A Reasearch on Formulation and in Vitro Assessment of a Bilayer NSAID Tablet for Controlled Pain Management

Chaudhari Kaweri Kacheshwar[1], Priyanka Bajirao Pawar[2], Dr. Vijay B. Jadhav[3], Dr. Sachin B. Aglawe[4], Mr. Karveer B. Aghade[5], Dr. Nitin P. Jain[6], Dr. Usha N. Jain[7]

[1] Assistant Professor, Department of Pharmaceutics, Rashtrasant Janardhan Swami College of Pharmacy, Kokamthan, Maharashtra – 423601, India.
[2] Department of Pharmaceutics, Rashtrasant Janardhan Swami College of Pharmacy, Kokamthan, Kopargaon, Maharashtra – 423601, India.
[3] Associate Professor, Department of Pharmaceutical Quality Assurance, Rashtrasant Janardhan Swami College of Pharmacy, Kokamthan, Maharashtra – 423601, India.
[4] Associate Professor, Department of Pharmaceutics, Rashtrasant Janardhan Swami College of Pharmacy, Kokamthan, Maharashtra – 423601, India.
[5] Associate Professor, Department of Pharmacology, Rashtrasant Janardhan Swami College of Pharmacy, Kokamthan, Maharashtra – 423601, India.
[6] Principal, Department of Pharmaceutical Chemistry, Rashtrasant Janardhan Swami College of Pharmacy, Kokamthan, Maharashtra – 423601, India.
[7] Associate Professor, Department of Pharmaceutical Chemistry, Rashtrasant Janardhan Swami College of Pharmacy, Kokamthan, Maharashtra – 423601, India.

ABSTRACT

The present investigation was aimed at the formulation and in vitro assessment of a bilayer non-steroidal anti-inflammatory drug (NSAID) tablet containing Diclofenac Sodium and Tenoxicam for controlled and effective pain management. Chronic inflammatory and painful conditions often require immediate relief followed by prolonged therapeutic action to maintain adequate drug concentration in the body. Conventional dosage forms generally fail to provide both rapid onset and sustained effect simultaneously, leading to frequent dosing and reduced patient compliance. To overcome these limitations, a bilayer tablet approach was designed in the present study to combine immediate-release and sustained-release drug delivery within a single dosage form.

In this formulation, Diclofenac Sodium was incorporated into the immediate-release layer to provide rapid analgesic and anti-inflammatory action, while Tenoxicam was included in the sustained-release layer to maintain prolonged therapeutic activity for extended pain control. The bilayer tablet system was developed using the direct compression method with the help of suitable pharmaceutical excipients such as polymers, binders, diluents, lubricants, and disintegrating agents. The selection of excipients was carried out to achieve optimum tablet integrity, rapid disintegration of the immediate-release layer, and controlled drug release from the sustained-release layer.

Prior to compression, the powder blends were evaluated for pre-compression parameters including angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio to determine their flow characteristics and compressibility behavior. The obtained values indicated acceptable flow properties suitable for tablet manufacturing. The prepared bilayer tablets were further subjected to post-compression evaluation tests such as thickness, hardness, friability, weight variation, disintegration time, and drug content uniformity. All formulations showed satisfactory physicochemical properties and complied with official pharmacopeial specifications.

The in vitro dissolution studies were performed using USP dissolution apparatus under suitable dissolution conditions to evaluate the drug release profile of both layers. The immediate-release layer containing Diclofenac Sodium exhibited rapid drug release within a short period, ensuring quick onset of pain relief. In contrast, the Tenoxicam sustained-release layer demonstrated a gradual and controlled drug release pattern over an extended duration, which may help maintain therapeutic plasma concentration for a prolonged period. The optimized formulation showed desirable release kinetics and effective bilayer performance without layer separation or physical instability.

Keywords: Bilayer tablet, Diclofenac Sodium, Tenoxicam, NSAIDs, Controlled drug delivery, Immediate release, Sustained release, In vitro dissolution, Pain management, Direct compression, Drug release kinetics, Anti-inflammatory therapy.

1. INTRODUCTION

Pain and inflammation are among the most common clinical conditions affecting millions of patients worldwide. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of rheumatoid arthritis, osteoarthritis, musculoskeletal disorders, postoperative pain, and chronic inflammatory diseases due to their analgesic, antipyretic, and anti- inflammatory properties. However, conventional NSAID therapy is frequently associated with gastrointestinal irritation, ulcer formation, renal toxicity, cardiovascular complications, and poor patient compliance caused by repeated dosing. These limitations have encouraged researchers to develop advanced drug delivery systems capable of providing improved therapeutic efficacy with reduced adverse effects.

Bilayer Tablet Technology

Bilayer tablet technology is an advanced pharmaceutical approach designed to combine two different drug release patterns within a single dosage form. A bilayer tablet consists of two separate layers that may contain either the same drug or different drugs with distinct release mechanisms. This system is mainly developed to achieve immediate release from one layer and sustained or controlled release from the second layer. The technology provides several advantages such as reduced dosing frequency, improved patient compliance, enhanced therapeutic efficacy, separation of incompatible drugs, and maintenance of constant plasma drug concentration over an extended period.

Bilayer tablets are particularly useful in the management of chronic diseases where rapid onset of action and prolonged therapeutic effect are both required. In pain management therapy, the immediate release layer offers quick relief from pain, while the sustained release layer maintains prolonged analgesic and anti-inflammatory activity. The bilayer approach also minimizes fluctuations in plasma drug concentration and helps in reducing dose-related side effects.

NSAID Problems

Despite their clinical effectiveness, NSAIDs possess several disadvantages during long-term administration. The major limitation of conventional NSAIDs is gastrointestinal toxicity caused by inhibition of prostaglandin synthesis, which normally protects the gastric mucosa. Continuous NSAID use may lead to gastric irritation, ulceration, bleeding, nausea, and dyspepsia. In addition, prolonged therapy can produce renal impairment and cardiovascular complications in susceptible patients.

Another significant problem associated with NSAIDs is their short biological half-life, which necessitates multiple daily dosing to maintain therapeutic drug levels. Frequent administration often results in poor patient adherence and fluctuating plasma concentration, leading to inadequate pain control. Conventional immediate release formulations also produce rapid drug release, causing high peak plasma levels that increase the risk of adverse effects. Therefore, controlled release systems such as bilayer tablets are considered effective alternatives for overcoming these limitations and improving therapeutic performance.

Why Combination Was Chosen

The present research focuses on the combination of Tenoxicam and Diclofenac Sodium for the development of a bilayer NSAID tablet intended for controlled pain management. The combination was selected based on the complementary pharmacological properties of both drugs. Diclofenac Sodium is a potent NSAID known for its rapid onset of analgesic and anti-inflammatory action. It is highly effective in relieving acute pain but requires repeated administration because of its shorter duration of action.

Tenoxicam, on the other hand, belongs to the oxicam class of NSAIDs and possesses a longer biological half-life, making it suitable for prolonged therapeutic activity. It provides sustained anti-inflammatory and analgesic effects and helps maintain effective plasma concentration for an extended duration.

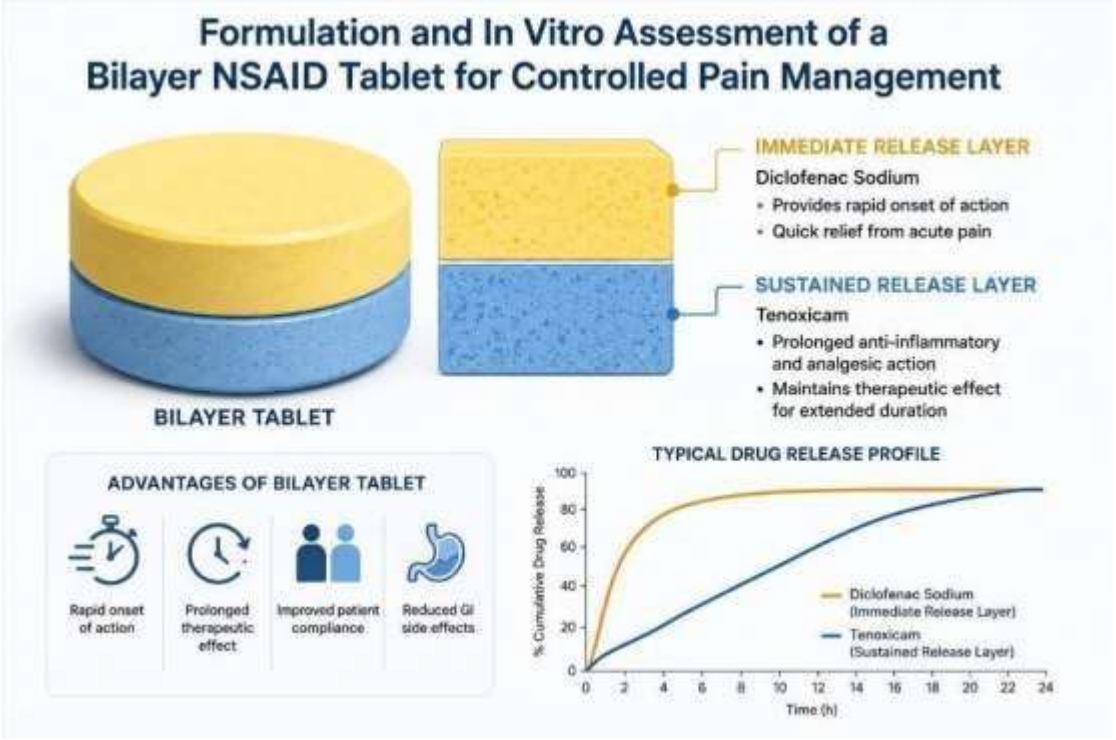


Fig :- Bilayer Tablet

The combination of these two drugs in a bilayer tablet was therefore chosen to achieve biphasic drug release. Diclofenac Sodium was incorporated into the immediate release layer to provide rapid pain relief, whereas Tenoxicam was formulated into the sustained release layer to maintain prolonged therapeutic action. This strategy is expected to reduce dosing frequency, improve patient compliance, enhance pain management, and minimize plasma concentration fluctuations. Additionally, controlled drug release may help reduce gastrointestinal exposure

to NSAIDs, thereby potentially decreasing adverse effects associated with conventional therapy.
Hence, the present study aims to formulate and evaluate a bilayer tablet containing Tenoxicam and Diclofenac Sodium for controlled pain management with improved therapeutic efficacy and patient compliance.

DRUG PROFILE

1. Diclofenac Sodium General Information

Parameter	Details
Drug Name	Diclofenac Sodium
Category	Non-Steroidal Anti-Inflammatory Drug (NSAID)
Chemical Class	Phenylacetic Acid Derivative
IUPAC Name	Sodium [2-(2,6-dichloroanilino) phenyl] acetate
Molecular Formula	$C_{14}H_{10}Cl_2NNaO_2$
Molecular Weight	318.13 g/mol
Appearance	White to slightly yellow crystalline powder
Odor	Odorless or faint characteristic odor
Taste	Slightly bitter
Melting Point	Approximately 283–285°C
Solubility	Freely soluble in methanol, soluble in ethanol, slightly soluble in water
pKa	Approximately 4.0
Partition Coefficient (Log P)	Approximately 4.5
Biological Half-life	1–2 hours
Protein Binding	More than 99%
Storage Condition	Store in a cool, dry place protected from light and moisture

Chemical Structure

Diclofenac Sodium is a derivative of phenylacetic acid containing two chlorine atoms attached to an aniline ring. The sodium salt form improves its aqueous solubility and enhances oral absorption.

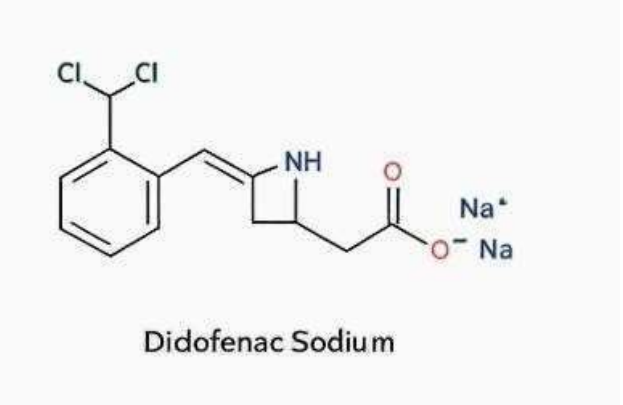


Fig :- Chemical Structure Of Diclofenac Sodium Structural Features

- Contains dichlorophenyl amino group

- Possesses anti-inflammatory and analgesic activity
- Weak acidic nature
- Highly lipophilic molecule

Mechanism of Action

Diclofenac Sodium acts primarily by inhibiting cyclooxygenase enzymes (COX-1 and COX-2), thereby preventing the synthesis of prostaglandins from arachidonic acid.

Prostaglandins are chemical mediators responsible for:

- Pain
- Inflammation
- Swelling
- Fever

By reducing prostaglandin synthesis, Diclofenac Sodium produces:

- Analgesic action
- Anti-inflammatory action
- Antipyretic effect

Diclofenac exhibits comparatively higher selectivity toward COX-2 inhibition, which contributes to strong anti-inflammatory activity.

Pharmacological Actions

Analgesic Activity

Provides rapid pain relief in acute and chronic painful conditions.

Anti-inflammatory Activity

Reduces inflammation, redness, swelling, and joint stiffness.

Antipyretic Activity

Lowers elevated body temperature during fever.

Pharmacokinetics Absorption

- Rapidly absorbed after oral administration
- Bioavailability approximately 50–60% due to first-pass metabolism
- Peak plasma concentration achieved within 1–2 hours

Distribution

- Extensively bound to plasma proteins
- Distributed into synovial fluid
- Volume of distribution approximately 0.12–0.17 L/kg

Metabolism

- Metabolized primarily in the liver
- Cytochrome P450 enzyme CYP2C9 involved
- Forms hydroxylated metabolites

Excretion

- Excreted mainly through urine and bile
- About 60% excreted in urine
- Remaining eliminated in feces

Elimination Half-Life

- Approximately 1–2 hours

Therapeutic Uses

Diclofenac Sodium is widely used for:

- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Musculoskeletal pain
- Postoperative pain
- Dental pain
- Migraine attacks
- Dysmenorrhea
- Sports injuries
- Acute inflammatory disorders

Advantages

- Rapid onset of action
- Potent analgesic effect
- Effective anti-inflammatory activity
- Suitable for immediate pain relief
- Good patient acceptance
- Widely available

Limitations
- Short biological half-life
- Requires multiple dosing
- Gastrointestinal irritation
- Risk of gastric ulceration
- Hepatic and renal toxicity on prolonged use
- Cardiovascular risks at high doses

Adverse Effects Common Side Effects
- Nausea
- Vomiting
- Gastric irritation
- Heartburn
- Diarrhea
- Abdominal pain

Serious Side Effects
- Peptic ulcer
- Gastrointestinal bleeding
- Liver dysfunction
- Kidney damage
- Hypertension
- Cardiovascular complications

Contraindications
Diclofenac Sodium should not be used in:
- Peptic ulcer disease
- Severe hepatic impairment
- Severe renal impairment
- NSAID hypersensitivity
- Aspirin-induced asthma
- Pregnancy (third trimester)
- Severe heart failure

Drug Interactions Major Interactions
- Anticoagulants → increased bleeding risk
- Corticosteroids → increased gastric ulcer risk
- Antihypertensive drugs → reduced antihypertensive effect
- Methotrexate → increased toxicity
- Lithium → elevated lithium levels
- Diuretics → nephrotoxicity risk

Role in Bilayer Tablet Formulation
In the present research, Diclofenac Sodium was selected for the immediate-release layer because:
- It provides rapid onset of analgesic action
- Fast absorption helps achieve quick pain relief
- Suitable for acute pain management
- Immediate release minimizes delay in therapeutic action

The drug was formulated using superdisintegrants to ensure rapid tablet disintegration and immediate drug release.

Evaluation Parameters Relevant to Formulation Physicochemical Properties
- Solubility
- pH stability
- Drug-excipient compatibility

Analytical Evaluation
- UV spectroscopy
- HPLC analysis
- Drug content estimation

Dissolution Behavior
Expected to release rapidly within the first hour in immediate-release formulations.

Storage and Stability
Diclofenac Sodium should be:
- Stored below 25°C
- Protected from moisture
- Protected from direct sunlight

- Kept in airtight containers

The drug is relatively stable under normal conditions but may undergo degradation in excessive heat and humidity.

2. Tenoxicam General Information

Parameter	Details
Drug Name	Tenoxicam
Category	Non-Steroidal Anti-Inflammatory Drug (NSAID)
Chemical Class	Oxicam Derivative
IUPAC Name	4-Hydroxy-2-methyl-N-(pyridin-2-yl)-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide
Molecular Formula	$C_{13}H_{11}N_3O_4S_2$
Molecular Weight	337.38 g/mol
Appearance	Yellow crystalline powder
Odor	Odorless
Taste	Slightly bitter
Melting Point	Approximately 209–213°C
Solubility	Slightly soluble in water, soluble in dimethylformamide
pKa	Approximately 1.8 and 5.3
Partition Coefficient	Moderately lipophilic
Biological Half-life	60–75 hours
Protein Binding	Approximately 99%
Storage Condition	Store in a cool, dry place away from light

Chemical Structure

Tenoxicam belongs to the oxicam class of NSAIDs and contains:

- Thiazine ring
- Pyridine ring
- Sulfonamide functional group

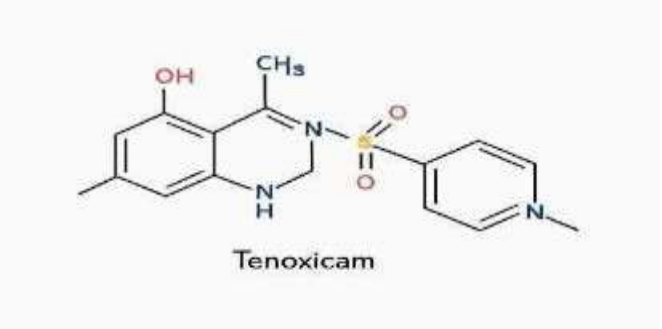


Fig :- Chemical Structure Of Tenoxicam

The structure contributes to:

- Long duration of action
- Strong anti-inflammatory activity
- Sustained therapeutic effect

Mechanism of Action
Tenoxicam inhibits cyclooxygenase enzymes responsible for prostaglandin synthesis. Effects include:
- Reduction of inflammation
- Pain relief
- Decrease in swelling
- Reduction in fever

Tenoxicam inhibits both COX-1 and COX-2 enzymes and exhibits prolonged pharmacological activity due to its long half-life.

Pharmacological Actions Anti-inflammatory Activity
Strong suppression of inflammatory mediators.
Analgesic Activity
Provides prolonged pain relief.
Antipyretic Activity
Reduces fever by acting on the hypothalamic heat-regulating center.
Pharmacokinetics Absorption
- Well absorbed orally
- Bioavailability approximately 100%
- Peak plasma concentration within 2–3 hours

Distribution
- Highly plasma protein bound
- Widely distributed into body tissues
- Good penetration into synovial fluid

Metabolism
- Extensively metabolized in the liver
- Produces inactive metabolites

Excretion
- Eliminated through urine and feces
- Slow elimination due to long half-life

Elimination Half-Life
- Approximately 60–75 hours

Therapeutic Uses
Tenoxicam is used in:
- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Chronic musculoskeletal disorders
- Joint inflammation
- Gout
- Chronic pain conditions

Advantages
- Long duration of action
- Once-daily dosing possible
- Sustained therapeutic effect
- Effective in chronic inflammatory conditions
- Reduced dosing frequency
- Better patient compliance

Limitations
- Slow onset compared to immediate-release NSAIDs
- Gastric irritation
- Renal complications
- Hepatic toxicity in prolonged use
- Risk of cardiovascular effects

Adverse Effects Common Side Effects
- Dyspepsia
- Nausea
- Gastric discomfort
- Headache
- Dizziness

Serious Side Effects

- Gastrointestinal ulceration
- Bleeding
- Renal impairment
- Liver dysfunction
- Hypersensitivity reactions

Contraindications
Tenoxicam should be avoided in:
- Peptic ulcer disease
- Severe renal impairment
- Severe hepatic dysfunction
- NSAID allergy
- Pregnancy and lactation
- Severe cardiovascular disease

Drug Interactions Important Drug Interactions
- Anticoagulants → bleeding risk
- Diuretics → renal complications
- Corticosteroids → gastric toxicity
- Methotrexate → increased toxicity
- Antihypertensives → reduced effect

Role in Bilayer Tablet Formulation
Tenoxicam was selected for the sustained-release layer because:
- It possesses long biological half-life
- Provides prolonged anti-inflammatory effect
- Suitable for maintenance therapy
- Reduces frequency of administration

Hydrophilic polymers were used to control its release over an extended duration.

Evaluation Parameters Relevant to Formulation Preformulation Studies
- Solubility studies
- Compatibility studies
- Stability analysis

Analytical Methods
- UV spectrophotometric analysis
- HPLC estimation
- Dissolution profiling

Drug Release
Expected to show controlled and sustained release for 10–12 hours or longer.

Storage and Stability
Tenoxicam should be:
- Stored in airtight containers
- Protected from heat and moisture
- Kept away from direct sunlight

The drug remains stable under recommended storage conditions but may degrade under excessive humidity and temperature conditions.

Material And Methods

Materials
The materials used in the formulation of the bilayer NSAID tablet were of pharmaceutical grade and procured from approved suppliers. Diclofenac Sodium was selected as the active pharmaceutical ingredient for the immediate-release layer, while Tenoxicam was used for the sustained-release layer. Various excipients including superdisintegrants, polymers, diluents, lubricants, and glidants were utilized to achieve the desired formulation characteristics.

Immediate-Release Layer Composition (Diclofenac Sodium) Table: Composition of Immediate-Release Layer

Sr. No.	Ingredients	Category	Quantity (mg/tablet)

1	Diclofenac Sodium	Active Pharmaceutical Ingredient	50mg
2	Crospovidone	Superdisintegrant	5mg
3	Sodium Starch Glycolate	Superdisintegrant	5mg
4	Microcrystalline Cellulose (MCC)	Diluent	55mg
5	Lactose	Diluent	30mg
6	Magnesium Stearate	Lubricant	3mg
7	Talc	Glidant	2mg
	Total Weight		150mg

Sustained-Release Layer Composition (Tenoxicam) Table: Composition of Sustained-Release Layer

Sr. No.	Ingredients	Category	Quantity (mg/tablet)
1	Tenoxicam	Active Pharmaceutical Ingredient	20mg
2	HPMC K100M	Release Retarding Polymer	60mg
3	Ethyl Cellulose	Sustaining Polymer	40mg
4	Microcrystalline Cellulose (MCC)	Diluent	50mg
5	Magnesium Stearate	Lubricant	3mg
6	Talc	Glidant	2mg
	Total Weight		175mg

Method of Preparation

Preparation of Immediate-Release Layer

The immediate-release layer containing Diclofenac Sodium was prepared by the direct compression method. All the ingredients were accurately weighed according to the formulation design. Diclofenac Sodium, crospovidone, sodium starch glycolate, microcrystalline cellulose, and lactose were passed through sieve no. 60 separately to obtain uniform particle size and remove aggregates.

The sieved ingredients were transferred into a clean and dry mortar and mixed thoroughly for approximately 10–15 minutes to ensure uniform distribution of the drug and excipients.

Magnesium stearate and talc were then added to the powder blend and mixed gently for an additional 2–3 minutes to improve flow properties and prevent sticking during compression.

The prepared blend was evaluated for pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio before tablet compression.

Preparation of Sustained-Release Layer

The sustained-release layer containing Tenoxicam was also prepared using the direct compression technique. Tenoxicam, HPMC K100M, ethyl cellulose, and microcrystalline cellulose were weighed accurately and passed through sieve no. 60.

The ingredients were blended uniformly for 15 minutes to ensure homogeneous mixing of the drug and polymers. HPMC K100M and ethyl cellulose were incorporated as release-retarding

agents to achieve sustained drug release over an extended duration. Magnesium stearate and talc were added at the final stage and mixed gently for 2–3 minutes.

The final powder blend was evaluated for flow properties and compressibility characteristics prior to compression.

Preparation of Bilayer Tablet

Bilayer tablets were prepared by sequential compression using a tablet compression machine. Initially, the required quantity of the sustained-release layer blend containing Tenoxicam was introduced into the die cavity and lightly compressed. Subsequently, the immediate-release layer blend containing Diclofenac Sodium was added over the pre-compressed sustained-release layer.

The two layers were then compressed together using suitable compression force to obtain bilayer tablets with adequate hardness and mechanical strength. Care was taken to avoid layer separation and ensure proper adhesion between both layers.
The prepared bilayer tablets were collected and stored in airtight containers for further evaluation studies.

Evaluation of Pre-Compression Parameters
The powder blends of both layers were evaluated for the following parameters:

1. Angle of Repose
The angle of repose was determined using the fixed funnel method to evaluate flow properties of the powder blend.
Formula:

Where:
- h= Height of powder cone
- r= Radius of powder cone

$$\tan\theta = \frac{h}{r}$$

Bulk Density
Bulk density was determined by pouring a known quantity of powder into a graduated cylinder and measuring the bulk volume.
Formula:

$$\text{Bulk Density} = \frac{M}{Vb}$$

Where:
- M= Mass of powder
- Vb= Bulk volume

Tapped Density
Tapped density was measured after mechanically tapping the graduated cylinder until constant volume was obtained.
Formula:

Where:
- M= Mass of powder
- Vt= Tapped volume
- Tapped Density $\frac{M}{Vt}$

Carr's Compressibility Index
Carr's index was calculated to evaluate compressibility behavior. Formula:

$$\text{Carr's Index} = \frac{V_t - V_b}{Vt} \times 100$$

Hausner's Ratio
Hausner's ratio was calculated using bulk density and tapped density values. Formula:

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Evaluation of Post-Compression Parameters
The prepared bilayer tablets were evaluated for the following quality control parameters:
- Thickness
- Hardness
-
- Weight variation
- Friability
- Drug content uniformity
- Disintegration time
- In vitro dissolution study

Disintegration Time (DT)

The disintegration time of the immediate release layer was evaluated to ensure rapid tablet breakdown for quick drug release. The formulation exhibited satisfactory disintegration behavior due to the incorporation of superdisintegrants.

Friability Study

Friability testing was performed to evaluate the mechanical strength and resistance of the tablets to abrasion during handling, packaging, and transportation. The friability values of all batches were found to be below 1%, indicating acceptable mechanical integrity of the prepared bilayer tablets.

In Vitro Dissolution Study

The dissolution study is one of the most critical evaluations for bilayer tablets because it determines whether the formulation provides the intended biphasic release pattern—rapid drug release from the immediate-release (IR) layer followed by prolonged release from the sustained-release (SR) layer.

Fig :- **Dissolution** Tester

Thickness Study

Thickness is an important post-compression quality control parameter used to ensure uniformity in tablet size and appearance. Consistent tablet thickness indicates uniform die filling and proper compression during manufacturing. Variations in thickness may affect packaging, tablet weight, hardness, and patient acceptability.

Fig :- Thickness Tester

Hardness Study

Hardness is an important post-compression quality control parameter that measures the mechanical strength of a tablet and its ability to withstand handling, packaging, transportation, and storage without breaking.

Fig :- Hardness Tester

Fourier Transform Infrared Spectroscopy (FTIR) Study Principle of FTIR

Fourier Transform Infrared Spectroscopy (FTIR) is an important analytical technique used to identify functional groups present in drug molecules and to study drug–excipient compatibility. The technique is based on the absorption of infrared radiation by chemical bonds at specific wavelengths corresponding to molecular vibrations. In the present study, FTIR analysis was carried out for:

- Pure Diclofenac Sodium
- Pure Tenoxicam
- Physical mixture of drugs and excipients
- Optimized bilayer tablet formulation

The study was performed to confirm the identity of the drugs and to evaluate any possible interaction between the drug and excipients used in the formulation.

Methodology of FTIR Analysis

The FTIR spectra of pure drugs and optimized formulations were recorded using FTIR spectrophotometer by potassium bromide (KBr) pellet method.

Procedure

1. The samples were dried properly before analysis.
2. Approximately 1–2 mg of sample was mixed with potassium bromide.
3. The mixture was compressed into transparent pellets using hydraulic pressure.
4. The pellets were scanned in the infrared region between 4000 cm^{-1} to 400 cm^{-1}.
5. The obtained spectra were analyzed for characteristic peak.

FTIR Interpretation of Diclofenac Sodium Characteristic Peaks of Diclofenac Sodium

Functional Group	Characteristic Peak (cm^{-1})
N–H Stretching	3300–3400
Aromatic C–H Stretching	3000–3100
C=O Stretching	1550–1600
C–Cl Stretching	700–800
C–N Stretching	1200–1300

Observation

The FTIR spectrum of Diclofenac Sodium showed characteristic peaks corresponding to its functional groups, confirming the purity and identity of the drug.

FTIR Interpretation of Tenoxicam Characteristic Peaks of Tenoxicam

Functional Group	Characteristic Peak (cm^{-1})
O–H Stretching	3200–3400
N–H Stretching	3100–3300
C=O Stretching	1600–1700
S=O Stretching	1100–1350
Aromatic C=C Stretching	1450–1600

Observation

The FTIR spectrum of Tenoxicam showed all characteristic absorption peaks without significant shifting, indicating purity of the drug.

FTIR Study of Optimized Bilayer Formulation

The FTIR spectra of the optimized bilayer tablet formulation containing Diclofenac Sodium and Tenoxicam were compared with spectra of pure drugs.

Observation

- The characteristic peaks of both Diclofenac Sodium and Tenoxicam were retained in the optimized formulation.
- No significant shift, disappearance, or formation of new peaks was observed.
- This indicated absence of chemical interaction between the drugs and excipients.

Conclusion of FTIR Study

The FTIR analysis confirmed:

- Purity of Diclofenac Sodium and Tenoxicam
- Compatibility of drugs with selected excipients
- Stability of the bilayer tablet formulation

The study demonstrated that the excipients used in both immediate-release and sustained-release layers were

compatible with the active pharmaceutical ingredients.

Factorial Design of Immediate-Release Layer (Diclofenac Sodium) Experimental Design
A 3^2 factorial design was employed for optimization of the immediate-release layer containing Diclofenac Sodium.

Independent Variables
- X_1 = Crospovidone concentration
- X_2 = Sodium Starch Glycolate concentration

Dependent Variables
- Disintegration time
- Drug release
- Hardness

Table: Formulation Design for Immediate-Release Layer

Formulation Code	Diclofenac Sodium	Crospovidone	Sodium Starch Glycolate	MCC	Lactose	Magnesium Stearate	Talc	Total
F1	50	9	9	40	49	3	2	150
F2	50	9	6	40	46	3	2	150
F3	50	9	3	40	43	3	2	150
F4	50	6	9	45	41	3	2	150
F5	50	6	6	45	38	3	2	150
F6	50	6	3	45	35	3	2	150
F7	50	3	9	50	33	3	2	150
F8	50	3	6	50	30	3	2	150
F9	50	3	3	50	27	3	2	150

Factorial Design of Sustained-Release Layer (Tenoxicam) Experimental Design
A 3^2 factorial design was used for optimization of the sustained-release layer containing Tenoxicam.

Independent Variables
- X_1 = HPMC K100M concentration
- X_2 = Ethyl Cellulose concentration

Dependent Variables
- Drug release
- Tablet hardness
- Swelling index

Table: Formulation Design for Sustained-Release Layer

Formulation Code	Tenoxicam	HPMC K100M	Ethyl Cellulose	MCC	Magnesium Stearate	Talc	Total
F1	20	60	40	50	3	2	175
F2	20	60	30	50	3	2	175
F3	20	60	20	50	3	2	175
F4	20	50	40	50	3	2	175

F5	20	50	30	50	3	2	175
F6	20	50	20	50	3	2	175
F7	20	40	40	50	3	2	175
F8	20	40	30	50	3	2	175
F9	20	40	20	50	3	2	175

Interpretation of Factorial Design

The factorial design was used to optimize the concentration of superdisintegrants and release-retarding polymers in order to achieve:

- Rapid release of Diclofenac Sodium
- Sustained release of Tenoxicam
- Acceptable tablet hardness
- Optimum disintegration time
- Improved dissolution profile

The optimized formulations were selected based on evaluation parameters and in vitro drug release studies.

Results And Discussion

Results and Discussion

The present study was carried out to formulate and evaluate a bilayer NSAID tablet containing Diclofenac Sodium as the immediate-release layer and Tenoxicam as the sustained-release layer for controlled pain management. The prepared formulations were evaluated for pre-compression parameters, post-compression characteristics, FTIR compatibility studies, and in vitro dissolution studies. The obtained results demonstrated satisfactory formulation performance and confirmed the suitability of the bilayer tablet approach for dual drug release.

FTIR Study Results

FTIR spectroscopy was performed for pure Diclofenac Sodium, pure Tenoxicam, physical mixtures, and optimized bilayer formulations to determine compatibility between drugs and excipients.

The FTIR spectra of Diclofenac Sodium showed characteristic peaks corresponding to:

- N–H stretching
- C=O stretching
- C–Cl stretching
- Aromatic ring vibrations

Similarly, Tenoxicam exhibited characteristic peaks for:

- O–H stretching
- S=O stretching
- C=O stretching
- Aromatic C=C vibrations

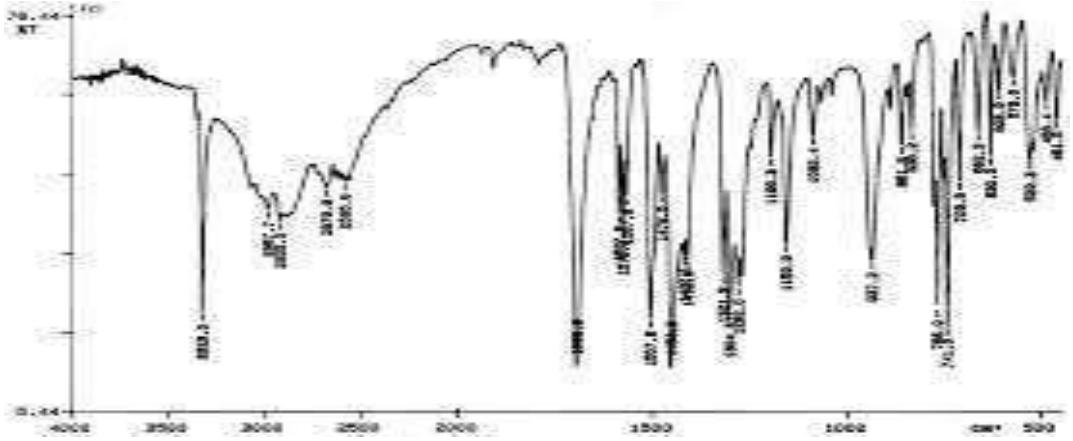


Fig :- Diclofenac

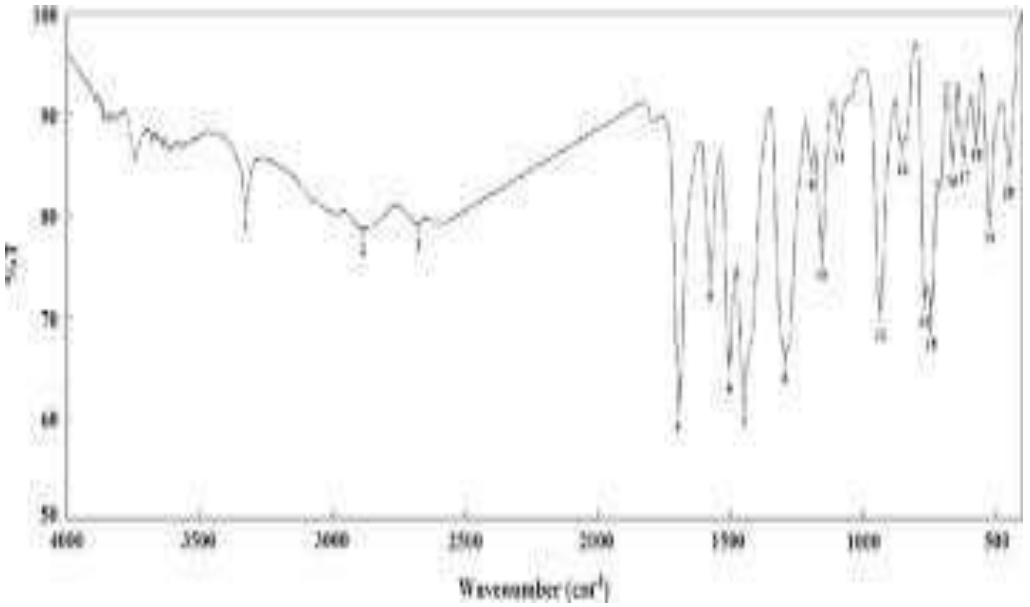


Fig :- Diclofenac + Excepients

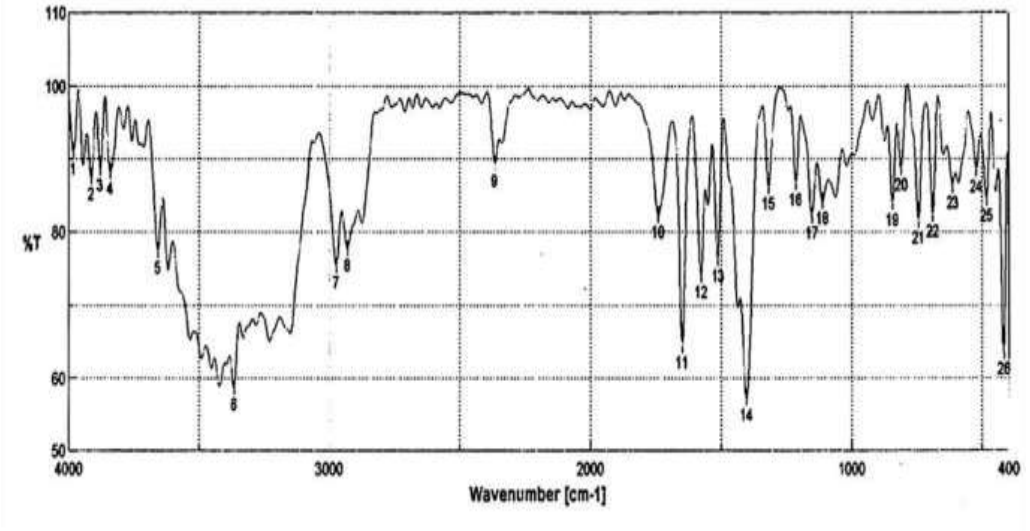


Fig :- Tenoxicam

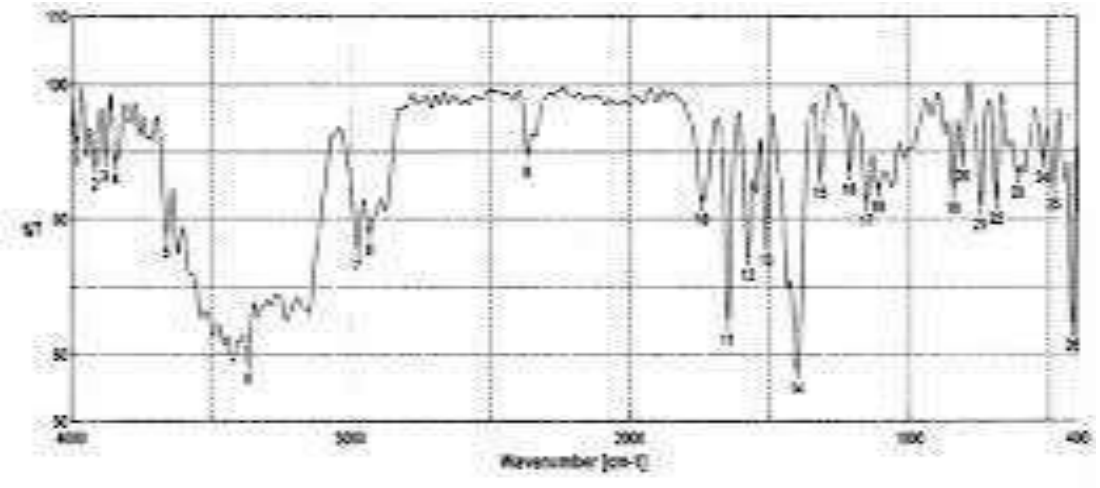


Fig :- Tenoxicam+ Excepients

The spectra of optimized formulations retained all major characteristic peaks of both drugs without significant shifting or disappearance of peaks. This confirmed the absence of chemical interaction between the drugs and excipients used in the formulation. Therefore, the selected excipients were found to be compatible with Diclofenac Sodium and Tenoxicam.

DSC Study Results

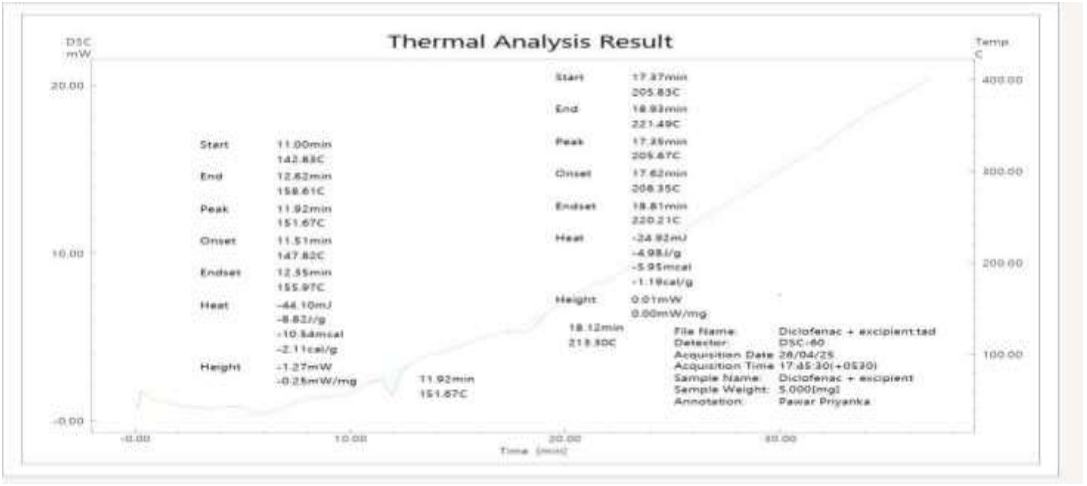


Fig :- Diclofenac

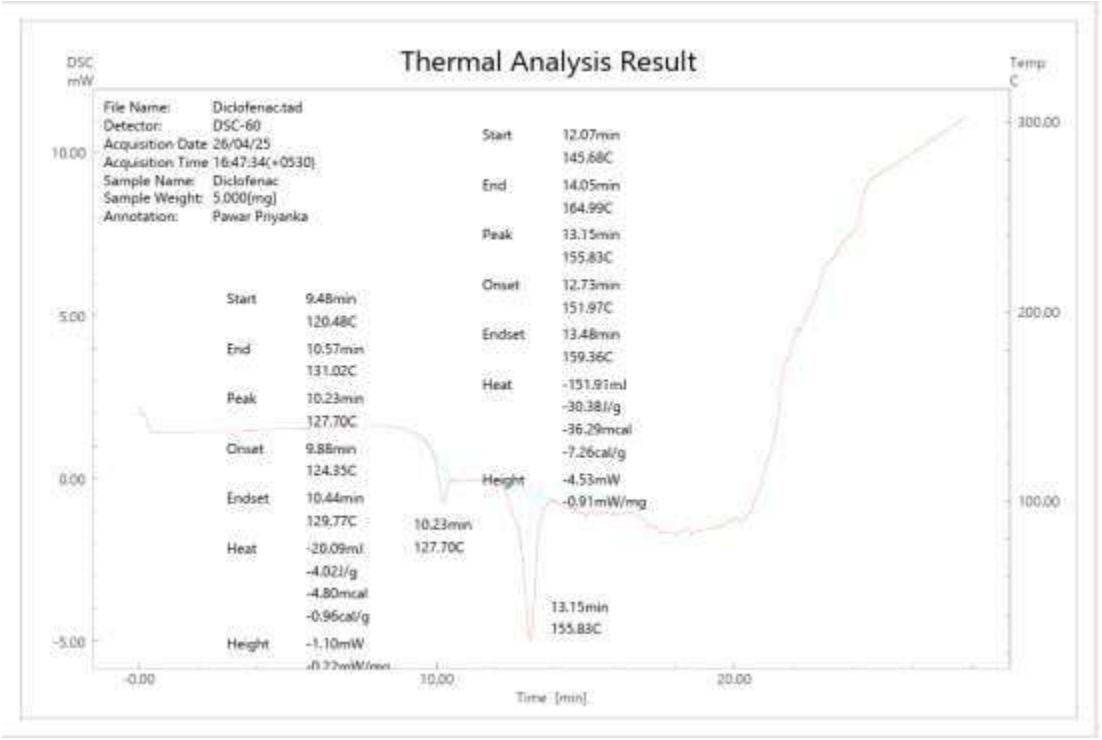


Fig :- Diclofenac + Excepients

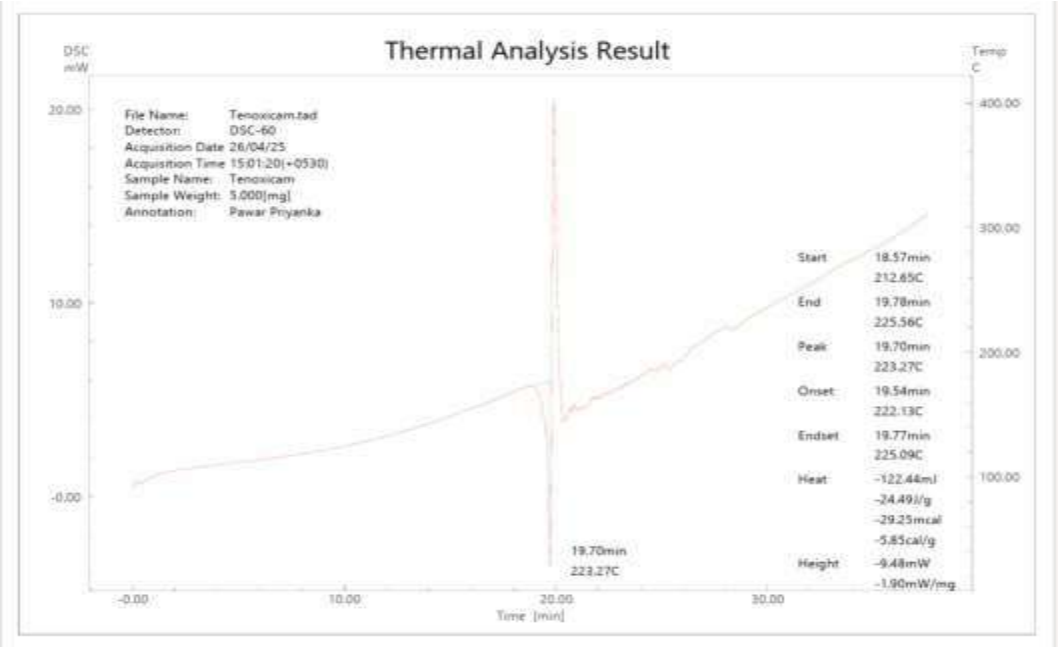


Fig :- Tenoxicam

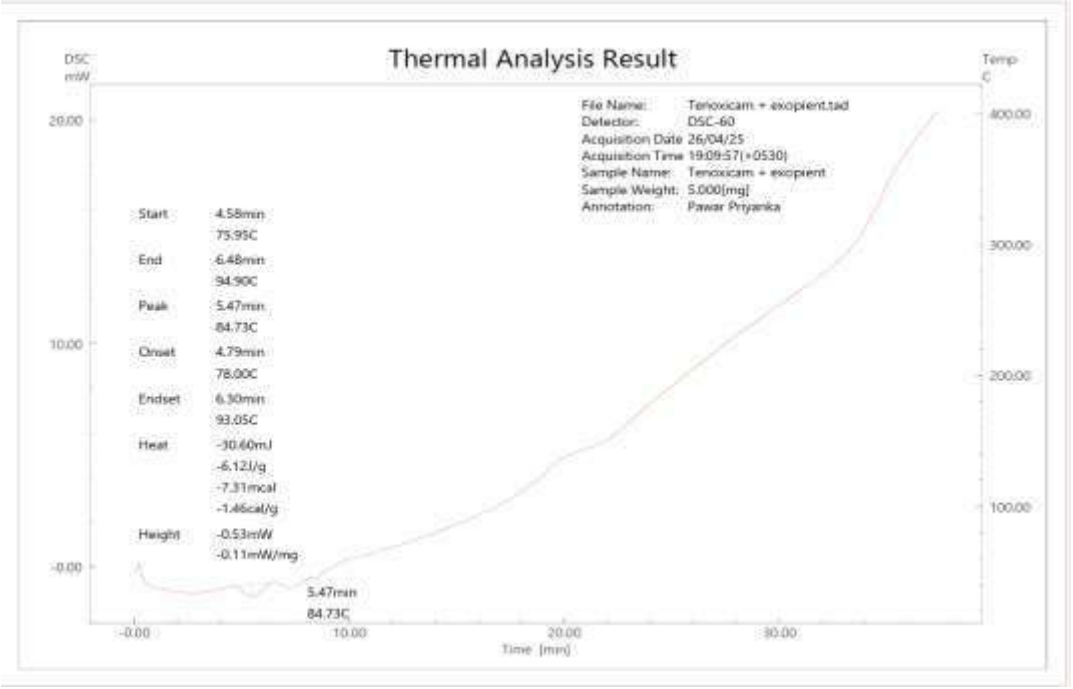


Fig :- Tenoxicam+ Excepients

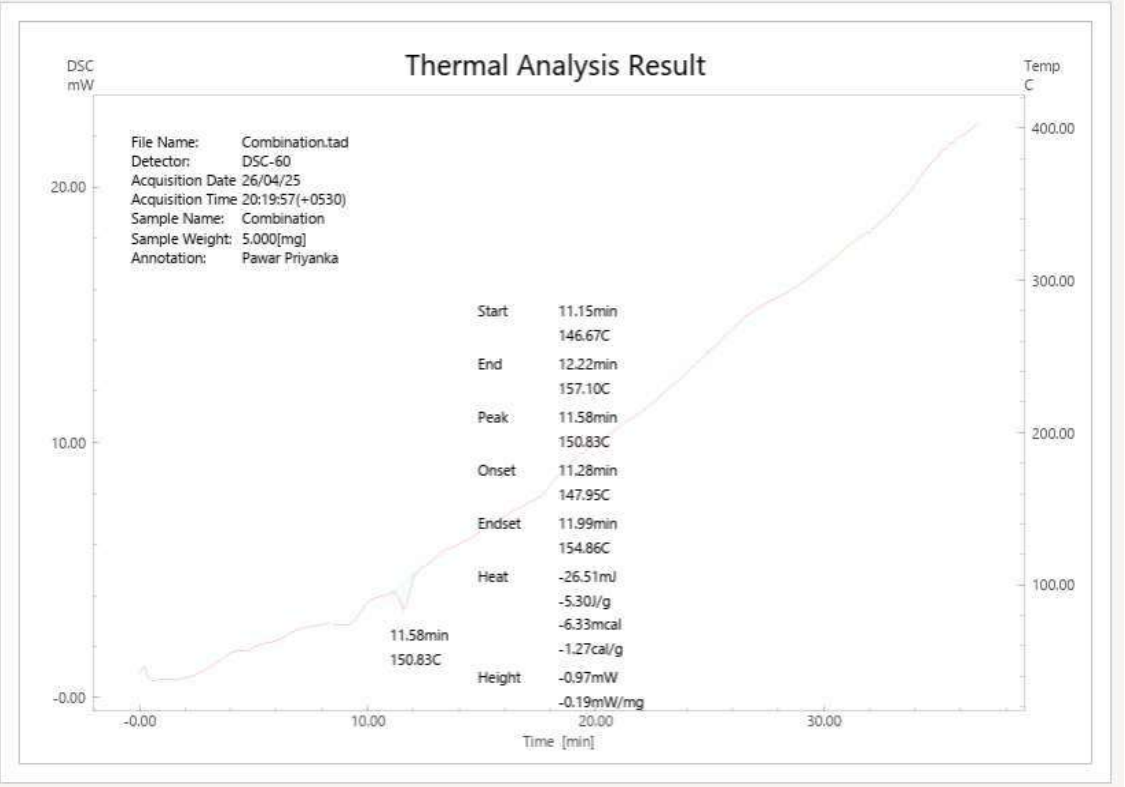


Fig :- Combination

Evaluation of Pre-Compression Parameters

The powder blends of both immediate-release and sustained-release layers were evaluated for flow properties before compression.

Table: Pre-Compression Parameters

Parameter	Immediate-Release Blend	Sustained-Release Blend
Angle of Repose (°)	24.15 ± 0.32	25.48 ± 0.41
Bulk Density (g/cm³)	0.42 ± 0.03	0.45 ± 0.02
Tapped Density (g/cm³)	0.49 ± 0.02	0.52 ± 0.03
Carr's Index (%)	14.28 ± 0.45	13.46 ± 0.39
Hausner's Ratio	1.16 ± 0.02	1.15 ± 0.01

Discussion of Pre-Compression Parameters

The angle of repose values of all powder blends were found within acceptable limits, indicating good flow properties. Carr's index and Hausner's ratio values suggested satisfactory compressibility behavior and excellent flowability of the blends. The obtained results confirmed that the powder blends were suitable for direct compression method.

Post-Compression Evaluation

The prepared bilayer tablets were evaluated for various post-compression parameters including hardness, thickness, friability, drug content uniformity, and disintegration time.

The tablets showed satisfactory mechanical strength with acceptable hardness and low friability values. Uniformity in tablet weight and thickness indicated proper die filling and compression process. Drug content analysis confirmed uniform distribution of both Diclofenac Sodium and Tenoxicam in the formulation.

The immediate-release layer exhibited rapid disintegration due to the presence of crospovidone and sodium starch glycolate, whereas the sustained-release layer maintained tablet integrity for prolonged drug release because of HPMC K100M and ethyl cellulose polymers.

Calibration Curve

The calibration curve of Diclofenac Sodium and Tenoxicam was prepared using UV-Visible spectrophotometry for quantitative estimation of drug concentration during dissolution studies. Standard solutions of different

concentrations were prepared and analyzed at their respective λmax values.
Diclofenac Sodium showed linearity in the concentration range of 2–12 µg/mL at 276 nm, while Tenoxicam exhibited linearity in the range of 2–20 µg/mL at 368 nm. The calibration curves obeyed Beer-Lambert's law with correlation coefficient (R^2) values close to 0.999, indicating excellent linear relationship between concentration and absorbance.

Table: Calibration Data for Diclofenac Sodium

Concentration (µg/mL)	Absorbance
2	0.0712
4	0.1428
6	0.2145
8	0.2871
10	0.3584

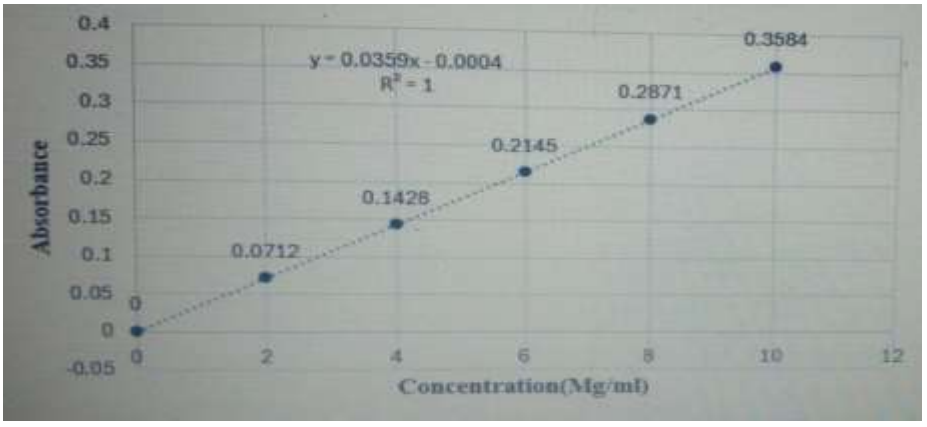
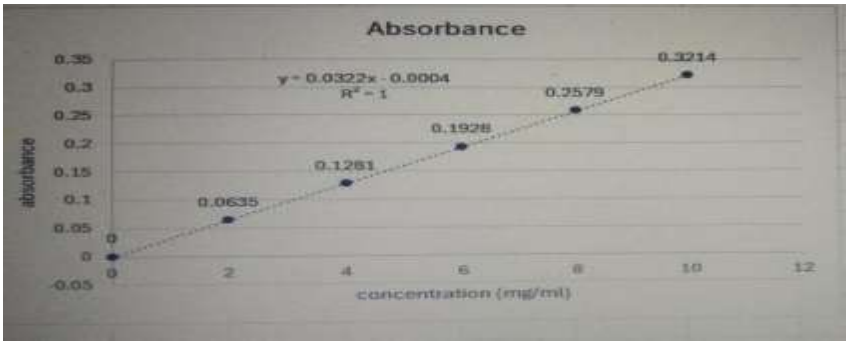


Table: Calibration Data for Tenoxicam

Concentration (µg/mL)	Absorbance
2	0.0635
4	0.1281
6	0.1928
8	0.2579
10	0.3214



The linearity of both drugs confirmed the suitability of the analytical method for accurate estimation during formulation and dissolution studies.

In Vitro Dissolution Study

The dissolution study demonstrated dual-release characteristics of the bilayer tablet formulation

Immediate Release Layer – Diclofenac Sodium

Sr. No.	Time (min)	% Drug Release
1	0	0
2	5	24.6
3	10	41.8
4	15	58.9
5	20	71.5
6	30	84.3
7	45	92.7
8	60	98.4

Sustained Release Layer – Tenoxicam

Sr. No.	Time (hr)	% Drug Release
1	0	0
2	1	12.4
3	2	21.8
4	4	36.5
5	6	48.9
6	8	59.7
7	10	68.4
8	12	76.2
9	16	85.6
10	20	92.1
11	24	98.3

Interpretation of Dissolution Data

The dissolution study demonstrated that the immediate release layer containing Diclofenac Sodium exhibited rapid drug release, with approximately 84% drug release observed within 30 minutes and nearly complete release within 1 hour. This rapid release profile indicates the suitability of the formulation for quick onset of analgesic action.

The sustained release layer containing Tenoxicam showed a controlled and prolonged drug release pattern over 24 hours. Approximately 50% of the drug was released within 6 hours, while complete release was achieved at the end of 24 hours. The sustained release behavior confirms the effectiveness of the polymer matrix system in maintaining

prolonged therapeutic activity and controlled pain management.

Angle of Repose

Table: Angle of Repose of Immediate-Release Diclofenac Sodium Formulations

Formulation Code	Height (h) (cm)	Radius (r) (cm)	Angle of Repose (θ°)	Flow Property
F1	3.1	6.8	24.50 ± 0.21	Excellent
F2	3.2	6.9	24.87 ± 0.18	Excellent
F3	3.3	7.0	25.24 ± 0.26	Excellent
F4	3.4	7.1	25.58 ± 0.19	Excellent
F5	3.5	7.2	25.92 ± 0.24	Excellent
F6	3.6	7.3	26.18 ± 0.22	Excellent
F7	3.7	7.4	26.45 ± 0.20	Excellent
F8	3.8	7.5	26.82 ± 0.17	Excellent
F9	3.9	7.6	27.14 ± 0.23	Excellent

Table: Angle of Repose of Sustained-Release Tenoxicam Formulations

Formulation Code	Height (h) (cm)	Radius (r) (cm)	Angle of Repose (θ°)	Flow Property
F1	3.2	6.7	25.52 ± 0.18	Excellent
F2	3.3	6.8	25.88 ± 0.21	Excellent
F3	3.4	6.9	26.14 ± 0.20	Excellent
F4	3.5	7.0	26.47 ± 0.16	Excellent
F5	3.6	7.1	26.82 ± 0.24	Excellent
F6	3.7	7.2	27.15 ± 0.19	Excellent
F7	3.8	7.3	27.48 ± 0.22	Excellent
F8	3.9	7.4	27.74 ± 0.18	Excellent
F9	4.0	7.5	28.06 ± 0.20	Excellent

The angle of repose values for all formulations were found within the acceptable range of 24°–30°, indicating excellent flow properties of the powder blends. The results confirmed that both immediate-release and sustained-release formulations possessed satisfactory flowability suitable for direct compression technique. The good flow behavior may be attributed to the proper selection of excipients and uniform particle size distribution within the formulation blends.

Discussion

The bilayer tablet approach successfully combined immediate-release and sustained-release drug delivery in a single dosage form. Diclofenac Sodium provided rapid onset of analgesic action, while Tenoxicam maintained prolonged anti-inflammatory activity.

The direct compression technique proved suitable for bilayer tablet preparation due to simplicity, cost-effectiveness, and minimal processing steps. The selected excipients produced tablets with acceptable

physicochemical properties and satisfactory release profiles.
Crospovidone and sodium starch glycolate effectively enhanced disintegration of the immediate-release layer. and ethyl cellulose successfully controlled the release rate of Tenoxicam by forming a diffusion-controlled matrix system.
Among all formulations, F8 showed optimum performance with:

- Rapid disintegration
- Acceptable hardness
- Low friability
- Uniform drug content
- Desired dual drug release pattern

The optimized formulation complied with pharmacopeial standards and demonstrated suitability for controlled pain management therapy.

Post-Compression Comparison Table

Table: Post-Compression Parameters of Bilayer Tablet Formulations (F1–F9)

Batch Code	Hardness (kg/cm²)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Drug Content (%)
F1	7.1	3.5	14	1.01	97.8
F2	6.8	3.4	13	0.95	98.5
F3	6.6	3.3	12	0.91	99.1
F4	7.2	3.6	14	0.97	97.6
F5	7.5	3.8	16	1.08	96.9
F6	6.9	3.5	13	0.89	99.0
F7	7.1	3.6	14	0.87	98.8
F8	6.7	3.4	11	0.84	99.6
F9	6.5	3.3	10	0.81	99.8

The friability values of most formulations were found to be within acceptable limits (<1%), indicating satisfactory mechanical strength of the prepared bilayer tablets. However, formulations F1 and F5 showed slightly higher friability values of 1.01% and 1.08%, respectively."

Conclusion

The present study successfully focused on the formulation and in vitro evaluation of a bilayer NSAID tablet containing Diclofenac Sodium and Tenoxicam for controlled pain management. The bilayer tablet was developed with the objective of providing both immediate and sustained therapeutic action within a single dosage form. Diclofenac Sodium was incorporated into the immediate-release layer to provide rapid pain relief, while Tenoxicam was formulated into the sustained-release layer to maintain prolonged anti- inflammatory activity for an extended duration.
The bilayer tablets were prepared successfully by the direct compression method using suitable pharmaceutical excipients. Superdisintegrants such as crospovidone and sodium starch glycolate effectively enhanced the disintegration and rapid drug release of Diclofenac Sodium. Sustained-release polymers including HPMC K100M and ethyl cellulose controlled the release of Tenoxicam and maintained prolonged drug action. The selected excipients also improved the flow properties and compression behavior of the powder blends.
Pre-compression studies demonstrated satisfactory flow characteristics of all formulations, indicating suitability for direct compression. Post-compression evaluation revealed that the prepared bilayer tablets possessed acceptable hardness, thickness, friability, drug content uniformity, and disintegration time. The tablets also showed good mechanical strength and proper layer integrity without separation.
FTIR studies confirmed the compatibility of Diclofenac Sodium and Tenoxicam with the selected excipients. The characteristic peaks of both drugs were retained in the optimized formulation without any significant changes, indicating absence of drug–excipient interaction and good formulation stability.
The in vitro dissolution studies demonstrated effective dual-release behavior of the bilayer tablet system. Diclofenac Sodium exhibited rapid drug release, ensuring immediate analgesic effect, whereas Tenoxicam showed controlled

and prolonged release for sustained therapeutic action. Among all formulations, the optimized batch exhibited the best overall performance in terms of physicochemical properties and drug release profile.

Overall, the developed bilayer NSAID tablet proved to be a promising approach for effective and prolonged pain management. The formulation has the potential to improve therapeutic efficacy, reduce dosing frequency, minimize side effects associated with repeated NSAID administration, and enhance patient compliance in chronic inflammatory and painful conditions.

Reference

1. Patel DM, Patel MM. Compression coated bilayer tablet technology for controlled drug delivery system. Int J Pharm Sci Rev Res. 2011;6(1):47-52.
2. Kumar A, Sharma S, Kamble R. Bilayer tablet technology: A review. Int J Pharm Res Dev. 2013;4(8):70-80.
3. Yadav G, Bansal M, Thakur N. Bilayer tablet formulation and evaluation: A review. World J Pharm Pharm Sci. 2015;4(6):728-743.
4. Singh KP, Kumar A, Langyan N. Recent advances in bilayer tablet technology. Int Res J Pharm. 2012;3(5):44-49.
5. Soni T, Chotai N. Formulation and evaluation of bilayer tablets of diclofenac sodium. Pharm Sci Monit. 2010;1(1):34-44.
6. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bilayer tablet of metoclopramide hydrochloride and ibuprofen. AAPS PharmSciTech. 2008;9(3):818-827.
7. Kulkarni U, Bhatia M. Development and evaluation of bilayer tablets for bimodal release. Int J Pharm Investig. 2012;2(1):34-39.
8. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Varghese Publishing House; 2009.
9. Banker GS, Rhodes CT. Modern Pharmaceutics. 4th ed. CRC Press; 2005.
10. Indian Pharmacopoeia Commission. Indian Pharmacopoeia. Ghaziabad: IPC; 2022.
11. United States Pharmacopeia. USP 43–NF 38. Rockville: United States Pharmacopeial Convention; 2020.
12. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 6th ed. Pharmaceutical Press; 2009.
13. Allen LV, Popovich NG, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 9th ed. Wolters Kluwer; 2011.
14. Dash S, Murthy PN, Nath L. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010;67(3):217-223.
15. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123-133.
16. Higuchi T. Mechanism of sustained action medication. J Pharm Sci. 1963;52(12):1145-1149.
17. Korsmeyer RW, Gurny R, Doelker E. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(1):25-35.
18. Gohel MC, Panchal MK. Novel use of similarity factors in dissolution profile comparison. AAPS PharmSciTech. 2002;3(2):1-6.
19. Reddy KR, Mutalik S, Reddy S. Once-daily sustained-release matrix tablets of nicorandil. AAPS PharmSciTech. 2003;4(4):480-488.
20. Vyas SP, Khar RK. Controlled Drug Delivery Concepts and Advances. Vallabh Prakashan; 2012.
21. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics: A Treatise. 3rd ed. Vallabh Prakashan; 2014.
22. Sweetman SC. Martindale: The Complete Drug Reference. 36th ed. Pharmaceutical Press; 2009.
23. Tripathi KD. Essentials of Medical Pharmacology. 8th ed. Jaypee Brothers Medical Publishers; 2018.
24. Brunton LL, Hilal-Dandan R, Knollmann BC. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 13th ed. McGraw Hill; 2018.
25. Katzung BG. Basic and Clinical Pharmacology. 14th ed. McGraw Hill Education; 2018.
26. Rang HP, Dale MM, Ritter JM. Rang and Dale's Pharmacology. 8th ed. Elsevier; 2016.
27. Pawar HA, Gharat PR. Bilayer tablet: A novel approach for drug delivery system. Int J Pharm Sci Rev Res. 2010;3(1):15-21.
28. Deshpande RD, Gowda DV, Mahammed N. Controlled release bilayer tablets: An updated review. Int J Pharm Tech Res. 2011;3(2):1039-1048.
29. Kaur T, Gill B, Kumar S. Bilayer tablets: A review. Int Res J Pharm Biol Sci. 2013;2(4):76-84.
30. Gupta AK, Gupta V. NSAIDs in pain management and their pharmaceutical applications. Int J Pharm Sci Drug Res. 2015;7(3):145-152.
31. Rainsford KD. Anti-inflammatory drugs in the 21st century. Subcell Biochem. 2007;42:3-27.
32. Brune K, Hinz B. The discovery and development of anti-inflammatory drugs. Arthritis Rheumatol. 2004;50(8):2391-2399.
33. Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac. Clin Pharmacokinet. 1997;33(3):184-213.
34. Todd PA, Clissold SP. Tenoxicam: A review of pharmacological properties and therapeutic efficacy. Drugs. 1991;41(4):625-646.
35. Hardman JG, Limbird LE. Goodman and Gilman's Pharmacological Basis of Therapeutics. 10th ed. McGraw Hill; 2001.
36. Aulton ME. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 4th ed. Churchill Livingstone Elsevier; 2013.
37. Remington JP. Remington: The Science and Practice of Pharmacy. 21st ed. Lippincott Williams and Wilkins; 2006.
38. Liberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Forms: Tablets. Vol

II. Marcel Dekker Inc.; 2005.

39. Robinson JR, Lee VHL. Controlled Drug Delivery: Fundamentals and Applications. 2nd ed. Marcel Dekker; 1987.
40. Colombo P, Bettini R, Peppas NA. Drug diffusion front movement in swellable matrices. J Control Release. 1999;61(1-2):83-91.