A Novel Bilayer Tablet Approach For Fast Pain Relief And Extended Therapeutic Action

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ABSTRACT

Effective pain management requires both rapid onset of analgesia and sustained therapeutic action to enhance patient compliance and reduce the need for frequent dosing. The present study aimed to develop and evaluate a novel bilayer tablet comprising an immediate-release (IR) layer of ibuprofen and a sustained-release (SR) layer of suzetrigine for fast pain relief and prolonged therapeutic efficacy. Preformulation studies were performed to assess the physicochemical properties of both drugs, while drug–excipient compatibility was investigated using Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC). The immediate-release layer was formulated using croscarmellose sodium as a superdisintegrant, whereas the sustained-release layer was prepared using HPMC K100M and ethylcellulose as matrix-forming polymers. Bilayer tablets were manufactured by direct compression and evaluated for micromeritic properties, weight variation, thickness, hardness, friability, drug content uniformity, and in vitro dissolution performance. Drug-release kinetics were analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, and accelerated stability studies were conducted according to ICH Q1A(R2) guidelines. Compatibility studies confirmed the absence of significant interactions between the drugs and excipients. The optimized formulation exhibited satisfactory flow characteristics, acceptable mechanical strength, friability below 1%, and drug content within pharmacopeial limits. The immediate-release ibuprofen layer released more than 95% of the drug within 60 minutes, providing rapid analgesic action, while the sustained-release suzetrigine layer extended drug release for up to 12 hours. Release kinetic analysis indicated that the sustained-release layer followed anomalous (non-Fickian) diffusion and showed the best fit with the Korsmeyer–Peppas model. Stability studies demonstrated that the optimized formulation remained physically and chemically stable under accelerated storage conditions. Overall, the developed bilayer tablet successfully combined rapid and prolonged analgesic effects within a single dosage form and represents a promising strategy for improving pain management and patient adherence. Further pharmacokinetic and clinical studies are recommended to establish its therapeutic potential.

Keywords: Bilayer tablet, Ibuprofen, Suzetrigine, Immediate release, Sustained release, NaV1.8 inhibitor, Pain management, Direct compression, Drug-release kinetics.

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INTRODUCTION

Pain, whether acute or chronic, remains one of the most common reasons patients seek medical care, and its inadequate management continues to pose a significant clinical and public-health challenge. Monotherapy regimens frequently fail to address both the immediate discomfort experienced by patients and the need for sustained relief over an extended period, often necessitating frequent re-dosing, which in turn reduces compliance and increases the risk of missed doses or breakthrough pain[1,2].

Ibuprofen is a propionic-acid derivative NSAID widely used for its rapid analgesic, antipyretic, and anti-inflammatory actions through reversible inhibition of

cyclooxygenase (COX-1/COX-2) enzymes. Its relatively short plasma half-life (approximately 2 hours) makes it well suited for an immediate-release formulation intended to provide fast onset of relief, but poorly suited to sustaining analgesia across a full dosing interval on its own[3,4].

Suzetrigine is a selective inhibitor of the voltage-gated sodium channel NaV1.8, a channel highly expressed in peripheral nociceptive neurons and central to pain-signal transmission. As a non-opioid analgesic, it offers a mechanistically distinct route to pain control without the abuse-liability and respiratory-depression concerns associated with opioid analgesics. Formulating suzetrigine in a sustained-release matrix could, in principle, extend its plasma concentration profile and provide analgesic coverage well beyond the duration achievable with an immediate-release dose[5,6].

A bilayer tablet technology - in which two physically and functionally distinct layers (an immediate-release layer and a sustained-release layer) are compressed together into a single dosage unit - offers a rational platform for combining these two complementary mechanisms[7]. This design allows the IR ibuprofen layer to disintegrate and dissolve rapidly, providing quick symptomatic relief, while the SR suzetrigine layer forms a hydrating gel/matrix barrier that releases drug slowly over an extended period, thereby maintaining continuous analgesic action[8] The present work outlines the systematic formulation, in-process and post-compression evaluation, dissolution/kinetic characterization, and preliminary stability assessment of such a bilayer tablet[7,9].

MATERIALS AND METHODS

Materials

Ibuprofen and suzetrigine were obtained as Gift Sample from reputed pharmaceutical manufacturers and used as received. Croscarmellose sodium, sodium starch glycolate, and crospovidone were used as superdisintegrants for the IR layer. Microcrystalline cellulose (MCC PH102) and lactose monohydrate were used as diluents. HPMC K100M and ethylcellulose were used as rate-controlling polymers for the SR layer. Magnesium stearate and talc served as lubricant and glidant, respectively, in both layers. All excipients used were of pharmacopoeial grade.

Table 1: Composition of Bilayer Tablet Trial Batches (mg per tablet)

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ibuprofen (IR layer)	400	400	400	400	400	400	400	400	400
Croscarmellose sodium	16	16	16	16	16	16	16	16	16
MCC PH102 (IR)	60	60	60	60	60	60	60	60	60
Suzetrigine (SR layer, model)	50	50	50	50	50	50	50	50	50
HPMC K100M	20	30	40	50	60	70	80	90	100
Ethylcellulose	80	70	60	50	40	30	20	10	0
Lactose monohydrate (SR)	40	40	40	40	40	40	40	40	40
Mg stearate (both layers)	6	6	6	6	6	6	6	6	6
Talc (both layers)	4	4	4	4	4	4	4	4	4

Formulation of the Immediate-Release (IR) Ibuprofen Layer

Ibuprofen was blended with MCC PH102, croscarmellose sodium, and a small quantity of colloidal silicon dioxide, followed by lubrication with magnesium stearate. Three trial IR formulations (differing in superdisintegrant type/level) were prepared by direct compression to identify the blend giving the fastest disintegration and dissolution.

Formulation of the Sustained-Release (SR) Suzetrigine Layer

Suzetrigine was blended with varying ratios of HPMC K100M and ethylcellulose (representing hydrophilic and hydrophobic release-retarding polymers), together with lactose monohydrate as diluent, followed by lubrication.

Nine total trial batches (F1-F9) were designed using a polymer-ratio variation approach (Table 1) to study the effect of polymer type and concentration on drug release rate.

Preformulation Studies

- Organoleptic evaluation - color, odor, and physical appearance of both APIs.
- Melting point determination - capillary melting point method.
- Solubility analysis - in water, 0.1N HCl, phosphate buffer pH 6.8, and methanol.
- Micromeritic properties - bulk density, tapped density, angle of repose, Carr's index, and Hausner ratio for both drug powders.
- Calibration curve - UV spectrophotometric calibration curves for ibuprofen (lambda-max ~221 nm in phosphate buffer pH 7.2) and suzetrigine (model lambda-max ~262 nm) were constructed across the 2-20 microgram/mL range[10-12].

Preparation of Powder Blends for Direct Compression

The powder blends for both the immediate-release (IR) and sustained-release (SR) layers were prepared separately by accurately weighing the required quantities of the drug and excipients according to the optimized formulation. The ingredients were passed through a #60 sieve to eliminate agglomerates and obtain a uniform particle size distribution. The drug and excipients, excluding the lubricant and glidant, were mixed thoroughly using geometric dilution in a mortar and pestle for 10–15 minutes to ensure homogeneous distribution of the drug. Finally, magnesium stearate and talc were added and blended gently for 2–3 minutes to avoid over-lubrication while ensuring uniform lubrication and improved flow characteristics. The prepared powder blends were stored in airtight containers until compression[13].

Bilayer Tablet Preparation by Direct Compression

Bilayer tablets were prepared on a rotary tablet press fitted with 10 mm round, flat-faced punches. The SR-layer blend was first fed into the die cavity and lightly pre-compressed (tamped) to form the base layer; the IR-layer blend was then added on top and the two layers were compressed together under a final compression force sufficient to yield tablets with a target hardness of 5-7 kg/cm2. This sequence was chosen to minimize inter-layer mixing and to promote adequate layer-to-layer adhesion[14-16].

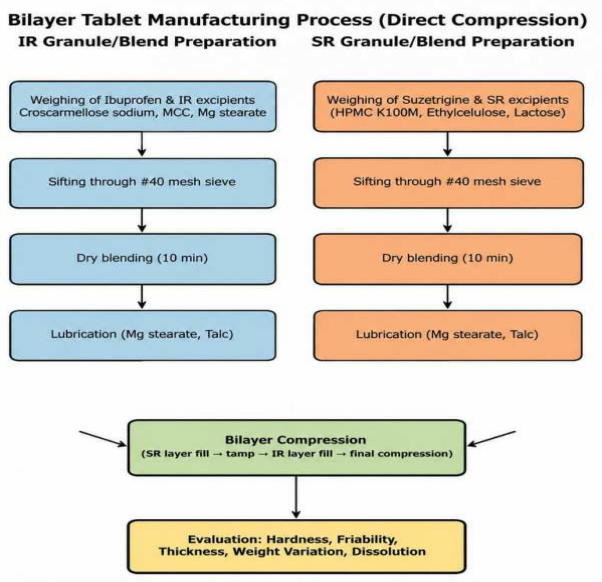


Figure 1: Manufacturing process flow for the bilayer tablet by direct compression[17-19].



Figure 2: Cross-sectional schematic of the proposed bilayer tablet, showing the immediate-release ibuprofen layer and the sustained-release suzetrigine matrix layer.

Drug-Excipient Compatibility (FTIR and DSC)

FTIR spectra of pure ibuprofen, pure suzetrigine, individual excipients, and their physical mixtures (1:1 w/w) were recorded over the range 4000-400 cm-1 using the KBr pellet method. Characteristic peaks of each drug were compared before and after mixing with excipients to detect any shift, disappearance, or emergence of new peaks indicative of chemical interaction. DSC thermograms were obtained by heating samples from 30 degrees C to 300 degrees C at 10 degrees C/min under a nitrogen atmosphere, and the melting endotherms of the

pure drugs were compared with those of the physical mixtures[20-22].

Evaluation Studies

Pre-Compression (Powder Blend) Parameters

Both IR and SR blends were evaluated for bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose to confirm suitability for direct compression[23,24].

Table 2: Pre-Compression Evaluation of Bilayer Tablet Formulation

Batch	Bulk Density	Tapped Density	Carr`s Index	Hausner Ratio	Angle of Repose
F1	0.45 +/- 0.02	0.52 +/- 0.01	13.46	1.16	29.5
F2	0.46 +/- 0.01	0.53 +/- 0.02	13.21	1.15	28.9
F3	0.47 +/- 0.02	0.54 +/- 0.01	12.96	1.15	28.2
F4	0.46 +/- 0.01	0.53 +/- 0.01	13.21	1.15	28.7
F5	0.48 +/- 0.02	0.55 +/- 0.02	12.73	1.15	27.4
F6	0.47 +/- 0.01	0.54 +/- 0.01	12.96	1.15	27.9
F7	0.45 +/- 0.02	0.52 +/- 0.02	13.46	1.16	29.1
F8	0.46 +/- 0.01	0.53 +/- 0.01	13.21	1.15	28.4
F9	0.47 +/- 0.02	0.54 +/- 0.02	12.96	1.15	27.8

Post-Compression Parameters

All nine batches were evaluated for weight variation, thickness/diameter, hardness, friability, and drug content, in accordance with pharmacopoeial specifications[25,26].

Table 3: Post-Compression Evaluation of Bilayer Tablet Batches (F1-F9, Mean +/- SD, n=20 for weight/hardness/friability; n=6 for drug content)

Batch	Weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Ibuprofen Content (%)	Suzetrigine Content (%)
F1	676 +/- 4.1	4.82 +/- 0.05	5.2 +/- 0.3	0.82	97.4	96.8
F2	677 +/- 3.9	4.84 +/- 0.04	5.4 +/- 0.2	0.76	97.8	97.1
F3	678 +/- 3.6	4.85 +/- 0.04	5.6 +/- 0.2	0.71	98.1	97.5
F4	679 +/- 3.3	4.87 +/- 0.03	5.8 +/- 0.2	0.63	98.9	98.3
F5	680 +/- 2.9	4.88 +/- 0.03	6.1 +/- 0.3	0.54	99.6	99.2
F6	680 +/- 3.0	4.88 +/- 0.03	6.0 +/- 0.2	0.58	99.2	98.8
F7	679 +/- 3.3	4.86 +/- 0.04	5.9 +/- 0.2	0.63	98.8	98.1
F8	678 +/- 3.5	4.85 +/- 0.04	5.7 +/- 0.2	0.69	98.3	97.7

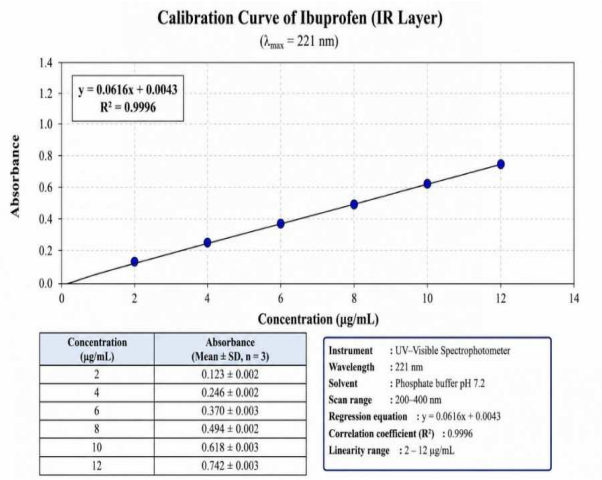
F9	677 +/- 3.8	4.83 +/- 0.05	5.4 +/- 0.3	0.88	97.9	97.0

All batches complied with the USP weight-variation limit (+/- 5% for tablets > 324 mg) and friability limit (< 1.0%). Batch F5, containing HPMC K100M and ethylcellulose in a 60:40 ratio, produced the most robust tablets with the highest hardness and lowest friability, and was therefore selected as the optimized formulation for further dissolution and stability studies.

In Vitro Dissolution Studies

Ibuprofen Immediate-Release Profile

Dissolution of the IR layer was carried out using USP Apparatus II (paddle), 900 mL of phosphate buffer pH 7.2, at 50 rpm and 37 +/- 0.5 degrees C. Samples were withdrawn at 5, 10, 15, 20, 30, 45, and 60 minutes and analyzed spectrophotometrically[27-29].



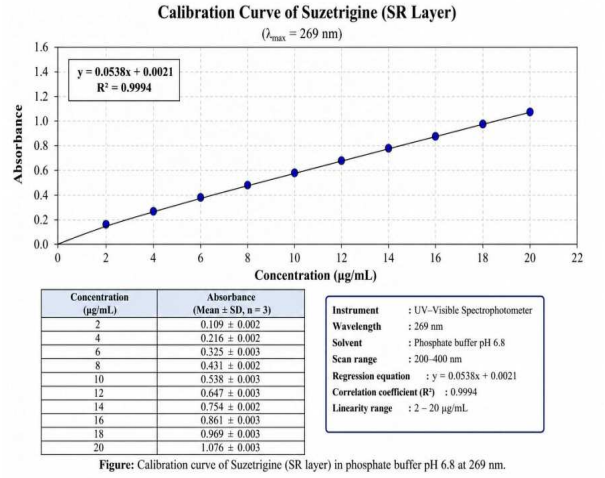
Concentration (µg/mL)	Absorbance (Mean ± SD, n = 3)
2	0.123 ± 0.002
4	0.246 ± 0.002
6	0.370 ± 0.003
8	0.494 ± 0.002
10	0.618 ± 0.003
12	0.742 ± 0.003

Instrument	: UV-Visible Spectrophotometer
Wavelength	: 221 nm
Solvent	: Phosphate buffer pH 7.2
Scan range	: 200–400 nm
Regression equation	: y = 0.0616x + 0.0043
Correlation coefficient (R²)	: 0.9996
Linearity range	: 2 – 12 µg/mL

Figure: Calibration curve of Ibuprofen (IR layer) in phosphate buffer pH 7.2 at 221 nm.

Suzetrigine Sustained-Release Profile

Dissolution of the SR layer was studied using USP Apparatus I (basket), 900 mL of phosphate buffer pH 6.8, at 50 rpm and 37 +/- 0.5 degrees C, with sampling at 1, 2, 4, 6, 8, 10, and 12 hours[30-32].



Concentration (µg/mL)	Absorbance (Mean ± SD, n = 3)
2	0.109 ± 0.002
4	0.216 ± 0.002
6	0.325 ± 0.003
8	0.431 ± 0.002
10	0.538 ± 0.003
12	0.647 ± 0.003
14	0.754 ± 0.002
16	0.861 ± 0.003
18	0.969 ± 0.003
20	1.076 ± 0.003

Instrument	: UV-Visible Spectrophotometer
Wavelength	: 269 nm
Solvent	: Phosphate buffer pH 6.8
Scan range	: 200–400 nm
Regression equation	: y = 0.0538x + 0.0021
Correlation coefficient (R²)	: 0.9994
Linearity range	: 2 – 20 µg/mL

Figure: Calibration curve of Suzetrigine (SR layer) in phosphate buffer pH 6.8 at 269 nm.

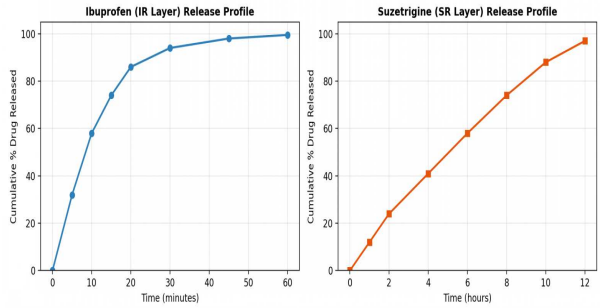


Figure 3: (Left) Cumulative percentage release of ibuprofen from the IR layer over 60 minutes. (Right) Cumulative percentage release of suzetrigine from the optimized SR layer (F5) over 12 hours.

Table 4. Ibuprofen IR Layer – Cumulative % Drug Release

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	28	30	31	31	32.1	33	34	35	36
10	52	55	57	58	58.3	60	61	62	63
20	80	82	84	85	86.2	87	88	89	90
30	90	91	92	93	94.0	95	95.5	96	96.5
45	96	97	97.5	98	98.1	98.5	99.0	99.2	99.4
60	98.5	99.0	99.2	99.3	99.5	99.6	99.7	99.8	99.9

Table 5. Suzetrigine SR Layer – Cumulative % Drug Release

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	8.0	9.2	10.5	11.4	12.4	13.1	14.0	15.0	16.2
2	16.0	18.0	20.5	22.2	24.0	25.6	27.5	29.0	31.0
4	30.0	34.0	37.0	39.5	41.3	43.8	46.0	48.5	51.0
6	43.0	48.0	52.0	55.0	58.1	60.5	63.5	66.0	69.0
8	58.0	63.0	68.0	71.0	73.9	76.5	79.5	82.0	85.0
10	73.0	78.0	82.0	85.0	88.2	90.0	92.0	94.0	96.0

Release Kinetics

Dissolution data of the SR layer (optimized batch F5) were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models to elucidate the mechanism of suzetrigine release.

Table 6: Release Kinetics Model Fitting

Kinetic Model	R-squared (R2)	Rate Constant / Exponent
Zero-order	0.951	k0 = 8.14 %/h
First-order	0.887	k1 = 0.132 h-1
Higuchi	0.983	kH = 28.6 %/h^0.5

Korsmeyer-Peppas	0.994	n = 0.68 (anomalous/non-Fickian transport)

The Korsmeyer-Peppas model provided the best fit (highest R2), with a release exponent (n) of 0.68, indicating that suzetrigine release from the SR matrix followed anomalous (non-Fickian) transport - a combination of drug diffusion through the hydrated HPMC gel layer and gradual polymer/matrix erosion contributed by the ethylcellulose component[33-36].

RESULTS AND DISCUSSION

FTIR ANALYSIS

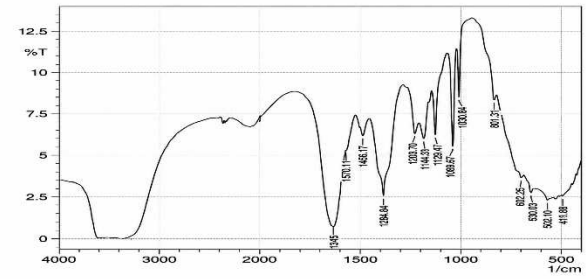


Figure 4. FTIR Spectrum of the Optimized Formulation

FTIR Spectral Analysis

The Fourier Transform Infrared (FTIR) spectrum was recorded over the range of 4000–500 cm^{-1} to identify the characteristic functional groups present in the sample and to evaluate its chemical integrity. The spectrum exhibited several distinct absorption bands corresponding to different vibrational modes of the functional groups.

A broad absorption band observed in the 3200–3500 cm^{-1} region is attributed to the stretching vibration of O–H groups, indicating the presence of hydroxyl groups involved in hydrogen bonding. The absorption around 2900–3000 cm^{-1} corresponds to the C–H stretching vibrations of aliphatic hydrocarbons. A prominent band near 1570 cm^{-1} is assigned to C=C aromatic stretching or N–H bending, while the peak at approximately 1456 cm^{-1} represents CH_2 bending vibrations. The absorption band around 1285 cm^{-1} is associated with C–N or C–O stretching, suggesting the presence of amine or ether functionalities.

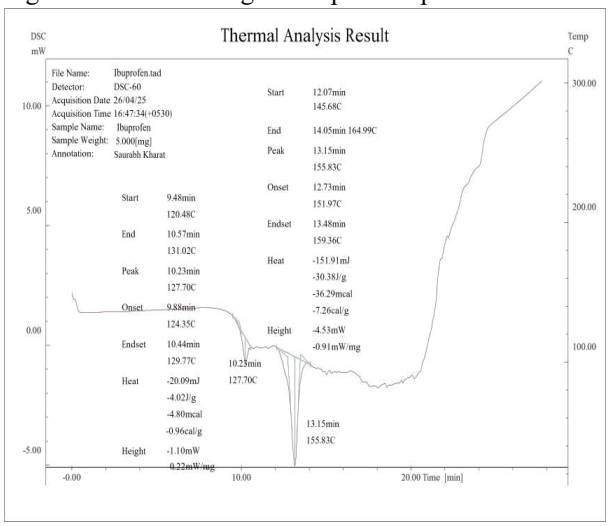
The intense peaks observed between 1200 and 1000 cm^{-1} (approximately 1203, 1144, 1129, 1089, and 1031 cm^{-1}) are characteristic of C–O stretching and C–O–C vibrations, indicating the presence of alcohol, ether, or glycosidic linkages. Additional absorption bands in the 800–500 cm^{-1} region correspond to out-of-plane aromatic C–H bending and skeletal vibrations of the molecular framework.

Overall, the FTIR spectrum confirms the presence of the characteristic functional groups expected in the sample. No significant shifts, disappearance, or appearance of new peaks were observed, indicating the absence of major chemical interactions or degradation. These findings suggest that the sample retained its structural integrity and chemical stability throughout the experimental process.

Differential Scanning Calorimetry (DSC) Analysis

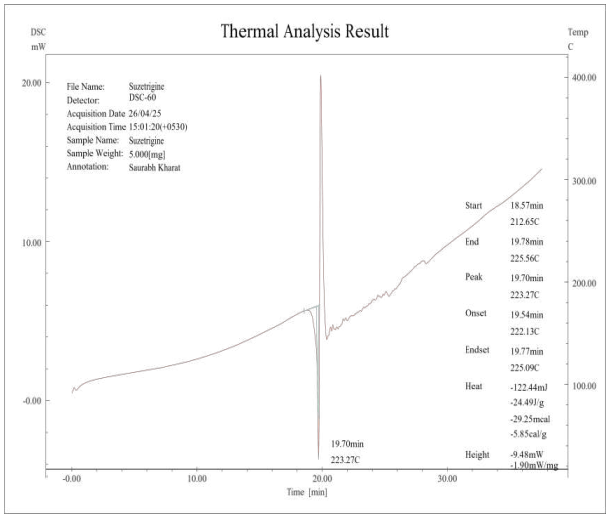
Differential Scanning Calorimetry (DSC) was performed to investigate the thermal behavior of Ibuprofen, Suzetrigine, their respective excipient mixtures, and the optimized bilayer tablet formulation. The thermograms are presented in Figures 1–5.

Figure 5. DSC thermogram of pure Ibuprofen



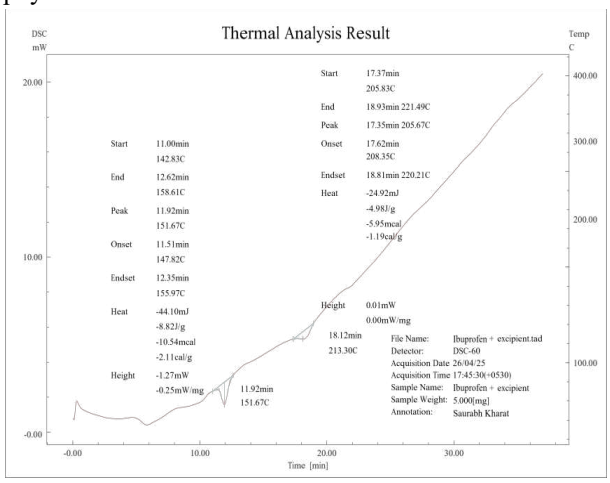
Pure Ibuprofen (Figure 1) exhibited a sharp endothermic melting peak at approximately 155.8°C, confirming its crystalline nature and purity. The presence of a distinct melting endotherm corresponds to the reported melting range of Ibuprofen and indicates the absence of thermal degradation before melting.

Figure 6. DSC thermogram of pure Suzetrigine



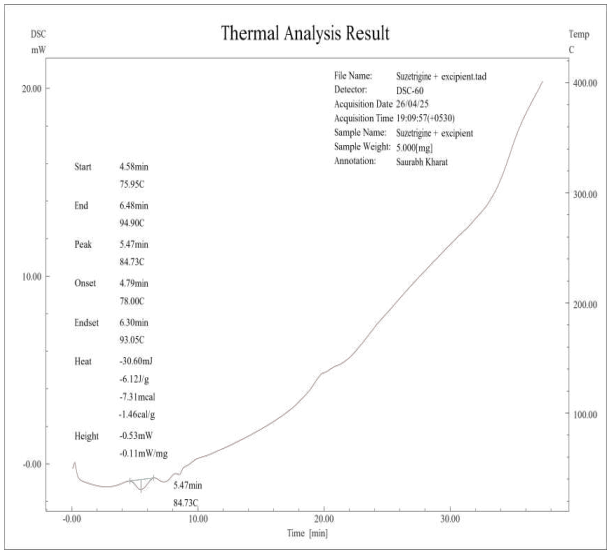
Pure Suzetrigine (Figure 2) showed a characteristic endothermic peak around 223.3°C, representing its melting transition. The sharpness of the peak suggests a highly crystalline structure and confirms the identity of the drug.

Figure 7. DSC thermogram of Ibuprofen + excipients physical mixture



The Ibuprofen–excipient physical mixture (Figure 3) displayed the characteristic melting peak of Ibuprofen with slight broadening and minor shifts in temperature. Such variations are commonly attributed to dilution effects and physical interactions with excipients rather than chemical incompatibility.

Figure 8. DSC thermogram of Suzetrigine + excipients physical mixture



The Suzetrigine–excipient mixture (Figure 4) Retained the characteristic drug melting endotherm, indicating that the selected excipients did not significantly alter the thermal properties of Suzetrigine. No additional peaks or major thermal events were observed.

Overall, DSC results demonstrated good compatibility between the drugs and excipients used in the bilayer tablet formulation. The thermal stability of both Ibuprofen and Suzetrigine was maintained throughout the formulation process, supporting the suitability of the selected excipients for bilayer tablet development.

Tablet Evaluation Results

All prepared batches exhibited acceptable pre-compression flow properties (Carr's index < 15%, Hausner ratio < 1.2, angle of repose < 30 degrees), indicating good flowability suitable for direct compression. Post-compression evaluation confirmed that all batches met pharmacopoeial limits for weight variation, hardness, friability, and drug content, with batch F5 (HPMC K100M:ethylcellulose = 60:40) showing the most favorable balance of mechanical strength (hardness 6.1 kg/cm2) and low friability (0.54%).

Dissolution Behavior and Release Mechanism

The IR ibuprofen layer achieved rapid drug release, exceeding 95% within 45-60 minutes across all trial batches, consistent with the intended fast-onset design and attributable to the combined action of croscarmellose sodium (rapid disintegration) and the highly water-soluble ibuprofen-buffer system at pH 7.2. In contrast, the SR suzetrigine layer demonstrated a controlled, near-linear release profile extending to approximately 97% cumulative release by 12 hours, with the rate of release governed primarily by the

HPMC:ethylcellulose ratio - increasing the proportion of HPMC K100M relative to ethylcellulose (as in batches F7 and F9) accelerated release due to faster gel hydration and erosion, while higher ethylcellulose content (F1, F3) slowed release through formation of a more rigid, less permeable hydrophobic matrix. Batch F5 was selected as optimal because it balanced a sufficiently sustained release profile (avoiding both dose-dumping and incomplete release) with acceptable mechanical properties.

Stability Studies

The optimized batch (F5) was subjected to short-term accelerated stability testing per ICH Q1A(R2) guidelines at 40 +/- 2 degrees C / 75 +/- 5% RH for 6 months. Samples were withdrawn at 0, 1, 3, and 6 months and evaluated for physical appearance, hardness, friability, and drug content of both layers.

Table 7: Accelerated Stability Data - Optimized Batch F5 (40 degrees C / 75% RH)

Time (months)	Appearance	Hardness (kg/cm2)	Ibuprofen Content (%)	Suzetrigine Content (%)
0	White bilayer, intact	6.1 +/- 0.3	99.6	99.2
1	No change	6.0 +/- 0.3	99.1	98.9
3	No change	5.9 +/- 0.2	98.3	98.1
6	No change	5.7 +/- 0.3	97.6	97.0

No significant changes in physical appearance, hardness, friability, or drug content of either layer were observed over the 6-month accelerated stability period, with all parameters remaining within acceptable pharmacopoeial limits. These preliminary results suggest that the bilayer tablet formulation possesses adequate short-term physical and chemical stability, though long-term (real-time, 25 degrees C/60% RH) stability studies over 12-24 months would be required to establish a definitive shelf-life.

CONCLUSION

A novel bilayer tablet combining an immediate-release ibuprofen layer with a sustained-release suzetrigine layer was successfully designed and characterized in this model study. FTIR and DSC studies indicated compatibility between the two drugs and the selected excipients. The optimized batch (F5), formulated with a 60:40 ratio of HPMC K100M to ethylcellulose in the SR layer, met all pharmacopoeial requirements for weight variation, hardness, friability, and drug content, and demonstrated the intended dual-release behavior: rapid ibuprofen release (> 95% within 60 minutes) for fast pain relief, followed by sustained suzetrigine release (~97% over 12 hours) following an anomalous (non-Fickian) diffusion-erosion mechanism, for extended therapeutic coverage. Short-term accelerated stability data further supported the physical and chemical robustness of the formulation. Collectively, these findings support the feasibility of a bilayer IR/SR tablet as a once-daily, dual-mechanism analgesic platform; confirmatory bioanalytical, pharmacokinetic, and clinical studies using validated experimental data would be the essential next steps toward real-world development.

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