IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF CURCUMIN TRANSDERMAL PATCHES FOR THE TREATMENT OF ARTHRITIS

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ABSTRACT : To create and assess transdermal patches loaded with curcumin and made using plant extracts for the treatment of arthritis. An improved arthritis medication is curcumin extract. Transdermal patches are composed of hydrophobic semi-synthetic material. The polymer plays a crucial role in the drug delivery process when it comes to the solvent evaporation approach. The transdermal patches containing curcumin extract are made using the solvent evaporation process, which also uses dibutyl phthalate as a plasticizer and ethyl cellulose as a polymer. One of the most efficient methods of supplying drugs to the body is through the use of transdermal drug delivery systems (TDDS), which restrict the site of administration and even lower the quantity and number of doses required to produce the desired systemic treatment through local skin application. One of the more novel drug delivery systems that has attracted attention recently is the transdermal method. Its benefits over the oral route of administration include non-invasiveness, high bioavailability, elimination of the first pass metabolism, lack of discomfort, and little to negligible side effects.

KEYWORDS :Transdermal patches,curcumin,dibutyl phthalate

INTRODUCTION

The most common method of administering drugs is orally. Despite this, there are several drawbacks, such as first pass metabolism, medication degradation in the gastrointestinal system as a result of enzymes, pH, etc. To overcome these issues, a novel a medication distribution mechanism was created. This transdermal administration method involves the preparation of medicated adhesive patches that, when applied to the skin, distribute a therapeutically appropriate dosage of medication.

TRANSDERMAL PATCH

An adhesive medication patch applied above the skin that delivers a precise dosage of medication through the skin and into the bloodstream at a predetermined rate of release to the body is called a transdermal patch. Now, The most widely used transdermal device on the market is mostly composed of semi-permeable membranes known as patches. Transdermal drug delivery systems (TDDS), also referred to as "transdermal patches" or "skin patches," are dosage forms intended to distribute a therapeutically effective quantity of medication across the skin and bloodstream of a patient.

MAIN INGREDIENTS USED FOR THE PREPARATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. Liners: Before using, the liner should be removed because it protects the patches during storage.

2. Adhesive: This helped to bind the patch's constituent parts together as well as

attaching the patch to the skin.

3. Membrane: This regulates the drug's release from the patches using multiple layers. Another name for it is the permeation enhancer.

4. Drug: The release liner and drug reservoir are in direct touch.

5. Backing: protects the patches from the outside environment.

ADVANTAGE

1. A consistent infusion of a drug is administered over an extended period of time via transdermal medication.

2. Transdermal drug input can produce a similar therapeutic effect at a lower daily dose than required, for example, if the drug is administered orally.

3. These systems enable self-administration.

4. Their physical characteristics, distinguishing marks, and bodily presence allow them to be quickly and simply recognized in emergency situations (such as an unconscious, comatose, or nonresponsive patient).

5. They are applicable to medications having a limited therapeutic range.

6. Extended duration of action that lowers the frequency of dosage.

7. Easier administration of medications that might usually need frequent dosage.

8. Enhancement of bioavailability.

DISADVANTAGES

A lot of medications, particularly those with hydrophilic properties, penetrate the skin too slowly to be therapeutically effective.

2. Unsuitable for high dosages of drugs.

3. The type of patch and the surrounding circumstances may affect adhesion.

4. Reactions including skin irritation and hypersensitivity could happen.

5. It is not possible to give medications that need high blood levels. In addition to these restrictions, the product's high price is a significant barrier to its widespread use.

IDEAL PROPERTIES OF TRANSDERMAL PATCHES

1. Non allergic, non irritating , or toxic

2. Rapid working.

3. The body exhibits no pharmacological activity.

4. Carry out one-way work.

5. The skin's barrier qualities need to fully and quickly restore after removal.

6. Compatible with medications and excipients.

7. Cosmetically acceptable.

PLANT PROFILE

TURMERIC

As a member of the Zingiberaceae family, turmeric (Curcuma longa) is perhaps the most important plant used in herbal medicine.The Arabic term "Kourkoum," which implies saffron, is the source of the Latin name "Curcuma." It expands in the warm,situations that are humid and call for lots of water. It has big, oblong leaves and a short pseudostem. There is a parent, or mother, rhizome and several branching subsidiary rhizomes within the subterranean rhizome. Turmeric's vivid yellow color also gives it the nickname "Indian saffron." Turmeric's main constituent, diferuloylmethane, or curcumin, is a yellow pigment that gives it its unique qualities.Turmeric plants have long, simple leaves with long petioles, or leaf stems, and grow to a height of about one meter (3.3 feet)... The leaves emerges from the branching rhizomes that are slightly below the soil's surface, the leaves emerge. Younger rhizomes are pale, whereas older rhizomes are slightly scaly and brown in color. While young rhizomes are pale from yellow to orange-brown. The tiny yellow-orange blossoms are carried in the axils of waxy bracts, which are often light green or somewhat purple in hue. It was used as a spice and a perfume in antiquity. The rhizome smells like pepper, tastes warm and slightly bitter, and is a bright orange-yellow color that stains well. In addition to Africa, it is grown in China, India, Indonesia, Thailand, and other tropical countries.Based on the region of production, the two primary commercial varieties of turmeric in India are "Madras" and "Alleppey" turmeric. While the British and Middle Eastern markets favor Madras turmeric, which has less curcumin and volatile oils, the United States imports Alleppey turmeric as a spice and food colorant. Madras turmeric is ideal for curry powder and mustard paste because of its brighter, lighter yellow color. The "Bengal" variety is mostly utilized as a coloring agent. Turmeric has historically been utilized in Eastern Asian medical systems, including traditional Chinese medicine, as well as Ayurveda and other traditional Indian medical systems. It was customary in India to utilize for conditions pertaining to the joints, digestive system, skin, and upper respiratory tract.

SYNONYMS

Saffron Indian; haldi (Hindi); Curcuma; Rhizoma cur-cumae.

BIOLOGICAL SOURCE

Turmeric is the dried as well as fresh rhizome of plant known as Curcuma longa Linn. (syn.C.domestica Valeton)., belonging to family Zingiberaceae.

GEOGRAPHICAL SOURCE

Native to southern India and Indonesia, turmeric is widely cultivated on the mainland and in the islands of the Indian Ocean. India is a leading producer and exporter of turmeric in the world. Andhra Pradesh, Tamil Nadu, Orissa, Karnataka, West Bengal, Gujarat, Meghalaya,

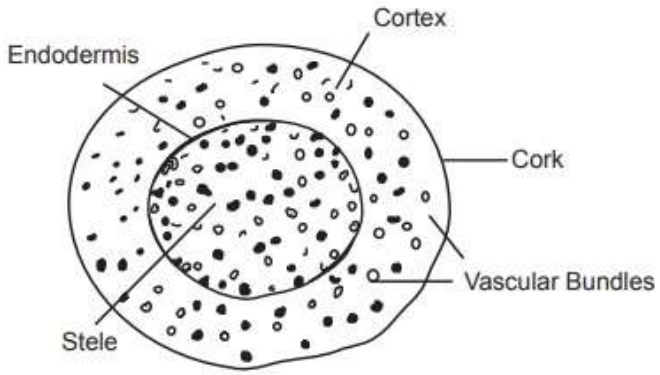
Maharashtra, Assam are some of the important states cultivating turmeric, of which, Andhra Pradesh alone occupies 38.0% of area and 58.5% of production. During 2013-2014, the country produced 12.29 lakh tonnes of turmeric from an area of 2.34 lakh ha.

TAXONOMICAL CLASSIFICATION

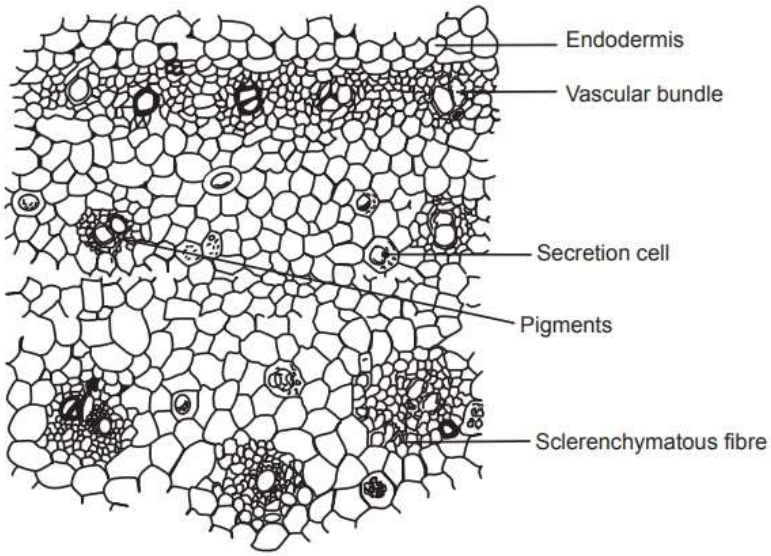
Kingdom	Plantae
Clade	Angiosperms
Subkingdom	Tracheobionts
Division	Mangoliophyta
Order	Zingiberales
Family	Zingiberaceae
Genus	Curcuma
Species	longa
Scientific name	Curcuma longa

MACROSCOPICAL AND MICROSCOPICAL CHARACTERS OF TURMERIC

The main rhizomes are cylindrical, pyriform, rectangular, or pear-shaped, and frequently have small branches. The term "bulb" or "round" turmeric refers to the rhizomes. The secondary, tapering on, more cylindrical, lateral branches rhizomes, which are referred to as "fingers," are 4-5 cm long and 1-2 cm wide at both ends. The long fingers are cut into manageable pieces, and the bulbous and finger-shaped portions are separated. They undergo a curing and polishing procedure after being cleaned from fibrous roots and dirt adhering to them. The fracture has a horny look, with a waxy, resinous cut surface. Wrinkled lengthwise and with a bright yellow to brown outer surface. There is a distinct smell and an aromatic, pungent, and bitter taste. However, the transverse portion of the microscopical features comprises the majority of spherical, thin-walled parenchyma cells, sporadic vascular bundles, distinct endodermis, a few layers of cork grown beneath the epidermis, and sporadic, brownish-filled oleoresin cells are the characteristics of rhizomes. The cells that make up the epidermis have thick walls and are shaped like cubes with different sizes. The sub-epidermal layers give rise to the cork cambium, and the epidermis persists long after the cork develops. Typically, cork is made up of four to six layers of parenchymatous cells, which are thin-walled, brick-shaped cells. Grain contains the parenchyma of the cortex and pith. transformed into a paste, containing occasionally long, lens-shaped, unmodified starch granules with a diameter of 4–15 µm. Oil cells have suberized walls and can hold amorphous resinous masses or orange-yellow globules of a volatile oil. Cortical vascular bundles are of the collateral type and are dispersed. In the pith region, the vascular bundles are primarily dispersed and form a discontinuous ring just under the endodermis. Few of the vessels have an annular or reticulate structure; most of the vessels have spiral thickenings



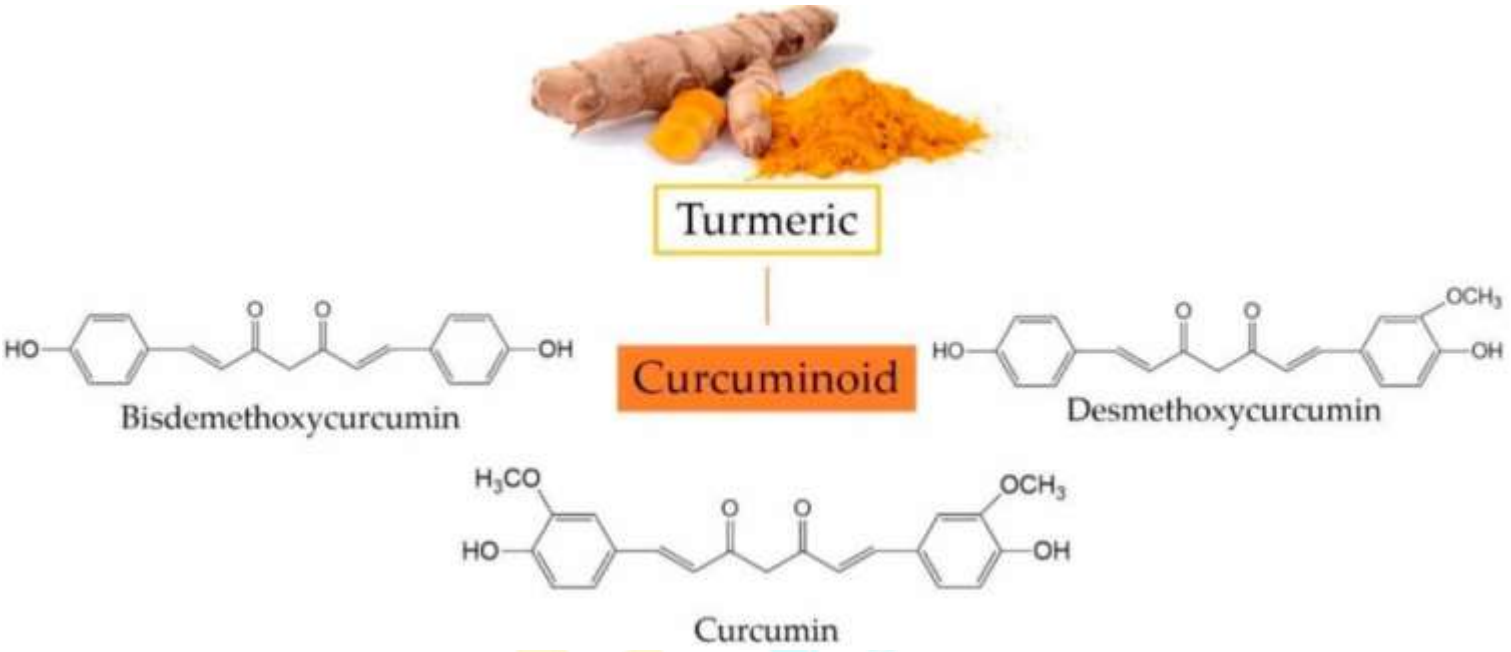
T.S. (schematic) of turmeric rhizome



Transverse section of turmeric rhizome

Chemical Constituents

Carbohydrates (69.4%), protein (6.3%), fat (5.1%), minerals (3.5%), αphellandrene (1%), zingiberene (25%), sabinene (0.6%), cineole (1%), and sesquiterpenes (53%),mixture of three curcuminoids [i.e., curcumin I ($C_{21}H_{20}O_6$, diferuloylmethane, 94%), curcumin II ($C_{20}H_{18}O_5$, demethoxycurcumin, 6%) and curcumin III ($C_{19}H_{16}O_4$, bis-demethoxycurcumin, 0.3%)]



COMPONENT COMPOSITION

Carbohydrates, fats, proteins, fibre, minerals, volatile and nonvolatile oils, moisture, and curcuminoids.

Curcumin (curcumin I), demethoxycurcumin (curcumin II), bis-demethoxycurcumin (curcumin III), and cyclocurcumin (curcumin IV)

Essential oils like mixture of sesquiterpene ketones and alcohols, d-sabinene, a-phellandrene, cineole, borneol, and zingiberene. Approximately 70% of curcuminoids is the diferuloylmethane, curcumin, Cyclocurcumin has poor biological activity, Exact composition is still unclear. Proximate analysis of turmeric reveals that the herb contains 6–13% moisture, with 60–70% carbohydrate, 6–8% protein, 5–10% fat, 3–7% minerals (potassium, sodium, calcium, iron, phosphorus), and trace amounts of vitamins. Essential oils obtained by steam distillation represent 3–7% of the turmeric rhizome and mainly consist of terpenoids, including sesquiterpenoids (e.g., α-phellandrene, zingiberene), monoterpenoids (e.g., sabinene, cineol), and norsesquiterpenoids. There is also 3–5% curcuminoids, which comprises more than 50 structurally related compounds; the three principal ones being curcumin, demethoxycurcumin, and bisdemethoxycurcumin. In general, turmeric composition varies according to the soil conditions used in cultivation, with Indian turmeric being regarded as having superior quality and high curcumin content. Curcuminoids and essential oils are classified as secondary metabolites produced by Curcuma plants, with well-defined bioactivity.

COMPOSITION (W/W)

Curcuminoids	1-6%
Volatile (essential) oils	3-7%
Fiber	2-7%
Mineral matter	3-7%
Protein	6-8%
Fat	5-10%
Moisture	6-13%
Carbohydrates	60-70%

USES

Due to its well-known anti-inflammatory qualities, turmeric may be beneficial for treating inflammatory diseases like arthritis. Turmeric has been shown in studies to alter cytokines, which are proinflammatory cells that can lower inflammation. Among those suffering from osteoarthritis, the most prevalent kind of arthritis. Turmeric is said to have a wide range of therapeutic benefits in Ayurvedic traditions, including as boosting the body's general energy, reducing gas, getting rid of worms, enhancing digestion, controlling menstruation, and breaking up gallstones. Additionally, it is used in folk medicine to cure, prevent, and manage a number of disorders, including psoriasis, diabetes, arthritis, cancer, diarrhea, inflammation, hepatobiliary diseases, and gastric and peptic ulcers. Antibacterial, antiviral, anti-inflammatory, anticancer, antioxidant, antiseptic, cardioprotective, hepatoprotective, nephroprotective, radioprotective, and digestive properties are among the properties of turmeric.

MATERIAL

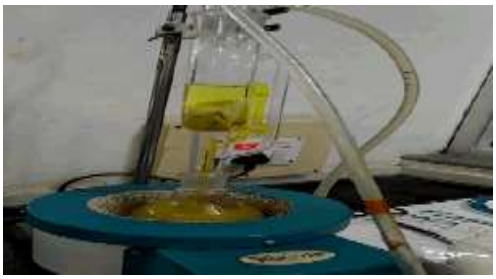
SR. NO	INGREDIENT	FOR 1 PATCH	FOR 4 PATCHES	ROLES
1	curcumin	0.04 ml	0.16 ml	pain relief, inflammatory conditions
2	dibutyl phthalate	0.3 ml	1.2 ml	plasticizer
3	ethanol	5 ml	20 ml	solvent
	ethyl cellulose	0.9 gm	3.6 gm	coating agent, film-former, stabilizer
5	Sodium lauryl sulfate	0.09 gm	0.36 gm	Surfactant, Wetting surfaces,
6	Polyethylene glycol	1 ml	4 ml	Surfactants, Emulsifiers,
7	Chloroform	15 ml	60 ml	Solvent
8	Menthol	0.1 gm	0.4 ml	Topical agent to prevent skin infections

METHODOLOGY

Procedure for Preparation of Transdermal patches

Extraction process of Curcumin :

1. Extract about 50 g of turmeric powder with 95% alcohol in a Soxhlet assembly until all the coloring matter is extracted.
2. Distil off alcoholic extract to a semi solid brown colored mass (about 4.5%).
3. Dissolve the curse extract in 50 ml of benzene and extract twice with equal volume of 0.1% sodium hydroxide solution.
4. Combine the alkaline extract and acidity with dilute hydrochloric acid. A yellow colored precipitate is formed. Allow it to settle for about 15 minutes.
5. After setting of precipitate, concentrate the extract by boiling on water bath and at the same time dissolving precipitate in boiling water. During this process of boiling, the resinous material would agglomerate and form lumpy mass.
6. Filter the solution in hot condition and concentrate, filter to very small volume and finally cool to get curcumin (1.5%). Curcumin is an orange - yellow crystalline powder with m.p. 183°C . It is insoluble in cold water, ether and soluble in alcohol and glacial acetic acid . It dissolves in concentrate sulphuric acid and gives yellow - red coloration. In 0.1 N sodium hydroxide, it gives deep brown color**.**



Soxhlet Extractor Unit

METHODS FOR PREPARATION OF TRANSDERMAL PATCH

I. Solvent Evaporation Method
II. Asymmetric TPX Membrane Method
III. Circular Teflon Mould Method

Procedure of Transdermal patches (Solvent Evaporation Method)

1. The patches were prepared by Solvent Evaporation Technique.

2. Drug is dissolved in Chloroform (5ml) along with dibutylphthalate (0.3 ml) and menthol [0.1 ml (5% w/v in ethanol)] .

3. This solution was then added to polymeric base prepared by dissolving in ethyl cellulose (paraffin) 900 mg and (PEG) sodium lauryl sulfate (90mg) in Chloroform (5 ml) and stirred continuously to get uniform solution.

4. The final volume was made to 10 ml with chloroform.

5. Definite volume (5.5 ml) of the above solution was then poured into siliconized glass mould and dried at room temperature for 30 minutes to obtain film .

Advantage of solvent extraction method :

1. High oil yield: n-hexane solvent is sprayed onto the oil cake via the nozzle of the solvent extraction method, and both the solvent and the oil cake in the extractor are fully

Together, the solvent and oil are separated using high heat and negative pressure. In certain cases, the solvent extraction process can be repeated again, significantly increasing the oil yield, which can reach 99%.

2. High extraction efficiency: The solvent extraction method has a high extraction efficiency and can effectively remove compounds that are difficult to dissolve in other solvents as well as target components from edible oil, such as vitamins and fatty acids.

3. Broad range of application: the solvent extraction method may be used with a variety of edible oil types, including rice bran oil, peanut oil, soybean oil, and so forth.

4. High profit: Solvent extraction yields more profits than other extraction techniques.

approach works well for production on a huge scale. First, it reduces costs for the manufacturer in terms of solvent recycling and reuse; second, it can yield more profits in terms of plant construction since different edible oils can be extracted with a single investment. (Source to read: Plant that processes soybean oil)

Disadvantage of solvent extraction method :

1. High Cost: Drawback of the solvent extraction method is its high cost. Its rather complex procedure necessitates the use of specialized technology and equipment, which raises manufacturing costs expense. Furthermore, the production environment needs to meet greater standards for the solvent extraction procedure. The construction of solvent extraction factories needs to adhere to the specifications of Class A explosion-proof workshops. In comparison to the pressing approach, the investment cost is larger.

2. Environmental impact: The solvent extraction method uses a lot of solvents, which might contaminate the environment if not handled carefully or recovered entirely.

EVALUATION PARAMETERS

A. Physicochemical evaluation

B. Invitro

A. Physicochemical evaluation :

1. Thickness :

The thickness of the drug prepared patches is measured by the digital travelling microscope ,dial/ screw gauge at different points of patch and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

2. Weight variation :

Weight 4 patches and then weight single patch. The variation in the weight is considered as the weight variation.

3. Folding endurance :

Folding repeatedly at a same point until it breaks . The number of times it could be folded is its folding endurance value.

4. Flatness :

One strip is cut from the center and two from each side end of the patches .The length of each strip is measured and variation in length is measured by constriction is equivalent to 100 percent flatness.

5. Percentage of moisture content :

First take a weight of empty china dish and then poured a drug into a China dish and weight it. After that apply heat to China dish containing the drug and note the reading after burning the drug. The difference in the initial and final is the moisture content percent.

6. Surface pH :

The pH of the patch was found to be 5.15 by using pH meter apparatus.

B. Invitro :

1. Drug content by UV

A 5 cm film is cut into small pieces, put into a 100 m² buffer (ph74) and shaken continuously for 24 hours then whole solution is ultrasonicated for spectrophotometrically at 425 nm.

RESULT AND DISCUSSION

Evaluation result of Transdermal patches

1. Weight variation :

The results shows that the weight is in ranges given below :

Patches	Thickness
F1	0.50 µm
F2	0.48 µm
F3	0.51 µm
F4	1.50 m

2. Folding Endurance

The results shows that the folding endurance is in ranges given below:

Patches	Folding endurance
F1	4
F2	4
F3	6
F4	5

3. Flatness

Formula:- % constriction= $I_1 – I_2/I_1 *100$

I_2 = Final length of each strip

I_1 = Initial length of each strip

SR NO.	I_1	I_2	%
F1	2.6	2.46	5.38%
F2	2.48	2.32	6.45%
F3	2.5	2.30	8%
F4	2.53	2.42	4.34%

% constriction $=I_1- I_2/I_1 *100$

= 2.53 – 2.42 / 2.53 * 100

= 0.11 / 2.53 * 100

= 0.0434 * 100

= 4.3478 %

The percentage flatness of the formulation was found to be 4.3478% for the F4 which is comparatively better than the other patches.

4. Moisture Content

% moisture content= initial weight - final weight / final weight * 100

Empty porcelain = 43.39 gm

Porcelain with drug (Initial weight) = 44.31 gm

After incineration (Final weight) = 43.87 gm

= 44.31 – 43.87

= 0.44

% moisture content = initial weight - final weight / final weight * 100

= 44.31 – 43.87 / 43.87 * 100

= 0.44 / 43.87 * 100

= 0.01002 * 100

= 1.002 %

The percentage moisture content of the formulation was found to be 1%

1. Surface PH

The PH of the patch was found to be 5.15 and 5.90 by using PH meter apparatus.

2. Drug content by UV

Patches	Drug content
F_3	46.6%
F_4	53%

The percentage drug content of the formulation was found to be in the range of 46.6% to 53% by comparing F_4 has good drug content

PH of Transdermal patch

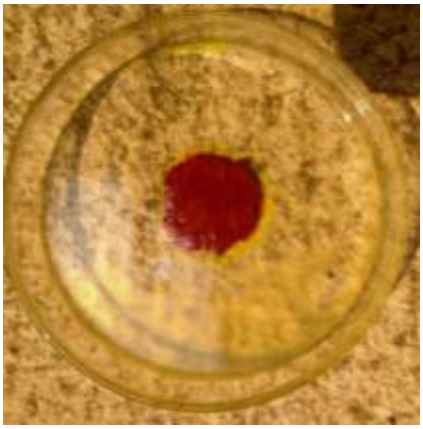
Empty Porcelain

Porcelain with drug

Incineration of drug

After incineration

Moisture Content



Transdermal Patches

CONCLUSION

Curcumin transdermal patches were made using a semi-synthetic hydrophobic polymer. The patches were smooth, flexible, and transparent. Curcumin dissolves quite well in ethanol. Of the different batches, the weight fluctuation and thickness show that the drug's polymeric solution is evenly distributed throughout the patches. Nonetheless, the strength and integrity of the patch were not negatively impacted by the moisture absorbed. They are kept stable and shielded from becoming totally dry and brittle regions by their low moisture content. The patch's outstanding physical integrity is indicated by its % flatness, and its exceptional flexibility is revealed by its folding endurance. A transdermal patch containing curcumin for arthritis was made and evaluated. This study indicates that the formulation of the Curcumin transdermal patch for arthritis satisfies long-term stability research and additional clinical trials are encouraged for this formulation in order to meet all requirements for pain alleviation and arthritis.

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