FORMULATION AND EVALUATION OF A GASTRO-PROTECTED BILAYER TABLET OF TRAMADOL AND INDOMETHACIN

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Abstract

The present study aimed to develop and evaluate a gastro-protected bilayer tablet containing Tramadol Hydrochloride and Indomethacin to provide combined analgesic and anti-inflammatory therapy through sustained and site-specific drug delivery. Tramadol Hydrochloride, a highly water-soluble analgesic, was incorporated into a sustained-release layer, whereas poorly water-soluble Indomethacin was formulated into a gastro-protected layer designed to restrict drug release in acidic gastric conditions and promote release after transition to intestinal pH. Preformulation studies confirmed the identity and physicochemical characteristics of both drugs. FTIR analysis indicated retention of characteristic drug functional groups without major evidence of chemical incompatibility. UV-visible calibration curves demonstrated satisfactory linearity over 2–20 µg/mL for both drugs. Five bilayer formulations (F1–F5) were prepared by varying HPMC K100M and ethyl cellulose in the Tramadol layer and sodium starch glycolate in the Indomethacin layer. Pre-compression parameters indicated acceptable flow and compressibility of the powder blends. The prepared tablets exhibited satisfactory physical characteristics, including adequate hardness, friability below 1%, uniform weight, and consistent drug content. Tramadol Hydrochloride demonstrated polymer-dependent sustained release over 12 h, while Indomethacin showed effective gastro-protection, with only 2.91–3.76% drug release during the initial 2 h in 0.1 N HCl, followed by rapid release in phosphate buffer pH 6.8. Among the formulations, F3 exhibited the most desirable dissolution profile, releasing 96.28 ± 1.39% Tramadol Hydrochloride at 12 h and 99.14 ± 1.06% Indomethacin at 4 h. Overall, F3 was identified as the optimized formulation,

demonstrating the feasibility of bilayer technology for combined sustained and gastro-protected drug delivery.

Keywords: Tramadol Hydrochloride; Indomethacin; Bilayer tablet; Gastro-protection; Sustained-release drug delivery.

INTRODUCTION

1.1.Overview of Oral Drug Delivery Systems

Oral drug delivery is one of the most widely accepted and extensively utilized routes for the administration of therapeutic agents. The popularity of the oral route is primarily associated with its convenience, ease of administration, patient acceptance, relatively low manufacturing cost, and suitability for both immediate and long-term pharmacotherapy. Compared with parenteral routes, oral administration generally eliminates the need for specialized personnel and invasive procedures, thereby improving patient compliance, particularly during prolonged treatment.

The gastrointestinal tract provides a large physiological surface for drug absorption. Following oral administration, a dosage form undergoes a series of processes including disintegration, dissolution, drug release, permeation across the gastrointestinal membrane, and subsequent entry of the drug into the systemic circulation. The efficiency of these processes is influenced by physicochemical properties of the drug as well as physiological conditions within the gastrointestinal tract [1].

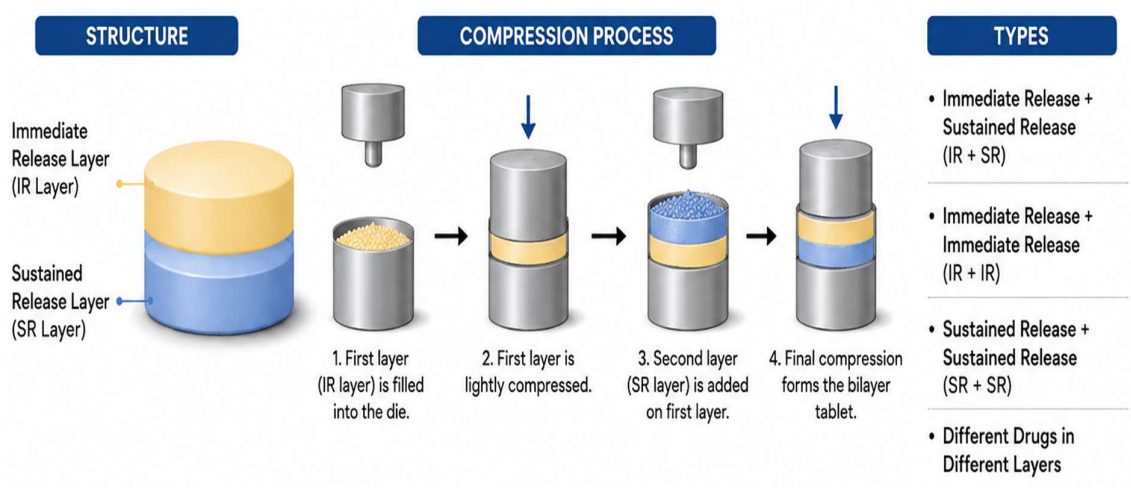

Figure 1: Bilayer tablet drug delivery system

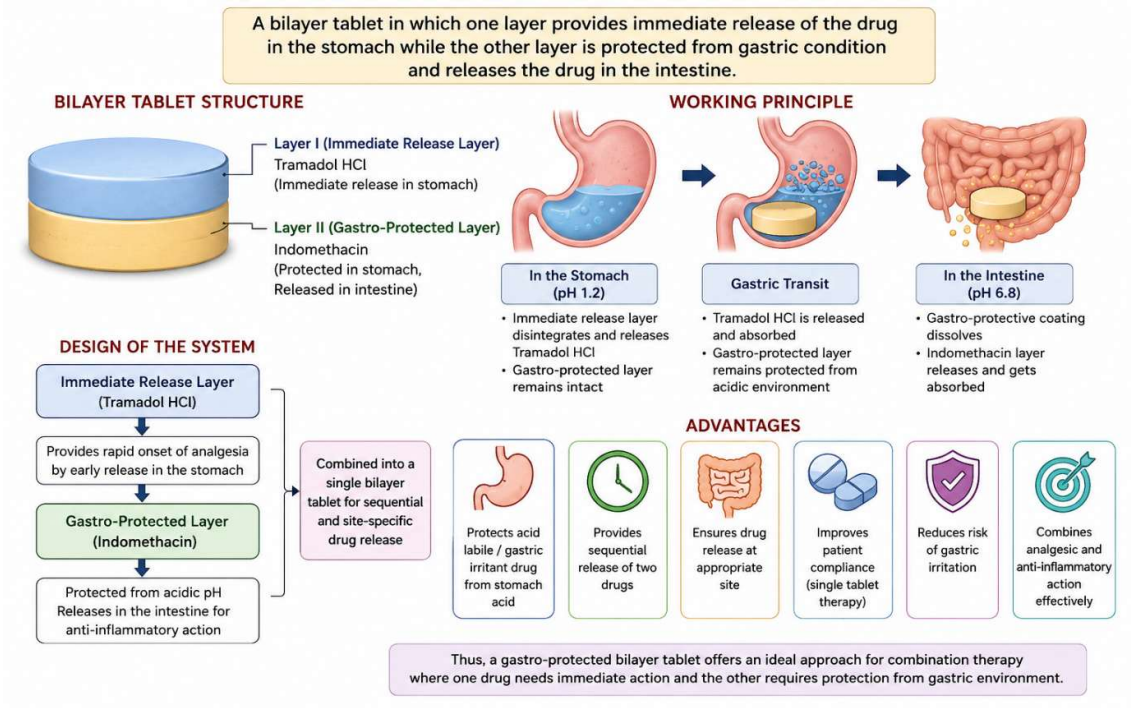

Figure 2: Concept of gastro-protective drug delivery system

1.1.Aim

To formulate and evaluate a gastro-protected bilayer tablet containing Tramadol Hydrochloride and Indomethacin for improved analgesic and anti-inflammatory therapy with reduced gastric irritation and enhanced drug release characteristics.

1.2. Objectives

- To perform preformulation studies of tramadol hydrochloride and indomethacin including organoleptic evaluation, melting point determination, and solubility studies.
- To study the compatibility between drugs and excipients using FTIR spectroscopy.
- To formulate a sustained-release layer of tramadol hydrochloride using suitable polymers.
- To formulate a gastro-protected indomethacin layer using enteric coating approach to minimize gastric irritation.
- To prepare bilayer tablets by direct compression technique using suitable excipients and polymers.
- To evaluate the prepared bilayer tablets for pre-compression and post-compression parameters such as flow properties, hardness, friability, thickness, weight variation, and drug content.
- To perform in vitro dissolution studies and analyze the drug release profile of the formulated bilayer tablets.

SCOPE OF THE STUDY

The present study focused on the formulation and evaluation of a gastro-protected bilayer tablet containing Tramadol Hydrochloride and Indomethacin for improved analgesic and anti-inflammatory therapy. The study aimed to develop a bilayer tablet capable of providing dual therapeutic action with reduced gastric irritation associated with indomethacin.

The work included preformulation studies such as organoleptic evaluation, melting point determination, solubility studies, and drug–excipient compatibility analysis. Suitable polymers and excipients were selected for the preparation of sustained-release and gastro-protected layers. The bilayer tablets were formulated using direct compression technique followed by enteric coating method.

The prepared formulations were evaluated for various pre-compression parameters including angle of repose, bulk density, tapped density, Carr’s index, and Hausner’s ratio. Post-compression evaluation such as hardness, friability, thickness, weight variation, and drug content uniformity was also carried out. The study further included in vitro dissolution studies to assess the drug release profile in different dissolution media.

The developed bilayer tablet was expected to improve therapeutic efficacy, enhance patient compliance, and reduce gastrointestinal side effects associated with conventional indomethacin therapy.

Table 1: Drug profile of Tramadol hydrochloride

S. No	Parameter	Description
1	Category	Centrally acting opioid analgesic
2	Chemical Name	(±)-cis-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride
3	Molecular Formula	$C_{16}H_{25}NO_2 \cdot HCl$
4	Molecular Weight	299.84 g/mol
5	Appearance	White crystalline powder
6	Solubility	Freely soluble in water and methanol
7	Melting Point	180–184 °C
8	Mechanism of Action	Acts by binding to μ-opioid receptors and inhibiting reuptake of norepinephrine and serotonin
9	Biological Half-Life	Approximately 5–7 h
10	Therapeutic Use	Management of moderate to severe pain
11	Dose	50–100 mg
12	Storage Condition	Store in a cool and dry place

Table 2: Drug profile of Indomethacin

S. No	Parameter	Description
1	Category	Non-steroidal anti-inflammatory drug (NSAID)

2	Chemical Name	1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid
3	Molecular Formula	$C_{19}H_{16}ClNO_4$
4	Molecular Weight	357.79 g/mol
5	Appearance	Yellow crystalline powder
6	Solubility	Slightly soluble in water; soluble in methanol and ethanol
7	Melting Point	152–154 °C
8	Mechanism of Action	Inhibits cyclooxygenase enzyme and suppresses prostaglandin synthesis
9	Biological Half-Life	Approximately 4–5 h
10	Therapeutic Use	Anti-inflammatory, analgesic, and antipyretic agent
11	Dose	25–50 mg
12	Storage Condition	Store in tightly closed container protected from light

Excipients

S. No	Excipient	Category/Function
1	HPMC K100M	Sustained-release polymer
2	Ethyl cellulose	Release retardant
3	Microcrystalline cellulose	Diluent
4	Sodium starch glycolate	Superdisintegrant
5	Lactose monohydrate	Diluent

6	Polyvinylpyrrolidone K30	Binder
7	Talc	Glidant
8	Magnesium stearate	Lubricant
9	Eudragit L100	Enteric coating polymer
10	Dibutyl phthalate	Plasticizer
11	Isopropyl alcohol	Solvent
12	Acetone	Co-solvent

METHODOLOGY

1.1.Organoleptic Evaluation

The samples of Tramadol Hydrochloride and Indomethacin were examined visually for their physical appearance, colour, odour, and texture. The observations were recorded to confirm the purity and identity of the drugs prior to formulation development.

1.2.Determination of Melting Point

The melting point of tramadol hydrochloride and indomethacin was determined by capillary tube method. A small quantity of each drug was filled separately into one end of a capillary tube previously sealed at one side. The capillary tube was placed in a melting point apparatus and heated gradually. The temperature at which the drug sample completely melted was recorded as the melting point. The experiment was carried out in triplicate and the average value was calculated.

1.3.Solubility Studies

Solubility studies were performed to determine the solubility behaviour of the drugs in various solvents. Excess quantity of tramadol hydrochloride and indomethacin was added separately into test tubes containing distilled water, methanol, ethanol, 0.1 N hydrochloric acid, and phosphate buffer pH 6.8. The mixtures were shaken continuously using a mechanical shaker for 24 h at room temperature to achieve equilibrium. The solutions were then filtered through

Whatman filter paper and suitably diluted. The absorbance was measured using UV-visible spectrophotometer at the respective λmax values and solubility was determined.

1.4.Drug–Excipient Compatibility Studies

Fourier Transform Infrared spectroscopy was carried out to investigate the compatibility between the drugs and excipients used in the formulation. The pure drugs and their physical mixtures with excipients were mixed individually with potassium bromide and compressed into translucent pellets using a hydraulic press. The pellets were scanned using FTIR spectrophotometer in the range of 4000–400 cm^{-1}. The obtained spectra were analyzed for the presence of characteristic peaks and any possible interaction between the drugs and excipients

1.5.Preparation of Tramadol Sustained-Release Layer

The sustained-release layer containing tramadol hydrochloride was prepared by direct compression method. The required quantities of tramadol hydrochloride, HPMC K100M, ethyl cellulose, and microcrystalline cellulose were weighed accurately and passed through sieve no. 60 separately to obtain uniform particle size distribution. All the sieved ingredients were transferred into a mortar and blended uniformly for 15 min to ensure homogenous mixing. Polyvinylpyrrolidone K30 was added as binder and mixed thoroughly. Talc and magnesium stearate were added finally as glidant and lubricant, respectively, and the blend was mixed gently for an additional 3–5 min. The prepared powder blend was stored in airtight containers until further use.

Table 3: Formulation of bilayer tablet

Ingredients (mg)	F1	F2	F3	F4	F5
Tramadol Sustained-Release Layer					
Tramadol Hydrochloride	100	100	100	100	100
HPMC K100M	40	50	60	70	80
Ethyl cellulose	20	25	30	35	40

Microcrystalline cellulose	70	55	40	25	10
Polyvinylpyrrolidone K30	10	10	10	10	10
Talc	5	5	5	5	5
Magnesium stearate	5	5	5	5	5
Indomethacin Gastro-Protected Layer					
Indomethacin	50	50	50	50	50
Sodium starch glycolate	10	12.5	15	17.5	20
Microcrystalline cellulose	55	52.5	50	47.5	45
Lactose monohydrate	40	40	40	40	40
Polyvinylpyrrolidone K30	10	10	10	10	10
Talc	5	5	5	5	5
Magnesium stearate	5	5	5	5	5
Total Tablet Weight (mg)	**425**	**425**	**425**	**425**	**425**

1.6.Preparation of Indomethacin Immediate-Release Layer

The indomethacin layer was prepared by direct compression method. Accurately weighed quantities of indomethacin, sodium starch glycolate, lactose monohydrate, and microcrystalline cellulose were passed through sieve no. 60 individually. The ingredients were blended

thoroughly for 15 min in a mortar to achieve uniform distribution of the drug and excipients. Polyvinylpyrrolidone K30 was added and mixed uniformly. Talc and magnesium stearate were added at the final stage and mixed gently for 3 min to improve flow properties and reduce friction during compression. The prepared blend was preserved in airtight containers for subsequent compression.

1.7.Compression of Bilayer Tablets

The bilayer tablets were prepared using a rotary tablet compression machine fitted with suitable punches and dies. Initially, the accurately weighed quantity of tramadol sustained-release layer blend was introduced into the die cavity and lightly compressed to form the first layer. Subsequently, the weighed quantity of indomethacin layer blend was added carefully over the pre-compressed tramadol layer. Final compression was then carried out to obtain bilayer tablets of desired hardness and thickness. The prepared tablets were visually inspected for any physical defects such as capping, lamination, cracking, or layer separation. The tablets were collected and stored in airtight containers for further evaluation.

1.8.Enteric Coating of Bilayer Tablets

Enteric coating was performed to provide gastro-protection to the indomethacin-containing layer and to minimize gastric irritation. The coating solution was prepared by dissolving Eudragit L100 in a mixture of isopropyl alcohol and acetone under continuous stirring. Dibutyl phthalate was added as plasticizer and the solution was stirred until a clear homogeneous coating solution was obtained. The prepared bilayer tablets were loaded into a conventional coating pan. The coating solution was sprayed uniformly onto the rotating tablets under controlled conditions. The inlet temperature and pan speed were maintained appropriately throughout the coating process to ensure uniform coating distribution.

The coating process was continued until the desired percentage weight gain was achieved. The coated tablets were dried at room temperature for 24 h to remove residual solvents and stored in airtight containers.

1.9.Evaluation of Powder Blend

1.9.1. Angle of Repose

The angle of repose was determined by fixed funnel method. The powder blend was allowed to flow through a funnel fixed at a particular height onto a flat surface until a cone-shaped heap was formed. The height and radius of the powder cone were measured and the angle of repose was calculated.

$$\theta = \tan^{-1} (h/r)$$

1.9.2. Bulk Density

Accurately weighed quantity of powder blend was transferred into a graduated measuring cylinder and the untapped volume was recorded. Bulk density was calculated using the following formula:

$$\text{Bulk Density (BD)} = W / V_0$$

Where:

- W = weight of the powder (g)
- V_0 = initial bulk volume (mL)

1.9.3. Tapped Density

The measuring cylinder containing powder blend was tapped mechanically until a constant volume was obtained. The tapped volume was noted and tapped density was calculated.

$$\text{Tapped Density (TD)} = W / V_f$$

Where:

- W = weight of powder (g)
- V_f = final tapped volume (mL)

1.9.4. Carr's Compressibility Index

Carr's compressibility index was determined from bulk density and tapped density values.

$$\text{Carr's Index (\%)} = (TD - BD / TD) \times 100$$

1.9.5. Hausner's Ratio

Hausner's ratio was calculated to evaluate flow properties of the powder blend.

Hausner's Ratio=TD/BD [61, 62]

1.10. Evaluation of Bilayer Tablets

1.10.1. Thickness

The thickness of tablets was determined using Vernier calipers. Three tablets were selected randomly and their thickness was measured individually. The average thickness was calculated.

1.10.2. Hardness

The hardness of tablets was measured using Monsanto hardness tester. Tablets were placed between the anvils of the tester and force was applied until the tablet broke. The hardness was recorded in kg/cm^2.

1.10.3. Friability

Friability test was carried out using Roche friabilator. Pre-weighed tablets were placed in the friabilator and rotated at 25 rpm for 4 min. After completion of the test, the tablets were dedusted and reweighed. Percentage friability was calculated.

1.10.4. Weight Variation Test

Twenty tablets were selected randomly and weighed individually using digital balance. The average weight was calculated and individual tablet weights were compared with the average weight.

1.10.5. Drug Content Uniformity

Ten tablets were weighed and powdered finely. Powder equivalent to one tablet was accurately weighed and transferred into a volumetric flask containing suitable solvent. The solution was sonicated for complete drug extraction and filtered through Whatman filter paper. Appropriate dilutions were prepared and analyzed using UV-visible spectrophotometer at the respective wavelengths.

1.10.6. In Vitro Dissolution Study

The in vitro dissolution study was performed using USP type II paddle dissolution apparatus. The dissolution medium consisted of 900 mL of 0.1 N hydrochloric acid for the initial 2 h followed by phosphate buffer pH 6.8 for the remaining period. The temperature was maintained at 37 ± 0.5 °C and the paddle speed was adjusted to 50 rpm. At predetermined time intervals, 5 mL samples were withdrawn and replaced immediately with equal volume of fresh dissolution medium maintained at the same temperature. The withdrawn samples were filtered, diluted appropriately, and analyzed spectrophotometrically at suitable wavelengths for tramadol hydrochloride and indomethacin. The cumulative percentage drug release was calculated and dissolution profiles were plotted

RESULTS AND DISCUSSION

1.11. Physical Appearance and Organoleptic Characteristics

The physical characteristics of Tramadol Hydrochloride and Indomethacin were evaluated visually for appearance, colour, odour, and texture.

Table 4: Physical appearance and organoleptic characteristics of drugs

Parameter	Tramadol Hydrochloride	Indomethacin
Physical appearance	Crystalline powder	Crystalline powder
Colour	White to off-white	Pale yellow to yellow
Odour	Odourless	Practically odourless
Texture	Fine, crystalline powder	Fine, crystalline powder

Tramadol Hydrochloride was observed as a white to off-white, fine crystalline powder with no characteristic odour, whereas Indomethacin appeared as a pale-yellow to yellow, fine crystalline powder and was practically odourless. The observed physical characteristics were consistent with the expected descriptions of the respective drug substances. No unusual discoloration, visible contamination, agglomeration, or abnormal physical characteristics were observed. These preliminary observations indicated that both drug samples possessed acceptable organoleptic characteristics and were considered suitable for further preformulation investigations. However, organoleptic examination alone does not establish chemical purity

and was therefore supported by melting-point, solubility, and subsequent analytical characterization.

1.12. Determination of Melting Point

The melting points of Tramadol Hydrochloride and Indomethacin were determined in triplicate using the capillary tube method.

Table 5: Melting-point determination of Tramadol Hydrochloride and Indomethacin

Drug	Trial 1 (°C)	Trial 2 (°C)	Trial 3 (°C)	Mean ± SD (°C)
Tramadol Hydrochloride	180.2	181.0	180.6	180.60 ± 0.40
Indomethacin	152.4	153.1	152.8	152.77 ± 0.35

The melting point of Tramadol Hydrochloride was found to be 180.60 ± 0.40°C, while Indomethacin exhibited a melting point of 152.77 ± 0.35°C. The narrow variation among the three measurements demonstrated good repeatability of the capillary melting-point determination.

The experimentally obtained melting temperatures were close to the characteristic melting behavior expected for the respective drug substances. A relatively sharp melting range is generally indicative of a well-defined crystalline material, whereas substantial impurities may broaden or depress the observed melting range. The absence of a pronounced melting-point depression therefore provided preliminary support for the identity and acceptable quality of the drug samples. Nevertheless, melting point should be considered a preliminary identification and purity assessment rather than definitive evidence of chemical purity.

1.13. Solubility Studies

The equilibrium solubility of Tramadol Hydrochloride and Indomethacin was evaluated in distilled water, methanol, ethanol, 0.1 N HCl, and phosphate buffer pH 6.8 after shaking for 24 h.

Table 6: Solubility profile of Tramadol Hydrochloride and Indomethacin

Solvent/Medium	Tramadol HCl (mg/mL), Mean ± SD	Solubility behaviour	Indomethacin (mg/mL), Mean ± SD	Solubility behaviour
Distilled water	482.6 ± 8.4	Freely soluble	0.012 ± 0.002	Practically insoluble
Methanol	168.4 ± 4.7	Soluble	28.64 ± 0.72	Soluble
Ethanol	82.7 ± 3.1	Soluble	17.82 ± 0.51	Soluble
0.1 N HCl	526.3 ± 9.6	Freely soluble	0.006 ± 0.001	Practically insoluble
Phosphate buffer pH 6.8	451.8 ± 7.9	Freely soluble	1.86 ± 0.08	Slightly soluble

The solubility study demonstrated a marked difference between the two active pharmaceutical ingredients. Tramadol Hydrochloride exhibited high aqueous solubility, with representative equilibrium solubilities of 482.6 ± 8.4 mg/mL in distilled water, 526.3 ± 9.6 mg/mL in 0.1 N HCl, and 451.8 ± 7.9 mg/mL in phosphate buffer pH 6.8. It also showed appreciable solubility in methanol and ethanol, with values of 168.4 ± 4.7 and 82.7 ± 3.1 mg/mL, respectively. This high aqueous solubility is consistent with the hydrochloride salt form of tramadol and is favorable for dissolution after release from an oral tablet.

In contrast, Indomethacin demonstrated very poor aqueous solubility, showing only 0.012 ± 0.002 mg/mL in distilled water and 0.006 ± 0.001 mg/mL in 0.1 N HCl. Its extremely low solubility under acidic conditions can be attributed to its weakly acidic nature, because the drug remains predominantly unionized at low pH and therefore exhibits limited aqueous solubility.

A substantial increase in Indomethacin solubility was observed in phosphate buffer pH 6.8, where the representative solubility reached 1.86 ± 0.08 mg/mL. At a pH above its acidic pKa, a greater proportion of Indomethacin becomes ionized, thereby increasing its apparent aqueous solubility. This pH-dependent behavior is particularly relevant to the proposed gastro-protected formulation because the drug exhibits considerably more favorable dissolution conditions in intestinal-pH medium than in acidic gastric medium.

Indomethacin also exhibited substantially greater solubility in the organic solvents, with values of 28.64 ± 0.72 mg/mL in methanol and 17.82 ± 0.51 mg/mL in ethanol. These observations reflect the comparatively lipophilic nature of the molecule and may also support the selection of a suitable organic solvent during analytical method development where required.

Overall, the preformulation investigations demonstrated distinct physicochemical characteristics of the two drugs. Tramadol Hydrochloride showed high aqueous solubility, whereas Indomethacin demonstrated poor aqueous solubility with pronounced pH-dependent improvement at pH 6.8. Together with the melting-point and organoleptic observations, these results support the suitability of the samples for subsequent preformulation characterization and development of the proposed gastro-protected bilayer tablet of Tramadol Hydrochloride and Indomethacin.

1.14. Calibration Curve of Tramadol Hydrochloride and Indomethacin

Calibration curves of Tramadol Hydrochloride and Indomethacin were constructed using standard solutions in the concentration range of 2–20 µg/mL. Absorbance was measured at the respective analytical wavelength of each drug, and absorbance was plotted against concentration. The linearity of the calibration curves was evaluated using the regression equation and coefficient of determination (R^2).

1.14.1. Calibration Curve of Tramadol Hydrochloride

The calibration data for Tramadol Hydrochloride showed a progressive increase in absorbance with increasing drug concentration.

Table 7: Calibration data of Tramadol Hydrochloride

S. No.	Concentration (µg/mL)	Absorbance*
1	2	0.099
2	4	0.176
3	6	0.254
4	8	0.391
5	10	0.483

6	12	0.599
7	14	0.637
8	16	0.774
9	18	0.836
10	20	**0.971**

The calibration curve showed a nearly linear relationship between concentration and absorbance over the investigated range. Linear regression analysis provided the equation:

$y = 0.0482x - 0.0087$

with a coefficient of determination of:

$R^2 = 0.9951$

The R^2 value of 0.9951 indicated a strong correlation between Tramadol Hydrochloride concentration and absorbance. The absorbance increased from 0.099 at 2 µg/mL to 0.971 at 20 µg/mL, demonstrating concentration-dependent optical response throughout the selected analytical range.

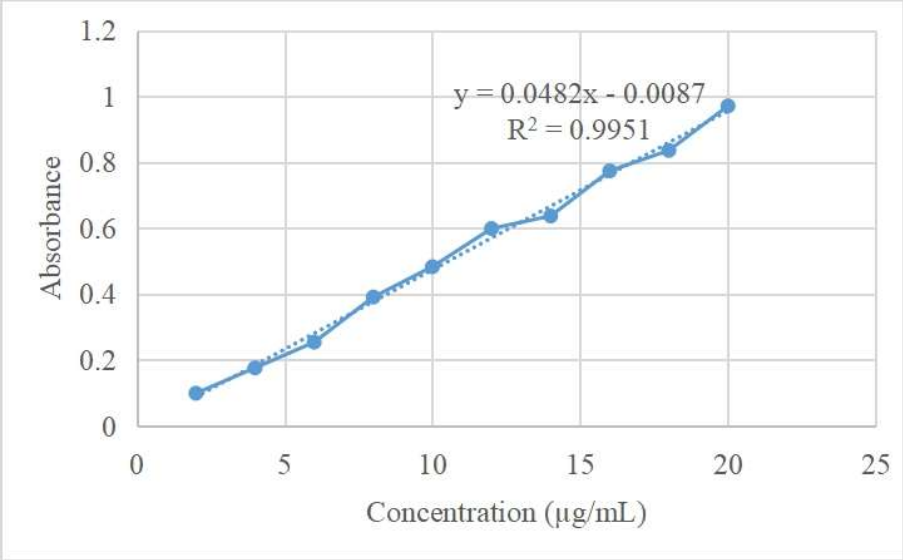

Figure 3: Calibration Curve of Tramadol Hydrochloride

Minor deviations of individual experimental points from the regression line were observed, which can occur because of normal analytical variation associated with solution preparation, dilution, pipetting, and spectrophotometric measurement. Nevertheless, the high R^2 value demonstrated satisfactory linearity of the calibration curve.

Therefore, the obtained calibration relationship was considered suitable for quantitative estimation of Tramadol Hydrochloride in subsequent formulation studies, including drug-content determination and in vitro dissolution analysis.

1.14.2. Calibration Curve of Indomethacin

The calibration curve of Indomethacin was similarly constructed over the concentration range of 2–20 µg/mL

Table 8: Calibration data of Indomethacin

S. No.	Concentration (µg/mL)	Absorbance*
1	2	0.109
2	4	0.175
3	6	0.261

4	8	0.337
5	10	0.489
6	12	0.596
7	14	0.638
8	16	0.746
9	18	0.896
10	20	0.997

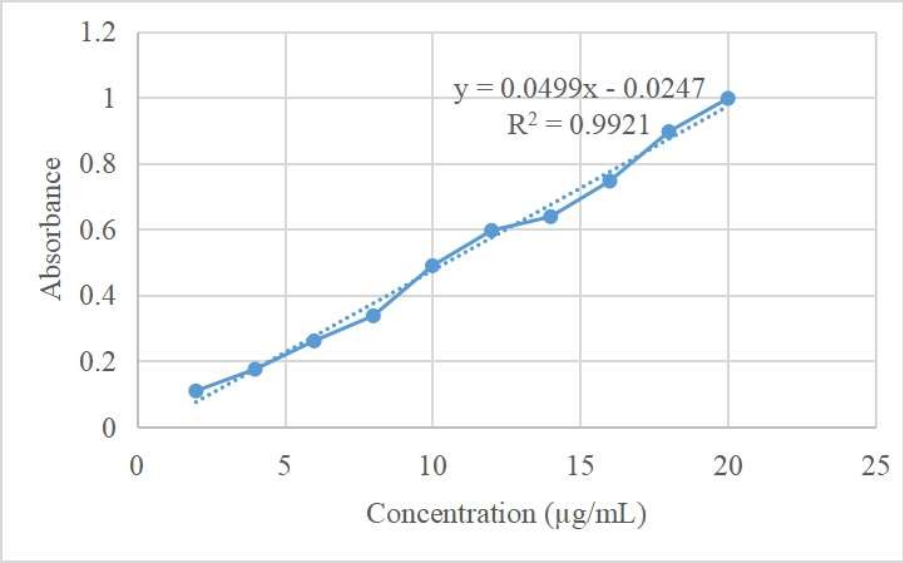

Figure 4: Calibration Curve of Indomethacin

A concentration-dependent increase in absorbance was observed throughout the investigated range. Regression analysis of the calibration data produced the equation:

$y = 0.0499x - 0.0247$

with a coefficient of determination of:

$R^2 = 0.9921$

The absorbance increased from 0.109 at 2 µg/mL to 0.997 at 20 µg/mL, demonstrating a strong positive relationship between Indomethacin concentration and absorbance. The R^2 value of 0.9921 indicated satisfactory linear correlation across the selected concentration range.

Some experimental points showed small deviations from the regression line, particularly within the intermediate concentration range. Such variations may arise from experimental factors including preparation of serial dilutions, pipetting variability, solvent or blank effects, and instrumental measurement. However, the overall concentration–absorbance relationship remained strongly linear.

The calibration curve was therefore considered suitable for the quantitative determination of Indomethacin during subsequent formulation evaluation and in vitro drug-release studies.

1.15. FTIR Spectrum of Pure Indomethacin

The FTIR spectrum of pure Indomethacin exhibited several characteristic absorption bands corresponding to the major functional groups present in the drug molecule. A broad absorption region was observed approximately between 3400 and 3200 cm^{-1}, attributable predominantly to the O–H stretching vibration of the carboxylic acid group. The broad nature of this region is consistent with hydrogen bonding commonly associated with carboxylic acid functionalities.

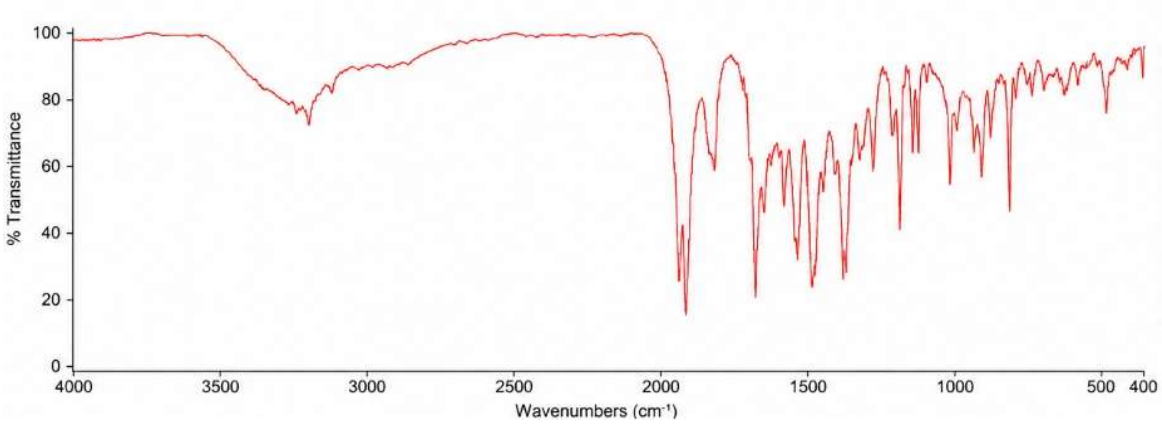

Figure 5: FTIR spectrum of pure Indomethacin

A prominent and intense absorption was observed in the carbonyl region at approximately 1710–1690 cm^{-1}, corresponding principally to C=O stretching of the carboxylic acid group. Additional strong absorption in the approximately 1680–1650 cm^{-1} region can be associated with the carbonyl-containing benzoyl functionality of Indomethacin. These carbonyl absorptions constitute important characteristic regions for identification of the drug.

Absorption bands appearing around 1600–1500 cm^{-1} were attributable mainly to aromatic C=C skeletal stretching vibrations. Multiple distinct absorptions were observed throughout this region, reflecting the aromatic structural components of Indomethacin.

The spectrum also displayed several intense peaks in the approximately 1450–1300 cm^{-1} region, which can be assigned to combinations of C–H bending, C–N vibrations, and carboxylic acid-related vibrations. Strong absorptions within approximately 1300–1000 cm^{-1} were consistent with C–O/C–N stretching and fingerprint vibrations of the molecule.

Numerous well-defined bands were further observed below 1000 cm^{-1}, representing aromatic C–H out-of-plane deformation and other fingerprint vibrations. The presence of multiple characteristic bands throughout the fingerprint region provided additional support for the identity of Indomethacin.

Overall, the spectrum demonstrated the principal functional-group regions expected for Indomethacin, particularly the broad carboxylic O–H region, strong carbonyl absorption, aromatic skeletal vibrations, and characteristic fingerprint bands. The obtained FTIR profile therefore supported the identity of the Indomethacin sample used for formulation development.

Table 9: FTIR data of pure Indomethacin

wavenumber (cm^{-1})	**Assignment**
3400–3200	O–H stretching of carboxylic acid
3000–2850	Aromatic/aliphatic C–H stretching
1710–1690	Carboxylic acid C=O stretching
1680–1650	Additional carbonyl-related stretching
1600–1500	Aromatic C=C skeletal vibrations
1450–1300	C–H bending/C–N and associated vibrations
1300–1000	C–O/C–N and fingerprint vibrations
<1000	Aromatic deformation/fingerprint region

1.16. FTIR Spectrum of Pure Tramadol Hydrochloride

The FTIR spectrum of pure Tramadol Hydrochloride also showed a characteristic pattern with prominent absorption bands across the functional-group and fingerprint regions. A broad and relatively intense absorption was visible approximately in the 3500–3200 cm^{-1} region. This region is primarily associated with O–H stretching, with the spectral appearance also influenced by the hydrochloride salt environment and hydrogen bonding.

Bands in the approximately 3000–2800 cm^{-1} region were associated with aliphatic C–H stretching vibrations arising from methyl, methylene, and related groups within the Tramadol structure. The spectrum showed substantial absorption in this region, consistent with the aliphatic character of the molecule.

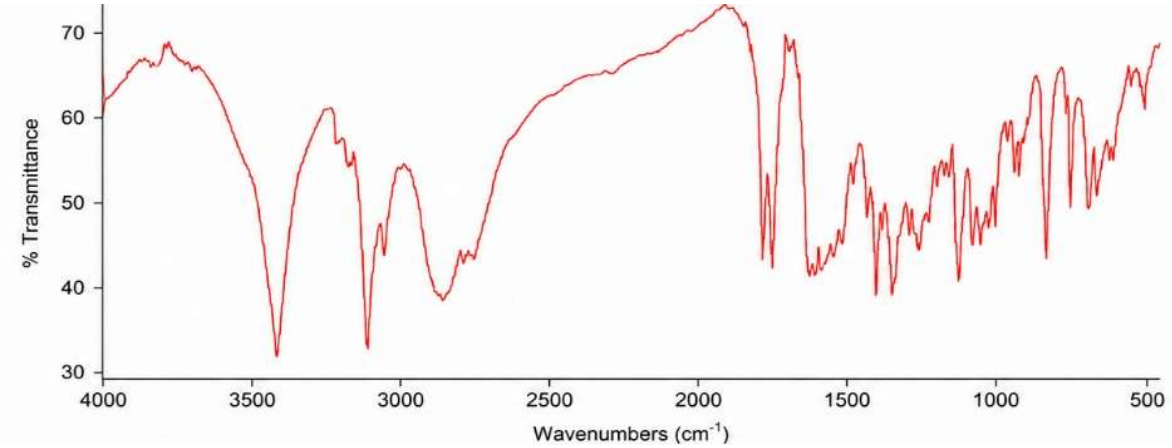

Figure 6: FTIR spectrum of pure Tramadol Hydrochloride

Absorptions appearing around approximately 1600–1450 cm^{-1} were attributable mainly to aromatic ring skeletal vibrations and C–H deformation. Multiple peaks within this region reflect overlapping molecular vibrations and contribute to the characteristic spectral profile of Tramadol HCl.

A particularly complex group of absorptions was evident between approximately 1450 and 1000 cm^{-1}. These bands can be attributed to combinations of C–N stretching, C–O stretching of the ether functionality, C–O vibrations associated with the alcohol-containing structure, and

C–H deformation. The strong fingerprint pattern in this region represents an important characteristic feature of Tramadol HCl.

Additional bands below approximately 1000 cm^{-1} corresponded to aromatic C–H out-of-plane bending and other skeletal/fingerprint vibrations. These characteristic absorptions remained clearly distinguishable in the spectrum.

The overall spectral profile was consistent with the functional groups expected in Tramadol Hydrochloride. The presence of the broad hydroxyl-associated region, aliphatic C–H bands, aromatic skeletal vibrations, and prominent C–O/C–N fingerprint absorptions provided supportive evidence for identification of the pure drug before formulation.

Major observed/assigned FTIR regions of pure Tramadol HCl

Table 10: FTIR data of pure Tramadol Hydrochloride

wavenumber (cm^{-1})	Assignment
3500–3200	O–H stretching/hydrogen-bonded region
3000–2800	Aliphatic C–H stretching
1600–1450	Aromatic skeletal/C–H deformation vibrations
1450–1200	C–N stretching and C–H bending
1250–1000	C–O/C–N stretching and fingerprint vibrations
1000–700	Aromatic C–H deformation
<700	Skeletal/fingerprint vibrations

1.17. FTIR Spectrum of Tramadol HCl + Indomethacin Final Formulation Blend

The FTIR spectrum of the final formulation blend was compared with those of the individual pure drugs to investigate whether the formulation process and presence of excipients produced major alterations in the characteristic functional groups of Tramadol HCl and Indomethacin.

The formulation spectrum showed a broad absorption around approximately 3400 cm^{-1}, which can be associated with overlapping O–H stretching and hydrogen-bonded vibrations originating from the drugs and potentially hydroxyl-containing excipients. Compared with the pure drug spectra, changes in the width and intensity of this region are expected in a multicomponent formulation because several components can contribute overlapping hydroxyl-associated absorptions.

Table 11: FTIR data of the final formulation blend

FTIR region (cm^{-1})	Pure Indomethacin	Pure Tramadol HCl	Final formulation	Interpretation
3500–3200	Broad O–H region	Strong/broad O–H region	Broad band retained	Overlapping O–H/hydrogen bonding
3000–2800	C–H stretching	C–H stretching	Retained	Aliphatic/aromatic C–H groups preserved
1710–1650	Strong carbonyl bands	No corresponding major drug carbonyl	Strong carbonyl region retained	Supports retention of Indomethacin carbonyl functionality
1600–1450	Aromatic skeletal bands	Aromatic skeletal/deformation bands	Multiple bands retained	Characteristic aromatic regions remain represented
1450–1200	Fingerprint vibrations	C–N/C–H vibrations	Multiple overlapping bands	Contributions from drugs and excipients
1250–1000	C–O/C–N-related bands	Strong C–O/C–N region	Characteristic bands retained/overlapped	Supports preservation of major Tramadol-associated functionality

<1000	Complex fingerprint region	Complex fingerprint region	Multiple bands retained	Expected overlapping fingerprint pattern

Bands were retained in the approximately 3100–2800 cm^{-1} region, corresponding predominantly to C–H stretching vibrations. Their presence in the formulation indicated retention of the aliphatic and aromatic structural features contributing to these bands.

Most importantly, a prominent carbonyl absorption remained evident at approximately 1700 cm^{-1}, consistent with retention of the characteristic carbonyl functionality of Indomethacin. The preservation of a strong absorption within this region is important because disappearance or major displacement of the characteristic carbonyl band could suggest substantial alteration of the drug's chemical environment.

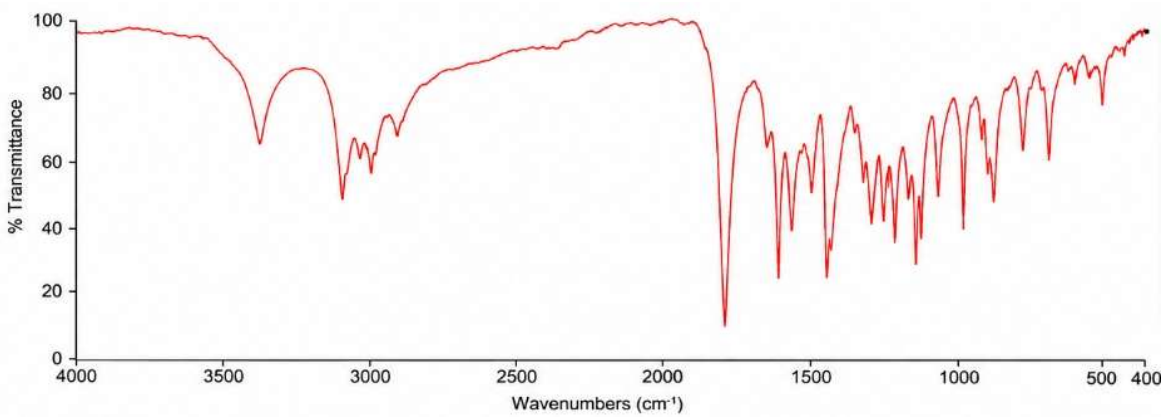

Figure 7: FTIR spectrum of the final formulation blend

Several absorptions were observed between approximately 1600 and 1450 cm^{-1}, corresponding to overlapping aromatic skeletal vibrations and other characteristic vibrations of the two drugs and formulation excipients. The formulation spectrum also retained numerous distinct bands within approximately 1450–1000 cm^{-1}, encompassing the C–O, C–N, C–H bending, and fingerprint regions associated with Tramadol HCl, Indomethacin, and the excipients.

The fingerprint region of the formulation was more complex than that of either individual drug. This is expected because the final formulation contains multiple chemical components, each

contributing its own vibrational bands. Consequently, certain pure-drug peaks showed differences in intensity, broadening, partial overlap, or small apparent shifts. Such variations can arise from physical mixing, dilution of the drugs by excipients, overlapping absorption bands, and intermolecular hydrogen bonding within the formulation.

Importantly, the supplied spectrum does not show an obvious complete loss of the major recognizable functional-group regions of the two active ingredients. In particular, the Indomethacin-associated carbonyl region and the Tramadol-associated hydroxyl/C–O/C–N regions remained represented in the final blend. No clearly identifiable entirely new major absorption region was apparent that, by itself, would demonstrate formation of a new covalent chemical species.

The comparison therefore provides preliminary evidence of drug–excipient compatibility in the final formulation. The observed differences in peak intensity and shape are reasonably attributable to overlapping bands and physical/intermolecular interactions within the multicomponent matrix rather than clear evidence of chemical degradation. FTIR alone, however, cannot conclusively establish compatibility or exclude all interactions; complementary techniques such as DSC or other solid-state/stability studies would strengthen this conclusion.

1.18. Pre-compression Evaluation of Tramadol HCl Powder Blends

The pre-compression characteristics of the Tramadol HCl sustained-release layer and Indomethacin layer were evaluated separately for formulations F1–F5. Bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio were determined to assess the packing ability, compressibility, and flow characteristics of each blend before bilayer tablet compression. The results and corresponding discussion for each parameter are presented together below.

Table 12: Pre-compression parameters of Tramadol HCl blends

Formulation	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Angle of Repose (°)	Carr's Index (%)	Hausner's Ratio

F1	0.48 ± 0.01	0.55 ± 0.01	25.8 ± 0.6	12.73	1.15
F2	0.47 ± 0.01	0.55 ± 0.01	26.9 ± 0.5	14.55	1.17
F3	0.46 ± 0.01	0.55 ± 0.01	28.1 ± 0.7	16.36	1.20
F4	0.45 ± 0.01	0.55 ± 0.01	29.4 ± 0.6	18.18	1.22
F5	0.44 ± 0.01	0.55 ± 0.01	30.8 ± 0.8	20.00	1.25

1.18.1. Bulk Density

The bulk density of the Tramadol HCl sustained-release blends ranged from 0.44 ± 0.01 to 0.48 ± 0.01 g/cm³. The highest bulk density was observed for F1 (0.48 ± 0.01 g/cm³), followed by F2 (0.47 ± 0.01 g/cm³), F3 (0.46 ± 0.01 g/cm³), F4 (0.45 ± 0.01 g/cm³), and F5 (0.44 ± 0.01 g/cm³).

A gradual reduction in bulk density was therefore observed from F1 to F5. This trend corresponded with the progressive increase in HPMC K100M from 40 to 80 mg and ethyl cellulose from 20 to 40 mg, together with the reduction of microcrystalline cellulose from 70 to 10 mg. The increasing proportion of polymeric material resulted in a comparatively more voluminous powder bed with reduced initial packing efficiency. Nevertheless, the bulk-density values indicated satisfactory packing characteristics for subsequent tablet compression.

1.18.2. Tapped Density

The tapped density of the Tramadol HCl formulations was approximately 0.55 ± 0.01 g/cm³ across F1–F5. Tapped density was consistently higher than bulk density because mechanical tapping reduced the void spaces between particles and promoted rearrangement into a more closely packed powder bed.

The difference between bulk and tapped density became progressively greater from F1 to F5. This indicated that the higher-polymer formulations underwent greater rearrangement during tapping. The increasing amounts of HPMC K100M and ethyl cellulose, accompanied by decreasing MCC content, may have contributed to the comparatively loose initial packing

observed in F4 and F5. The tapped-density results nevertheless demonstrated adequate packing behavior of all Tramadol HCl blends.

1.18.3. Angle of Repose

The angle of repose ranged from 25.8 ± 0.6° to 30.8 ± 0.8°. F1 showed the lowest angle of repose of 25.8 ± 0.6°, while F5 showed the highest value of 30.8 ± 0.8°. The values increased progressively through F2 (26.9 ± 0.5°), F3 (28.1 ± 0.7°), and F4 (29.4 ± 0.6°).

The relatively low angles obtained for F1 and F2 indicated good powder flow. Although the angle increased with increasing polymer concentration, the remaining formulations retained acceptable flow characteristics. The increase toward F5 may be related to the greater proportion of HPMC K100M and ethyl cellulose, which increased interparticulate friction and cohesiveness. The simultaneous decrease in MCC may also have contributed to the observed reduction in flowability.

Thus, although F1 exhibited the most favorable flow, all formulations showed angles of repose compatible with direct compression.

1.18.4. Carr's Index

Carr's index increased from 12.73% in F1 to 20.00% in F5. Intermediate values of 14.55%, 16.36%, and 18.18% were obtained for F2, F3, and F4, respectively.

F1 demonstrated good flow and packing characteristics based on its relatively low Carr's index. The progressive increase in Carr's index from F1 to F5 indicated increasing compressibility and cohesiveness of the powder blends. This trend corresponded closely with the increase in polymer concentration and reduction in MCC.

Although F5 showed the highest Carr's index, its value of 20.00% still indicated a blend that could be processed by direct compression, particularly in the presence of the incorporated glidant and lubricant. Overall, the Carr's index values confirmed acceptable flow and compressibility of the Tramadol HCl blends.

1.18.5. Hausner's Ratio

The Hausner's ratio ranged between 1.15 and 1.25. F1 exhibited the lowest value of 1.15, followed by F2 (1.17), F3 (1.20), F4 (1.22), and F5 (1.25).

The results followed the same trend as Carr's index. Lower values for F1 and F2 reflected comparatively better powder flow and lower cohesiveness, whereas the gradual increase toward F5 indicated greater interparticulate interaction as the polymer concentration increased.

Since the Hausner's ratio remained at or below 1.25 for all formulations, the Tramadol HCl sustained-release blends were considered to possess acceptable flow properties for compression. F1 demonstrated the most favorable flow characteristics, while F5 showed comparatively reduced but still acceptable flow.

1.19. Pre-compression Evaluation of Indomethacin powder blend

Table 13: Pre-compression parameters of Indomethacin blends

Formulation	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Angle of Repose (°)	Carr's Index (%)	Hausner's Ratio
F1	0.52 ± 0.01	0.59 ± 0.01	24.9 ± 0.5	11.86	1.13
F2	0.51 ± 0.01	0.59 ± 0.01	25.6 ± 0.6	13.56	1.16
F3	0.50 ± 0.01	0.59 ± 0.01	26.4 ± 0.5	15.25	1.18
F4	0.49 ± 0.01	0.59 ± 0.01	27.3 ± 0.7	16.95	1.20
F5	0.48 ± 0.01	0.59 ± 0.01	28.2 ± 0.6	18.64	1.23

1.19.1. Bulk Density

The bulk density of the Indomethacin blends ranged between 0.48 ± 0.01 and 0.52 ± 0.01 g/cm^3. F1 exhibited the highest value of 0.52 ± 0.01 g/cm^3, whereas F5 exhibited the lowest value of 0.48 ± 0.01 g/cm^3.

A gradual reduction in bulk density occurred as the concentration of sodium starch glycolate increased from 10 to 20 mg and MCC decreased from 55 to 45 mg. The reduction was relatively small because lactose monohydrate was maintained at a constant concentration of 40 mg throughout the formulations.

The bulk-density values of the Indomethacin blends were slightly higher than those of the Tramadol HCl blends. This difference can be attributed to the absence of large quantities of high-viscosity polymer and the continued presence of appreciable quantities of MCC and lactose in the Indomethacin layer.

1.19.2. Tapped Density

The tapped density was approximately 0.59 ± 0.01 g/cm³ for the Indomethacin formulations and was consistently greater than the corresponding bulk-density values. This demonstrated that the powder particles underwent rearrangement and closer packing when subjected to mechanical tapping.

The difference between bulk and tapped density gradually increased from F1 to F5, suggesting a modest increase in powder compressibility. This change corresponded with the increasing concentration of sodium starch glycolate and decreasing concentration of MCC.

Overall, the tapped-density results indicated satisfactory packing characteristics of all five Indomethacin blends and supported their suitability for uniform filling of the second layer during bilayer compression.

1.19.3. Angle of Repose

The angle of repose varied from 24.9 ± 0.5° to 28.2 ± 0.6°. F1 showed the lowest value, while F5 exhibited the highest. Values for F2, F3, and F4 were 25.6 ± 0.6°, 26.4 ± 0.5°, and 27.3 ± 0.7°, respectively.

All five formulations therefore demonstrated generally good flow characteristics. A small increase in the angle of repose occurred as the sodium starch glycolate concentration increased. The fine particulate nature of sodium starch glycolate can increase interparticle contact and modestly increase cohesiveness at higher concentrations.

Despite this trend, the angle of repose remained below approximately 30° for all Indomethacin formulations, indicating favorable flow for direct compression and consistent die filling.

1.19.4. Carr's Index

Carr's index values ranged from 11.86 to 18.64%. F1 showed the lowest Carr's index of 11.86%, while F5 exhibited the highest value of 18.64%. Values increased progressively through F2 (13.56%), F3 (15.25%), and F4 (16.95%).

The relatively low values obtained for F1 and F2 indicated good flow and packing properties. The progressive increase from F1 to F5 suggested a modest increase in cohesiveness as sodium starch glycolate concentration increased and MCC decreased.

Nevertheless, all formulations remained within an acceptable range for tablet manufacture, indicating that the powder blends were capable of satisfactory flow and compression without requiring extensive additional flow modification.

1.19.5. Hausner's Ratio

Hausner's ratio ranged from 1.13 to 1.23. F1 exhibited a value of 1.13, followed by F2 at 1.16, F3 at 1.18, F4 at 1.20, and F5 at 1.23.

The gradual increase was consistent with the trends observed for angle of repose and Carr's index. F1 possessed the most favorable flow characteristics, whereas F5 showed comparatively greater cohesiveness. However, all ratios remained below 1.25, supporting acceptable flowability of the Indomethacin powder blends.

1.19.6. Comparison Between Tramadol HCl and Indomethacin Layer Blends

The two layers demonstrated some differences in their pre-compression characteristics because of their substantially different excipient compositions. The Indomethacin blends generally exhibited slightly better flow than the Tramadol HCl sustained-release blends.

The bulk density of the Tramadol blends ranged from 0.44–0.48 g/cm³, compared with 0.48–0.52 g/cm³ for the Indomethacin blends. Similarly, the angle of repose ranged from 25.8–30.8° for Tramadol HCl and 24.9–28.2° for Indomethacin, indicating comparatively better flow of the latter.

Carr's index ranged from 12.73–20.00% for Tramadol HCl compared with 11.86–18.64% for Indomethacin, while Hausner's ratios were 1.15–1.25 and 1.13–1.23, respectively. These findings consistently indicated slightly greater cohesiveness in the Tramadol HCl sustained-release blends.

The difference was most pronounced toward F4 and F5 because the Tramadol layer contained increasing quantities of HPMC K100M and ethyl cellulose, together with a substantial reduction in MCC. In contrast, the Indomethacin layer retained considerable quantities of MCC and a constant 40 mg of lactose monohydrate, contributing to comparatively favorable flow.

Despite these differences, both layer blends exhibited acceptable pre-compression properties throughout F1–F5. The results indicated adequate flow, packing, and compressibility for sequential die filling and direct compression. This is particularly important for bilayer tablet manufacture because reproducible flow of each individual blend is required to achieve consistent layer weight, dose uniformity, mechanical integrity, and overall tablet quality.

1.20. Evaluation of Bilayer Tablets

The prepared bilayer tablets F1–F5 were evaluated for various post-compression quality-control parameters, including thickness, hardness, friability, weight variation, and drug content. These parameters are important for establishing the physical integrity, manufacturing reproducibility, dose uniformity, and overall quality of the prepared tablets.

1.20.1. Thickness

The thickness of the prepared bilayer tablets was measured using Vernier calipers and the results are presented below.

The mean thickness of the bilayer tablets ranged from 4.72 ± 0.04 to 4.91 ± 0.06 mm. A small progressive increase in tablet thickness was observed from F1 to F5. This variation can be associated mainly with changes in the composition of the Tramadol sustained-release layer,

particularly the progressive increase in HPMC K100M and ethyl cellulose.

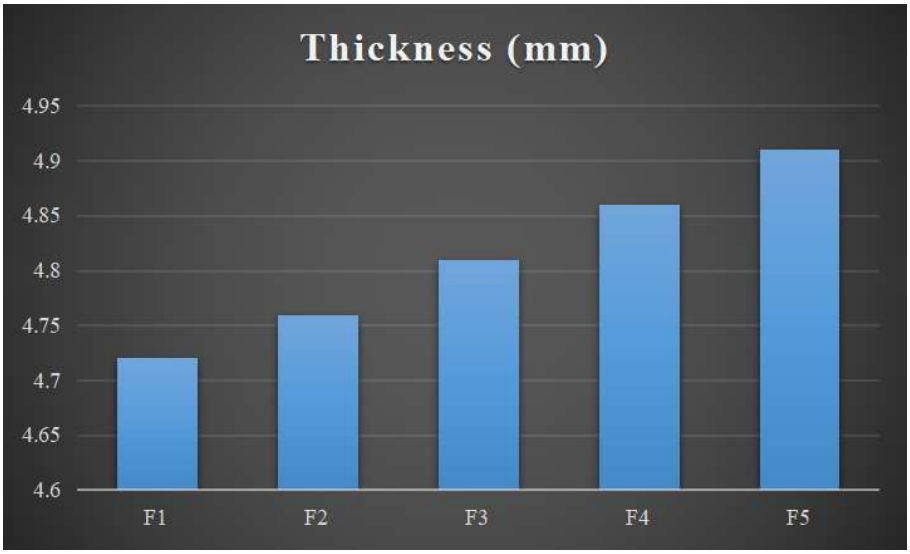

Figure 8: Thickness of the bilayer tablets

Although the total tablet weight was maintained at 425 mg, differences in the bulk density, packing behavior, and compressibility of the constituent excipients can produce small variations in the final tablet dimensions. The low standard deviation obtained for each formulation demonstrated good reproducibility of the compression process. No excessive variation in thickness was observed, indicating satisfactory die filling and compression of both layers.

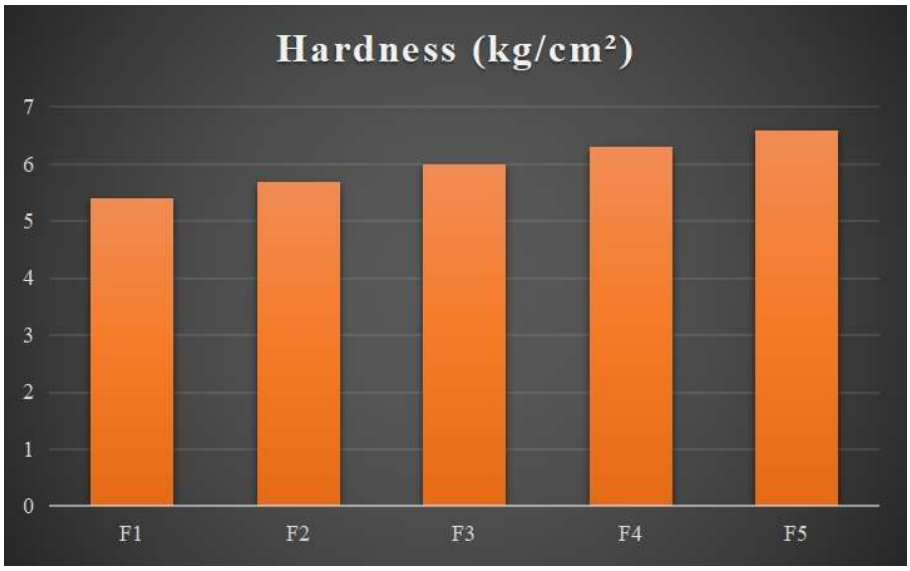

Figure 9: Hardness of the bilayer tablets

1.20.2. Hardness

The mechanical strength of the bilayer tablets was evaluated using a Monsanto hardness tester.

The hardness of the prepared tablets ranged between 5.4 ± 0.18 and 6.6 ± 0.19 kg/cm², indicating adequate mechanical strength of all formulations. A gradual increase in hardness was observed from F1 to F5.

The increasing hardness may be related to the progressively higher concentrations of HPMC K100M and ethyl cellulose in the Tramadol sustained-release layer. These polymeric materials can contribute to formation of a coherent compact during compression. PVP K30 present in both layers also contributed to particle binding and tablet strength.

F5 exhibited the highest hardness of 6.6 ± 0.19 kg/cm², whereas F1 showed the lowest value of 5.4 ± 0.18 kg/cm². Despite these differences, all tablets possessed sufficient strength to withstand handling, coating, packaging, and subsequent evaluation. Importantly, no visible capping, cracking, lamination, or separation of the two layers was observed, indicating satisfactory interlayer adhesion.

Figure 10: Friability of the bilayer tablets

1.20.3. Friability

Friability was determined to evaluate the resistance of the prepared tablets to abrasion and mechanical stress.

The percentage friability of the bilayer tablets ranged from 0.41 to 0.72%. All formulations showed friability values below 1%, demonstrating satisfactory resistance to abrasion and mechanical damage.

A progressive decrease in friability was observed from F1 to F5, which corresponded with the increasing tablet hardness. F1, with the lowest hardness, showed the highest friability of 0.72%, whereas F5, having the greatest hardness, demonstrated the lowest friability of 0.41%.

The inverse relationship between hardness and friability was expected because stronger interparticulate bonding generally improves resistance to mechanical abrasion. The results indicated that all formulations possessed adequate mechanical integrity for subsequent enteric coating, handling, storage, and packaging.

Table 14: Post-compression evaluation of Bilayer Tablets

Formulation	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Average Weight (mg)	Tramadol HCl (%)	Indomethacin (%)
F1	4.72 ± 0.04	5.4 ± 0.18	0.72	424.6 ± 3.2	98.62 ± 0.74	98.31 ± 0.69
F2	4.76 ± 0.05	5.7 ± 0.21	0.64	425.2 ± 3.0	99.14 ± 0.68	98.86 ± 0.72
F3	4.81 ± 0.04	6.0 ± 0.17	0.56	425.5 ± 2.8	99.48 ± 0.61	99.27 ± 0.64
F4	4.86 ± 0.05	6.3 ± 0.20	0.48	424.8 ± 2.6	99.21 ± 0.66	99.51 ± 0.58
F5	4.91 ± 0.06	6.6 ± 0.19	0.41	425.3 ± 2.5	98.94 ± 0.71	99.08 ± 0.67

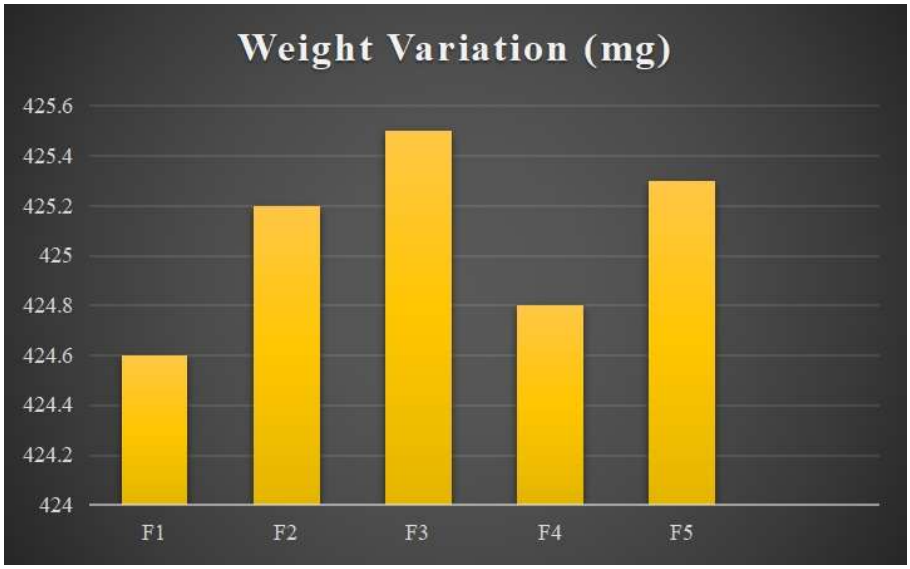

Figure 11: Weight variation of the bilayer tablets

1.20.4. Weight Variation

The weight variation test was performed using 20 tablets from each formulation. The target total weight of each bilayer tablet was 425 mg.

The average tablet weights ranged from 424.6 ± 3.2 to 425.5 ± 2.8 mg, which were very close to the theoretical target weight of 425 mg. The maximum individual deviations remained small across all formulations.

The low variability in tablet weight indicated consistent powder flow and uniform die filling during sequential compression of the Tramadol and Indomethacin layers. This finding was also consistent with the acceptable pre-compression flow characteristics previously observed for both layer blends.

F5 showed the lowest variability, with an average tablet weight of 425.3 ± 2.5 mg, while F1 showed slightly greater variation at 424.6 ± 3.2 mg. Nevertheless, the observed variation was minor for all formulations, indicating satisfactory control of tablet weight during the bilayer compression process.

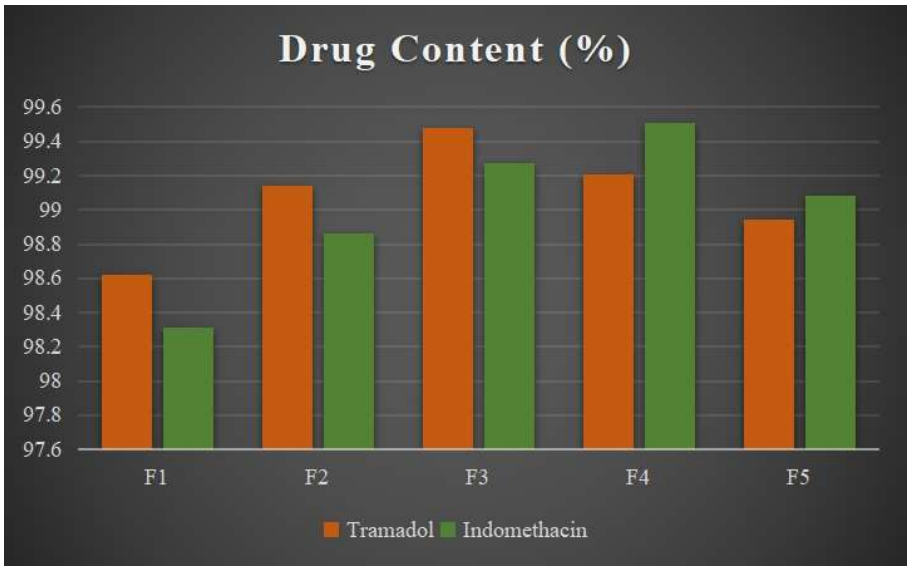

Figure 12: Drug content of the bilayer tablets

1.20.5. Drug Content Uniformity

The prepared tablets were analyzed separately for Tramadol Hydrochloride and Indomethacin content. The theoretical drug content per tablet was 100 mg of Tramadol Hydrochloride and 50 mg of Indomethacin.

The Tramadol Hydrochloride content ranged from 98.62 ± 0.74 to 99.48 ± 0.61%, while the Indomethacin content ranged from 98.31 ± 0.69 to 99.51 ± 0.58%. The values were close to the respective theoretical drug contents and showed only minor differences among formulations.

F3 exhibited the highest Tramadol HCl content of 99.48 ± 0.61%, while F4 showed the highest Indomethacin content of 99.51 ± 0.58%. The relatively low standard deviations indicated homogeneous distribution of both active pharmaceutical ingredients within their respective layers.

The results suggested that the 15-min blending process provided satisfactory drug distribution before compression and that sequential bilayer compression did not produce substantial variability in drug loading. Uniform drug content is particularly important in bilayer tablets because each active pharmaceutical ingredient is incorporated into a separate layer and must remain uniformly distributed throughout manufacturing.

1.20.6. In Vitro Drug Release Study of Tramadol Hydrochloride

The in vitro dissolution profiles of the prepared bilayer tablets F1–F5 were evaluated using a USP Type II paddle dissolution apparatus. The tablets were initially exposed to 900 mL of 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 for the remaining dissolution period. The temperature was maintained at 37 ± 0.5°C, and the paddle speed was maintained at 50 rpm.

Samples were withdrawn at predetermined intervals and analyzed using a UV-visible spectrophotometer. Tramadol Hydrochloride was analyzed at 271 nm, while Indomethacin was analyzed at 320 nm. The cumulative percentage drug release was calculated using the respective calibration curves.

The Tramadol HCl layer contained increasing concentrations of HPMC K100M and ethyl cellulose from F1 to F5. Accordingly, a progressive reduction in the rate of drug release was expected as the polymer concentration increased.

Table 15: Cumulative percentage release of Tramadol HCl from F1–F5

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
0	0.00	0.00	0.00	0.00	0.00
1	15.42 ± 0.81	12.86 ± 0.69	10.24 ± 0.58	8.17 ± 0.51	6.35 ± 0.43
2	27.68 ± 1.12	23.14 ± 0.96	19.37 ± 0.84	15.72 ± 0.76	12.48 ± 0.65
3	40.83 ± 1.28	35.26 ± 1.17	30.62 ± 1.02	25.48 ± 0.91	21.36 ± 0.82
4	52.64 ± 1.36	46.18 ± 1.25	40.76 ± 1.14	34.53 ± 1.06	29.47 ± 0.93
6	70.28 ± 1.52	63.72 ± 1.43	57.84 ± 1.31	50.36 ± 1.24	43.61 ± 1.15
8	84.76 ± 1.68	78.42 ± 1.56	72.63 ± 1.48	64.27 ± 1.39	56.48 ± 1.31
10	94.32 ± 1.74	89.67 ± 1.69	85.46 ± 1.57	77.68 ± 1.51	69.74 ± 1.43
12	99.18 ± 1.21	97.36 ± 1.32	96.28 ± 1.39	89.54 ± 1.46	82.36 ± 1.52

A clear polymer-dependent sustained-release pattern was observed for Tramadol Hydrochloride. At 2 h, the cumulative release ranged from 12.48 ± 0.65% for F5 to 27.68 ± 1.12% for F1, demonstrating that increasing the amount of HPMC K100M and ethyl cellulose progressively restricted the initial release of the drug.

F1, containing the lowest amounts of HPMC K100M (40 mg) and ethyl cellulose (20 mg), exhibited the fastest release. Approximately 52.64 ± 1.36% was released within 4 h, increasing to 84.76 ± 1.68% at 8 h and 99.18 ± 1.21% at 12 h. The relatively rapid release can be attributed to the lower polymer concentration and higher MCC content, which facilitated penetration of dissolution medium into the tablet matrix.

Increasing the HPMC K100M and ethyl cellulose content in F2 and F3 produced progressively greater retardation of drug release. HPMC K100M hydrates in aqueous medium and develops a viscous gel layer surrounding the matrix. Drug molecules must subsequently diffuse through this hydrated polymeric barrier. Ethyl cellulose, being relatively hydrophobic, further restricts penetration of dissolution medium and drug diffusion.

F3 demonstrated a well-controlled release pattern, with 19.37 ± 0.84% release at 2 h, 40.76 ± 1.14% at 4 h, 57.84 ± 1.31% at 6 h, 72.63 ± 1.48% at 8 h, 85.46 ± 1.57% at 10 h, and 96.28 ± 1.39% at 12 h. Thus, F3 provided sustained drug release throughout the complete 12-h period without either excessively rapid initial release or incomplete final release.

In contrast, the higher polymer concentrations in F4 and F5 produced excessive retardation. At 12 h, F4 released 89.54 ± 1.46%, whereas F5 released only 82.36 ± 1.52%. The greater amount of HPMC K100M produced a thicker and more viscous hydrated gel barrier, while the higher ethyl cellulose concentration increased the hydrophobic character of the matrix. Consequently, water penetration and diffusion of Tramadol HCl were substantially reduced.

The Tramadol release results therefore indicated that F3 provided the most balanced sustained-release profile, achieving approximately 96% drug release over 12 h.

1.20.7. In Vitro Drug Release Study of Indomethacin

The Indomethacin component was designed for gastro-protection to minimize drug release under acidic gastric conditions. Accordingly, very limited release was expected during the initial 2-h acid stage, followed by rapid release after exposure to phosphate buffer pH 6.8.

Table 16: Cumulative percentage release of Indomethacin from F1–F5

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
0	0.00	0.00	0.00	0.00	0.00
1	1.84 ± 0.21	1.67 ± 0.18	1.52 ± 0.17	1.43 ± 0.16	1.35 ± 0.15
2	3.76 ± 0.32	3.42 ± 0.29	3.18 ± 0.27	3.06 ± 0.25	2.91 ± 0.24
2.25	27.64 ± 1.18	31.86 ± 1.24	36.52 ± 1.31	40.78 ± 1.38	44.63 ± 1.42

2.5	51.72 ± 1.43	57.86 ± 1.51	63.48 ± 1.57	68.84 ± 1.62	73.46 ± 1.68
2.75	72.83 ± 1.56	78.34 ± 1.61	83.76 ± 1.68	87.92 ± 1.72	90.68 ± 1.76
3	88.46 ± 1.63	91.72 ± 1.68	95.64 ± 1.54	97.18 ± 1.47	98.26 ± 1.39
4	97.52 ± 1.28	98.36 ± 1.17	99.14 ± 1.06	99.38 ± 0.98	99.52 ± 0.94

During the initial 2-h exposure to 0.1 N HCl, all formulations demonstrated minimal Indomethacin release. At the end of the acid stage, cumulative release ranged between 2.91 ± 0.24 and 3.76 ± 0.32%. The low release during this period demonstrated satisfactory gastro-resistant behavior and indicated that the protective barrier effectively restricted exposure of Indomethacin to the acidic dissolution medium.

After replacement of the acidic medium with phosphate buffer pH 6.8, a marked increase in Indomethacin release was observed. This behavior was consistent with the pH-responsive nature of the gastro-protective system. At the higher intestinal pH, the enteric polymer became increasingly ionized and soluble, permitting exposure of the underlying Indomethacin-containing layer to the dissolution medium.

The amount of sodium starch glycolate increased from 10 mg in F1 to 20 mg in F5, producing a progressive increase in the rate of post-gastric drug release. Sodium starch glycolate functions as a superdisintegrant and rapidly absorbs water and swells after exposure of the tablet layer to dissolution medium.

F1, containing only 10 mg of sodium starch glycolate, showed the slowest post-gastric release, reaching 51.72 ± 1.43% at 2.5 h and 88.46 ± 1.63% at 3 h. Increasing the superdisintegrant concentration accelerated drug release in F2–F5.

F3, containing 15 mg of sodium starch glycolate, showed a desirable balance between gastro-protection and subsequent rapid intestinal release. Only 3.18 ± 0.27% of Indomethacin was released during the initial 2 h, whereas release rapidly increased to 63.48 ± 1.57% at 2.5 h, 83.76 ± 1.68% at 2.75 h, 95.64 ± 1.54% at 3 h, and 99.14 ± 1.06% at 4 h.

F4 and F5 showed even faster release after the acid stage because of their higher sodium starch glycolate content. Although rapid intestinal release is desirable for the immediate-release Indomethacin component, increasing the superdisintegrant beyond the F3 level provided only a relatively small additional improvement in final drug release.

The dissolution study demonstrated two distinct release characteristics within the developed formulation. Tramadol Hydrochloride showed sustained release over 12 h, whereas Indomethacin showed minimal release during the initial 2-h gastric phase followed by rapid release after exposure to pH 6.8.

The difference in release behavior was primarily governed by the functional excipients incorporated into the respective layers. In the Tramadol layer, HPMC K100M and ethyl cellulose provided sustained release by forming hydrophilic and hydrophobic diffusion barriers. Increasing their concentrations progressively reduced the release rate.

In the Indomethacin layer, the gastro-protective barrier restricted release under acidic conditions, whereas sodium starch glycolate facilitated rapid disintegration and release after exposure to intestinal-pH conditions.

This dual-release behavior is consistent with the intended pharmaceutical objective of the bilayer system: prolonged delivery of the centrally acting analgesic Tramadol HCl combined with delayed, subsequently rapid delivery of the anti-inflammatory drug Indomethacin.

Based on the combined dissolution profiles, F3 was selected as the optimized formulation. F3 contained 60 mg HPMC K100M and 30 mg ethyl cellulose in the Tramadol sustained-release layer, together with 15 mg sodium starch glycolate in the Indomethacin layer.

The Tramadol component of F3 demonstrated controlled release of 19.37 ± 0.84% at 2 h, 40.76 ± 1.14% at 4 h, 57.84 ± 1.31% at 6 h, 72.63 ± 1.48% at 8 h, 85.46 ± 1.57% at 10 h, and 96.28 ± 1.39% at 12 h. This profile was more appropriately sustained than F1 and F2, while providing substantially more complete 12-h release than F4 and F5.

Simultaneously, the Indomethacin component of F3 showed only 3.18 ± 0.27% release during the initial 2-h acidic phase, demonstrating satisfactory gastro-protection. Following exposure to phosphate buffer pH 6.8, release increased rapidly and reached 95.64 ± 1.54% at 3 h and 99.14 ± 1.06% at 4 h.

Therefore, F3 demonstrated the most appropriate overall balance between sustained Tramadol HCl release, gastric restriction of Indomethacin release, and rapid post-gastric Indomethacin availability. Considering these dissolution characteristics together with its satisfactory pre-compression and post-compression properties, F3 was considered the optimized formulation among F1–F5.

SUMMARY AND CONCLUSION

- The present study was undertaken to develop a gastro-protected bilayer tablet containing Tramadol Hydrochloride and Indomethacin for combined analgesic and anti-inflammatory therapy. The formulation was designed to provide sustained delivery of Tramadol HCl together with gastro-protected delivery of Indomethacin.
- Preliminary characterization showed Tramadol HCl as a white to off-white crystalline powder and Indomethacin as a pale-yellow to yellow crystalline powder. Their melting points were 180.60 ± 0.40°C and 152.77 ± 0.35°C, respectively, supporting the identity and acceptable quality of the drug samples.
- Solubility studies revealed distinctly different characteristics of the two drugs. Tramadol HCl exhibited high aqueous solubility, whereas Indomethacin showed very poor solubility in water and 0.1 N HCl but improved solubility in phosphate buffer pH 6.8, supporting the rationale for post-gastric release.
- FTIR analysis demonstrated the characteristic functional-group regions of both pure drugs. Comparison with the final formulation spectrum showed retention of the major recognizable bands of Tramadol HCl and Indomethacin, with no obvious evidence of major chemical incompatibility within the limitations of FTIR analysis.
- UV-visible calibration curves were established over the concentration range of 2–20 µg/mL. Tramadol HCl followed the regression equation $y = 0.0482x - 0.0087$ ($R^2 = 0.9951$), whereas Indomethacin showed $y = 0.0499x - 0.0247$ ($R^2 = 0.9921$), demonstrating satisfactory linear relationships for quantitative analysis.
- Five formulations, F1–F5, were developed with a constant dose of 100 mg Tramadol HCl and 50 mg Indomethacin. HPMC K100M and ethyl cellulose were varied in the sustained-release Tramadol layer, while sodium starch glycolate was varied in the Indomethacin layer to modify post-gastric drug release.

- Pre-compression evaluation of the Tramadol HCl blends showed bulk densities of 0.44–0.48 g/cm³, angles of repose of 25.8–30.8°, Carr's indices of 12.73–20.00%, and Hausner's ratios of 1.15–1.25. These findings indicated acceptable flow and compressibility for direct compression.
- The Indomethacin blends showed comparatively favorable flow, with bulk densities of 0.48–0.52 g/cm³, angles of repose of 24.9–28.2°, Carr's indices of 11.86–18.64%, and Hausner's ratios of 1.13–1.23. All formulations were therefore suitable for sequential filling during bilayer compression.
- The prepared bilayer tablets exhibited uniform dimensions, with thickness ranging from 4.72 ± 0.04 to 4.91 ± 0.06 mm. Tablet hardness increased from 5.4 ± 0.18 to 6.6 ± 0.19 kg/cm², indicating adequate mechanical strength and satisfactory interlayer integrity.
- Friability values ranged from 0.41 to 0.72%, remaining below 1% for all formulations. Average tablet weights were close to the theoretical 425 mg core-tablet weight, indicating consistent die filling and reproducible bilayer compression.
- Drug-content analysis demonstrated uniform distribution of both active ingredients. Tramadol HCl content ranged from 98.62 ± 0.74 to 99.48 ± 0.61%, while Indomethacin content ranged from 98.31 ± 0.69 to 99.51 ± 0.58%, demonstrating satisfactory drug incorporation.
- The Tramadol HCl dissolution profiles showed a clear polymer-dependent sustained-release pattern. Increasing HPMC K100M and ethyl cellulose progressively reduced drug release, with F1 releasing 99.18 ± 1.21% at 12 h compared with 82.36 ± 1.52% from the highest-polymer formulation F5.
- The gastro-protected Indomethacin component showed only 2.91–3.76% release during the initial 2 h in 0.1 N HCl, demonstrating effective restriction of drug release under acidic conditions. Following transfer to phosphate buffer pH 6.8, rapid Indomethacin release occurred, reaching approximately 97.52–99.52% by 4 h.
- Among the formulations, F3 demonstrated the most balanced dissolution performance. It released Tramadol HCl progressively to 96.28 ± 1.39% at 12 h, while Indomethacin release was restricted to 3.18 ± 0.27% at 2 h and subsequently increased to 95.64 ± 1.54% at 3 h and 99.14 ± 1.06% at 4 h.
- Based on the collective preformulation, pre-compression, post-compression, drug-content, and dissolution findings, F3 was selected as the optimized formulation. The study demonstrates the feasibility of a bilayer approach for combining sustained Tramadol HCl

delivery with gastro-protected Indomethacin delivery, although further stability and in vivo studies would be required to establish long-term performance and therapeutic benefit.

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