A Review Article of Curcumin Transdermal Patch

Utkarsh R. Mandage.[1]*, Indrayani S. Pagare[2], Anushka S. Deore[3]

[1]Lecturer, Department of Pharmacognosy, Ravindra Vidya Prasarak Mandal Institute of Pharmacy, Dwarka, Nashik, India.
[2]Principal, Department of QA, Ravindra Vidya Prasarak Mandal Institute of Pharmacy, Dwarka, Nashik, India.
[5] Assistant Professor, Department of Pharmacognosy, MET's Institute of Pharmacy, Adgaon, Nashik, India.

ABSTRACT

Currently herbal medications are the subject of various investigations on innovative drug delivery systems. The framework used to administer transdermal curcumin medicine was created and assessed. . Curcumin is also known as diferuloylmethane (94%) in science with molecular formula C21H2006. It comes from the subterranean stem of the Curcuma longa plant, which is naive to East India. Curcumin, the main curcuminoid in turmeric, makes up about 2-5% of the spice and contributes significantly to its therapeutic effects and distinctive yellow color. Preformulation studies, encompassing solubility, compatibility, and description investigations, were assessed of the medication curcumin. Mostly, the transdermal patches were prepared by using, a solvent evaporation method. Several Physiological and Invitro evaluation parameters are studied like thickness, weight variation,
flatness, surface pH, moisture uptake, etc. of the transdermal patches. Curcumin contains several types of pharmacological actions like anti-inflammatory, anti-fungal, anti-oxidant, anti-cancer etc. In future, curcumin is widely used in the world as a medicine like anti- oxidant property used in the formulations of cosmetic products. Curcumin's characteristics make it in high demand in both the domestic and foreign markets. In India, curcumin value of about 43 billion rupees. nhancing the bioavailability of curcumin increases its market worth. This review mainly focuses on the curcumin properties, mechanisms, enhancement of bioavailability, transdermal preparation, and their evaluation.

KEYWORDS: Curcumin, Transdermal patch, Pharmacological actions.

INTRODUCTION

Over the past two decades, there have been considerable advancements in controlled release medication delivery for therapeutic medicines. Initially, controlled release medication delivery research concentrated on developing zero-order devices. Advancements in technology have made it possible to give medications at a consistent rate across time, from days to years.[1] As a novel and enticing substitute for oral and parenteral drug administration, transdermal drug delivery uses the skin as the drugs absorption medium.[2]

Currently, transdermal drug delivery system (TDDS) has become one of the most extensively researched means of unobtrusive drug delivery into the body via the skin, as opposed to traditional direct administration techniques that involve needle-based injections. TDDS has fundamentally changed the delivery of numerous therapeutic drugs, particularly in reducing pain, hormone therapy, and treatment of disorders of the coronary and neurological systems.[3,4]

Figure 1: Advantages of TDDS.[5]

Figure 2: Disadvantages of TDDS.[6]

Topical treatments often contain medicines that act locally on tissues around the application site. Skin has been a popular option for continuous medication administration due to its ease of application and ability to precisely control the rate of drug entrance into the body. Poor patient compliance is a common issue in clinical practice, including oral, IV, and IM dose forms.[7,8]

Transdermal drug delivery systems (TDDS), often known as "transdermal patches" or "skin patches," are dosage forms that release a therapeutic amount of medicine via the skin and bloodstream of a patient. A transdermal patch is an adhesive pharmaceutical patch that releases medication into the circulation at a set rate. Patches are the most common

type of semi-permeable membranes used in transdermal devices.[9]

Curcumin, a turmeric pigment, is a rare natural substance that has been researched both physiologically and chemically by scientists. This is the most common turmeric derivative used in India.[10] Turmeric, a medicinal plant (Curcuma longa) from the ginger family (Zingiberaceae), has medical advantages. Curcumin (Diferuloylmethane) is a yellow-colored active ingredient found in the rhizomes of turmeric (C. longa Linn). (family: Zingiberaceae).[11,12] This study focuses on current developments in chemistry, pharmacology, pharmacokinetics, toxicology, side effects, and appropriate dose of curcumin and curcumin transdermal patch and use of permeation enhancers in curcumin transdermal patch.

CURCUMIN

Curcuma longa linn (Zingiberaceae) is generally known as 'Indian saffron'. Turmeric's rhizomes, roots, and leaves are utilized for health benefits.[13] Turmeric contains a substance known as curcumin, which is obtained by solvent extraction and purification of the crystallization extract. Curcumin is a chemical compound consisting of (1E,6E)-1,7bis (4-hydroxy-3-methoxy phenyl) hepta- 1,6-dione-3,5-dione. Because of its anti-bacterial, anti- oxidant, anti-inflammatory, anti-viral, anti-fungal, hyperlipidemic, wound-healing, and hepatoprotective qualities, curcumin is used in medicine. Despite having a wide range of pharmacological actions, curcumin has been found to have a low aqueous solubility because of its long first pass metabolism and partition coefficient of 3.2. This limits its therapeutic efficacy.[14]
Curcumin reduces inflammation and free radicals in the skin by inhibiting nuclear factor (KB). Curcumin therapy also shortened wound healing time, and enhanced the accumulation of collagen and enhanced fibroblast and vascular density in wounds. This improves regular and impaired wound healing.[15] Curcumin suppresses anti-inflammatory action by inhibiting NF-kB activation via IkB kinase activity. An early investigation found that the hydroxyphenyl unit in curcumin has anti-inflammatory properties. The existence of a hydroxyphenyl group in compounds similar to curcumin, particularly in the 2-position, supports their chemoprotective effect by inducing Phase II detoxifying enzymes, indicating antitumor potential.[16,17]

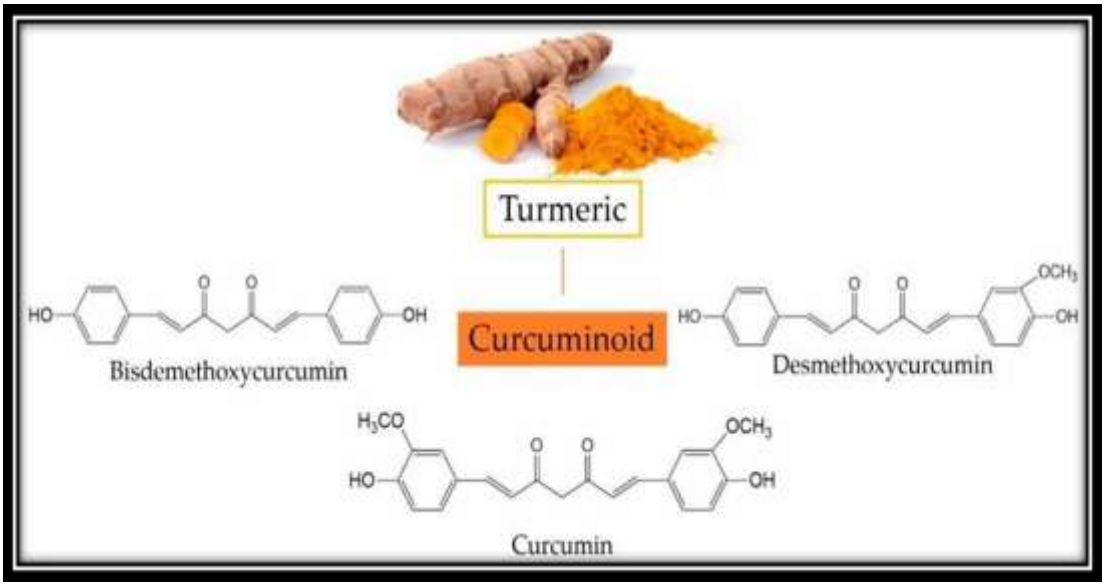

Figure 3: Three major curcuminoids of turmeric.[18]

Table 1: Physical and chemical properties of curcumin.[19]

PHYSICAL AND CHEMICAL PROPERTIES	CURCUMIN
Molecular formula	C21H20O6
Molecular weight	368.35g/mol
Melting point	183°C (361.4°F)
color	Yellow
Solubility in water	Low

Odor	Odorless
Taste	Slightly bitter
Stability	Chemically unstable
Class	Polyphenolic compound
Isomer	Different geometric isomer

Figure 4: Metabolic Pathways of Curcumin.[20] PHARMACOKINETIC OF CURCUMIN[21]

Absorption: Low intestinal absorption due to its lipophilic nature

Absorption rate: After oral administration 60-66%

Metabolism: Undergo first pass metabolism via glucuronidation and sulfation

Clearance: Rapidly clear from the body.

Curcumin's therapeutic application is restricted due to its lack of solubility and quick metabolism, which result in low bioavailability. It is susceptible to the blood-brain barrier.

EXTRACTION PROCESS OF CURCUMIN

Table 2: Various Extraction processes of Curcumin.[22]

METHOD	CONDITION AND PRINCIPLES	SOURCE OF EXTRACTION
Soxhlet extraction	Percolation (boiler and reflux	Mother liquor/ curcumin oleoresin was collected from a local oleoresin industry
Antisolvent Supercritical solution (SAS)	Carbon dioxide supercritical	Dried rhizomes collect from India and China
Microwave assisted extraction	Microwave energy for analyte partition	Dried rhizomes from India
Steam distillation	Fractional distillation based on boiling point	Dried rhizomes obtained in Brazil
Hydro distillation	Vaporization- Condensation cycle	Dried rhizomes obtained in Brazil
Liquid-liquid microextraction	Aqueous two-phase extraction using imidazolium and ultrasound	Mixture of curcuminoids obtained commercially

Pharmacological actions and their mechanisms

Pharmacological action	Mechanism of Action	Reference
Anti-Inflammatory	Curcumin regulates many transcription factors, cytokines, protein kinases, adhesion molecules, redox state, and enzymes that have been associated to inflammation. It also exerts its anti-inflammatory function by blocking multiple molecules that play a role in	[23,24]

	inflammation.	
Anti-Bacterial	A range of periodontopathic bacteria as well as the activities of the proteinases Lys- and Arg- specific Porphyromonas gingivitis (KGP and RGP, respectively) are inhibited by curcumin. Curcumin inhibited the homotypic P. gingivitis and the dose-dependent biofilm development of Streptococcus Gordonii The growth of bacteria was nearly entirely inhibited at extremely low levels of curcumin. Following curcumin treatment at the MIC, numerous characteristics of a bacterial apoptosis-like response were noted, such as membrane depolarization, Ca 2+ influx, PS exposure, and DNA fragmentation. Curcumin induces a bacterial reaction related to apoptosis by generating reactive oxygen species and damaging DNA.	[25]
Antioxidant	Curcumin's antioxidant activity was assessed using a range of in-vitro antioxidant assays,	[23,25]
	including hydrogen peroxide scavenging, 1,1-diphenyl-2-picryl-hydrazyl free radical (DPP.H) scavenging, 2,2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical scavenging action, N, N-dimethyl-p-phenylenediamine dihydrochloride (DMPD) radical scavenging activity, ferric thiocyanate determination of total antioxidant activity, Fe3+ – Fe2 + transformation method for total reducing capacity, superoxide anion radical scavenging through the use of riboflavin/methionine/illuminate system, hydrogen peroxide scavenging, and ferrous ions (Fe2+) chelating activities. Curcumin increases the activity of antioxidant enzymes including SOD, CAT, and GPx and inhibits ROS-generating enzymes like LOX, COX, and xanthine oxidase.	

Anti-diabetic	Curcumin's antioxidant properties may contribute to its antidiabetic action. Improves diabetes-induced endothelial dysfunction by reducing superoxide generation and inhibiting vascular protein kinase C. Curcumin inhibits reactive oxygen species (ROS) that cause oxidative damage. Curcumin reduces oxidative stress-induced cell death by activating antioxidant enzymes including heme oxygenase-1 (HO-1).	[23,26]
Gastrointestinal Activity	Curcuma longa contains two constituents that have been shown to have multiple beneficial impacts on the gastrointestinal tract: sodium curcuminate, which inhibits intestinal spasm, and p-tolymethylcarbinol, which increases the secretion of gastrin, bicarbonate, and pancreatic enzymes. Turmeric has also been shown to be able to inhibit the formation of ulcers caused by stress, alcohol, indomethacin, pyloric ligation, and reserpine, significantly raising the amount of gastric wall mucus in rats exposed to these gastrointestinal insults.	[23]
Cardioprotective Activity	Turmeric's antioxidant properties help defend the cardiovascular system by reducing triglyceride and cholesterol levels, reducing the vulnerability of low-density lipoprotein (LDL) to lipid peroxidation, and preventing platelet aggregation. Giving 18 atherosclerotic rabbits a low dosage	[27]

	of turmeric extract (1.6–3.2 mg/kg body weight daily) has been shown to reduce LDL's sensitivity to lipid peroxidation. The larger dose reduces cholesterol and triglyceride levels but does not reduce lipid peroxidation of low- density lipoprotein (LDL). It lowers plasma cholesterol and triglyceride levels. The possible impact of turmeric extract on cholesterol levels might be attributed to a reduction in the intestinal absorption of cholesterol and an increase in the liver's transformation of cholesterol into bile acids. Curcuma longa reduces platelet aggregation by inhibiting thromboxane production and potentiating the formation of prostacyclin.	

Hepatoprotective Activity	Due to its antioxidant properties and capacity to inhibit the production of pro-inflammatory cytokines, turmeric exhibits hepatoprotective and reno-protective qualities akin to those of silymarin. Research conducted on animals has demonstrated the protective effects of turmeric against a range of hepatotoxic insults, such as carbon tetrachloride (TCE), galactosamine, acetaminophen (paracetamol), and Aspergillus aflatoxin.	[28]
Anti-Cancer	**Breast cancer** BRCA1 mutations occur 55–65% of the time, whereas BRCA2 mutations occur 45–50% of the time. Curcumin and 45 mg of dimethyl sulfoxide (DMSO) together prevented the growth of gastrointestinal tumors and decreased the prevalence of BRCA gene mutations. **Pancreatic cancer** The medicine Gemcitabine has been used in conjunction with nano-formulated curcumin to suppress tumor development. **Lung cancer** Curcumin inhibits NF-kB activity. This nuclear factor is activated by carcinogens and can cause inflammation, chemoresistance, radioresistance, invasion, transformation of the cell, and/or metastasis. It can also decrease apoptosis. **Skin cancer** In female CD-1 mice, topical administration of curcumin plus the tumor stimulator TPA twice a week for 20 weeks significantly reduced the	[29] [30] [31,32]
	development of papillomas. TPA-induced tumor promotion was significantly inhibited by small amounts of curcumin (20 or 100 nmol). Dietary delivery of 2% turmeric effectively reduced the growth of cutaneous tumors caused by TPA and DMBA in female Swiss mice.	

Lupus nephritis treatment	Lupus nephritis is an autoimmune illness with polyclonal B cell hyperactivity and impaired T cell function. Although immunosuppressive and steroid medication can be effective, the illness may recur. In a randomized and placebo-controlled research, the impact of oral turmeric supplementation on 24 patients with relapsing or refractory biopsy-proven lupus nephritis was examined. Patients with recurrent or refractory lupus nephritis may benefit from short-term turmeric supplementation as a safe adjuvant treatment, since it can reduce hematuria, proteinuria, and systolic blood pressure. To better elucidate these effects of turmeric, longer-term clinical research including more individuals are needed.	[33,34]

TRANSDERMAL PATCH

A transdermal patch is an adhesive patch that is medicated and applied to the skin to enter the bloodstream and release a predetermined amount of medication at a predetermined rate. When a drug is administered transdermally it undergoes first pass metabolism, improving its bioavailability and requiring fewer doses than when it is administered orally.[35,36] Patches are one type of transdermal preparation. Compared to other transdermal preparations, patch preparation offers a number of benefits, including increased safety, ease of use, painlessness, and better dosage precision.[37]

ADVANTAGES OF TRANSDERMAL PATCH[38,41]

1. Patches are non-invasive, comfortable, and easy to place.
2. The drug can be taken for an extended period of time.
3. Dosage frequency is decreased since a single patch delivers the drug persistently for a longer amount of time.
4. There are no interactions between drugs and food, drinks, or other microorganisms in the gastrointestinal system.
5. Suitable for senior citizens who have trouble swallowing medicines.
6. Beneficial for drugs that minimize side effects and are disagreeable to swallow. In the event of toxicity, drug administration can be halted by taking off the patch.
7. It is possible to self-administer patches.

DISADVANTAGES OF TRANSDERMAL PATCH[38,41]

1. Giving high dosages (more than 10 mg/day) might be challenging.
2. Ionic medications are challenging to administer using a transdermal drug administration method.
3. It is not appropriate to use drugs with a molecular weight more than 500 Dalton using the transdermal medication delivery method.
4. Drug concentrations too high might irritate skin. Producing high amounts of plasma medication can be difficult.
5. Long-term adherence results in discomfort for the patients.
6. Medication with abnormally high or low partition coefficients finds it difficult to get into the bloodstream.

BASIC COMPONENTS OF TRANSDERMAL PATCH

Table 3: Different components of Transdermal patch.[42]

BASIC COMPONENT	FUNCTION	EXAMPLES
Polymer matrix	The polymer controls the medication's release from the transdermal drug delivery mechanism.	Hydroxy propyl methyl cellulose (HPMC), Polyvinyl alcohol (PVA), Polypropylene etc.
Drug or Active pharmaceutical ingredient	Give pharmacological effect	Nicotine, Fentanyl, Nitroglycerine, Curcumin etc.
Penetration enhancer	Change the skin's barrier characteristics to a drug's flow, increasing the permeability of the skin	Pluronic F68, sodium lauryl sulfate, ethanol, dimethyl sulfoxide etc.
Plasticizer	Decrease the polymer film's brittleness	Polyethylene glycol, Glycerol, Propylene glycol, dibutyl phthalate etc
Backing laminate	These are mainly used to provide the support to drug.	Polyurethane (flexible), Polyester films, Aluminum foil, Polypropylene resin etc.
Rate controlling membrane	Control Drug release from the product and its delivery to the skin for penetration.	Poly-2-hydroxyethyl methacrylate (PHEMA), chitosan etc.
Adhesive layer	The adhesive coating secures the transdermal device to the skin's surface, providing its retention under the different mechanical forces.	Mainly three classes of polymers are used- Acrylic type, Silicon type and Polyisobutylene polymer
Release liner	Release liners are a protective covering that must be taken off prior to product application.	Teflon, polyester, and silicone are a few types of release liners.

EVALUATION OF TRANSDERMAL PATCHES

- ✓ Thickness of patch
- ✓ Weight uniformity test
- ✓ Folding endurance
- ✓ Content uniformity test
- ✓ Moisture uptake
- ✓ Shear adhesion test
- ✓ Water vapor transmission studied (WVT)
- ✓ Rolling ball tack test

- ✓ Quick stick (peel-tack) test
- ✓ Probe tack test

1. **Weight uniformity test**: An electronic balance was used to determine the weight of each of the three patches that were removed from each batch.

2. **Water vapor transmission test:** Using an adhesive that contained one gram of fused calcium chloride as a desiccant, the film was adhered to the glass vial. The vial was then put in a desiccator with a saturated potassium chloride solution (relative humidity: 84%). Periodically, the vial was removed and weighed.[43]

3. **Thickness of patch:** A screw gauge was used at various locations on the patch to measure its thickness. Three randomly chosen patches were utilized from each formulation. It was established what the average thickness of one patch.[43]

4. **Percentage moisture content:** After being individually weighed, the produced films were stored for 24 hours at room temperature in a desiccator filled with fused calcium chloride. The film was weighed once again, and the following formula was used to determine the % moisture content:
Percentage moisture content = [initial weight – final weight / final weight] × 100.
5. **Percentage moisture uptake:** After being stored for 24 hours at room temperature in a desiccator, the weighted films were subjected to 84% relative humidity using a saturated potassium chloride solution. Lastly, the films were weighed, and the following formula was used to determine the % moisture uptake:
Percentage moisture uptake = [final weight-initial weight / initial weight] × 100

6. **Rolling back tack test:** Rolling back tack tester is an instrument which is used to test the tackiness of the pressure adhesive coated on the films, transdermal patches, tapes etc.[44]
The scale is divided into three zones:

0-100mm indicates the High tacking zone

100-200mm indicates the Medium tacking zone 200-300mm indicates the Low tacking zone

7. **In-Vitro drug release studies:** The fabricated film was placed over the egg membrane, the manufactured film was connected to the diffusion cell such that the drug-releasing surface of the cell faced the receptor compartment, which held 50 milliliters of sodium lauryl sulphate solution at 32±10C. Magnetic stirring was used to mix the elution media. At prearranged intervals, the 5 ml aliquots were taken out and replaced with an equal volume of sodium lauryl sulphate solution. The drug content of the samples was determined using a UV spectrophotometer set at 429 nm.[45]

8. **Quick stick (peel-tack) test:** The peel tack test calculates the amount of force required to remove an adhesive's bond from the surface it has been applied to. The film is pulled away from the backing material at a pace of 12 inches per minute at a 90° angle to determine the peel force needed to break the binding between an adhesive and substrate.[46]

CONCLUSION

The foregoing information demonstrates that curcumin is a beneficial chemical present in turmeric that has attracted attention for potentially advantageous health benefits. The results showed curcumin have various pharmacological functions which increase their market worth in future. Localized effect of curcumin is enhanced by using the transdermal preparation which absorbs at the site of action.

RESULT

The curcumin source, pharmacological actions and their mechanisms, extraction process were studied. The transdermal patch preparation and their evaluation methods were also studied. Methods of enhancing the bioavailability using permeation enhancers were assessed. Briefly studied about all the parameters and worldwide market worth of curcumin were done.

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