International Research Journal of Education and Technology

Peer Reviewed Journal

ISSN 2581-7795

Formulation and Evolution Of Herbal Anti-Microbial Transdermal Patch By using Curcumin

PROF. HARISHCHANDRE S.S, ASANE VARAD ARUN, KOLHE PRASAD, ABHANG RAJU ANIL

DR. KOLPE INSTITUTE OF PHARMACY KOLPEWADI, KOPERGAON, MAHARASHTRA.

Abstract:

The transdermal patch exhibited promising antimicrobial properties, with the ability to release curcumin in a sustained manner, ensuring prolonged contact with the skin surface. Additionally, the patch demonstrated reduced irritation and good skin adhesion properties, making it a viable option for topical antimicrobial therapy. The results suggest that curcumin-loaded herbal transdermal patches can be a potential alternative for treating skin infections, providing a more localized and effective treatment compared to conventional oral or topical antibiotics. Herbal remedies, particularly those derived from plant-based compounds, offer a promising solution to combat microbial infections with minimal side effects. This study focuses on the formulation and evolution of a herbal antimicrobial transdermal patch utilizing curcumin, the active compound found in *Curcuma longa*. Curcumin is known for its broad-spectrum antimicrobial, anti-inflammatory, and antioxidant properties, making it an ideal candidate for transdermal delivery systems.

Keyword: Transdermal Patch, Curcuma Longa, Broad-Spectrum Antimicrobial, Antioxidant.

Introduction:

1.1Traditional Medicine System:

Traditional medicine refers to any ancient and culturally based healthcare practice differing from scientific medicine and is largely transmitted orally by communities of different cultures.[1] The World Health Organization (WHO) observes that it is difficult to assign one definition to the broad range of characteristics and elements of traditional medicine, but that a working definition is essential. It thus concludes that the traditional medicines[include] diverse health practices, approaches, knowledge and beliefs incorporating plant, animal and mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being,as well as to treat, diagnose or prevent illness.[2]

1.1.1. Traditional System of Medicines[3]

- Ayurveda
- Unani
- Homeopathy
- Siddha

1.1.2Turmeric in Traditional System of Medicine:

Turmeric is believed to have a variety of medicinal benefits in Ayurvedic practises, including boosting the body's overall energy, antimicrobial and anti-inflammatory actions, relief from gas and worms, improved digestion, control of menstruation, removal of gallstones, and relief from arthritis. It is employed as an antibacterial agent and an antiseptic in several South Asian nations for wounds, burns, and bruises. Applying turmeric on a piece of burned cloth and placing it over a wound helps to clean and speed up the healing process in some countries. Turmeric is used in India to treat skin issues and cleanse the blood in addition to its Ayurvedic uses. Several sunscreens are currently made with turmeric as an ingredient. Turmeric-based face creams are produced by several global corporations.[4]

Turmeric has a long history of use in Ayurvedic medicine as a remedy for a number of respiratory ailments, including asthma, allergies, and bronchial hyperactivity, as well as for liver problems, anorexia, rheumatism, diabetic wounds, runny noses, coughs, and sinusitis. It is used in traditional Chinese medicine to treat illnesses linked to stomach discomfort). Turmeric has long been used to treat sprains and swelling as advised by Ayurveda .Turmeric is also used by unani practitioners to remove phlegm or kapha and to widen blood vessels to enhance blood flow. [5]

1.2Novel Drug Delivery System:

The goal of the Novel Drug Delivery System is to quickly deliver the required drug concentration to the proper place in the body in a therapeutic quantity. Over a certain treatment period, the drug delivery system must distribute the medicine at a pace dictated by the body. [6]

The prime areas of research and developments for NDDS are,

- Liposomes,
- Niosomes,
- Nanoparticles,
- Transdermal drug delivery
- Implants,
- Oral system,
- Microencapsulation/Microcapsules.

Novel drug delivery system can be divided into classes:

1. Sustained diffusion drug delivery system
2. Controlled diffusion drug delivery system

1.2.1. Merits of drug delivery system

1. Better treatment of many chronic illnesses. Eg. Cancer, Asthma, Arthritis.
2. Increased Bio- availability.
3. Biocompatibility.
4. Better patient compliance effect from the reduction in the number and frequency of doses needed to maintain the want therapeutic responses.

1.3.Transdermal Drug Delivery System:

The term "TDDS" refers to self-contained, discrete dose forms that, when applied to undamaged skin, transport the drug(s) to the systemic circulation through the skin at a regulated rate. For powerful, low-molecular-weight therapeutic medicines that cannot tolerate the harsh environment of the gastrointestinal system and/or are vulnerable to significant firstpass liver metabolism, transdermal drug delivery is a potential method of administration.[7]

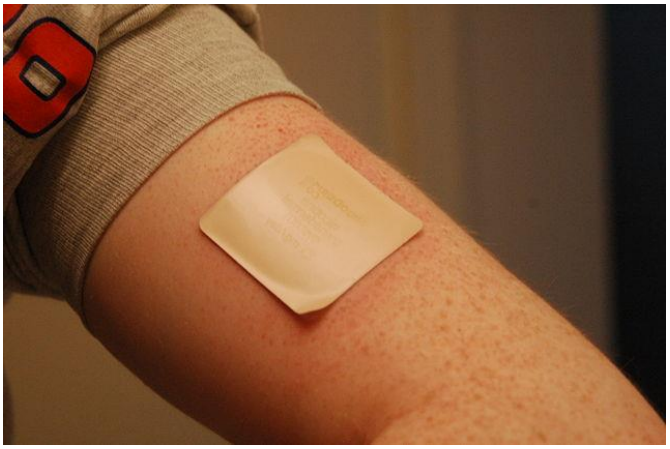


Fig No 01

Transdermal drug delivery systems are topically applied medications in the form of patches that release medications for systemic effects at a set and regulated rate. An alternate method of medicine administration is offered by a transdermal drug delivery device, which can have either an active or passive design. Pharmaceuticals may now be given across the skin barrier thanks to these devices. The transdermal patch is best shown in fig.1.[8]
The medication will continue to diffuse into the blood for a considerable amount of time, keeping the consistent concentration of drug in the blood flow, due to the high concentration on the patch and low concentration in the blood. [9]

HISTORY:

The first Transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness. The FDA has approved, till 2003, more than transdermal patch products, spanning 13 molecules 3. The US Transdermal market approached $1.2 billion in 2001. It was based on 11 drug molecules: fentanyl nitroglycerin, estradiol, ethinylestradiol, nor- ethindroneacetate, testosterone, clonidine, nicotine lidocaine, prilocaine, and scopolamine. 4. Two new, recently approved Transdermal patch products (a contraceptive patch containing ethinyl estradiol and nor-elgestromin, and a patch to treat overactive bladder containing oxybutynin.)

1.3.1Advantages of TDDS[10]
This approach to drug delivery offers many advantages over traditional methods some of this are-
• This type of drug delivery system technique also permits lower pharmacological dosages since the transdermal channel has a shorter metabolisation pathway than the stomach system.
• The patch also enables continuous dosing as opposed to the ups and downs in medicine level common to oral treatments.

1.3.2Disadvanatges Of TDDS[11]
• The medication that required high blood levels cannot be used, and it can even irritate or sensitise the skin.
• The adhesives could be difficult to wear and might not stick properly to all types of skin.

1.4. Pathway of Transdermal Permeation

The permeation of drugs through the skin includes the diffusion through the intact epidermis and through the skin appendages, ie., hair follicles and sweat glands, which form shunt pathways through the intact epidermis. However, these skin appendages occupy only 0.1% of the total human skin surface and the contribution of this pathway is usually considered to be small (with only a few exceptions having been noted). As stated above, drug permeation through the skin is usually limited by the Stratum corneum. Two pathways through the intact barrier may be identified (Fig No.4) the intercellular lipid route between the corneocytes and the transcellular route crossing through the corneocytes and the intervening lipids that is, in both cases the permeant must diffuse at some point through the intercellular lipid matrix, which is now recognized as the major determinate of percutaneous transport rate [12].

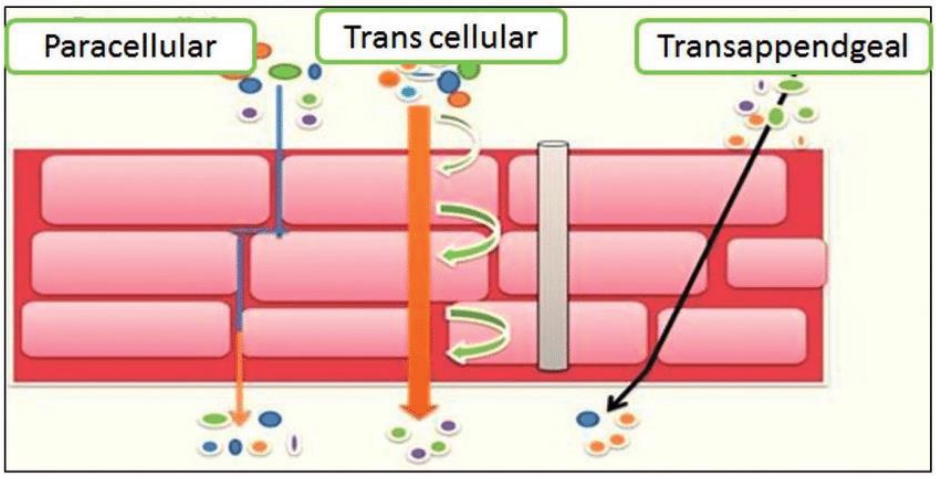


Fig. Drug penetrate into skin

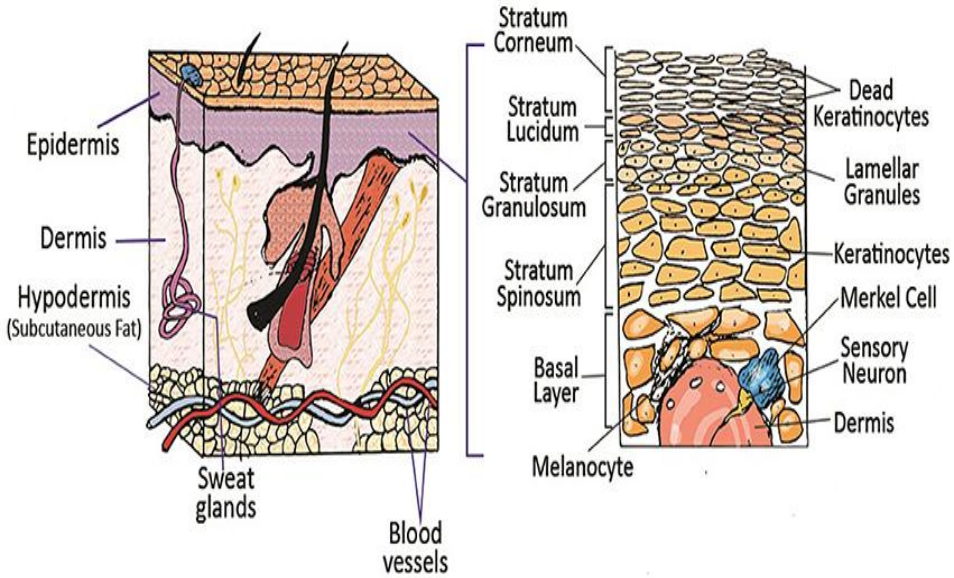


Fig. Structure of skin

Three potential entry "MACRO ROUTES" to the viable tissue.

1. Via the sweat ducts.
2. Across the continuous stratum corneum (diffusion).
3. Through the hair follicles with their associated sebaceous glands.

Route of drug penetration into skin:

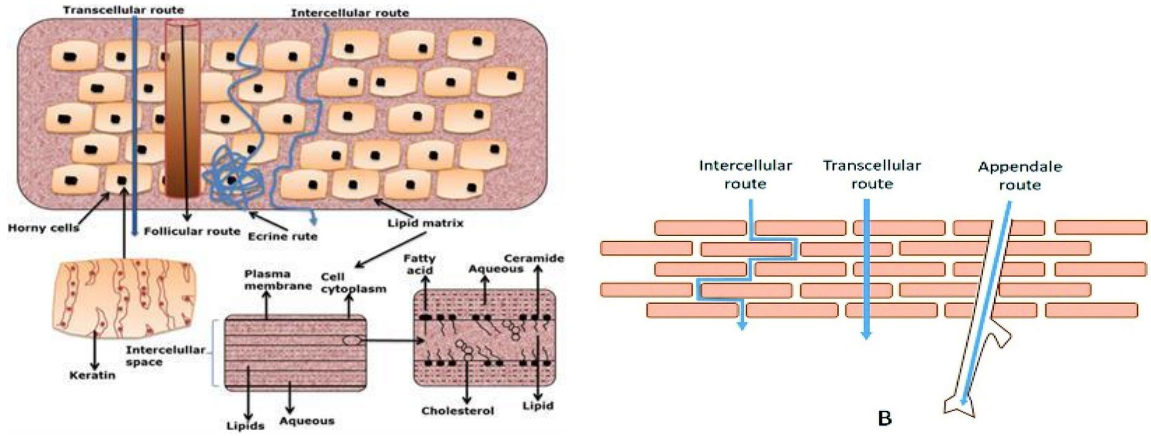


Fig. Route of drug penetration into skin

1. Transcellular permeation through the stratum corneun
2. Intercellular permeation through the stratum corneum
3. Transappendageal permeation via hair follicle, sebaceous & sweat gland.

Materials employed/Formulation/ Components transdermal patch:

1. Polymer matrix/ matrices
2. The drug
3. Pressure sensitive adhesives
4. Permeation enhancers
5. Excipients/ other supportive materials

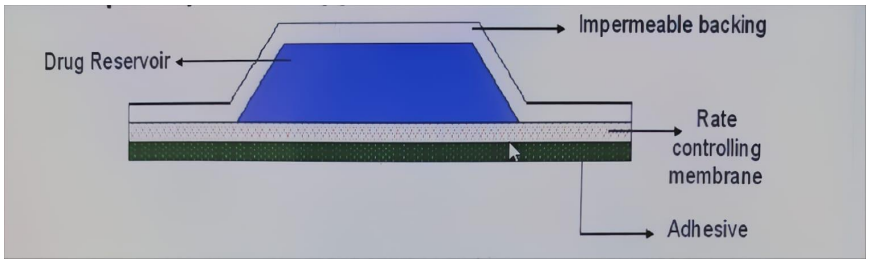


Fig. Parts Of Transdermal patch

A .Polymer matrix: The polymer is formulated either as a matrix/ reservoir to controls the release of the drug from the device.

Ideal characters:

1. The polymer molecular weight, glass transition temperature and chemical functionality must allow proper diffusion & release of drug
2. It should be stable, non reactive with the drug, easily nanufactured and fabricated into the delired product
3. The polymer and its degradation products must be non toxic or non antagonistic to the host.

4. The mechanical properties of the polymer should not deteriorate excessively when the large amount of the active agents are incorporated into it.
The polymers used in the transdermal drug delivery systems are
1. Natural polymers - Cellulose derivatives ,zein , gelatin , shellac ,waxes, proteins , gums and their derivatives , natural rubber starch etc.
2. Synthetic elastomers- Poly butadiene , hydrin rubber , poly siloxane silicone rubber , nitrile , acrylonitrile ,butyl rubber, butadiene Neoprene etc.
3. Synthetic polymers- Polyvinyl chloride, polyethylene, poly propylene, polyacrylate ,polyamide ,polyurea, polyvinyl pyrrolidone, poly methyl methaacrylate

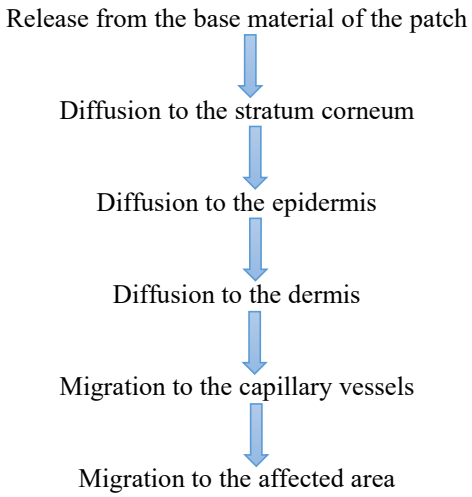
B. Drug:
For successful development of a transdermal drug delivery, the following are the desirable properties of a drug. Physicochemical properties.- It is generally accepted that the best drug candidates for passive adhesive Transdermal patches must be Non-ionic.
Low molecular weight (less than 1000 Daltons), Adequate solubility in oil and water .
Low melting point (less than 200°C) Potent (dose ideally less than 10 mg per day).

C. Permeation enhancers: These are the compounds which promote skin permeability by altering the skin as a barrier to the fl of a desired penetrant (drug).
1.These are also known as accelerants /sorption promoters. Ideal properties: 1. Should work rapidly.
2. The activity and duration of effect should be both predictable and reproducible.
3. should not have pharmacological activity
4. Should wqsk unidirectionally (prevent loss of endogenous material from body).
5. When removed form skin, the barrier properties should return both rapidly and fully.

D. Other supportive material

a. **Release liner**
b. **Backing layer**
c. **Semi permeable membrane**
d. **Packing substrate**

1.4.1.Skin Permeation Mechanism:



PLANT PROFILE:

Herbal Drug Name: Turmeric
Biological Source: Turmeric is a product of **Curcuma longa**, a rhizomatous herbaceous perennial plant.
Part used : Fruit

Fig. Curcumin

Family : Zingiberaceae
Synonyms : Curcuma domestica, Curcuma longa.
Generic Name: Curcumin
Chemical Constituent: The distinct yellow colour of turmeric comes from the pigment curcurmin (CUR), 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, and two curcuminoids, demethoxycurcumin (DEM) and bisdemethoxycurcumin (BIS)

Properties : Antioxidant, Anti-Inflammatory, Antimicrobial Effects.

Description

Colour: Curcumin is a yellowish crystalline, odourless
Odour : Odourless powder
Taste: Peppery, somewhat bitter
Nature: Hydrophobic nature

Solubility: curcumin is poorly soluble in water. However, it is easily soluble in organic solvents.

Biological activity : Curcuminoids from turmeric and their derivatives have been shown to possess a wide range of biological activities including antioxidant, anti-inflammatory, anticancer, antimicrobial, neuroprotective, cardioprotective and radioprotective effects.

• Medical use :
The active ingredient in Curcuma plant xanthorrhiza oil and the golden spice turmeric (Curcuma longa) is curcumin, commonly known as diferuloylmethane. It is a very pleiotropic chemical that also has antimicrobial, anti-inflammatory, hypoglycaemic, antioxidant, and wound-healing properties. Curcumin has been studied for the

therapy and supportive care of a variety of clinical disorders, including proteinuria, breast cancer, multiple myeloma, depression, and non-small cell lung cancer (NSCLC), as a result of these qualities. Despite having been shown to be effective against numerous experimental models, curcumin's therapeutic efficacy has been shown to be constrained by its poor bioavailability caused by poor absorption, rapid metabolism, and rapid systemic elimination.[13]

CHEMICALS AND EQUIPMENNTS:

Table 1: List of Chemicals

Chemical Name	Uses
PECTIN	THICKENING AGENT
CARBOPOL	MUCOADHESIVE EFFECT
DMSO	PERMEATION ENHANCER
GLYCERIN	PLASTICIZER
OLEIC ACID	INCREASE ABSORPTION OF DRUG
TWEEN 80	SURFACTANT

Table 2: List of Equipment's:

Name of Equipments	Name of Manufacturer	Purpose
Dessicator	-	Moisture Content Studies
Digital Vernier Caliper	-	Patch Thickness Studies
Electronic Balance	Weighing Purpose	
Digital Ph meter	-	Surface Ph Studies
Filter Paper	-	Filtration
Magnetic Stirrer	LABOHOUSE INDIA	Diffusion Studies
UV Spectrophotometer	Labman Scientific Instruments	Determination of absorption maximum&concentration of active substance.

7. EXCIPIENT PROFILE:

1. PECTIN

The major terrestrial plant cell walls include pectin, of terrestrial plants include pectin, which is a structural heteropolysaccharide. A naturally generated biopolymer called pectin isincreasingly used more and more uses in the biotechnology and pharmaceutical sectors. It has been used successfully as an ingredient for thickening, a gelling agent, and a colloidal stabilizer in the food and beverage sector for many years. Pectin also possesses a number of distinctive qualities that have made it possible to use it as a matrix for the delivery and/or trapping of a range of medicines, proteins, and cells.

General properties of Pectin

A natural polymer is pectin. Pure water dissolves pectin. Pectinic and pectic acid monovalent cation (alkali metal) salts are typically soluble in water, whereas di and trivalent cation salts are either weakly soluble or insoluble.

Pharmaceutical uses of pectin

In the pharmaceutical industry, pectin gets often utilized. Pectin has an advantageous impact on blood cholesterol levels. To considerably decrease cholesterol, one needs to ingest at least 6 grammes of pectin each day. Pectin serves as a natural preventative measure against toxicity-related poisoning. It has been demonstrated to be successful at eliminating mercury as well as lead from the digestive system and respiratory organs. The duration of blood coagulation is shortened by intravenous pectin injection.

2. GLYCERIN

Synonyms: Croderol, E422, Glycerine, Glycon G-100, Kemstrene, Pricerine, 1,2,3- propanetriol,trihydroxy propane glycerine

Description: It is a viscous, transparent odour-free liquid that is clear and hygroscopic with a sweet flavour that is around 0.6 times sweeter than sucrose.

Typical properties:

Melting point: 17.80C

• Solubility: Soluble in water, methanol

Applications in Pharmaceutical Technology

It is utilized in a wide range of medicinal formulations, such as parenteral, topical, ophthalmic, and oral preparations. It is primarily employed for its humectant and emollient qualities in topical medicinal formulations and cosmetics. It primarily functions as a solvent in parenteral formulations.

3. Dimethyl Sulphoxide (DMSO)

Synonyms: Deltan, dimexide, dimethyl sulphoxide, DMSO; Kemsol, methylsulfoxide, Rimso-50; sulphinyl bismethane.

Applications in Pharmaceutical Formulation or Technology

Dimethyl sulfoxide is a highly polar substance that is aprotic, thus, it is deficient in acidic and basic properties. It has incomparable solvent properties for both organic as well as inorganic components, which are obtained from its capacity to associate with both ionic species and neutral molecules that are either polar or polarizable. Due to its capacity to remove bound water from the stratum corneum, dimethyl sulfoxide improves the topical penetration of medicines. As a result, lipids are extracted and protein configurations are altered. [14]

4. CARBOPOL

High molecular weight, cross-linked, and based on acrylic acid are carbopol polymers. These are acrylic acid polymers that have been linked together with poly alkenyl ethers or divinyl glycol. They are created from parent polymer particles with an average diameter ranging from 0.2 to 6.0 microns. When created, the flocculated agglomerates are incapable of being broken down into the final particles. A system consisting of networks of polymer chains connected by cross-linking can be thought of as each particle. The pH will be lower because the concentration increases the carboxyl concentration

8. EXPERIMENTAL WORK:

PROCEDURE FOR FORMULATION:

1. Extraction of curcumin from turmeric powder

15g of powdered form of turmeric was carefully added to a soxhlet apparatus along with 95:5 ethanol and water for 10 hours. The substance was then carefully filtered out following extraction. Then, the quantifiable amount of drug obtained was used to make transdermal patches.

Fig Extraction of curcumin from turmeric powder

2. Preparation of Transdermal Patch

40g of curcumin powder were combined. Curcumin, and three different ratios of pectin and carbopol have been paired to create transdermal patches. A calculated amount of water was heated on a water bath while a weighed amount of polymer was dissolved in it. The aforementioned mixture was given 40ml of extract (40ml of curcumin, respectively), which was thoroughly agitated to create a homogeneous mixture. Following that, 0.3 ml of glycerin and 0.3 ml of dimethyl sulfoxide were added. The amount of extract in each of the three batches was the same at 40ml. The product that emerged was put onto a Petri dish and allowed to air dry for 24 hours at room temperature. Using a knife, the patches were then skinned off of the Petri dish and stored in a desiccator. [15]

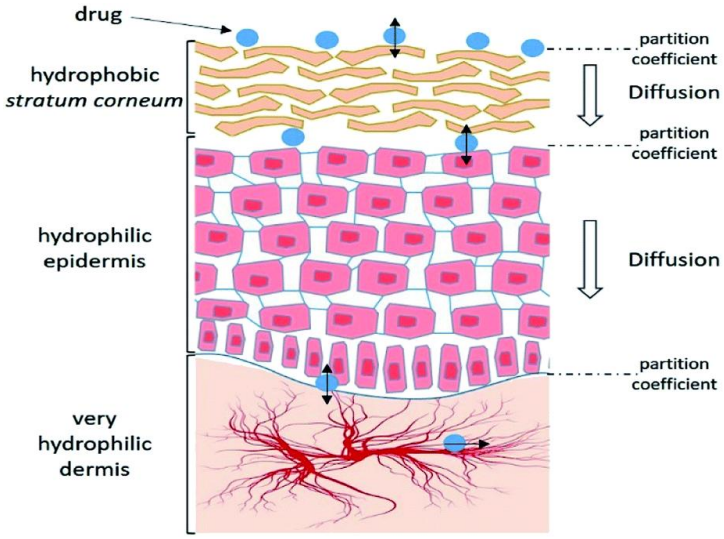


Fig. Drug penetrate skin layer

Table No. 03: Formula for TDDs. Ingredients :

Table 3: Formula for TDDs. Ingredients	**TP1**	**TP2**	**TP3**	**TP4**	**Category**
Curcuminn(mg)	40	40	40	40	**Drug**
Pectin(mg)	240	320	--	--	**Polymer**
Carbopol(mg)	--	--	240	320	**Polymer**
DMSO(ml	0.3	0.3	0.3	0.3	**Excipient**
Glycerin(ml)	0.3	0.3	0.3	0.3	**Excipient**
Water	q.s	q.s	q.s	q.s	**Solvent**

Fig. Sample, Extraction and Residue.

EVALUATION:

Physico- chemical evaluation of Transdermal patch :

1. Uniformity of weight
This was accomplished by weighing three separate patches from each batch, selecting a consistent size at random, and averaging their weights. The patch was tested after it had been dried at 60°C for four hours**.**

2. Thickness of the Patch
At multiple points on the patch, the thickness was measured using the digital vernier caliper. Three patches were chosen at random from each formulation. The overall thickness of an individual patch is calculated on average.

3. Drug content determination
A beaker with 100 ml of water that had been distilled was filled with the patches. Magnetic beads were used to stir the medium for 5 hours. The solution was then filtered and its drug content was assessed spectrophotometrically at 382 nm.

4. Folding Endurance
This was established by continuously folding one patch until it broke in the same location. The value of folding endurance was determined by how many times the patch could be folded in the same location without breaking.

5. Percentage Moisture uptake
The pieces were precisely weighed before being put in desiccators with aluminum chloride. The patch was removed and weighed after 24 hours. By dividing the end weight by the initial weight, the % moisture uptake was obtained. With respect to the initial weight. It is calculated by using the following formula.

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

6.Determination of surface pH:
The patches were kept in contact with 1 ml of distilled water for 2 hours at room temperature to allow them to swell. The pH of the patches was then measured by placing an electrode against their surface and letting it equilibrate for 1 minute.

Anti-Bacterial Activity
Principle
Discs infused with known antibiotic concentration are positioned on an agar plate that has been uniformly infested (or seeded) with a culture of the bacterium that will be examined. At 37°C, the plate is allowed to incubate for 18–24 hours. During this time, the antibacterial agent spreads throughout the agar and might stop any microbial growth. The effectiveness of susceptibility varies with the circumference of the disc's inhibitory zone. Tolerance exists in organisms that reach the disc's edge.

A) Materials Required- Peptone, Sodium Chloride, Dil. Sodium Hydroxide, Dil. Sulfuric acid, Agar, Distilled water, pH paper, Conical flask, Culture tubes, Glass rod, Non-absorbent cotton, Autoclave- Micropipette, Petri dishes, and Incubator.

B) Experimental condition -Organisms used: Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa. Media used: Nutrient Agar. Test used: AE patch Standard: Ciprofloxacin, Nystatin

C) Preparation of Nutrient Agar –Suspend 28g of nutrient agar powder in 1L of distilled water. Mix and dissolve them completely. Sterilize by autoclaving at 121•C for 15 min.Pour the liquid into the petri dish and wait for the medium to solidify.

D) Preparation of Paper Disc- The normal filter paper was cut and laid out with a 6.0 mm diameter using a normal punching machine. The paper discs were disinfected at 160°C in a hot air oven for one hour at 160°C in a hot air oven. The test solution was then applied to the paper disc.

Physicochemical evaluation :

1. Interaction studies

• Physicochemical evaluation
• In vitro evaluation
To create a stable product, both the drug and the excipients must be compatible with one another. The bioavailability and stability of the medicine are impacted by the interaction between the drug and excipients. Compatibility studies are crucial in formulating new excipients if they have never been utilised in formulations containing the active ingredient. By contrasting their physicochemical characteristics, such as assay, melting point, wave numbers, and

absorption maxima, thermal analysis, Fourier transform infrared spectroscopy (FTIR), ultraviolet (UV), and chromatographic techniques are used to conduct interaction investigations.

2.Thickness of the patch
The thickness of the resultant patch is measured by using a digital micrometer at multiple points of the patch and this assesses the average thickness and standard deviation for the same to make certain the thickness of the prepared patch.

3.Weight uniformity
Before testing, the produced patches must be dried at 60°C for 4 hours. A predetermined patch area must be divided into various patches and weighed using a digital balance. From the individual weights, the average weight and standard deviation values should be computed.

4.Folding endurance
A specified section of the strip is sliced, then folded repeatedly until it breaks. The value of folding endurance was determined by how many folds the film could withstand without breaking.

5.Percentage moisture content
The prepared patches are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature. After 24 h, the films are to be reweighed and the percentage moisture content determined by below formula,
Percentage moisture content (%) = [Initial weight - Final weight / Final weight] ×100

RESULTS AND DISCUSSIONS :

Table. Result and Discussions:

Sr.no.	Formulation code	Weight(g)
1.	**Pectin(P1)**	**0.46+-0.85**
2.	**Carbopol(P2)**	**0.41+- 0.65**

Sr.no.	Formulation code	Weight(g)
1.	**Pectin(P1)**	**0.49+- 0.23**
2.	**Carbopol(P2)**	**0.45+- 0.23**

CONCLUSION:

- Three batches of (P1, P2) extract of curcumin transdermal patches were formulated by solvent casting technique.
- To produce thin, clear, smooth, stable, and highly permeable transdermal patches, a variety of formulation parameters, Drug-Polymer ratios, and permeation enhancers were optimised.
- From the optimization, the best 2 formulations P1 & P2 were chosen based on physicochemical evaluation and in vitro drug diffusion study.
- 0.3ml of glycerin was added as a plasticizer to produce a flexible patch without having a key influence on their diffusion property. If the amount exceeds, the film loses its flexibility and become stiff.
- The plasticizer diffuses through the patch and softens the polymer particles. This softening increases latex coalescence and patch formation.

- All three batches were assessed for Percentage Moisture uptake, Percentage Moisture content, Thickness, Percentage Drug content, and Adhesive strength.
- The formulations P2 & p2 showed maximum % Moisture uptake, Moisture content, Thickness, folding endurance, % Drug content, Percent elongation, Tensile strength
- No significant difference in drug content was witnessed between the patches among the six formulations. This specifies the homogenous dispensing of the drug during the patch preparation.

REFERENCES:

1. Karunamoorthi K, Jegajeevanram K, Jerome X, Vijayalakshmi J,Melita L. Traditional medicinal system - Siddha: an indigenous health practice in the international perspectives. *International journal of Genuine Traditional Medicine*. 2012, Vol: 2(2):1-11.
2. Legal status of traditional medicine and complementary/ alternative medicine: a worldwide review (document who/edm/trm/2001.2). Geneva, world health organization,2001.
3. Ravishankar, B And Shukla, Indian Systems Of Medicine: A Brief Profile Complementary And Alternative Medicines V.J. *African. Journal of Traditionalmedicine. Cam* (2007), vol:4 (3): 319 – 337.
4. Jatav VS, Saggu JS, Jat RK, Sharma AK, Singh RP. Recent advances in development of transdermal patches. Pharmacophore Int. Res. J., 2011; 2(6): 287-297.
5. Joshi K, Selvaduary G. Transdermal drug delivery system and their use of polymers. MatE 175- Biomaterials. 1st Ed., 2008; 1-28.
6. Patel DS, Patel MV, Patel KN, Patel BA, Patel PA. Transdermal patches: a complete review on transdermal drug delivery system. Int. J Pharm Res. Scholars, 2012; 1(1): 55-71.
7. International Journal of Pharmaceutical Sciences and Research, 2290.
8. www.wikipedia.com.
9. Wokovich AM, Prodduturi S, Doub WH, Hussain AS, Buhse LF. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. Eup. J Pharm BioPharm, 2006; 64: 1-8.
10. Thejaswi C, Rao KM, Gobinath M, Radharani J, Hemafaith V, Venugopalaiah P. A review on design and characterization of proniosomes as a drug carrier. Int. J Advances Pharm Nanotechnology, 2011; 1(1): 16-19.
11. Arunachalam A, Karthikeyan M, Kumar DV, Pratap M, Sethuraman S, Kumar SA. Transdermal drug delivery system: review. Current Pharm Res., 2010; 1(1): 70-81.
12. Syeda Ayesha Fathima, Shireen Begum, Syeda Saniya Fatima.Transdermal Drug Delivery System , International Journal of Pharmaceutical and Clinical Research 2017,vol 9(1): 35-43.
13. Sharma A, Saini S, Rana AC. Transdermal drug delivery system: A review. Int. J Res Pharm Biomedical Sci., 2013; 4(1): (286-292).
14. Mali AD, Bathe R, Patil M. An updated review on transdermal drug delivery systems. Int. J advances Sci. Res., 2015; 1(06): 244-254.
15. Gaikwad AK. Transdermal drug delivery system: Formulation aspects and evaluation. Comprehensive J Pharm Sci., 2013; 1(1): 1-10.
16. Lende LK, Grampurohit ND, Gaikwad DD, Gadhave MV, Jadhav SL. Transdermal patches: a review. Int. J Pharm Res. Dev., 2011; 4(3): 96-103.

17. Shingade GM, Aamer Q, Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL, Gaikwad D. Review on: Recent Trends on Transdermal Drug Delivery System. J Drug Delivery Therapeutics, 2012; 2(1): 66-75.

18. Bathe R, Kapoor R. Transdermal drug delivery system: formulation, development and evaluation-An overview. Int. J Biomedical and Advance Res, 2015; 6(01): 1-10.

19. Tanwar and Sachdeva, IJPSR, 2016; 7(6): 2274-2290. E-ISSN: 0975-8232; P-ISSN: 2320-5148.

20. Yadav B, Sharma B, Saroha K. Transdermal patches: a discrete dosage form. Int. J Current Pharm Res., 2011; 3(3): 98-108.