyl Cellulose: used as stabilizers.
3. PEG 400: used as plasticizers.
4. DMSO: used as membrane penetration.
5. Ethanol: used in extraction process.

Preparation of Plant Extract: The dried plant material (leaves) is used for extraction. The fresh part of plant dried by air-cured method which is carried in the shade outdoors, after complete drying of leaves, make finelydivided powder by grinding method. Extraction of Colocasia esculenta done by hot-continuous method or soxhlet extraction method, in which 50gm of finely divided powder take and filled in extractor. Ethanol used as solvent in extraction which is filled in boiling flask, and condensers areconnected to it for condensation process. It takes 24hr to complete extraction process and extract collected in boiling flask. Collected extract evaporate on water bath for 2hr and we get concentrated extract[12.]

Fig.4. Grinding

Fig.5. Soxhlet extraction

Preparation of Herbal Transdermal Patches for Anti-Inflammatory Activity:

SOLVENT EVAPORATION TECHNIQUE: the Colocasia esculenta family areace matrix transdermal patches were fabricated by the solvent evaporation technique utilizing HPMC (0.142 g), and ethyl cellulose (0.142 g), respectively. In the process of formulation, initially the polymer was taken in a beaker with solvent i.e. water-ethanol (2:1) and was allowed to completely swell for a duration of one hour.Subsequently, with continuously stirring, ethyl cellulose 0.5ml was added. Afterward, the plasticizer(PEG 400) and permeation enhancer (DMSO) were added and mix uniformly for the few minutes' duration. Finally the drug (extract of Colocasia esculenta) was incorporated with continuous stirring to mix well. The resultant homogenous dispersion was spread over a filmformer with the help of a dragger. Inverted funnel placed over prepared film for partial evaporation and achieved fabricated dried films were wrapped in aluminium foil and stored in the desiccator for further study[18,19].

Fig.6. Solvent evaporation technique

Formula:

INGREDIENT	QTY TAKEN
Herbal drug	0.3 ml
HPMC	0.150 g
Ethyl cellulose	0.150 g
PEG-400	0.5 ml
DMSO	0.1 ml
Water: ethanol (2:1)	(4:2) ml

Table.3: Formula

Batches Prepared

Batch Code	B1	B2	B3
Herbal Drug	0.3ml	0.3ml	0.3ml
HPMC (mg)	0.150	0.5	1.0
EC (mg)	0.150	0.5	1.0
PEG 400 (ml)	0.5ml	0.5ml	0.5ml
DMSO (ml)	0.1ml	0.1ml	0.1ml
Water: ethanol (2:1)	4:2	4:2	4:2

Table.4. Batches prepared

Evaluation of Herbal Transdermal Patches:

Physical appearance: The prepared patches are physically examined for color, clarity and surface texture.

Thickness of the patch: The thickness of the drug loaded patch is calculated in different pointsby using a digital micrometer, or travelling microscope, dial gauge, screw gauge, and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch. Patch will have an equal thickness at every point. The variation of thickness within the patch and patch to patch can be calculated.

Moisture content: Individually weighed patches are kept in the desiccators having fused calcium-chloride at room temperature for 24 hours. After 24 Hours the patches are to be reweighed and percentage moisture content is calculated by the formula.

% Moisture content = (Initial weight – Final weight) X 100 / Initial weight

Moisture uptake: The weighed films are to be kept in desiccators at room temperature for 24hrs. containing saturated solution of potassium chloride in instruct to maintain 84% RH. After24 hrs. the films are to be reweighed and determined the percentage moisture uptake from thementioned.

%Moisture uptake = (Final weight – Initial weight X 100) / Initial weight

Folding endurance: This was determined by repeatedly folding the film at the same place until it broke. The number of period the films could be folded at the same place without breaking/ cracking gave the value of folding endurance.

Weight uniformity: A specified area of the patches was cut carefully in different parts and afterward weighed in a digital balance. The average weight and standard deviation values werecalculated from the individual weight.

Drug content determination: Amount of drug entrapped in a patch was determined by completely dissolving patch of size 2×2 cm^2 in 100ml phosphate buffer solution (PH 7.4).complete dissolution was achieved by placing the solution containing patch on shaker for about24 hours. Solution was then filtered and drug content was estimated spectrophotometrically at 210nm after suitable dilution.

Studies In-vitro permeation: Permeation studies are carried out in order to determinetransition of drug from patch to skin microcirculation. In this study synthetic membrane like cellulose nitrate was placed between the donor and receptor compartment of Franz diffusion cell. Receptor compartment was filled with phosphate buffer of ph. 7.4. transdermal patch wasplaced upon the cellulose nitrate membrane was towards the receptor compartment having phosphate buffer. The receiver compartment was maintained at room temperature and was continuously stirred with the help of magnetic stirrer. Samples were withdrawn at specific timeinterval and equal amount of phosphate buffer was replaced each time to maintain volume of receptor compartment at a constant level. Samples withdrawn were then analyzed for their absorbance and concentration was then calculated.

Skin irritation test: skin irritation studies were carried out in order to detect irritation and sensitization under conditions of maximal stress which may occur over a prolong contact withthe skin surface. Skin irritation test is done by using patch test on the back skin of volunteer. Patch(B1) (2×2 cm^2) was applied to the clean skin of the volunteer back and secured using adhesive tape. Volunteer was then kept under observation for a period of 4-6 hours to detect any sign of erythema, redness, sensitization or any other allergic reaction[19,20,21].

Result and Discussion:

1. **Characterization and identification of plant extract**

Physical Properties:

Color	Dark green
Odor	Pungent odor
Taste	Slightly metallic taste
Appearance	Slightly dense and oily in nature

Solubility Studies:

Water	**Ether**	**Ethanol**	**5%NaOH**	**5%HCL**	**H2SO4**
Soluble	Insoluble	Soluble	Sparingly soluble	Sparingly soluble	Insoluble

2. **Preliminary phytochemical screening of plant extract**

Sr. No.	**Plant constituents**	**Test / reagents**	**Colocasia esculenta extract**
1	Sterols	Salkowaski test Liebermann's test Libermann-Burchard test	+ + +
2	Alkaloids	Dragendorff's test Mayer's test Wagner's test Hager's test	- -
3	Saponins	Foam test Haemolysis test	- -
4	Glycoside	Borntrager's test	+
5	Tannins	Ferric chloride Lead acetate	+ +
6	Flavonoids	Shinoda test	+
7	Carbohydrates	Molisch test Barfoed's test Fehling's test	+ + +
8	Protein	Biuret test Xanthoproteic test	+ +
9	Amino acid	Ninhydrine test	+
10	Volatile oil	Solubility test Paper stain test	+ +

3. Calibration Curve

Determination of absorbance maxima for Colocasia esculenta extract

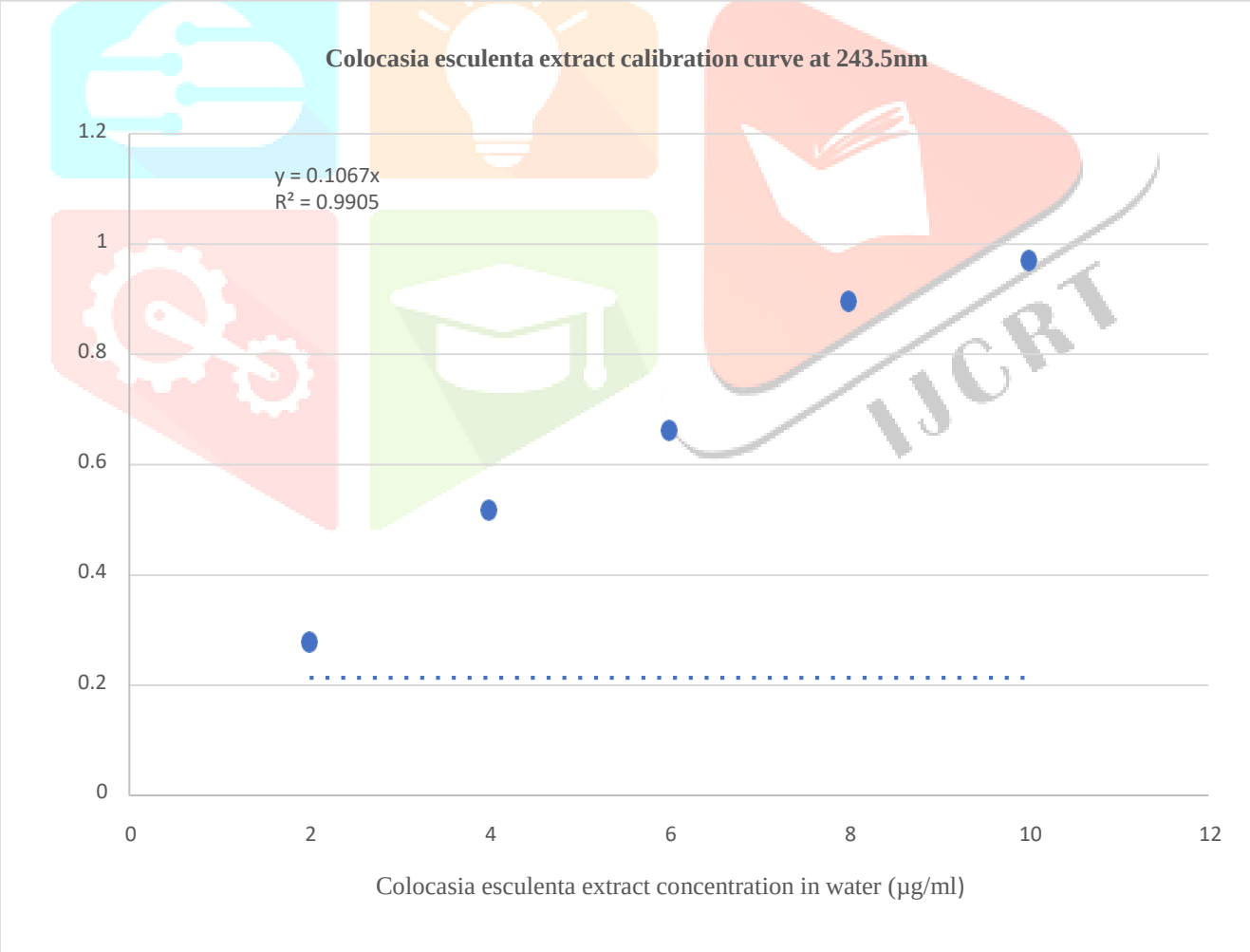
The UV scanning of Colocasia esculenta extract, family araceae, showed maximum absorbance i.e.243.5nm (λmax) which complies with the specification given in literature. The absorbance maxima of Colocasia esculenta extract concentration was found to be 243.5 nm (λmax).

Standard calibration curve of Colocasia esculenta extract

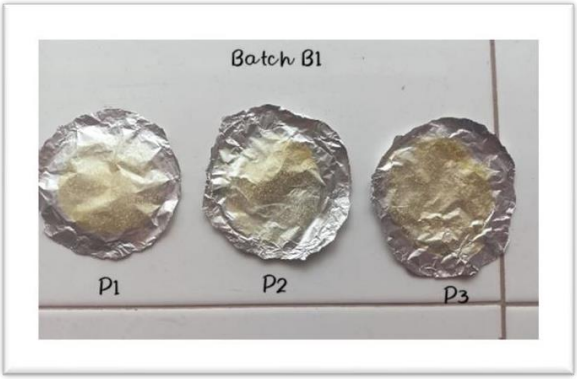
Standard calibration curve of Colocasia esculenta extract were prepared of 2µg/ml to 10µg/ml concentration in distilled water at 243.5nm λmax value. The absorbance vs. concentration was plotted and data was subjected to linear regression analysis. The standard calibration curve of drugin distilled water respectively.

Colocasia esculenta (243.5nm)

Concentration (µg/ml)	2	4	6	8	10
Absorbance	0.278	0.518	0.662	0.896	0.971



4. Evaluation And Characterization of Herbal Transdermal Patch



Physical Appearance

Batch code	B1
Colour	Pale Yellow
Clarity	Translucent
Texture	Slightly Rough

Thickness of Patch

Batch code	Thickness(mm)	Average
B1	0.150 0.162 0.154	0.155 ± 0.007mm

Moisture Content

Batch code	Initial weight	Final weight	% moisture content
B1	0.162gm	0.156gm	3.70%

Moisture Uptake

Batch code	Initial weight	Final weight	% moisture uptake
B1	0.162gm	0.169gm	4.32%

Folding Endurance

Batch code	Folding endurance	Average
B1	9 5 9 4 9 6	95 ± 1

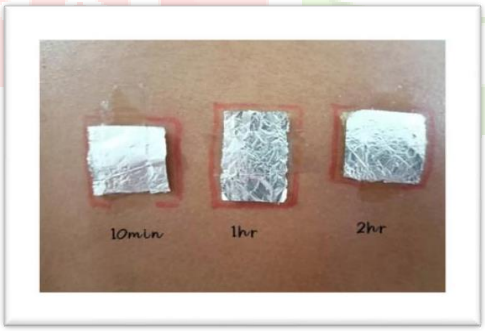
Weight Uniformity

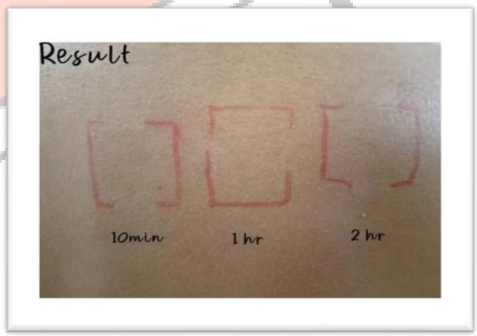
Batch code	Weight uniformity	Average
B1	0.159mg 0.162mg 0.165mg	0.162 ± 0.030gm

Drug Content Determination

Batch code	Absorbance	% Drug content
B1	0.8234	84.79%

Skin Irritation Studies

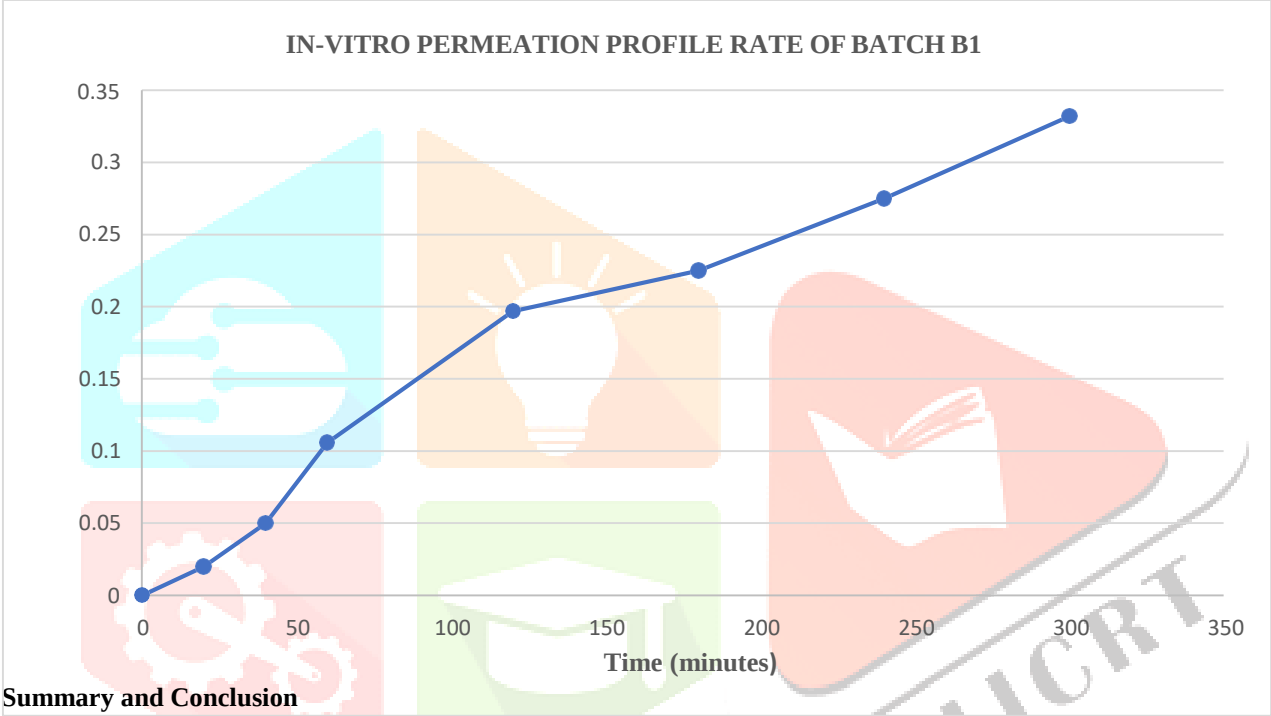




TIME	INTERPRETATION
10 Min	No Reaction
1 Hour	No Reaction
2 Hour	No Reaction

In-Vitro Permeation Studies

TIME (In minutes)	**ABSORBANCE** (In nm)
0	0.0
20	0.02
40	0.05
60	0.106
120	0.197
180	0.225
240	0.275
300	0.332



Summary and Conclusion

Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. Colocasia esculenta belonging to family araceae extract were used for its anti- inflammatory property. In the present investigation, herbal transdermal patches were formulated using HPMC and EC polymer by solvent evaporation technique. The physicochemical parameterslike flexibility, thickness, smoothness, weight variation, moisture content and folding endurance were evaluated. The developed formulation showed good physicochemical properties like thickness, weight variation, drug content, folding endurance, moisture content. In anti- inflammatory models, the formulation containing flavonoid fraction, tannin fraction, glycoside fraction and sterols exhibited significant anti-inflammatory activity and the promising anti-inflammatory activity may be attributed to high flavonoid content and sterols content which seemsto be responsible.

Conflicts of Interests: Nil

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