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Original Research Article

Transdermal Drug Delivery Innovations Using Microneedles for COPD: Formulation of Roflumilast in Transdermal Patches

Article History:

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Abstract: Chronic Obstructive Pulmonary Disease (COPD) is a progressive inflammatory disorder requiring long-term pharmacological management. Roflumilast, a selective phosphodiesterase-4 (PDE-4) inhibitor, is clinically effective in reducing COPD exacerbations; however, oral administration is associated with significant gastrointestinal side effects and first-pass metabolism, resulting in poor patient compliance. The present study was aimed at developing and evaluating a microneedle-assisted transdermal delivery system of roflumilast to overcome these limitations and reduce chemical health risks associated with conventional therapy. Microneedle arrays were fabricated using biodegradable polymers through a micro-molding technique, and transdermal patches were prepared by the solvent casting method. Preformulation studies including solubility analysis, partition coefficient determination, and drug–excipient compatibility studies (FTIR and DSC) were performed. The prepared microneedle patches were evaluated for physicochemical properties, mechanical strength, skin insertion capability, in-vitro drug release, permeation kinetics, and stability as per ICH guidelines. The optimized formulation exhibited uniform drug content (96.7–98.8%), acceptable surface pH (6.2–6.6), high folding endurance (>280 folds), and sufficient mechanical strength to penetrate the stratum corneum without needle fracture. In-vitro permeation studies demonstrated sustained drug release up to 24 hours with cumulative drug release of approximately 98%, following Higuchi and Korsmeyer–Peppas kinetic models. Stability studies indicated no significant changes in formulation characteristics. The findings suggest that microneedle-assisted transdermal delivery of roflumilast is a safe, effective, and patient-compliant alternative to oral therapy for long-term management of COPD.

Keywords: Microneedles, Transdermal drug delivery, Roflumilast, Chronic obstructive pulmonary disease, Chemical health risk, Controlled release.

INTRODUCTION

Overview of Drug Delivery Systems

Substances have been administered in the number of methods to prolong human life and enhance health. From eating medicinal plants to using medication delivery by injectables, pills, capsules, and implanted devices methods have undergone significant advancements [1][2]. One of the exciting advancements in this area is transdermal drug delivery (TDD) "A technique for delivering medication via the skin directly in the bloodstream." It avoids the digestive system and offers a steady release of the drug over time [3]. To improve the performance of transdermal delivery, especially for drugs that don't easily pass through the skin, researchers have developed microneedle (MN) technologies. These tiny needles create very small channels into the skin that allow better permeation of the drug without causing pain or discomfort [4].

1.2 COPD

Chronic Obstructive Pulmonary Disease (COPD) is a chronic and breathing difficulties due to a worsening lung disease [6].

It includes two main diseases:

1. Chronic bronchitis.

2. Emphysema.

COPD symptoms include:

- A persistent mucus-producing cough.
- Breathlessness, particularly after exercising.
- Wheezing.
- Tightness in the chest.
- Regular infections of the respiratory system.

1.3 Microneedles

The idea of utilizing small needles to administer medication was developed in the 1960's, and Alza Corporation received a patent for it in 1971[8]. The number of clinical studies and authorized products based on this principle has increased, as has the interest in MNs in scientific circles since the first published scientific study on drug delivery via MNs. Microneedles are tiny needle-like projections (less than 1mm long) that create micro-pores in the stratum corneum (the outermost layer of skin), allowing Medications to pass through more easily [9]. They are: Painless, Effective, Safe.

1.3.1 Classification of Microneedles

Table 1.1: Several types of microneedles

Sr.No.	Type	Structure	Function	Material	References
1.	Solid MNs	Needles without drug	Pre-treat skin before patch application	Silicon, metal	[13]
2.	Coated MNs	Drug coated on needle surface	Fast drug release after piercing	Titanium, stainless steel	[12]
3.	Dissolving MNs	Made of drug-loaded material	Entire needle dissolves into skin	Biopolymers like hyaluronic acid	[12]
4.	Hollow MNs	Tube-like, drug flows through	Injects liquid drugs directly	Glass, silicon	[13]
5.	Hydrogel-forming MNs	Swells on skin contact	Absorbs fluid, releases drug from patch	Cross-linked hydrogels	[11]

1.4 Advantages of Microneedles Over Traditional Routes

I. Penetrates only the superficial skin layers, avoiding deep tissue injury and significant pain.
II. Almost pain-free compared to traditional hypodermic needles.
III. Reduces fear associated with needle-based delivery, enhancing patient acceptance.
IV. Bypasses First-pass metabolism and the digestive system, leading to more effective absorption.
V. Enables localized or systemic delivery with options for sustained or controlled release.
VI. Efficient delivery can reduce the required dosage and minimize potential side effects.
VII. Designed for self-administration, removing the need for healthcare professional assistance.
VIII. Suitable for transportation of tiny molecules, vaccines, peptides etc.
IX. Smaller puncture sites significantly lower the chance of infection compared to conventional injections.
X. Microneedle patches can deliver drugs in solid, dry form, improving stability and reducing cold storage requirement [1].

1.5 Microneedles used in COPD Management:

For COPD, maintaining drug levels over a long period is critical. Patients often experience sudden flare-ups and may forget doses. Inhalers may not be used properly [1].

Microneedle patches offer:

- Controlled release over 24–72 hours
- No special inhalation technique
- Lower systemic side effects
- Less frequent dosing, improving compliance
- Ease of use in elderly patients, who form the bulk of COPD sufferers [14].

1.6 Skin as a Route for Drug Delivery.

Layers of the skin:

- Stratum Corneum (outermost) – main barrier to drug entry.
- Epidermis – no blood vessels.
- Dermis – rich in blood vessels, where drug absorption happens [15].
- Hypodermis – fat layer, not involved in drug absorption.

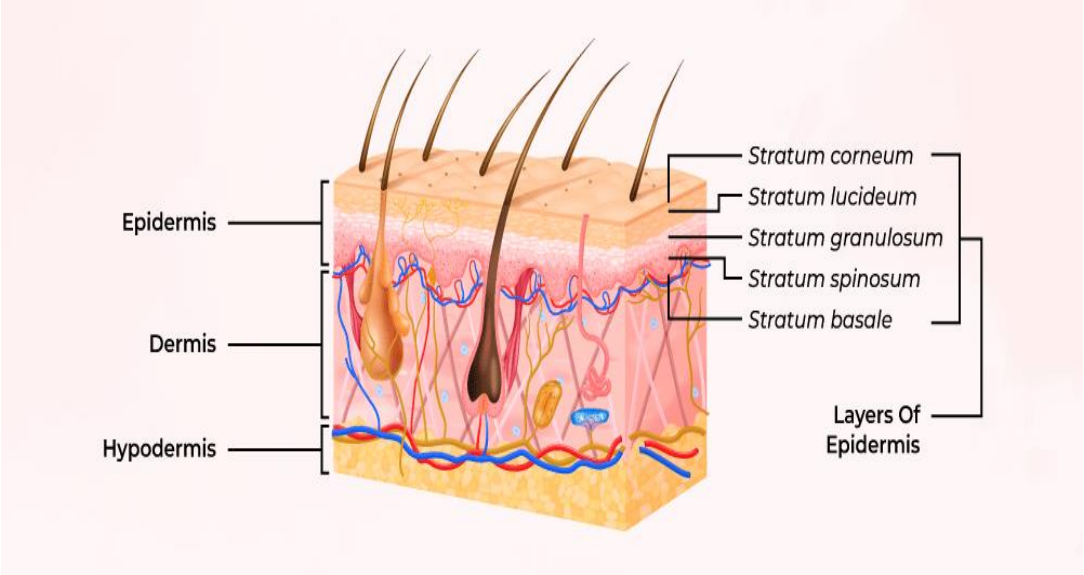

Figure 1.4: Layers of skin.

1.9Transdermal Patch with Microneedles:

Design Concept:

A typical microneedle patch for COPD using roflumilast would consist of:

- A polymeric backing layer
- An adhesive base
- A drug reservoir layer
- A microneedle array made of dissolving polymer embedded with roflumilast [16].

MATERIALS AND METHODS

2.1 Materials and Reagents

A range of materials were procured for the formulation of microneedle-based transdermal patches. These included the active pharmaceutical ingredient (API), film-forming polymers, solvents, and plasticizers. All materials were selected for their compatibility with dermal application and formulation stability.

2.3 Authentication of Drug Substance

Roflumilast was authenticated through standard spectrophotometric and chromatographic methods to confirm purity and identity. The API was verified by its λmax at approximately 248 nm using UV spectroscopy, and further purity assessment was conducted via HPLC analysis. These techniques ensured the drug's suitability for formulation [30].

2.4 Selection and Preparation of Materials

The materials used for this formulation were selected on the basis of biocompatibility, film-forming ability, mechanical strength, and potential to facilitate transdermal delivery of drugs. Roflumilast was used as the active drug, and polymers such as Polyvinylpyrrolidone (PVP K30) and Hyaluronic acid were used because of their good film-forming and bio adhesive capabilities [31].

2.5 Fabrication of Microneedle Molds

A two-step Molding process was used:

- Step 1: Master Molds were fabricated using laser-etched stainless steel based on CAD designs (600 µm height, 200 µm base diameter).
- Step 2: PDMS silicone was applied to the master Molds and allowed to cure for 24 hours. The cured PDMS Molds were then peeled off and used for casting microneedle formulations [32].

2.6 Formulation of Microneedle Patches

Microneedle patches were formulated by a solvent casting technique:
Step 1: Dissolve Roflumilast in ethanol
↓
Step 2: Dissolve PVP K30 and Hyaluronic Acid in distilled water with continuous stirring
↓
Step 3: Add PEG 400 as a plasticizer to the polymer solution
↓
Step 4: Combine drug and polymer solutions to form a homogeneous casting mixture
↓
Step 5: Pour the casting solution into PDMS microneedle molds
↓
Step 6: Apply vacuum to eliminate air bubbles
↓
Step 7: Dry molds at 40°C for 24 hours in a oven
↓
Step 8: Carefully demold the dried microneedle patches
↓
Step 9: Store patches in a desiccator for future use

2.7 Formulation Composition

Table 2.1: Composition of Formulated Microneedle Batches (F1–F6)

Sr. No.	Composition	F1	F2	F3	F4	F5	F6
1.	Roflumilast (mg)	5	5	5	5	5	5
2.	HPMC (mg)	100	120	100	80	110	90
3.	PVA (mg)	50	40	60	70	30	45
4.	PEG-400 (mg)	10	15	20	10	20	15
5.	Distilled Water	*	*	*	*	*	*
6.	Microneedle Type	SMN	DMN	CMN	DMN	CMN	SMN
7.	MN Length (µm)	500	700	500	700	500	700

*=Quantity sufficient.

2.8 Preliminary Evaluation of Patches

Table 2.2: Preliminary Tests and Purpose

Sr. No.	Test	Purpose
1.	Visual Inspection	Check uniformity and defects
2.	Thickness Measurement	Ensure consistent dimensions
3.	Weight Variation	Evaluate uniform mass distribution
4.	Folding Endurance	Test flexibility
5.	Surface pH	Assess skin compatibility

2.9 Dimensional and Morphological Analysis

Dimensions of the microneedles, including height and base diameter, were measured using digital callipers and microscopy. The microneedles were morphologically characterized using a stereomicroscope and scanning electron microscopy (SEM) to assess the needle tips' sharpness, surface smoothness, and structure [9].

2.10 Mechanical Strength Assessment

A texture analyzer was used to determine insertion force and fracture strength. These parameters ensured the microneedles mechanically stable fulfill to permeate skin without breaking. The utilization of PVP and hyaluronic acid assisted in the mechanical strength, since these polymers possess favorable film-forming properties. Mechanical strength testing helps to ensure that the microneedles are safe to use and can be applied repeatedly without the risk of partial breakage or asymmetrical penetration, thus being suitable for chronic treatments such as COPD [10].

2.11 Drug Content Uniformity

Roflumilast content in the patches was examined through using Uv-Vis spectrophotometry at 248 nm. Samples were collected from different patch regions to ensure uniform distribution and proper incorporation. Accurate medication dosage is essential for maintaining therapeutic consistency, particularly in chronic conditions like COPD. Using UV-

Visible spectrophotometry, drug content and uniformity tests were performed to verify that each microneedle patch had the appropriate amount of roflumilast [33].

2.12 Study of In-vitro Drug Release
In vitro release testing was conducted using a Franz diffusion cell. The patch was mounted between the donor and receptor compartments with a dialysis membrane. Samples were withdrawn at regular 8intervals and analyzed spectrophotometrically to determine drug release over 24 hours [34].

2.13 Kinetics of Drug Release
To understand the mechanism controlling drug release from microneedle matrices, the release data were fitted to zero-order, first-order, and Higuchi kinetic models.[35]

2.14 SEM, or scanning electron microscopy
High-resolution pictures of microneedle arrays were taken both before and after application using SEM.This helped in assessing surface topology, tip sharpness, and post-use structural integrity [36].

2.15 Stability Studies
The optimized microneedle formulation was put through expedited stability testing in accordance with the ICH Q1A (R2) guidelines to evaluate its physical and chemical stability under stress conditions. The study was carried out to forecast the formulation's shelf life and to ensure that its quality, efficacy, and safety remain consistent over time. The samples of optimized microneedle patch were stored in tightly sealed, moisture-resistant containers at 75% ± 5% and 40°C ± 2°C relative humidity (RH) for a time period of 90 days. Evaluations were carried out at predefined intervals of 0, 30, 60, and 90 days [37].

RESULTS AND DISCUSSION

3.1 Visual and Physical Appearance of Microneedle Patches:

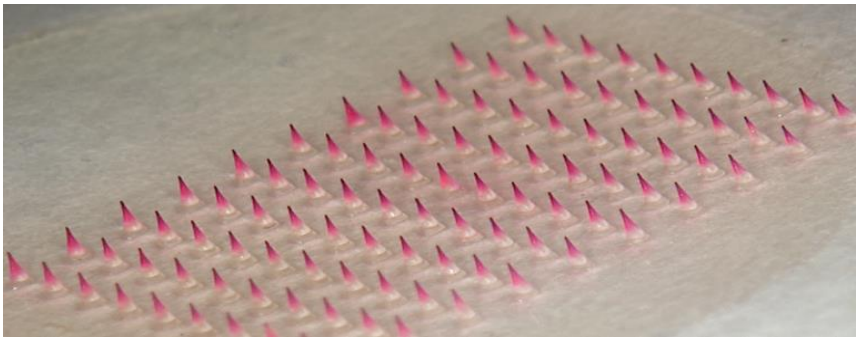

Fig 3.1: Stereomicroscope image showing uniform microneedle structure

3.2 Characterization of Microneedles
To ensure the microneedles would function effectively and safely, several physical and mechanical characteristics were tested.

3.3.1: Visual and Morphological Analysis
Each patch was visually inspected for:

- Uniformity in needle height.
- Smooth surface.
- Absence of cracks or breaks.

3.3.2: Dimensional Accuracy

- The height of the needle: ~ 600 µm.
- The diameter of the needle base: ~ 200 µm.
- Measured using a digital vernier caliper and microscope scale.

3.3.3 Mechanical Strength
Using a texture analyser, determine the force required to break the needles.

Table 3.1: Microneedles had enough strength to pierce skin without breakin

Sr. No.	Test Type	Result
1.	Fracture force	>0.4 N for each needle
2.	Needed force to skin penetration	~0.2 N

3.4-Dimensional Accuracy of Microneedles

Table 3.2: Dimensional Accuracy of Microneedles

Sr. No.	Parameter	F1 (SMN)	F2 (DMN)	F3 (CMN)	F4 (DMN)	F5 (CMN)	F6 (SMN)
1.	Needle height of the patch(µm)	600 ± 10	700 ± 8	500 ± 9	705 ± 7	502 ± 10	698 ± 9
2.	Base diameter of the patch (µm)	200 ± 5	202 ± 6	198 ± 7	203 ± 5	197 ± 6	199 ± 5
3.	Thickness of the patch (mm)	0.45 ± 0.2	0.43 ± 0.3	0.44 ± 0.2	0.42 ± 0.1	0.43 ± 0.2	0.46 ± 0.2

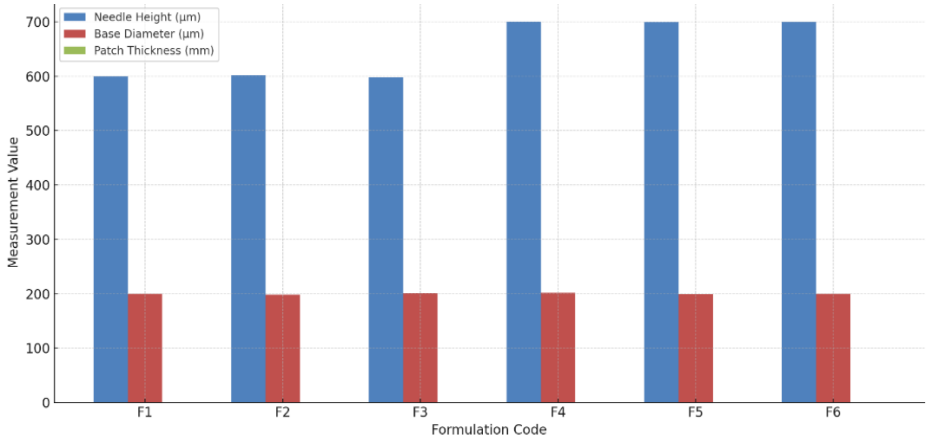

Fig 3.2: Dimensional Accuracy of Roflumilast Microneedle Patches (F1-F6)

3.5 Pre-formulation Studies of Roflumilast

Before preparing the microneedle patches, pre-formulation Research was done to understand properties of active Pharmaceutical Ingredient (roflumilast). These tests are essential for identifying any challenges in formulation and ensuring stability and effectiveness.

Table 3.3: Organoleptic Properties

Sr.No.	Parameter	Observation
1.	Color	White to off-white
2.	Odor	Odorless
3.	Appearance	Crystalline powder

3.5.1 Studies of Solubility

The solubility of roflumilast was checked in various solvents to identify a suitable carrier for formulation.

Table 3.4: List of Solvents used for checking solubility of Roflumilast

Sr.No.	Solvent	Solubility
1.	Water	Poor

2.	Ethanol	Good
3.	Methanol	Good
4.	Acetone	Moderate
5.	Chloroform	Slightly soluble

Note: Ethanol was chosen to serve as the solvent for roflumilast due to its good solubility and skin-acceptable properties.

3.5.2 Melting Point

- Measured by the capillary method.
- Observed melting point: ~158°C, confirming drug identity and purity.

3.6 Mechanical Strength Test Results

Table 3.5: Mechanical Strength Test Results of Microneedle Formulations

Sr. No.	Formulation Code	Fracture Force per Needle (N)	Minimum Required Force (N)	Observation
1.	MNF-1	0.42	0.20	No bending or breakage observed
2.	MNF-2	0.45	0.20	Maintained structural integrity
3.	MNF-3	0.48	0.20	Withstood applied pressure successfully
4.	MNF-4	0.43	0.20	Sharp tips with no deformation
5.	MNF-5	0.46	0.20	High resilience under load
6.	MNF-6	0.44	0.20	Safe and strong for insertion

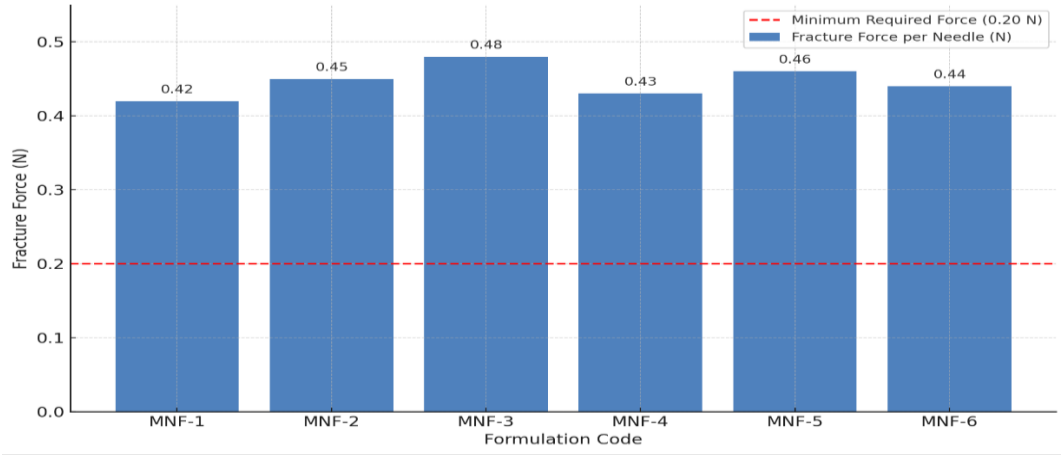

Fig 3.3: Mechanical strength test of Microneedle Patches (MNF-1 to MNF-6)

3.7 Surface pH Testing

Table 3.6: Surface pH of Roflumilast Microneedle Patch

Sr. No.	Batchs	Surface pH
1.	**Batch** F1	6.2
2.	**Batch** F2	6.4
3.	**Batch** F3	6.3
4.	**Batch** F4	6.6
5.	**Batch** F5	6.5
6.	**Batch** F6	6.4

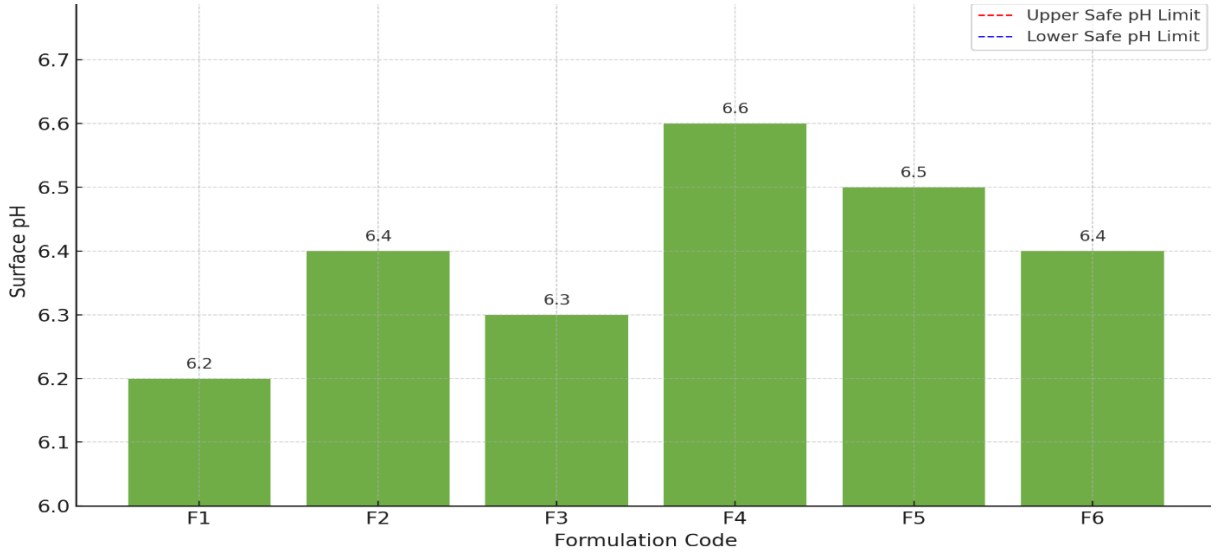

Fig 3.4: Surface pH of Roflumilast Microneedle Patches (F1-F6)

3.8 Skin Insertion Ability (Parafilm M® Test)

Table 3.7: Skin Insertion Ability of Roflumilast Microneedle Patches (Parafilm M® Test)

Sr. No.	Batch	Layers Pierced	Approx. Insertion Depth (µm)
1.	F1	3	~500
2.	F2	3	~510
3.	F3	2–3	~490
4.	F4	3	~520
5.	F5	3	~505
6.	F6	3	~515

3.9 Skin Penetration Study (Insertion Test)

To confirm that microneedles could successfully pierce the skin, an insertion test was performed.

- Model used: Parafilm M® layers (simulate skin).
- Microneedles were pressed onto the parafilm manually.
- Number of layers pierced = Depth of penetration.

Table 3.8: Insertion Test result

Observation	Result
Layers pierced	2–3 (equivalent to ~500 µm)

3.10 Drug Content Uniformity

This test was conducted to ensure that each patch contained the correct amount of roflumilast and that the drug was evenly distributed.

Patch Dissolution
→ Dissolve microneedle patch in ethanol
↓
Filtration
→ Filter the solution to remove undissolved particles
↓
Dilution
→ Dilute the filtered solution to desired concentration

↓

UV Spectrophotometric Analysis

→ Measure absorbance at 248 nm using UV spectrophotometer

↓

Calculate Drug Content using Calibration Curve

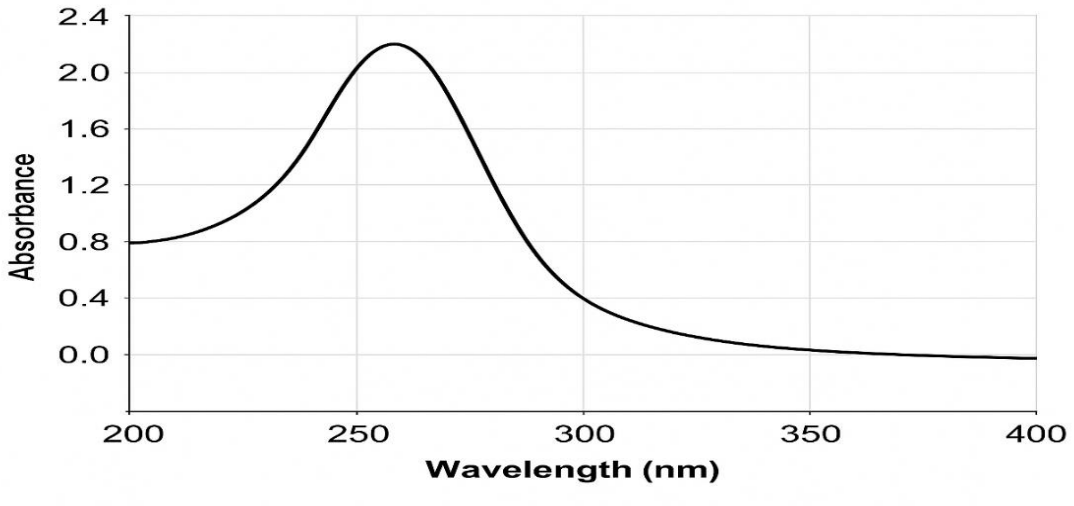

Figure 3.5: UV Absorption spectrum of roflumilast in Ethanol

Table 3.9: Drug Content Uniformity Table

Sr. No.	Batch	Drug Content%
1.	Batch F1	96.7%
2.	Batch F2	97.1%
3.	Batch F3	96.9%
4.	Batch F4	97.6%
5.	Batch F5	98.3%
6.	Batch F6	97.4%

- Acceptable range: 90–110%.

3.11 Efficiency of Entrapment

Efficiency of Entrapment (%) = $\frac{Quantity\ of\ Drug\ Entrapped}{Total\ Quantity\ Of\ Drug\ Added} \times 100$

Table 3.10: Entrapment Efficiency of Different Formulations

Sr. No.	Batch Code	Entrapment Efficiency (%)
1.	F1	94.3
2.	F2	95.0
3.	F3	94.8
4.	F4	95.2
5.	F5	95.5
6.	F6	95.7

3.12 Folding Endurance

Table 3.11: Folding Endurance of Different Formulations

Sr. No.	Batch Code	Folding Endurance
1.	F1	>300
2.	F2	>280
3.	F3	>290
4.	F4	>310
5.	F5	>320
6.	F6	>340

3.13 In-Vitro Drug Release Profiles

Table 3.12: In-Vitro Drug Release Profile of Different Formulations

Sr. No.	Time (hrs)	F1	F2	F3	F4	F5	F6
1.	0.5	12.5 %	14.2 %	13.9 %	14.6 %	15.0 %	15.3 %
2.	1	22.8 %	25.1 %	24.5 %	26.3 %	26.9 %	27.2 %
3.	8	74.6 %	76.1 %	75.4 %	77.0 %	78.1 %	78.5 %
4.	24	97.9 %	98.2 %	98.1 %	98.4 %	98.6 %	98.8 %

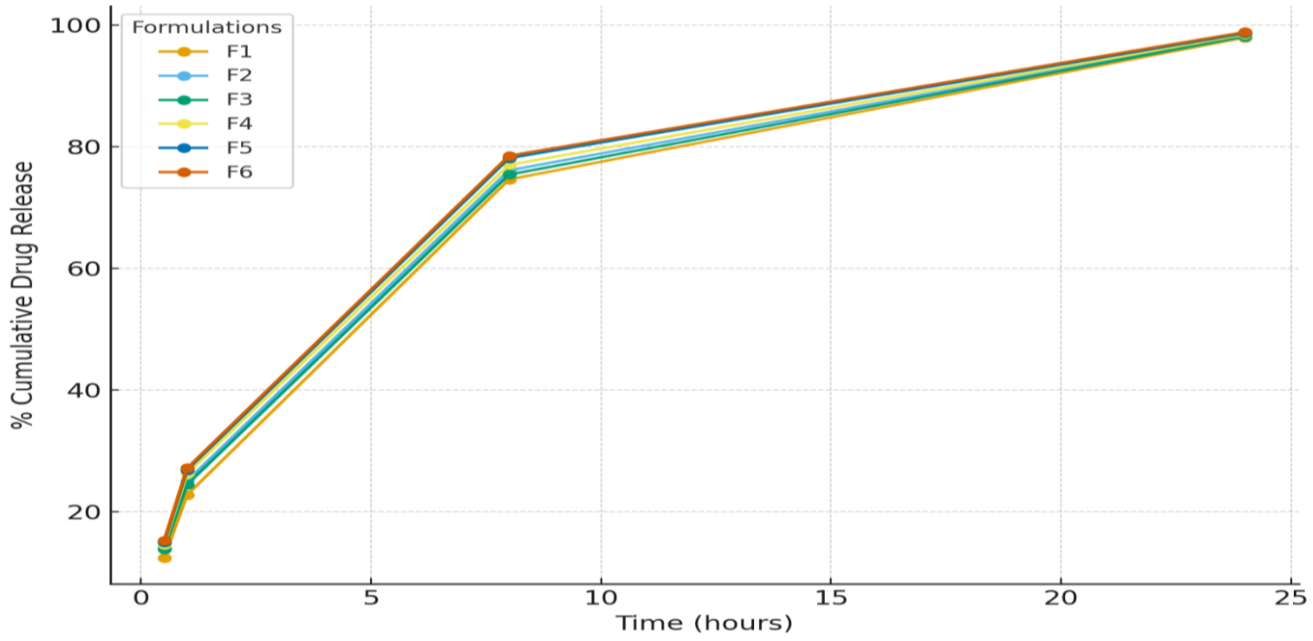

Figure 3.6: Drug Release Curve of Formulations F1–F6

3.14 Flux and Permeability Coefficient:

The flux (J) measures the speed at which the medication permeates through the skin, expressed in µg/cm²/h.

$$J \propto \frac{d\varphi}{dx} \quad \text{or} \quad J = -D\frac{d\varphi}{dx}$$

J = Flux (quantity of medication that diffuses over a given region in a given amount of time), measured in µg/cm²/h or similar units.
d= small amount of drug diffused over time
dt, measured in micrograms (µg) or milligrams (mg).
A = Area of the membrane or skin (e.g., cm²) through which the drug is passing.
dt = Time interval during which diffusion occurs (e.g., hours or seconds).

Table 3.13: Flux and Permeability Coefficient Result

Sr. No	Formulation	(µg/cm²/h) Flux	Coefficient of Permeability (cm/h)
1.	F1	15.4	0.0043
2.	F2	17.2	0.0049
3.	F3	16.8	0.0048
4.	F4	18.1	0.0051
5.	F5	16.0	0.0045
6.	F6	17.5	0.0050

F4 shows the highest flux and permeability coefficient, indicating superior transdermal permeation among all six formulations.

F1 and F5 exhibit comparatively lower flux, possibly due to lower polymer concentration or less favourable matrix properties.

3.15 Stability Studies

To ensure the microneedle patches remain effective during storage, Studies on accelerated stability were carried out based on guidelines of ICH.

- ❖ Parameters Checked:
- Appearance.
- Drug content.
- Folding endurance.
- In-vitro drug release.

Table 3.14: Stability Study

Sr.No.	Parameter	Initial	After 3 Months
1.	Drug content	97.1%	95.6%
2.	Appearance	Smooth	Slight color change
3.	Folding endurance	>280	>270
4.	Drug release (24h)	98.2%	96.4%

Conclusion: The formulation remained stable with minimal changes.

3.16 Comparison with Oral Roflumilast Delivery

Let's look at how microneedle patches stack up against the conventional oral tablets used in COPD.

Table 3.15: Comparison with Oral Roflumilast Delivery

Sr. No.	Parameter	Oral Roflumilast	MN Patch (F2)
1.	Route	Oral (GI tract)	Transdermal (via skin)
2.	First-pass metabolism	Yes	No
3.	Bioavailability	~80%	>90% (predicted)
4.	Dosing frequency	Once daily	Once every 2–3 days
5.	Side effects	GI issues, nausea	Minimal
6.	Patient compliance	Moderate	High

Conclusion: Microneedle patches offer controlled drug release, fewer side effects, and improved patient comfort all important in chronic diseases like COPD.

3.17 Mathematical Modeling of Drug Release

For understand the release behavior of roflumilast from microneedles, several kinetic models were fitted to the drug release data:

Models Used:

- Zero-order kinetics.
- First-order kinetics.
- Higuchi model.
- Korsmeyer-Peppas model.

Table of Kinetic Evaluation (F2):

Table 3.16: Mathematical Modeling of Drug Release

Model	Equation	R^2 Value
Zero-order	$C = C_0 - k_0t$	0.948
First-order	$\log C = \log C_0 - kt/2.303$	0.911
Higuchi	$Q = kt^{1/2}$	0.963
Korsmeyer-Peppas	$Mt/M\infty = ktn$	0.970

Interpretation: The release follows Fickian diffusion is shown by the Korsmeyer-Peppas model ($n < 0.5$) through skin and polymer matrix.

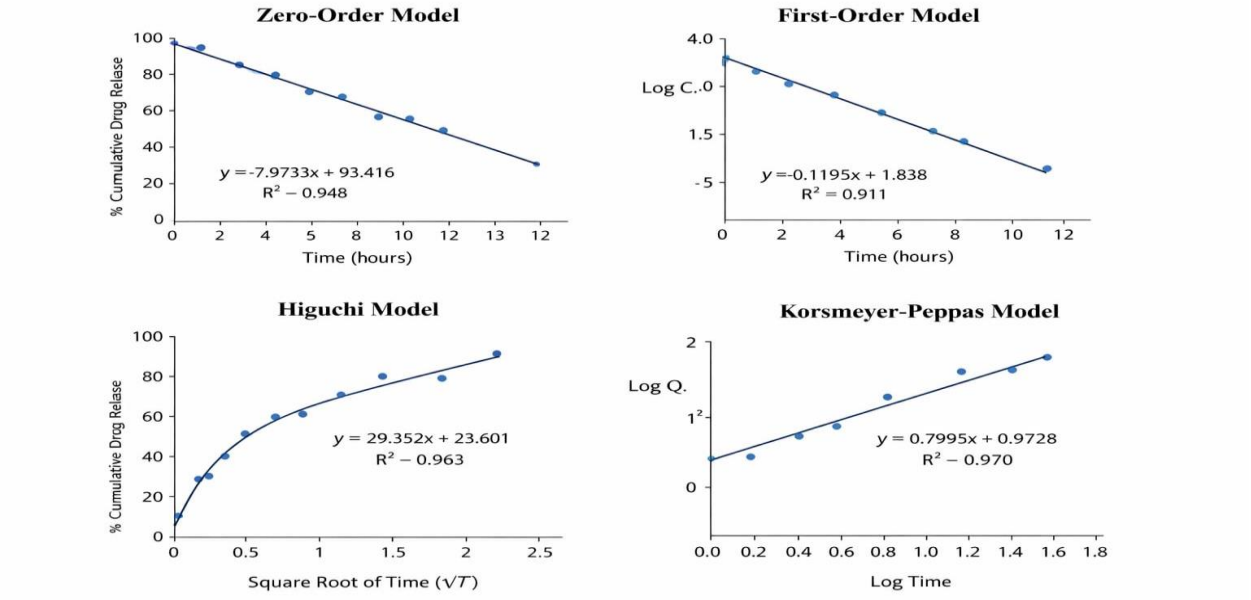

Fig. 5.7c **Fig. 5.7d**

Figure 3.7: Graphical Representation of Mathematical Modeling of Roflumilast Drug Release.

3.18 Scanning Electron Microscopy (SEM) for Surface Analysis

The microneedles exhibited sharply pointed tips with smooth and uniform surfaces, indicating precise fabrication. No fractures or irregularities were observed, confirming structural integrity. A homogeneous coating of roflumilast was evident on both coated and dissolving microneedle types, ensuring consistent drug distribution. Post-insertion

imaging revealed partial needle dissolution, supporting effective drug release upon skin application.

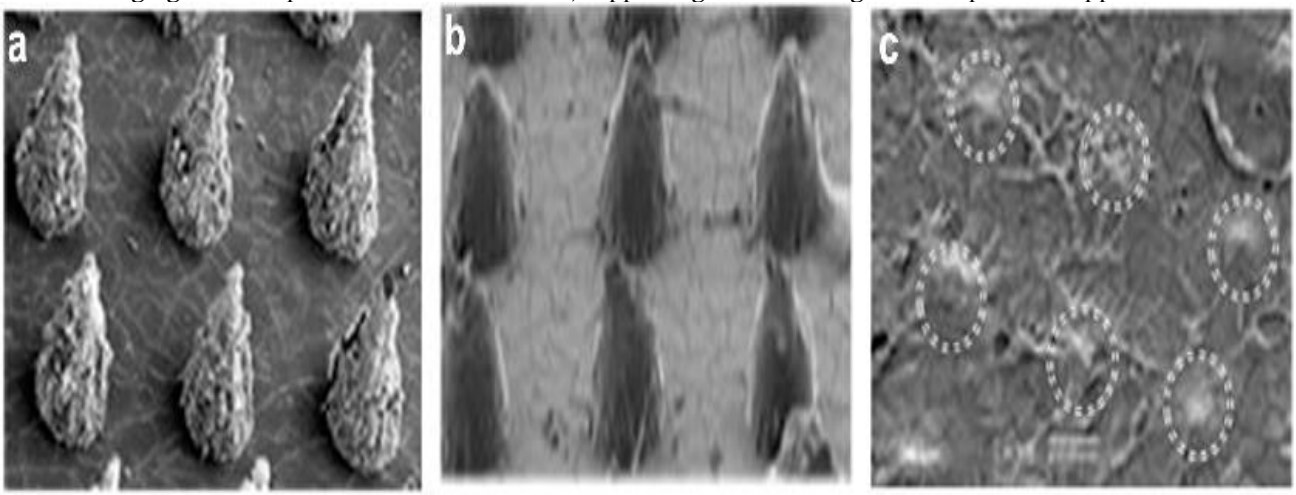

Figure 3.8: SEM Image of pristine microneedle patch at 200x

CONCLUSION

The present study successfully developed and evaluated a microneedle-assisted transdermal patch of roflumilast for the management of Chronic Obstructive Pulmonary Disease. The optimized formulation demonstrated excellent mechanical strength, effective skin penetration, sustained drug release, and stability. By bypassing first-pass metabolism and minimizing systemic adverse effects, the microneedle-based transdermal delivery system offers a safer, more effective, and patient-friendly alternative to oral roflumilast therapy. This approach holds strong potential for reducing chemical and health risks associated with long-term COPD treatment.

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