Formulation and Evaluations of Transdermal Patches of Mefenamic acid and Dicyclomine

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***Abstract*—Topically applied medications are known as transdermal drug delivery systems (TDDS). One significant issue that causes the transdermal patch to become unstable and reduces medication delivery is the crystallization of mefenamic acid. In order to prevent mefenamic acid from crystallizing, an additive (PVP K90) was utilized. Transdermal patches typically contain two medications, such as mefenamic acid and dicyclomine. The goal of the current study was to create and assess a novel transdermal formulation of dicyclomine and mefenamic acid, which are used to relax muscles and reduce discomfort, particularly during the menstrual cycle. Furthermore, tests on drug permeation and release (drug index) were conducted using Franze diffusion cell membranes and UV visible spectra, respectively.**

***Index Terms*—TDDS, Transdermal patch, mefenamic acid, dicyclomine, crystallization.**

I. INTRODUCTION

A medicated adhesive patch called a transdermal patch is applied to the skin to deliver a certain dosage of medication via the skin and into the bloodstream (1). Transdermal drug delivery systems (TDDS) are becoming more popular for both local therapeutic effects on ill skin (topical delivery) and systemic medication delivery. The drug's bioavailability is increased by avoiding hepatic first-pass metabolism, pH and emptying rate effects, and stomach discomfort, (2). Among the many noteworthy benefits of employing the skin as a location of medication delivery over many other drug administration routes are lowering the risk of systemic side effects by minimizing plasma concentrations when compared to oral therapy (3).

Mefenamic is a non-steroid anti-inflammatory medicine (NSAID) that is used to treat mild to moderate pain, including headaches, inflammation, muscular and joint pain, and menstrual cramps (dysmenorrhea). Dicyclomine is an anticholinergic medication that relaxes the muscles in the stomach and intestines to relieve cramps, spasms, and abdominal pain. Mefenamic acid typically results in adverse effects such heartburn, bloating gas, diarrhoea, nausea, vomiting, GI and stomach irritation, and occasionally GI bleeding. Transdermal patches are the most effective way to transfer the dose into the body in order to prevent this undesirable consequence. However, dicyclomine also exhibits a number of gastrointestinal and stomach-related negative effects, which is why certain nations have outlawed it. We employ dicyclomine transdermal as an antispasmodic and muscle relaxant to counteract this effect. The preparation's primary goal is to deliver the dose to the body without generating any gastrointestinal side effects. This patch mostly relieves menstruation pain and relaxes the muscles. To improve treatment results for dysmenorrhea, the transdermal delivery mechanism of mefenamic acid may be investigated for combination therapy with antispasmodic or other analgesic drugs.

Cutaneous delivery is one very effective way to deliver medication. The transdermal drug delivery system (TDDS) is a unique medicine administration approach in the pharmaceutical business because of its several advantages over other drug delivery methods (4). Conventional drug delivery system formulations require larger dosages and longer regimens to produce therapeutic results, and long-term regimens may cause serious side effects and ultimately poor patient

compliance (5). It is believed that an organism's skin serves as its first line of defence, protecting it from dangerous illnesses, toxic substances, and viruses found in the environment. Keratinocytes are encircled by several layers of lipid matrix that act as a barrier in the skin's upper stratum (15 μm). Furthermore, the skin serves as the main barrier that keeps most drugs out (6).

Mefenamic acid has a higher permeability because it is class 2 BCS. Dicyclomine is a class 1 BCS medication with high permeability and water solubility. Understanding the architecture and physiology of the skin may lead to the best design and development of dependable medication delivery systems. The skin is the largest part of the human body. The 20 square feet of human skin contain around one-third of the blood that circulates throughout the body (7).

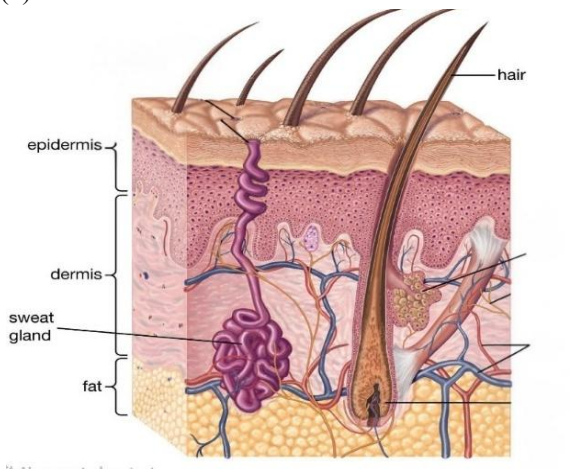

Figure 1. Skin Anatomy

Advantage

- Drug breakdown in acidic and basic environments is avoided by chemically hastening the GI environment.
- There is no GI distress, and unlike the oral route, this route is unaffected by factors like gastric emptying, intestinal motility, and transit time.
- Therefore, a smaller dose is required to avoid considerable presystolic metabolism (degradation in the GIT or by the liver).
- Enables the efficient use of medications with brief biological half-lives
- Decreased variability within and between patients
- Optimize the blood concentration-time profile to improve therapeutic efficacy and minimize fluctuations (fast spikes in low and high blood levels) (8).
- Improving patient compliance and lowering the frequency of doses

Disadvantage

- Large doses, such as more than 10 mg daily, are challenging to deliver.
- Ionic medications cause issues.
- Substances larger than 500 Dalton are not appropriate for TDDS (9).
- High concentrations of drugs might irritate the skin (10).
- Achieving a high plasma medication concentration is challenging.
- Patients experience discomfort due to long-term adherence.
- Medications having a high or extremely low partition coefficient are unable to enter the systemic circulation (11).

Uses

- Mainly used in menstrual cramps (dysmenorrhea).
- Stomach and abdominal pain due to spasms and discomfort.
- Pain from intestinal spasms.
- Colicky pain.
- Pain associated with gastrointestinal disorders (Inflammatory Bowel Disease).

II. DRUG AND EXCIPIENT PROFILE

1. Drug profile-

- Mefenamic acid

Sr. no	Use	Concentration (%)
1	Non-steroidal anti-inflammatory drug	20–90
2	Analgesic	5–20
3	Antipyretic	-

- Dicyclomine

Sr. no	Use	Concentration (%)
1	Antispasmodic	-
2	Anti cholinergic	5–20
3	Muscle relaxant	-

2. Excipient profile –

➢ PVP K30

Sr.no	Use	Concentration (%)
1	Carrier for drugs	10–25
2	Dispersing agent	Up to 5
3	Eye drops	2–10
4	Suspending agent	Up to 5
5	Tablet binder, Tablet diluent, or coating agent	0.5–5

➢ HPMC (Hydroxypropyl Methylcellulose)

Sr.no	Use	Concentration (%)
1	Film forming agent	-
2	Rate controlling membrane	-
3	Matrix Former	-
4	Moisture Barrier	-
5	Compatibility with plasticizer	-

Materials

PVP, K90 (Polyvinylpyrrolidone K-30), Mefenamic acid, Dicyclomine, HPMC (Hydroxypropyl Methylcellulose), Diethyl phthalate, Ethyl acetate, Ethanol were used

1.1. Drug/Excipients/Chemicals/Material

Sr no	Name	Grade	Quantities
	PVP K-30	-	0.4gm
	Mefenamic acid & Dicyclomine	-	0.2gm
	HPMC (Hydroxypropyl Methylcellulose)	--	5gm
	Glycerine	-	1.5ml
	Ethyl acetate	-	8ml
	Ethanol	-	6ml+

1.2. Equipment

Sr. No	Name of the equipment	Model & make
1	pH meter	Equip-Tronics
2	Hot air oven	-
3	Electronic Weighing Balance	SF400C
4	Dissolution apparatus	-
5	Petri dish	-
6	Sonicator	-

Method

Procedure

a. Solution 1

HPMC (Hydroxypropyl Methylcellulose) + Diethyl Phthalate

↓

Mixed

↓ **dissolve**

Ethyl acetate

b. Solution 2

Drug + PVP K 90 (1:2) dissolved in ethanol

Solution 1& 2 Homogenously **mixed** by mechanical stirrer

↓

Mixed solution sonicated for 30min to reduced bubbles

↓

Mixture poured into Petri dish

↓

Dried in hot air oven at 50 ± 2°C for 5 hrs

↓

At room temperature

The drug mefenamic acid matrix patches were peeled off from petri-dish

↓

Kept in a Desiccator

III. EVALUATION

1. Folding endurance

It is the number of times a patch can be folded repeatedly at the same place without breaking or cracking. It is mainly used to evaluate the flexibility & mechanical strength of transdermal patch in pharmaceutics.

Procedure (12)

- Cut the transdermal patch into a small strip of uniform size.
- Fold the strip repeatedly at the same place using fingers.
- Each fold (one complete fold and unfold) is counted as one cycle.
- Continue folding until the film breaks or develops cracks.
- Note down the number of folds required to break the film.
- That number is note down as the folding endurance of the film/patch.

2. Tensile strength

It is strength is the maximum stress that a path can withstand when stretched before it breaks.

Procedure (13)

- Cut the film or transdermal patch into a rectangular strip of uniform size.
- Measure and record the length, width, and thickness of the strip.
- Fix one end of the strip to a stable support and the other end to a tensile strength apparatus (or weights system).
- Apply force by adding weights and continue it until the film breaks.
- Note the force required to break the film.
- Calculate tensile strength using the formula:

$$\text{Tensile Strength} = \frac{\text{Breaking force}}{\text{Cross} - \text{sectional area}}$$

3. % elongation break test

The percentage elongation at break test is used to determine the extent to which a film or transdermal patch can be stretched before it breaks, expressed as a percentage of its original length.

Procedure (14)

- The percentage elongation break was calculated by noting the length just before the breaking point and the following formula was used to calculate the percentage elongation.

Percentage Elongation =

$$\frac{\text{Final length of strip} - \text{initial length of strip}}{\text{intial length of Initial}} \text{ X } 100$$

4. Thickness (15)

procedure

- The thickness of the transdermal patches was measured using a micrometre screw gauge.
- at three different places in 5 by 5cm area, and calculate the mean value (16).

5. Drug content

Amount of drug present in transdermal patches.

Procedure

- A 2cm x 2 cm size transdermal patch was dissolved in 100 ml ethyl acetate.
- The whole solution was then ultrasonicated for 30 min.
- Samples were diluted 5 times with ethyl acetate and filter using a cellulose acetate membrane, the drug's content was measured using spectrophotometry at a wavelength 353nm.

6. % Moisture content

The amount moisture (water content) present within transdermal formulation.

Procedure

- The prepared transdermal films were individually weighed and stored in a desiccator containing a fused saturated solution of potassium chloride for 24 hrs at room temperature.
- After 24 h, the patch was reweighed and the percentage moisture uptake.
- calculated using the following formula

$$\% \text{ Moisture content } \frac{\text{intial wt} - \text{final wt}}{\text{final wt}} \text{X} 100$$

7. Swelling study

Swelling study is also known as swelling index, the ability of patches to swell the moisture content from the environment or air.

Procedure (17),

- The formulated transdermal patches were weighed (W1) individually and incubated at 37 ± 0.5 ° C separately in agar gel (2%) plate.

- The patches were removed from the petri dish at regular time intervals of every 15 min up to 1 h and the excess water on the surface was removed carefully with filter paper.
- The swollen patches were reweighed (W2)
- calculated by using the formula.

$$\text{Swelling study} = \frac{W2 - W1}{W1}$$

IV. RESULTS AND DISCUSSION

Calibration curve

Solvent System	λmax	Equestion of straight line (y= mx+c)	Coefficient of regression
0.1 Sodium Hydroxide (NaOH)	285nm	y = (0.0582x - 0.0172)	R^2 = 0.9998

Table: Concentration and absorbance of mefenamic acid

Sr no.	Concertaton (µg/ml)	Absorbance
1	10	0.1212
2	20	0.2415
3	30	0.3616
4	40	0.4818
5	50	0.6021

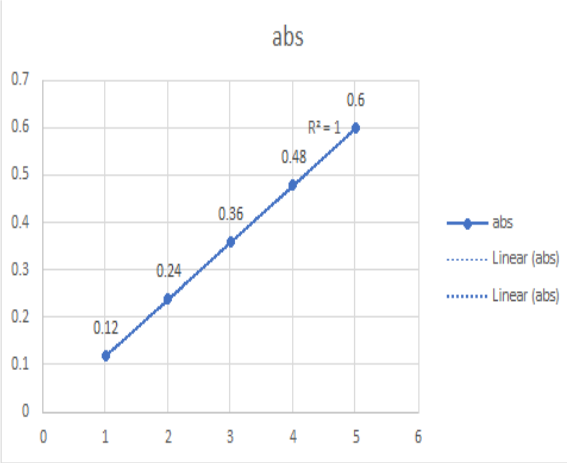

Figure 2: Calibration curve of mefenamic acid

λmax of mefenamic acid is 285 nm and equation of straight line is y = (0.0582x -0.0172) and coefficient of regression is R^2 = 0.9998

Folding Endurance: Report the number of times the patch could be folded at the same place without breaking. Higher values indicate better flexibility.
The increased folding endurance observed in formulations containing higher concentrations of [Glycerine] is attributed to the reduction in intermolecular forces between polymer chains, increasing film flexibility.

Tensile strength, which reflects the material's resistance to fracture under stress was found to be 12.4 MPa.
The observed enhancement in tensile strength is likely due to the uniform distribution of the polymer matrix, which facilitates a cohesive intermolecular network. This mechanical fortitude is critical, as it ensures that the patch remains intact when subjected to the mechanical strain of skin movement during patient use.

Percentage elongation break was found to be 15.2%.
Thickness and Weight Variation: The mean thickness and mean weight of patches across formulation was found to be 0.22 mm and 148mg respectively.
The thickness of the matrix is directly proportional to the total drug loading capacity. While reducing thickness enhances patient comfort, it must be balanced against the therapeutic requirement to deliver a consistent dose of Mefenamic Acid.

Drug Content Uniformity: The percentage of drug content across batches to ensure uniform distribution is found to be 97%.
By shifting from oral administration to a transdermal route, the formulation aims to bypass hepatic first-pass metabolism and minimize the prostaglandin-mediated gastrointestinal irritation commonly associated with oral Mefenamic Acid. These results demonstrate that a transdermal patch is a viable strategy for achieving steady-state plasma concentrations of the drug.

Moisture Content/Uptake: The percentage of moisture content/uptake of the patch is found to be 4% (w/w).
The moisture content analysis reveals that the residual water levels remained within the optimal therapeutic

window for all prepared patches. This controlled moisture level is essential for ensuring that the matrix retains its viscoelastic properties, allowing the patch to conform to the skin's surface without inducing mechanical failure. Furthermore, the stability of these values across different batches highlights the robustness of our vacuum-drying process, confirming that the drug delivery system is physically stable and ready for long-term storage.

Swelling index: The swelling index of the patch is found to be 14.4%.

Hydrophilic polymers (HPMC) contain functional groups (hydroxyl or carboxyl) that readily form hydrogen bonds with water, leading to higher swelling. If your study used a blend, explain how shifting the ratio allowed you to "tune" the swelling behaviour.

V. SUMMARY CONCLUSION

The present study focused on the formulation and evaluation of a Transdermal Drug Delivery System (TDDS) of mefenamic acid, a non-steroidal anti-inflammatory drug (NSAID) used for pain and inflammation.

Mefenamic acid was selected due to its short half-life, gastrointestinal side effects on oral administration, and suitability for controlled drug delivery. The TDDS was prepared using polymers such as HPMC (Hydroxypropyl Methylcellulose) and PVP K30, along with plasticizers like glycerine, and solvents such as ethanol and ethyl acetate.

The prepared patches showed uniform drug distribution, good mechanical strength, and desirable physicochemical characteristics, along with a controlled and prolonged drug release profile.

Among the formulations, the optimized patch showed better drug release profile and permeation characteristics, making it a promising alternative to conventional oral dosage forms. The results indicated that the formulated patches showed uniform drug distribution, good mechanical strength, and satisfactory flexibility.

TDDS of mefenamic acid is an effective and potential approach for pain management, offering improved therapeutic performance and better patient compliance.

REFERENCES

[1] Designing and Characterization of Drug free Patches for Transdermal Application. Bharkatiya M, Nema R, Bhatnagar M. 1, 2010, Vol. 2, pp. 35-39.

[2] Design and evalution of matrix type of transdermal patches of methotrexate. Balaji P, Thirumal M, Gowri R, Divya V, Ramaswamy V. 2012, Vol. 2, pp. 464-471.

[3] Percutaneous penetration enhancers: Local versus transdermal activity. Asbill CS, Michniak BB,. 2000, Vol. 3, pp. 36-41.

[4] Transdermal drug delivery system: Review. Lallit Samant, Anusha Bhaskar. 2, 2012, Vol. 5, p. 2012.

[5] Transdermal drug delivery system: A comprehensive review of innovative strategies, applications, and regulatory perspectives. Andrea Crasta, Tanvi Painginkar, Amatha Sreedevi, Sachin Dattram Pawar, Muddukrishna Badamane Sathyanarayana. july 2025, Vol. 24, p. 100245.

[6] Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review. A. Herman, A.P. Herman. 4, 2015, J. Pharm. Pharmacol, Vol. 67, pp. 473-485.

[7] Transdermal drug delivery In vitro using diffusion cells. L. Bartosova, J. Bajgar. 7, 2012, Vol. 19, pp. 4671-4677.

[8] Transdermal Drug Delivery System (Patch, Application in Present Scenario). Sandhu P., Bilandi A., Kataria S., Middha A.,. 4, 2011, Vol. 1, pp. 1139-1151.

[9] Transdermal Drug delivery system: An Overview. Niroj Shrestha, Nagasamy Venkates D. 2, 2012, Vol. 3.

[10] Recent Advances in Transdermal Drug Delivery System. Debjit Bhowmilk, Chiranjib, Marget Chandira. 1, 2010, Vol. 2, pp. 68-77.

[11] Blooming Pharma Industry with Transdermal Drug Delivery System. Sharma N., Parashar B., Mahajan U. 3, 2012, Vol. 2, pp. 262-278.

[12] Design and evaluation of transdermal films of atenolol. Bangale GS, Rathinaraj BS, Rajesh KS, Shinde GV, Umallkar DG, Rajveer CH. 2010, Vol. 2, pp. 593-604.

[13] Design and evalution of transdermal drug delivery of ketotifen fumarate. Shivaraj A, Selvaam RP Mani TT, Sivakumar T. 2010, Vol. 1, pp. 42-7.

[14] Formulation and Evalution of Transdermal Patches of Pantoprazole sodium. M.R. Shivalingam, Arul Balasubramanian, Kothai Ramalingam. 5, 2021, Vol. 13.
[15] Transdermal drug delivery system-design and evaluation. Keleb E, Sharma RK, Mosa EB, Aljahwi A-Az. 2010, Vol. 1, pp. 42-7.
[16] Formulations and evalution of transdermal films for the treatment of overactive bladder. Pandit V, Khanum A, Bhaskaran S, Banu V. 2009, Vol. 1, pp. 799-804.
[17] Crystallization inhibition of mefenamic acid for transdermal patches: Preliminary study. Suksaeree J., Siripornpinyo P., Chaiprasit S., Pichayakorn W. 2017, Thai J Pharm Sci, Vol. 41, pp. 49–52.
[18] Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol. Guyot M., Fawaz F. (1-2), 200, International Journal of Pharmaceutics, Vol. 204, pp. 171–182.
[19] Modeling and comparison of dissolution profiles. Costa P., Sousa Lobo J. 12, 2001, European Journal of Pharmaceutical Sciences., Vol. 13.
[20] Design, formulation and in vitro drug release from transdermal patches containing imipramine hydrochloride as model drug. Hadiniyan S, Kumar K, Nandy BC, Saxena R. 2017, Vol. 9, pp. 220-225.
[21] Formulation development, in vitro and in vivo evaluation of membrane controlled transdermal systems of glibenclamide. Mutalik S, Udupa N. 2005, Vol. 8, pp. 26-38.