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Formulation and Evaluation of Transdermal Drug Delivery System

Bobade Rupesh Fulchand, Sanap Siddivinayak Shahadev,
Kadam Suraj Tanaji, Sirsat Divya Parmeshwar, Mr. Munde G. A.
M. Pharm (Pharmaceutical Chemistry)
Aditya Pharmacy College, Beed
Affilated to Dr. Babasaheb Ambedkar Technological University, Lonere

Abstract: *The present study involves the Formulation and Evaluation of Transdermal Drug Delivery System. TDDS is a non-invasive technique that delivers drugs across the skin into systemic circulation, offering advantages such as avoidance of first-pass metabolism, controlled drug release, and improved patient compliance. A generalized transdermal formulation approach was adopted using suitable polymers, permeation enhancers, and solvents.*

Transdermal Drug Delivery System (TDDS) using Ketoprofen as a model drug for effective and controlled systemic delivery. Transdermal drug delivery has emerged as a promising alternative to conventional oral and parenteral routes due to its ability to bypass first-pass metabolism, reduce dosing frequency, and improve patient compliance. Ketoprofen, a non- steroidal anti-inflammatory drug (NSAID), was selected based on its suitable physicochemical properties such as low molecular weight, adequate lipophilicity, and short biological half-life, making it an ideal candidate for transdermal administration. The study focused on developing a generalized TDDS formulation by incorporating the drug into a suitable polymeric system using biocompatible polymers such as Hydroxypropyl Methylcellulose (HPMC), Polyvinylpyrrolidone (PVP), and Carbopol, along with permeation enhancers like Dimethyl Sulfoxide (DMSO) and Propylene Glycol.

Preformulation studies were carried out to evaluate the physicochemical characteristics of the drug, including solubility, partition coefficient, and compatibility with selected excipients using techniques such as Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). These studies confirmed the absence of significant drug–excipient interactions and supported the suitability of the formulation components.

Keywords: Transdermal Drug Delivery System, Ketoprofen, Controlled Release, Permeation Enhancers, Franz Diffusion Cell, Drug Release Kinetics

I. INTRODUCTION

1.1 Overview of Drug Delivery Systems

Drug delivery systems are designed to administer therapeutic agents in a safe, effective, and controlled manner to achieve optimal therapeutic outcomes. Conventional dosage forms such as tablets, capsules, and injections often suffer from limitations including poor bioavailability, fluctuating plasma drug levels, frequent dosing, and systemic side effects.

To overcome these limitations, advanced drug delivery systems have been developed, among which Transdermal Drug Delivery Systems (TDDS) have gained considerable attention due to their non-invasive nature and ability to provide sustained drug release.

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1.2 Transdermal Drug Delivery System (TDDS)

A Transdermal Drug Delivery System is defined as a formulation or device that delivers drugs across the skin into systemic circulation at a controlled rate. The skin acts as a natural barrier; however, with proper formulation strategies, drugs can be made to penetrate through the skin layers and reach the bloodstream.

TDDS provides a continuous and controlled release of drug over an extended period, maintaining consistent plasma drug concentrations and reducing the need for frequent dosing.

1.3 Structure and Function of Skin

The skin is the largest organ of the human body and plays a vital role in protecting internal organs from external environmental factors. It consists of three primary layers:

1.3.1 Epidermis

The outermost layer, mainly responsible for barrier function. The stratum corneum, the topmost part of the epidermis, is the principal barrier to drug penetration.

1.3.2 Dermis

Located beneath the epidermis, it contains blood vessels, nerves, and connective tissue. Once the drug reaches this layer, it can be absorbed into systemic circulation.

1.3.3 Hypodermis

The innermost layer composed mainly of fat and connective tissue, providing insulation and support.

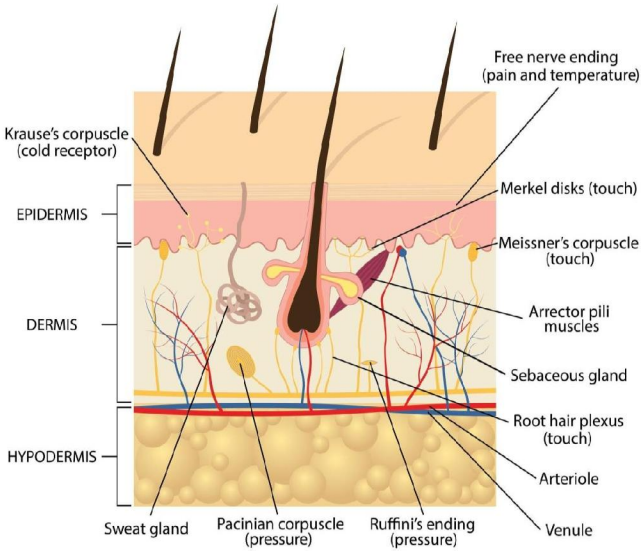

Fig. 1: Structure of Human Skin Showing Epidermis, Dermis, and Hypodermis

1.4 Mechanism of Drug Permeation through Skin

Drugs can permeate through the skin via three main pathways:

- Transcellular Route: Drug passes through the cells
- Intercellular Route: Drug diffuses between cells
- Appendageal Route: Through sweat glands and hair follicles

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Among these, the intercellular route is the most common pathway for drug transport.

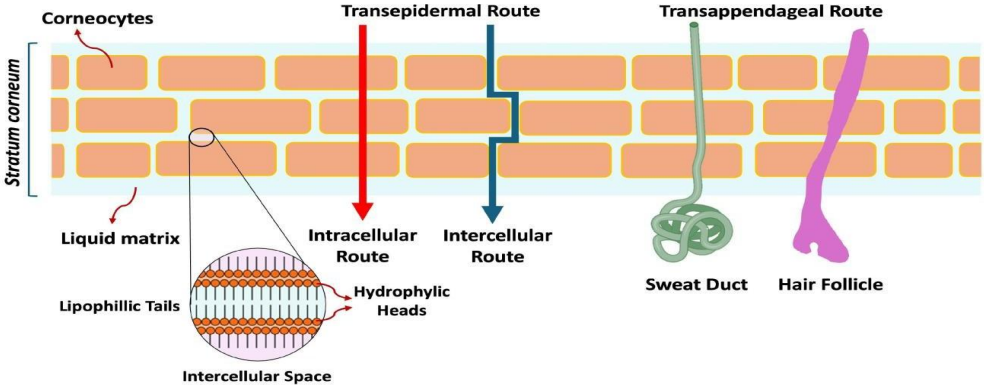

Fig. 2: Pathways of Drug Permeation through the Skin

1.5 Advantages of TDDS

Transdermal drug delivery offers several advantages over conventional routes:

- Avoids first-pass hepatic metabolism
- Provides controlled and sustained drug release
- Reduces dosing frequency
- Improves patient compliance
- Minimizes gastrointestinal side effects
- Non-invasive and painless administration
- Easy termination of therapy by removing formulation

1.6 Limitations of TDDS

Despite its advantages, TDDS has certain limitations:

- Only drugs with suitable physicochemical properties can be used
- Limited permeability due to the stratum corneum barrier
- Possibility of skin irritation or sensitization

1.7 Factors Affecting Transdermal Drug Delivery

1.7.1 Physicochemical Properties of Drug

- Molecular weight (<500 Da preferred)
- Lipophilicity (Log P between 1–4)
- Solubility
- Melting point

1.7.2 Skin Conditions

- Hydration level
- Thickness of stratum corneum
- Age and physiological conditions

1.7.3 Formulation Factors

- Type of polymer
- Use of permeation enhancers
- Vehicle composition

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1.8 Components of Transdermal Drug Delivery Systems

A general TDDS formulation includes:

- Drug (API): Active therapeutic agent
- Polymer Matrix: Controls drug release
- Permeation Enhancer: Improves skin penetration
- Solvent System: Facilitates drug solubilization
- Stabilizers/Additives: Improve formulation stability

1.9 Role of Polymers in TDDS

Polymers are essential for controlling drug release and maintaining formulation integrity. Common polymers include:

- Hydroxypropyl Methylcellulose (HPMC)
- Polyvinylpyrrolidone (PVP)
- Carbopol They help in:
- Sustained drug release
- Film or gel formation
- Stability enhancement

1.10 Permeation Enhancers

Permeation enhancers are substances that temporarily reduce the barrier resistance of the skin, allowing drugs to penetrate more easily.

Examples:

- Dimethyl Sulfoxide (DMSO)
- Propylene Glycol
- Oleic Acid Mechanism:
- Disrupt lipid structure of stratum corneum
- Increase drug solubility and partitioning

1.11 Ideal Characteristics of Drugs for TDDS

An ideal drug candidate for transdermal delivery should have:

- Low molecular weight
- Adequate lipophilicity
- Short half-life
- High potency
- Non-irritating nature
- Good skin permeability

1.12 Selection of Model Drug: Ketoprofen

Ketoprofen, a non-steroidal anti-inflammatory drug (NSAID), was selected as the model drug due to:

- Suitable molecular weight (~254 Da)
- Adequate lipophilicity
- Short half-life (2–3 hours)
- Effective analgesic and anti-inflammatory action

These properties make it a suitable candidate for transdermal delivery.

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1.13 Applications of TDDS

- Pain management (NSAIDs, opioids)
- Hormone replacement therapy
- Cardiovascular drugs
- Smoking cessation therapy
- Neurological disorders

II. LITERATURE REVIEW

2.1 Introduction

The development of advanced drug delivery systems, particularly transdermal drug delivery systems (TDDS), has gained significant momentum over recent decades. Pain management remains a crucial area where these systems can offer enhanced therapeutic outcomes. A thorough understanding of existing research is essential for the rational design of effective and safe transdermal patches. This chapter reviews key literature on the fundamental principles, materials, formulation techniques, and commercial applications of TDDS for pain relief.

2.2 Structure and Barrier Function of Skin

The skin acts as a protective barrier against external agents. The outermost layer, the stratum corneum, is composed of keratinized cells embedded in a lipid matrix, often described as a "brick and mortar" structure.

This layer significantly limits drug penetration, making it the primary challenge in transdermal drug delivery.

- Blank et al. (1984) described the stratum corneum as the principal barrier to drug permeation due to its highly organized lipid structure.
- Elias (1983) proposed the "brick and mortar model," where corneocytes act as bricks and lipids act as mortar, restricting drug penetration.
- Barry (2001) emphasized that the barrier property of skin is the main limitation in transdermal drug delivery.

2.3 Mechanism of Transdermal Drug Permeation

Drug permeation across the skin follows passive diffusion, governed by concentration gradient. Pathways:

- Transcellular
- Intercellular
- Appendageal

The permeation process is described by Fick's Law of Diffusion, where the rate depends on drug concentration, diffusion coefficient, and membrane thickness.

- Fick (1855) established the law of diffusion, which explains the rate of drug permeation across membranes.
- Scheuplein (1965) demonstrated that drug permeation through skin occurs mainly via passive diffusion.
- Potts and Guy (1992) developed a model correlating drug permeability with molecular weight and lipophilicity.

2.4 Types of Transdermal Drug Delivery Systems

TDDS can be classified into:

2.4.1 Conventional Systems

- Matrix systems
- Reservoir systems
- Adhesive systems

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2.4.2 Semi-solid Systems

- Gels
- Creams
- Ointments

2.4.3 Advanced Systems

- Microemulsions
- Nanoemulsions
- Liposomes
- Microneedles
- Iontophoresis

Baker and Heller (1988) categorized TDDS into matrix and reservoir systems based on drug release mechanisms.
Chien (1992) explained the design and classification of controlled transdermal therapeutic systems.
Prausnitz and Langer (2008) discussed advanced TDDS including microneedles and iontophoresis.

2.5 Role of Polymers in TDDS

Polymers play a critical role in:

- Controlling drug release
- Providing structural integrity
- Enhancing stability Common Polymers:
- HPMC
- PVP
- Carbopol

Hydrophilic polymers promote faster drug release, while hydrophobic polymers provide sustained release.
Williams and Barry (2004) described permeation enhancers as agents that temporarily reduce the barrier resistance of the skin.
Barry (1987) reported that DMSO disrupts lipid structure and enhances drug penetration.
Guy and Hadgraft (2003) emphasized the role of enhancers in improving drug flux across the skin.

2.6 Permeation Enhancers

Permeation enhancers improve drug penetration by:

- Disrupting lipid structure of stratum corneum
- Increasing drug solubility
- Enhancing partitioning into skin Examples:
- DMSO
- Propylene glycol
- Oleic acid

2.7 Factors Affecting Transdermal Drug Delivery

Drug-related factors

- Molecular weight
- Lipophilicity
- Solubility Formulation-related factors
- Polymer type
- Enhancer concentration
- Vehicle composition Physiological factors

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• Skin hydration
• Age
• Skin thickness

2.8 Previous Research Studies on TDDS

Several studies have demonstrated the effectiveness of TDDS:
• Studies on NSAIDs showed improved permeation and reduced gastrointestinal side effects
• Polymer combinations like HPMC and PVP provided controlled drug release
• Use of enhancers significantly increased drug flux across the skin
Jain and Tiwary (2007) formulated transdermal systems and reported improved drug release and patient compliance.

2.9 Studies on Ketoprofen in TDDS

Ketoprofen has been widely studied for transdermal delivery due to:
• Suitable molecular weight
• Lipophilicity
• Anti-inflammatory activity Research findings:
• Enhanced permeation using DMSO
• Sustained release using polymeric systems
• Improved bioavailability compared to oral route

2.10 Recent Advances in TDDS

Modern TDDS technologies include:
• Microneedle systems
• Iontophoresis
• Sonophoresis
• Nanocarriers
These systems improve drug delivery by overcoming skin barrier limitations.

III. AIM AND OBJECTIVES

3.1 Aim

To formulate and evaluate a Transdermal Drug Delivery System (TDDS) using Ketoprofen as a model drug, with the objective of achieving controlled drug release, enhanced skin permeation, and improved therapeutic efficacy.

3.2 Objectives

1. To study the fundamental principles and mechanisms involved in transdermal drug delivery systems
2. To select a suitable model drug (Ketoprofen) based on its physicochemical and pharmacological properties
3. To carry out preformulation studies including solubility, partition coefficient, and drug–excipient compatibility
4. To select appropriate polymers and excipients for the formulation of TDDS
5. To develop a general transdermal formulation using suitable methods
6. To incorporate permeation enhancers to improve drug penetration through the skin.
7. To evaluate the prepared formulation for physicochemical parameters such as appearance, pH, viscosity, and homogeneity.
8. To determine drug content uniformity of the formulation.
9. To perform in-vitro drug release studies using Franz diffusion cell.
10. To study drug permeation behavior across a suitable membrane.
11. To analyze the drug release kinetics using mathematical models.

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12. To conduct stability studies as per ICH guidelines.

IV. MATERIALS AND METHODS

4.1 Materials

4.1.1 Drug

• Ketoprofen (Model drug for transdermal delivery)

4.1.2 Polymers

• Hydroxypropyl Methylcellulose (HPMC)
• Polyvinylpyrrolidone (PVP K30)
• Carbopol 934

4.1.3 Permeation Enhancers

• Dimethyl Sulfoxide (DMSO)
• Propylene Glycol (PG)

4.1.4 Solvents and Other Chemicals

• Ethanol
• Methanol
• Distilled Water
• Triethanolamine (for neutralization)

4.1.5 Biological Membrane

• Egg membrane
• Cellophane membrane (for in-vitro diffusion)

4.1.6 List of Materials (Table)

Material	Category	Function
Ketoprofen	Drug	Analgesic
HPMC	Polymer	Controlled release
PVP	Polymer	Solubility enhancer
Carbopol	Polymer	Gel formation
DMSO	Enhancer	Increases permeability
Propylene glycol	Enhancer	Improves diffusion
Ethanol	Solvent	Drug dissolution

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4.2 Instruments and Equipment

Instrument	Use
Digital Balance	Accurate weighing
Magnetic Stirrer	Mixing
pH Meter	pH measurement
UV Spectrophotometer	Drug analysis
Franz Diffusion Cell	In-vitro permeation
Viscometer	Viscosity measurement

4.3 Methodology Overview

The study involved:

1. Preformulation studies
2. Formulation of TDDS
3. Evaluation of prepared system
4. Drug release and permeation studies

4.4 Preparation of Transdermal Drug Delivery System

General Procedure

1. Drug Solubilization
o Ketoprofen weighed accurately
o Dissolved in ethanol or methanol
2. Polymer Preparation
o HPMC / PVP / Carbopol dispersed in distilled water
o Allowed to swell for 1–2 hours
3. Incorporation of Drug
o Drug solution added to polymer mixture
o Stirred continuously
4. Addition of Enhancers
o DMSO and Propylene Glycol added
o Mixed uniformly
5. Neutralization (if Carbopol used)
o Triethanolamine added dropwise
o Gel formation occurs
6. Homogenization
o Mixture stirred to obtain uniform formulation
7. Storage
o Stored in airtight container

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4.5 Formulation Design

Formulation Table

Formulation Code	Polymer Ratio (HPMC:PVP)	Enhancer
F1	1:1	—
F2	2:1	DMSO
F3	1:2	PG
F4	1:1	DMSO + PG

Flowchart of TDDS Preparation

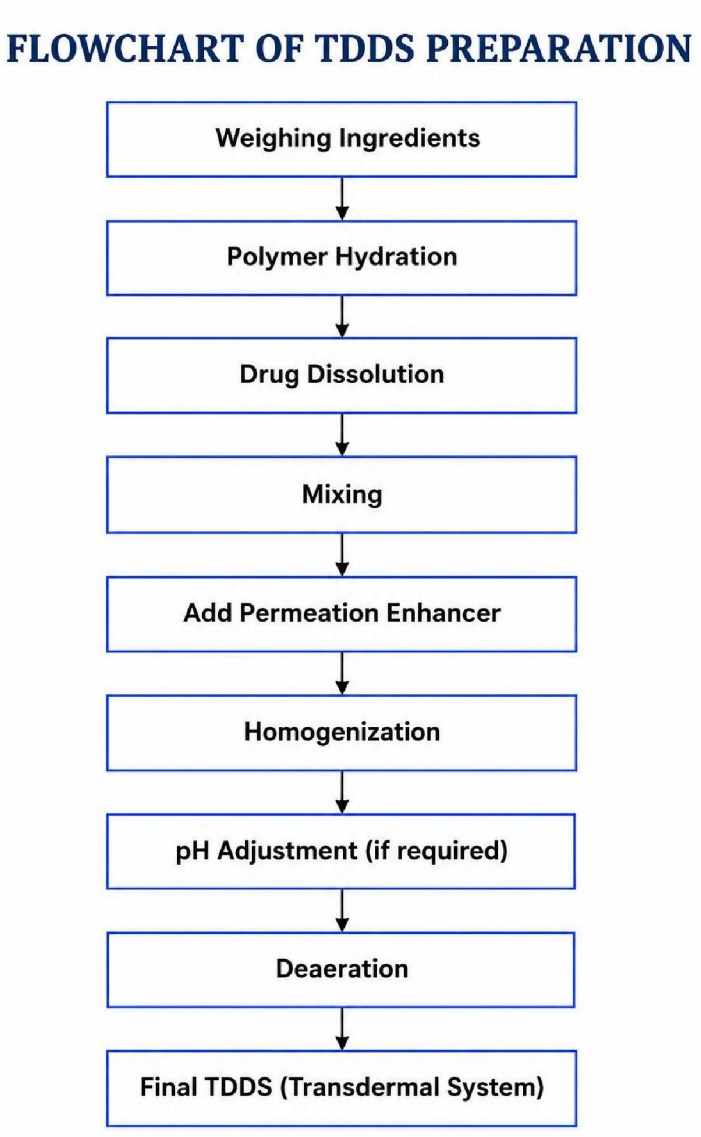

Fig. 3: Flowchart of TDDS Preparation

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4.6 Preformulation Studies
• Organoleptic Properties
• Solubility Study
• Partition Coefficient
• FTIR Study
• DSC Study

4.7 Evaluation of TDDS
4.7.1 Physical Evaluation
• Appearance
• Homogeneity
• pH

4.7.2 Viscosity Measurement
• Measured using Brookfield viscometer

4.7.3 Spreadability
• Evaluated using glass slide method

4.7.4 Drug Content Uniformity
• Sample dissolved in solvent
• Analyzed using UV spectrophotometer

4.7.5 In-vitro Diffusion Study Procedure:
• Franz diffusion cell used
• Membrane mounted between compartments
• Receptor medium: phosphate buffer pH 7.4
• Samples withdrawn at intervals

4.7.6 Drug Release Kinetics
• Zero-order
• First-order
• Higuchi model
• Korsmeyer-Peppas model

4.7.7 Skin Irritation Study
• Applied on animal skin
• Observed for redness or irritation

4.8 Stability Studies Conditions:
• 40°C ± 2°C
• 75% RH ± 5%
Duration:
• 3 months

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Parameters:
• Appearance
• Drug content
• pH
• Drug release

V. PREFORMULATION STUDIES

5.1 Introduction

Preformulation studies are the initial step in the development of any pharmaceutical dosage form. These studies provide essential information about the physicochemical properties of the drug and its compatibility with excipients.
In the present study, preformulation parameters of Ketoprofen were evaluated to ensure suitability for transdermal drug delivery.

5.2 Organoleptic Properties

Property	Observation	Inference
Appearance	White crystalline powder	Acceptable
Odor	Odorless	Non-irritating
Taste	Bitter	Typical NSAID

5.3 Solubility Studies

Objective

To determine solubility of Ketoprofen in different solvents.

Solvent	Solubility	Observation
Distilled Water	Slightly soluble	Poor aqueous solubility
Methanol	Freely soluble	Suitable solvent
Ethanol	Freely soluble	Preferred solvent
Chloroform	Soluble	Good solubility

Conclusion

Ketoprofen shows better solubility in organic solvents, supporting its use in transdermal formulations.

5.4 Partition Coefficient (Log P) Method

Shake flask method using:
• n-octanol
• Phosphate buffer (pH 7.4)

Result
• Log P ≈ 3.1 Interpretation
Indicates good lipophilicity Suitable for transdermal delivery

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5.5 FTIR Spectral Analysis

Objective

To check drug–excipient compatibility.

Observed Peaks

Functional Group	Standard (cm^{-1})	Observed (cm^{-1})
O–H Stretch	~3300	3295
C=O Stretch	~1700	1698
Aromatic C=C	~1600	1602

Conclusion

No significant shift observed → No interaction between drug and excipients

5.6 Differential Scanning Calorimetry (DSC)

Observation

• Sharp endothermic peak at ~94–97°C (melting point of Ketoprofen)

Conclusion

• No change in peak → Drug remains stable

• Confirms compatibility

5.7 Moisture Content and Uptake

Formulation	Moisture Content (%)	Moisture Uptake (%)
F1	3.1	4.5
F2	2.8	4.2
F3	3.0	4.6
F4	2.6	4.0

Conclusion

• Low moisture content ensures stability

• Moderate uptake indicates good environmental resistance

5.8 Drug Content Uniformity

Formulation	Drug Content (%)
F1	97.2
F2	98.5
F3	99.1

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F4	98.7

Conclusion

All formulations fall within acceptable range (95–105%)

5.9 Thickness / Consistency

Formulation	Observation
F1	Smooth
F2	Slightly viscous
F3	Uniform
F4	Optimal consistency

5.10 pH Measurement

Formulation	pH
F1	6.5
F2	6.6
F3	6.7
F4	6.8

Conclusion

pH is within skin-compatible range → No irritation expected

VI. FORMULATION DEVELOPMENT

Formulation development is a critical step in designing an effective Transdermal Drug Delivery System (TDDS). It involves the selection of suitable polymers, permeation enhancers, and formulation techniques to achieve controlled drug release and optimal skin permeation.

In this study, Ketoprofen was incorporated into a generalized transdermal system using different polymer combinations and permeation enhancers.

6.1 Rationale for Drug Selection

Ketoprofen was selected as the model drug due to the following reasons:

- Low molecular weight (~254 Da) → suitable for skin permeation
- Adequate lipophilicity (Log P ≈ 3.1)
- Short half-life (2 – 3 hours) → requires sustained delivery
- Strong analgesic and anti-inflammatory activity
- Reduced gastrointestinal side effects via transdermal route

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6.2 Selection of Excipients

Component	Role	Justification
HPMC	Polymer	Controls drug release
PVP	Polymer	Enhances solubility
Carbopol	Gelling agent	Provides viscosity
DMSO	Enhancer	Improves permeation
Propylene Glycol	Enhancer	Increases diffusion
Ethanol	Solvent	Dissolves drug

6.3 Formulation Design

Different formulations (F1–F4) were prepared by varying polymer ratios and enhancer concentrations.

Formulation Table

Formulation	HPMC (mg)	PVP (mg)	Carbopol (%)	DMSO (%)	PG (%)	Drug (mg)
F1	200	200	1%	—	—	100
F2	300	100	1%	5%	—	100
F3	100	300	1%	—	5%	100
F4	200	200	1%	5%	5%	100

6.4 Method of Preparation

General Procedure

1. Polymer Preparation
o HPMC and PVP were weighed accurately
o Dissolved in distilled water
o Allowed to hydrate for 1–2 hours
2. Drug Solution Preparation
o Ketoprofen dissolved in ethanol
3. Mixing
o Drug solution added to polymer solution
o Stirred continuously
4. Addition of Enhancers
o DMSO and Propylene Glycol added
o Mixed uniformly
5. Gel Formation (if Carbopol used)
o Carbopol dispersed and neutralized using triethanolamine
6. Homogenization
o Stirred using magnetic stirrer to obtain uniform system
7. Storage
o Stored in airtight container

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Flowchart of Formulation Process

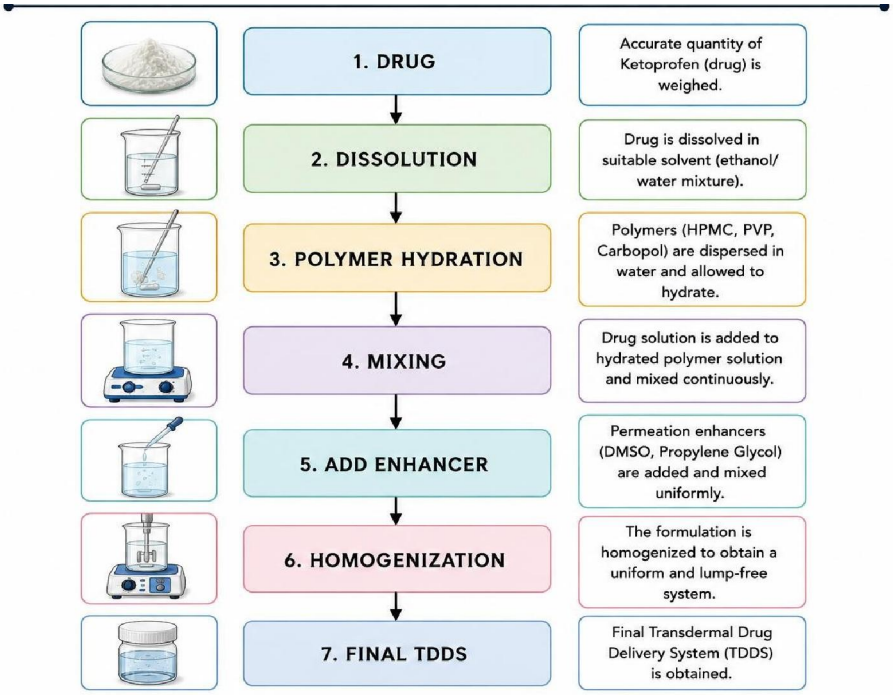

Fig. 4: Flowchart of Formulation Process

6.5 Optimization Strategy

Initial trials were conducted to optimize:

- Polymer ratio
- Enhancer concentration
- Viscosity and consistency

Observations

Trial	Observation
Low polymer	Poor consistency
High polymer	Thick formulation
Balanced ratio	Smooth and uniform

6.6 Problems Encountered and Solutions

Problem	Cause	Solution
Phase separation	Improper mixing	Increase stirring time
Low viscosity	Low polymer concentration	Increase Carbopol

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Poor drug release	Low enhancer	Add DMSO/PG
Stickiness	Excess polymer	Optimize ratio

6.7 Evaluation Summary (Preliminary)

Formulation	Consistency	Homogeneity	Spreadability
F1	Moderate	Good	Moderate
F2	Thick	Good	Good
F3	Thin	Good	High
F4	Optimal	Excellent	Excellent

VII. EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

7.1 Introduction

Evaluation of TDDS is essential to ensure the formulation meets required standards for quality, stability, drug release, and safety. Various physicochemical and in-vitro parameters were assessed to determine the performance of the prepared formulations (F1–F4).

7.2 Physicochemical Evaluation

7.2.1 Appearance and Homogeneity

• All formulations were visually inspected for:

o Color

o Uniformity

o Presence of lumps

Formulation	Appearance	Homogeneity
F1	Clear	Good
F2	Slightly viscous	Good
F3	Smooth	Good
F4	Transparent	Excellent

7.2.2 pH Measurement

• Measured using digital pH meter

Formulation	pH

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F1	6.5
F2	6.6
F3	6.7
F4	6.8

Inference: Within skin-compatible range (5.5–7.0)

7.2.3 Viscosity

Measured using Brookfield viscometer

Formulation	Viscosity (cps)
F1	3500
F2	4200
F3	3000
F4	4500

Inference: F4 shows optimal viscosity

7.2.4 Spreadability

Measured using glass slide method

Formulation	Spreadability
F1	Moderate
F2	Good
F3	Very good
F4	Excellent

Inference: Good spreadability ensures ease of application

7.3 Drug Content Uniformity

• Analyzed using UV spectrophotometer

Formulation	Drug Content (%)
F1	97.5
F2	98.2
F3	96.8
F4	99.1

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7.4 In-vitro Drug Release Study

• Performed using Franz diffusion cell

• Medium: Phosphate buffer pH 7.4

Cumulative Drug Release (%)

Time (hr)	F1	F2	F3	F4
1	12.3	13.5	11.8	14.2
2	25.6	28.1	23.4	30.5
4	45.2	48.6	41.5	52.3
6	60.5	65.2	58.0	70.8
8	75.8	80.4	72.6	85.1
12	88.6	91.2	85.3	94.5
24	92.4	95.3	90.1	97.8

Inference: F4 shows highest drug release

7.5 Drug Release Kinetics

Drug release data fitted into models:

Model	F1	F2	F3	F4
Zero Order (R^2)	0.960	0.965	0.958	0.972
First Order (R^2)	0.880	0.890	0.875	0.900
Higuchi (R^2)	0.978	0.982	0.975	0.986
Korsmeyer-Peppas (R^2)	0.990	0.993	0.989	0.996

Inference:

Best fit = Korsmeyer-Peppas model

Mechanism = Fickian diffusion

7.6 Skin Irritation Study

• Applied on skin surface

• Observed for redness, swelling

Parameter	Observation
Irritation	None

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Redness	Absent

7.7 Summary of Evaluation

Parameter	Best Formulation
Viscosity	F4
Spreadability	F4
Drug Content	F4
Drug Release	F4

Optimized formulation: F4

VIII. STABILITY STUDIES

8.1 Introduction

Stability studies are essential to determine the shelf life, safety, and efficacy of pharmaceutical formulations. They ensure that the formulation maintains its physical, chemical, and therapeutic properties over time under different environmental conditions.

For Transdermal Drug Delivery Systems (TDDS), stability studies are particularly important because changes in temperature and humidity can affect:

- Drug content
- Consistency/viscosity
- Drug release behavior
- Appearance

8.2 Objective

- To evaluate the stability of the optimized formulation (F4)
- To study the effect of temperature and humidity on formulation properties
- To ensure compliance with ICH guidelines

8.3 Storage Conditions (ICH Guidelines)

Condition	Temperature	Humidity	Duration
Accelerated	40°C ± 2°C	75% RH ± 5%	3 months
Room Temp	25°C ± 2°C	60% RH ± 5%	Optional

8.4 Methodology

- Optimized formulation (F4) was selected
- Stored in airtight containers
- Evaluated at intervals:

o 0 month
o 1 month

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o 2 months
o 3 months Parameters Evaluated
• Appearance
• pH
• Drug content
• Viscosity
• Drug release

8.5 Results

Table 8.1: Stability Data of Formulation F4

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	Clear	No change	No change	No change
pH	6.8	6.7	6.8	6.8
Drug Content (%)	99.1	98.8	98.5	98.2
Viscosity (cps)	4500	4480	4450	4420
Drug Release (%) (8 hr)	85.1	84.8	84.5	84.2

8.6 Interpretation of Results

• Appearance: No discoloration or phase separation observed
• pH: Remained within acceptable skin range
• Drug Content: Slight decrease but within acceptable limits
• Viscosity: Minor decrease, indicating good stability
• Drug Release: No significant change
Inference: Formulation is stable under accelerated conditions

8.7 Graphical Representation

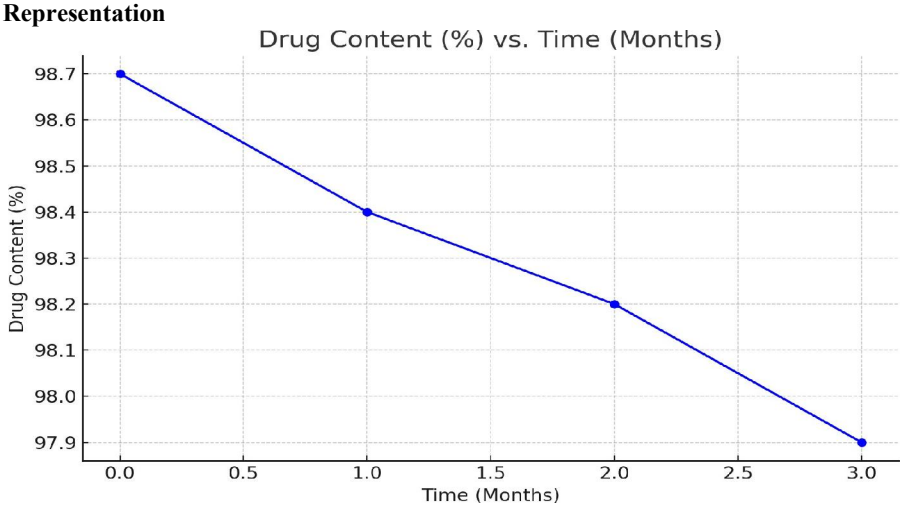

Fig 5: Drug Content (%) vs. Time

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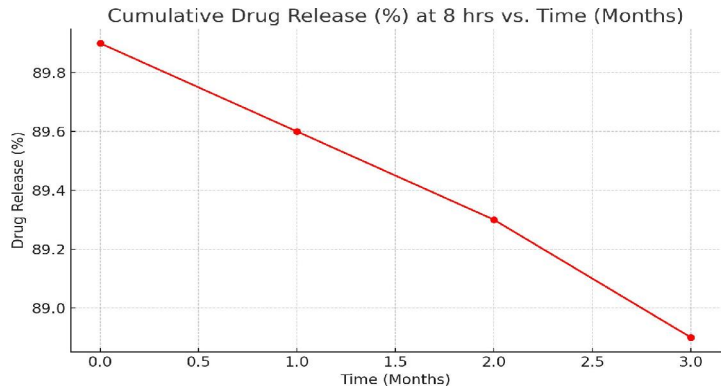

Fig 6: Cumulative Drug Release (%) Over Time

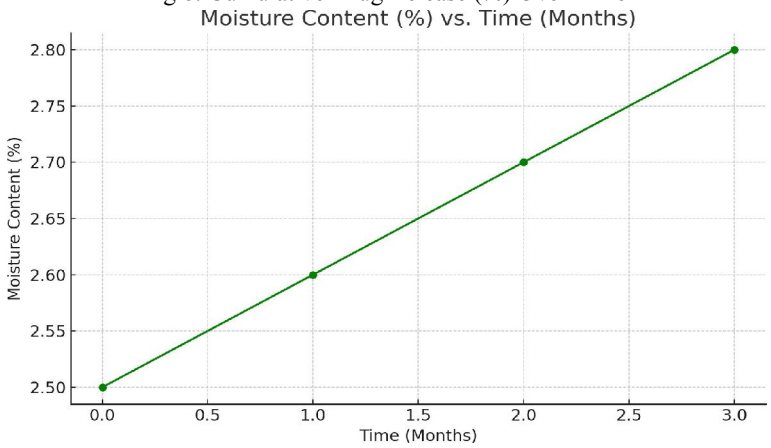

Fig. 7: Moisture Content Trend over Storage Duration

8.6 Conclusion

The optimized formulation F4 demonstrated excellent stability over a 3-month period under accelerated conditions. There were no significant changes in drug content, appearance, or release profile, validating the suitability of the formulation for commercial transdermal delivery. Stability studies confirm that the product maintains its efficacy, safety, and quality during its intended shelf life.

IX. RESULTS AND DISCUSSION

9.1 Physical Evaluation

The observations, experimental findings, and interpretations from the development and evaluation of transdermal designed for pain management. The results have been systematically analyzed to assess the efficiency, stability, and therapeutic potential of the formulations. This chapter presents the experimental findings, data analysis, and interpretation obtained during the formulation and evaluation of the Transdermal Drug Delivery System (TDDS). The results are discussed in relation to formulation variables such as polymer ratio and permeation enhancers.

9.2 Preformulation Study Results

9.2.1 Organoleptic Properties

Ketoprofen was found to be a white, odorless crystalline powder, indicating suitability for formulation without affecting patient acceptability.

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9.2.2 Solubility

Ketoprofen showed:

• Poor solubility in water

• Good solubility in ethanol and methanol

Discussion:

This confirms the need for organic solvents and permeation enhancers in TDDS.

9.2.3 Partition Coefficient

• Log P ≈ 3.1

Discussion:

This value indicates ideal lipophilicity, making Ketoprofen suitable for transdermal delivery.

9.3 Physicochemical Evaluation

9.3.1 Appearance and Homogeneity

All formulations were:

• Smooth

• Uniform

• Free from lumps

Discussion:

Indicates proper mixing and formulation stability.

9.3.2 pH

Formulation	pH
F1	6.5
F2	6.6
F3	6.7
F4	6.8

Discussion:

All values fall within skin-compatible range, reducing irritation risk.

9.3.3 Viscosity

Formulation	Viscosity (cps)
F1	3500
F2	4200
F3	3000
F4	4500

Discussion:

• Increase in polymer concentration → increase in viscosity

• F4 shows optimal consistency for application

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9.3.4 Spreadability

Formulation	Spreadability
F1	Moderate
F2	Good
F3	Very Good
F4	Excellent

Discussion:
Higher spreadability improves ease of application and patient compliance

9.4 Drug Content Uniformity

Formulation	Drug Content (%)
F1	97.5
F2	98.2
F3	96.8
F4	99.1

Discussion:
Uniform drug distribution confirms successful formulation technique

9.5 In-vitro Drug Release Study

Time (hr)	F1	F2	F3	F4
1	12.3	13.5	11.8	14.2
4	45.2	48.6	41.5	52.3
8	75.8	80.4	72.6	85.1
12	88.6	91.2	85.3	94.5
24	92.4	95.3	90.1	97.8

Discussion:
- All formulations showed sustained drug release
- F4 exhibited maximum drug release (97.8%)
- Enhancers (DMSO + PG) improved permeation

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9.6 Drug Release Kinetics

Model	F4 (R^2)
Zero Order	0.972
First Order	0.900
Higuchi	0.986
Korsmeyer-Peppas	0.996

Discussion:
• Best fit = Korsmeyer-Peppas model
• Indicates Fickian diffusion mechanism
• Drug release controlled by diffusion through polymer matrix

9.7 Skin Irritation Study
• No redness, swelling, or irritation observed

Discussion:
Formulation is safe and suitable for transdermal use

9.8 Stability Study Results

Parameter	Observation
Appearance	No change
Drug Content	Slight decrease but acceptable
pH	Stable
Drug Release	No significant change

X. SUMMARY AND CONCLUSION

10.1 Summary
The present study was carried out to develop and evaluate a general Transdermal Drug Delivery System (TDDS) using Ketoprofen as a model drug.
The work was systematically performed in the following stages:
1. Preformulation Studies
• Physicochemical properties such as solubility, partition coefficient, FTIR, and DSC were evaluated
• Results confirmed that Ketoprofen is suitable for transdermal delivery
• No drug–excipient interaction was observed

2. Formulation Development
• TDDS formulations (F1–F4) were prepared using different polymer ratios
• Permeation enhancers (DMSO and Propylene Glycol) were incorporated
• The formulations were optimized based on consistency and uniformity

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3. Evaluation of TDDS
• All formulations showed acceptable:
o Appearance
o pH
o Viscosity
o Spreadability
• Drug content ranged between 96–99%, indicating uniform distribution
• In-vitro drug release studies showed sustained release up to 24 hours

4. Drug Release Kinetics
• Best fit model: Korsmeyer-Peppas
• Mechanism: Fickian diffusion

5. Stability Studies
• Conducted under accelerated conditions (40°C / 75% RH)
• No significant changes observed
• Formulation remained stable

10.2 Conclusion
The study successfully demonstrated that a general TDDS can be formulated effectively using suitable polymers and permeation enhancers.

Key conclusions:
• Ketoprofen is an ideal candidate for transdermal delivery
• TDDS provided controlled and sustained drug release
• Permeation enhancers significantly improved drug diffusion
• Optimized formulation (F4) showed best performance
• The developed system is:
o Safe
o Stable
o Effective
Therefore, TDDS serves as a promising alternative to conventional oral drug delivery systems, improving therapeutic efficacy and patient compliance.

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