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Formulation and Evaluation of Bilayer Tablets of Vonoprazan Fumarate (IR) and Ibuprofen (SR) for Gastroprotective Nsaid Therapy

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Abstract: ***In this study, a bilayer tablet which combines Ibuprofen in a sustained-release layer and Vonoprazan in an immediate-release layer is designed and tested. In separate batches, three highly effective super-disintegrants - sodium starch glycolate, polyplasdone XL, and croscarmellose sodium - were utilised to formulate the IR layer at different concentration levels of 3%, 4%, and 5%. To ensure sustained drug release in accordance with USP guidelines, a combination of Ibuprofen and three hydrophilic matrix-forming polymers, namely HPMC K4M, HPMC K15M, and Hypromellose K100M CR Premium, was used at concentration levels of 15%, 20%, and 25% respectively, for the SR layer. The appearance, thickness, hardness, friability, drug content, weight uniformity, and in-vitro dissolution characteristics of the manufactured bilayer tablets have been evaluated. Formulation T9, containing 7.5 mg of croscarmellose sodium, produced outstanding results among the IR batches, achieving a 99.25% release of Vonoprazan within a 0.1 N HCl solution after a short period of just one hour. The batch containing 325 mg of Hypromellose K100M CR Premium showed the most successful sustained release in the SR layer, outperforming other studied formulations by releasing 99.12% of Ibuprofen over 12 hours, first in 0.1 N HCl for 2 hours and then in phosphate buffer with a pH of 7.2.***

Keywords: Bilayer tablet, Vonoprazan, Immediate release, Sustained release, Gastro protective NSAID Therapy

1. Introduction

Two distinct layers of a bilayer tablet contain specific active pharmaceutical ingredients (APIs) formulated to achieve a defined drug release pattern. The sustained-release layer prolongs medication release to maintain steady plasma concentrations[1], the immediate-release layer ensures rapid drug delivery for an initial therapeutic effect[2]. This design made it simpler to combine substances that are incompatible, moisture-sensitive, or thermolabile. In order to ensure tablet durability, efficacy, manufacturing possible outcomes, and greatest bioavailability, the right APIs and excipients must be chosen[3]. Key functional excipients enhance formulation performance, patient adherence, and aesthetic appeal. These examples include binders, superdisintegrants, flavouring agents, and colorants. A gradual API release can be facilitated by controlled-release drug delivery systems[4], which also maintain therapeutic plasma levels, reduce dosage frequency, and diminish adverse consequences after the first medication action4. Compared to traditional immediate-release formulations, these systems provide more long-lasting therapeutic outcomes through improved medication effectiveness and patient compliance[5].

Ibuprofen, a commonly prescribed nonsteroidal anti-inflammatory drug (NSAID), effectively alleviates pain and inflammation, but prolonged use can lead to stomach irritation and ulcers[6-7]. Strong gastro protection against NSAID-induced mucosal injury is provided by vonoprazan, a strong potassium-competitive acid blocker (P-CAB) that acts quickly to reduce stomach acid output[8-9].Vonoprazan equitable treatment in an immediate-release (IR) layer promises rapid acid inhibition before ibuprofen prolonged release, reducing the potential of stomach side effects[10]. This novel bilayer design optimizes therapeutic efficacy by incorporating dual-action therapy into a single dosage form, thereby enhancing patient adherence. This method is particularly beneficial for managing chronic pain, as long-term NSAID use necessitates concurrent stomach protection.

2. Materials and Methods

Material

Vonoprazan fumarate, ibuprofen, microcrystalline cellulose PH 102 and PH 101, L-HPC, HPMC K4M, HPMC K15M, and Hypromellose K100M CR Premium, Povidone K 30, Sodium starch glycolate, Polyplasdone XL, Croscarmellose sodium, Colloidal anhydrous silica M5P, and Magnesium stearate are used.

Methodology

The composition of bilayer tablets prepared using vonoprazan and ibuprofen

Table 1: Formulation table of Vonoprazan fumarate IR Layer

S.NO	Ingredients	T1	T2	T3	T4	T5	T6	T7	T8	T9
1	Vonoprazan Fumarate	26.723	26.723	26.723	26.723	26.723	26.723	26.723	26.723	26.723
2	Microcrystalline cellulose PH 102	110.73	109.23	107.73	110.73	109.23	107.73	110.73	109.23	107.73
3	L-Hydroxy propyl cellulose	6	6	6	6	6	6	6	6	6
4	Fumaric acid	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
5	Ferric oxide Yellow	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
6	Sodium starch glycolate	4.5	6	7.5	-	-	-	-	-	-
7	Polyplasdone XL	-	-	-	4.5	6	7.5	-	-	-
8	Croscarmelose sodium	-	-	-	-	-	-	4.5	6	7.5
9	Magnesium stearate	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55
Total weight of tablet (mg)		150	150	150	150	150	150	150	150	150

Table 2: Formulation table of Ibuprofen SR Layer

S. No	Ingredients	T1	T2	T3	T4	T5	T6	T7	T8	T9
1	Ibuprofen	800.00	800.00	800.00	800.00	800.00	800.00	800.00	800.00	800.00
2	Lactose Monohydrate	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00
3	Microcrystalline cellulose 101	174.00	109.00	44.00	174.00	109.00	44.00	174.00	109.00	44.00
4	HPMC K4M	195.00	260.00	325.00	-	-	-	-	-	-
5	HPMC K15M	-	-	-	195.00	260.00	325.00	-	-	-
6	Hypromellose K-100 M Premium CR	-	-	-	-	-	-	195.00	260.00	325.00
7	Povidone K -30	39.00	39.00	39.00	39.00	39.00	39.00	39.00	39.00	39.00
8	Purified Water	150.00	150.00	150.00	150.00	150.00	150.00	150.00	150.00	150.00
9	Croscarmelose sodium	26.00	26.00	26.00	26.00	26.00	26.00	26.00	26.00	26.00
10	Colloidal Anhydrous Silica	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00
11	Magnesium Stearate	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00
Total weight of tablet (mg)		1300	1300	1300	1300	1300	1300	1300	1300	1300

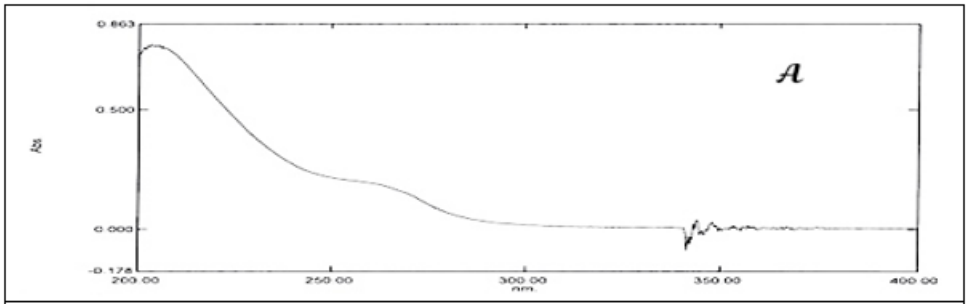
Preparation of vonoprazan granules:

A 30-mesh stainless steel sieve was used to sift Vonoprazan Fumarate, Microcrystalline Cellulose PH 102, and Hydroxypropyl Cellulose first, and the sifted components were then collected into two polyethylene bags throughout the tablet production process. Iron Oxide Yellow, Croscarmellose Sodium, Colloidal Anhydrous Silica, and Magnesium Stearate are consistently processed through a 60-mesh filtering process each time to standardize particle size. The initial mixture, comprising Vonoprazan Fumarate, Microcrystalline Cellulose, and L-HPC, is then placed in a double cone mixer and agitated for ten minutes. The pre-sifted Iron Oxide Red, Colloidal Silica, and Magnesium Stearate are then added, and the mixture is mixed for a further five minutes [29] to ensure adequate lubrication and prevent sticking issues during production, ultimately facilitating smooth tablet compression.

Preparation of ibuprofen granules:

Ibuprofen, lactose, and Microcrystalline Cellulose PH101 are first passed through a #24 mesh screen as part of the wet granulation process. The material is then placed in a Rapid Mixer Granulator (RMG) for a 5-minute mixing process. Povidone K-30 is dissolved in isopropyl alcohol (IPA) to create a binder solution, which is then added sequentially to the RMG, with further additions of IPA made as needed, and then mixed for a further two minutes. The wet mass is then sent to a Fluid Bed Dryer (FBD) for a 10-minute air drying period without applying heat. Any material that remains after passing granules through a #24 mesh is then milled using a multi-mill with a 1.0 mm screen and subsequently sieved. The granules must be dried in the FBD for 15 minutes at a temperature of 45°C (within a 40–50°C range) to reach a moisture content of 1.4–2.6% w/w. The dried granules have been blended with Hypromellose K100M Premium CR, Croscarmellose Sodium, and Colloidal Anhydrous Silica, which have been pre-sieved through a #30 mesh screen for a period of ten minutes using a Double Cone Blender. To guarantee an even distribution, the magnesium stearate (#60 mesh) is added last and mixed for three more minutes.

Development of analytical techniques for Ibuprofen and Vonoprazan Fumarate involves locating the absorption maxima: This entails acquiring the electromagnetic spectrum of the working standards by scanning between 200 and 400 nm against the blank element in the reagent for determining the absorption maxima. Every subsequent experiment is then conducted at the previously determined λ-max wavelength[11-12].



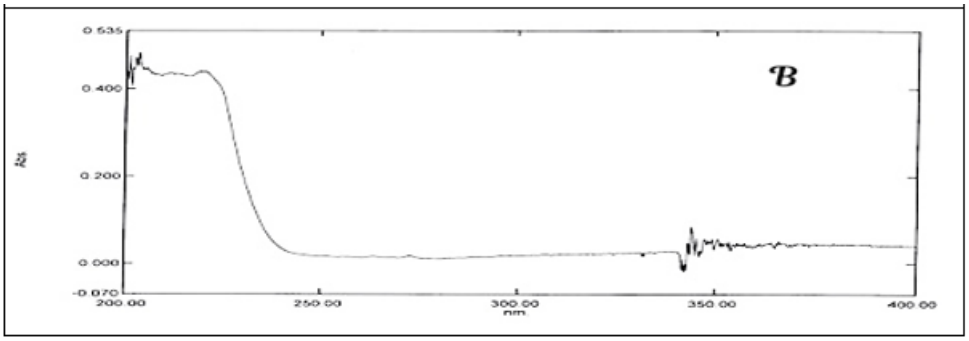


Figure 1: λ-max Scan of Vonoprazan Fumarate (A) and Ibuprofen (B)

The absorption maxima (λ-max) was found at 218 nm right after the working standards were scanned over a wavelength range of 20—400nm against a reagent blank. As a result, this ideal wavelength was implemented for precise and reliable analytical measurements in both the standard calibration curve and dissolution research.

Calibration curve for Vonoprazan Fumarate and Ibuprofen

To make sure that would establish a linear relationship between concentration and response and stand by precise drug quantification in succeeding analyses, a standard calibration curve was established by producing various concentrations of vonoprazan fumarate in 0.1 M HCl and measuring their absorbance[13].

A series of Ibuprofen solutions at different concentrations in methanol were put together to create the standard calibration curve[14]. HPLC analysis was then performed to ascertain the relationship between drug content and peak area ensure precise quantification a, as shown figure 2.

Table 3: Preparation of Standard Graph of Vonoprazan Fumarate and Ibuprofen

S. No	Vonoprazan Fumarate		Ibuprofen	
	Concentration mcg/mL	Peak Area	Concentration mcg/mL	Peak Area
1	0	0	0	0
2	10	1502514	9	945622
3	16	2500321	14.4	1532332
4	20	3125419	18	1915415
5	24	3750502	21.6	2298498
6	30	4752154	27	2905214

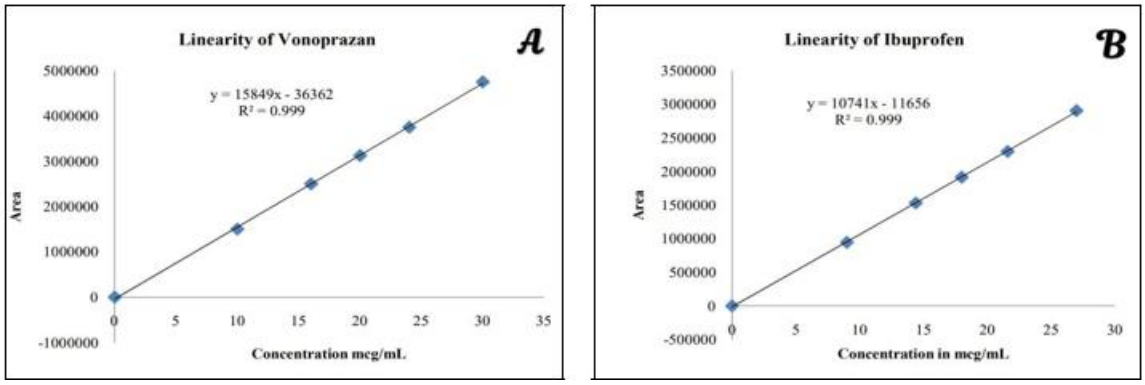


Figure 2: Standard curve for Vonoprazan Fumarate (A) and Ibuprofen (B)

Assay procedure:

Chromatographic Condition

The mobile phase was in circulation for a total of 20 minutes and comprised 0.05 M potassium dihydrogen phosphate buffer at a pH of 3.0 and acetonitrile in a 60:40 (v/v) ratio [15,16]. The detection technique was performed at a UV wavelength of 218 nm with a column temperature maintained at 25°C ± 2°C and an overall injection volume of 100 µL. The mobile phase circulated for a total coof0 minutes and represented 0.05 M potassium dihydrogen phosphate buffer (pH 3.0) and acetonitrile in a 60:40 (v/v) ratio [15, 17].

Preparation of Mobile Phase:

Standard preparation:

The Vonoprazan Standard Preparation:

Weigh exactly 27 mg as the working standard of vonoprazan fumarate precisely, then pour it into a 100 mL volumetric flask. To help ensure total dissolution, add suitable mobile phase, sonicate, and subsequently dilute to volume using the same mobile phase. To create a working standard with a final concentration of 27 µg/mL, further dilute this stock solution.

The Ibuprofen Standard Preparation:
To establish a final concentration of 100 µg/mL, precisely measure 800 mg of the Ibuprofen working standard, dissolve it in a compatible solvent, and then dilute the solution[14].

Test preparation:
After calculating the average weight of twenty tablets, they were finally pulverized into a fine powder. A fixed amount, equal to 800 mg of Ibuprofen and 20 milligrams of Vonoprazan, was introduced into a 100 mL volumetric flask. After adding 25 mL of diluent, the mixture was sonicated for 15 minutes to ensure complete dissolution. The volume was then changed after that level of compensation.

Procedure:
Separately, inject corresponding quantities of the test sample, standard solution, and diluent (blank) into the chromatographic apparatus. Determine which peak areas correspond to Vonoprazan and Ibuprofen by recording the outcomes of chromatograms. Determine how much Vonoprazan and Ibuprofen had been prescribed in the test preparation based on the peak areas that were obtained.

Procedure for dissolution testing:

Method of analysis
At each interval, 10 mL aliquots were withdrawn and immediately replenished with fresh medium and diluent[18-21]. The USP Type-II (Paddle) device was operated at a temperature of 37 degrees Celsius ± 0.5 degrees and a speed of 50 revolutions per minute. Specimens were collected at 5, 10, 15, 20, 30, 45, and 60 minutes (or until the full release occurred) for the immediate-release layer of Vonoprazan, and at 1, 2, 4, 8, and 12 hours (or until saturation or release completion took place) for the sustained-release layer of Ibuprofen. At each interval, 10 mL aliquots were collected and then replaced with new medium and diluent[18-21].

Procedure to feed preparing the Sample:
Insert each of the six tablets individually into the six dissolution containers that have been filled with the required dissolution medium and calibrated to a temperature of 37°C ± 0.5°C. Before turning the device over, make sure there are no air bubbles left on the tablet surfaces. Samples should be taken at a location between the revolving blade and the medium's surface after the pre-designated intervals, maintaining at least 1 cm from the vessel wall. To prevent any contamination, the obtained samples should be filtered using Whatman No. First, discard 5 mL of the liquid and then use 1 filter paper.

Standard Preparation:
Transfer 150 mg of the Ibuprofen working reference standard and approximately 20 mg of the Vonoprazan working reference standard into a 100 mL volumetric flask after properly weighing them. About 30 milliliters of the dissolution medium need to be used to dissolve the standards. Then, use the same medium to adjust the volume and genuinely mix. To get the final standard solution, further dilute 5 mL of this solution to 50 mL using the dissolution medium.

Chromatographic conditions:
With a Phenomenex C18 column (250 mm × 4.6 mm, 5 µm particle size) and a gradient pump mode, the chromatographic analysis was carried out at a flow rate of 1.0 mL/min. A UV wavelength of 218 nm was used for the detection, together with a 20 µL injection volume and a column temperature of 25°C ± 2°C. The mobile phase diluent was made up of 0.05 M potassium dihydrogen phosphate buffer and acetonitrile in a 60:40 (v/v) ratio, and the overall run time was set at 20 minutes [19-20].

Procedure and System Suitability:
Six injections of the standard solution are carried out, followed by the injections with the sample solutions and blank. The resolution between the two peaks must be at least 3.3.0 and the relative standard deviation (RSD) of the replicate standard injections cannot be greater than 2% for the system to be considered acceptable.

3. Results and Discussion

Pre-compression scenarios:

Table 4: Parameters of the Vonoprazan blend before compression

Code	B.D (g/mL)	T.D (g/mL)	Hausner's ratio	Comps. Index (%)	Angle of repose (ɵ)	Flow property
T1	0.495	0.657	1.33	24.66	43º 20'	PASSABLE
T2	0.544	0.654	1.2	16.82	38º 09'	FAIR
T3	0.526	0.638	1.21	17.55	37º 18'	FAIR
T4	0.518	0.618	1.19	16.18	38º 25'	FAIR
T5	0.511	0.612	1.2	16.5	32º 45'	GOOD
T6	0.568	0.665	1.17	14.59	33º 36'	GOOD
T7	0.518	0.615	1.19	15.77	34º 18'	GOOD
T8	0.553	0.636	1.15	13.05	33º 12'	GOOD
T9	0.622	0.718	1.15	13.37	32º 42'	GOOD

Table 5: Parameters of the Ibuprofen Blend Before Compression

Code	B.D (g/mL)	T.D (g/mL)	Hausner's ratio	Comps. Index (%)	Angle of repose (ɵ)	Flow property
T1	0.425	0.589	1.39	27.84	46 º 92'	POOR
T2	0.455	0.635	1.4	28.35	45º 75'	POOR
T3	0.477	0.642	1.35	25.7	41º 28'	PASSABLE
T4	0.578	0.685	1.19	15.62	36º 45'	GOOD
T5	0.556	0.663	1.19	16.14	35º 45'	GOOD
T6	0.555	0.685	1.23	18.98	35º 75'	GOOD
T7	0.577	0.698	1.21	17.34	34º 47'	GOOD
T8	0.542	0.689	1.27	21.34	34º 71'	GOOD
T9	0.552	0.684	1.24	19.3	34º 35'	GOOD

Drugs and excipient compatibility studies using FTIR:

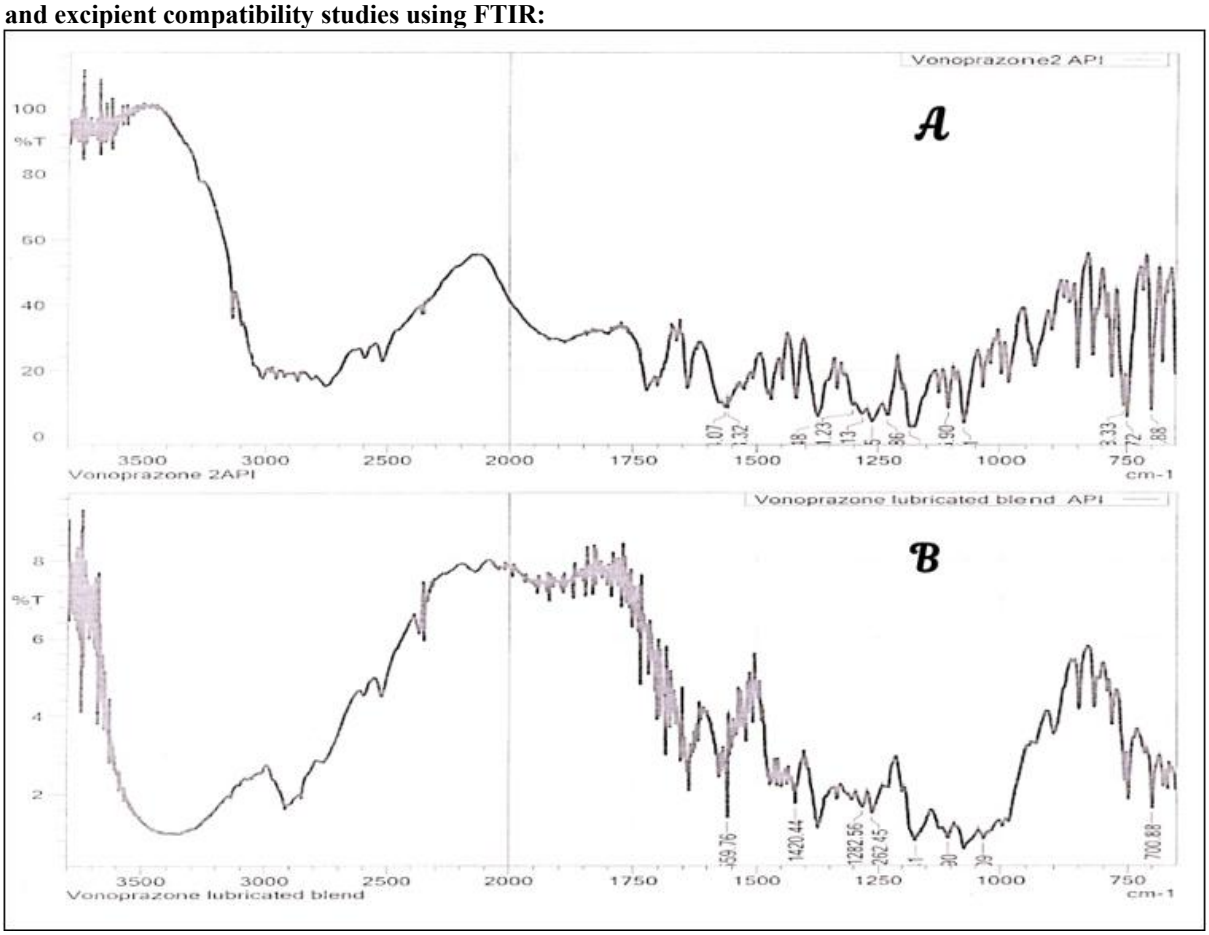


Figure 3: FTIR Spectra of pure Vonoprazan fumarate (A) and lubricated blend (B)

Studies were conducted to assess the potential interactions between excipients and the active pharmaceutical ingredients, specifically Ibuprofen and Vonoprazan fumarate, for the immediate-release (IR) and sustained-release (SR) formulations. The samples were formulated by hydraulically compressing crushed mixes containing potassium bromide (KBr) into pellets. Fourier-transform infrared (FTIR) spectroscopy was carried out at room temperature over the range of 400 to 4000 cm^{-1}. Prior to analysis, baseline corrections and spectrum smoothening were carried out22-23.

The objective of this study was to investigate any physical or chemical interactions between the active ingredients and excipients in the extended-release Ibuprofen matrix and the fast-release Vonoprazan layer formulations. FTIR spectroscopic analysis of Vonoprazan and its physical mixture with excipients showed no significant interactions, thus confirming the drug's compatibility with the formulation components.

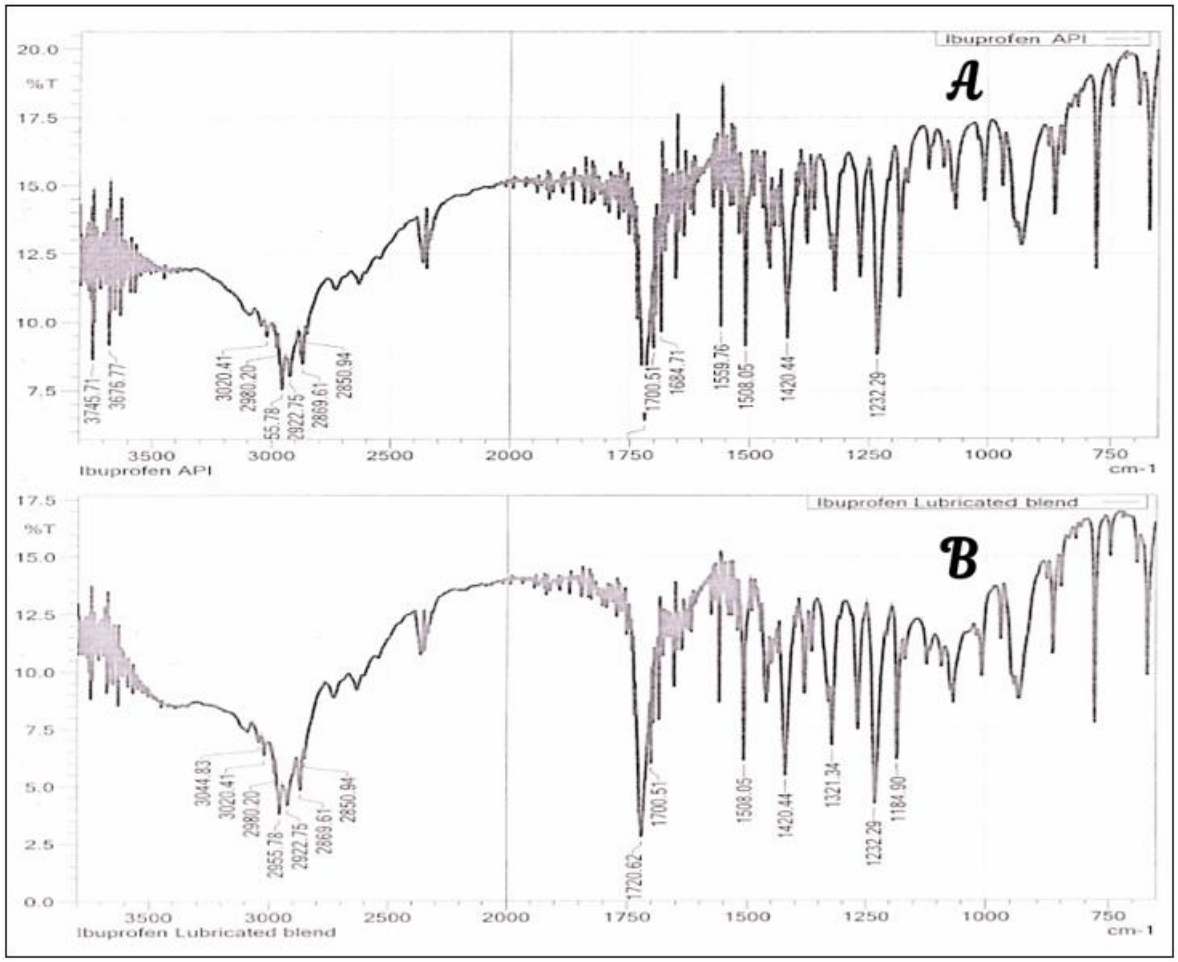


Figure 4: FTIR Spectra of pure Ibuprofen (A) and lubricated blend (B)

The FTIR spectral analysis of pure Ibuprofen and its physical mixture with excipients revealed no notable interactions, as the characteristic peaks of the drug remained unaltered, confirming compatibility between the drug and the formulation components.

Drug and excipient compatibility testing under accelerated environmental conditions (40°C / 75% RH).

A drug-excipient compatibility study was carried out over a four-week period under accelerated stability conditions, specifically 40°C ± 2°C and 75% ± 5% relative humidity. Different drug-excipient mixes were preserved under these circumstances and their physical attributes were evaluated periodically at pre-arranged times. To guarantee compatibility and stability, the observed changes in appearance, colour, and other physicochemical properties were compared with the original baseline information. This investigation ensures compatibility of excipients with formulation development by detecting any negative interactions under stress conditions [23-24].

Post Compression parameters:

Table 6: Evaluation of Bilayer Tablets of Vonoprazan IR and Ibuprofen SR (T1 to T9)

S. No	Tests	Specifications	T1	T2	T3	T4	T5	T6	T7	T8	T9
1	Description	Yellow / White colored oval shaped uncoated Bilayer tablet	Meet	Meet	Meet	Meet	Meet	Meet	Meet	Meet	Meet
2	Average weight (mg)	1450 mg ±3%	1452	1458	1452	1450	1457	1455	1452	1455	1453
3	Thickness (mm)	7.00mm ± 0.2mm	7.05	7.02	7.06	7.01	7.08	7.02	7.05	7.11	7.07
4	Hardness (kg/cm2)	NLT 5.0	10	11.5	9.85	10.5	11.05	10.5	12.5	11	10.5
5	Friability (% w/w)	NMT 1%	0.07	0.11	0.11	0.15	0.14	0.1	0.1	0.13	0.11
6	Weight variation (n=20)	±5% from the average weight	-2.5 to +2.1	-2.7 to +1.9	-2.7 to +1.5	-3.0 to +1.7	-2.3 to +1.9	-2.5 to +1.2	-2.7 to +1.5	-2.0 to +1.7	-1.3 to +1.9
7.	Assay										
	Vonoprazan Fumarate equivalent to Vonoprazan	90 – 110%	97.90%	97.20%	97.50%	98.10%	98.18%	97.2%	98.10%	98.70%	98.33%
	Ibuprofen	90 – 110%	97.75%	97.85%	98.30%	96.37%	97.90%	97.50%	98.20%	97.30%	98.52%

***In-vitro* Dissolution studies**

According to USP requirements[26-28], The assessment involved *in-vitro* dissolution testing to determinethe release of Ibuprofen and Vonoprazan at different times throughout the day.

Immediate release layer of Vonoprazan

Table 7: Comparative In-vitro release data for Vonoprazan IR layer T1 to T9 formulations.

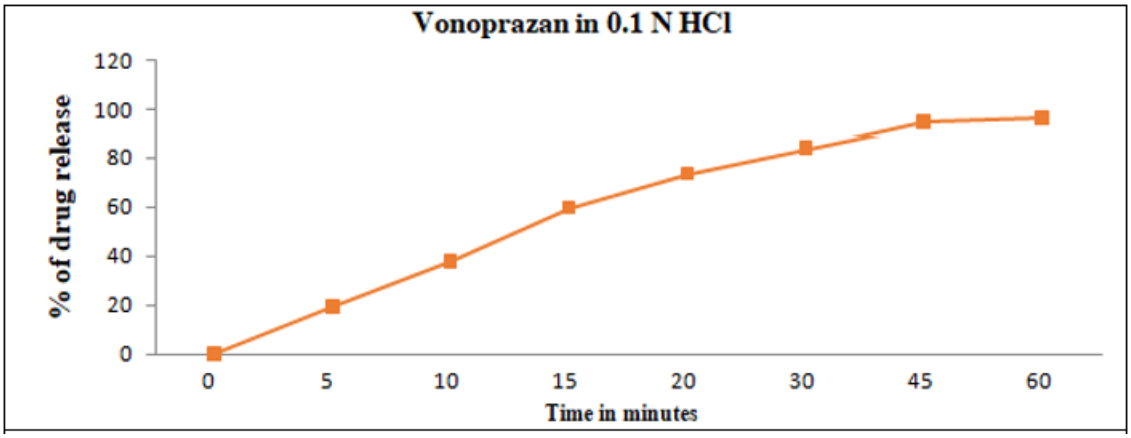
S. No	Formulation	Time (hr)	Amount of drug release (mg)	Cumulative % drug release
1	T1	1	17.73	88.65
2	T2	1	18.42	92.11
3	T3	1	19.15	95.75
4	T4	1	17.49	87.44
5	T5	1	18.32	91.58
6	T6	1	19.37	96.87
7	T7	1	18.73	93.64
8	T8	1	19.05	95.24
9	T9	1	19.87	99.33

Sustained release layer of Ibuprofen

Table 8: Comparative In-vitro release data for Ibuprofen T1 to T9 formulations.

S. No	Formulation	Amount of drug release (mg)					Cumulative % drug release				
		1hr	2hr	4hr	8hr	12hr	1hr	2hr	4hr	8hr	12hr
1	T1	605	686	762	785	791	75.6	85.8	95.3	98.2	98.9
2	T2	543	675	745	785	788	67.9	84.4	93.2	98.1	98.5
3	T3	461	682	739	783	790	57.6	85.2	92.4	97.8	98.8
4	T4	442	671	727	778	789	55.2	83.9	90.9	97.2	98.6
5	T5	188	652	740	786	792	23.5	81.6	92.5	98.3	99
6	T6	164	385	710	759	793	20.5	48.2	88.7	94.9	99.2
7	T7	177	421	681	765	791	22.1	52.6	85.1	95.7	98.8
8	T8	168	371	621	769	793	21	46.4	77.6	96.1	99.1
9	T9	126	268	452	650	793	15.8	33.5	56.5	81.2	99.1

While Vonoprazan fumarate reaching 99.33% release within the first hour, batch T9 bilayer tablet combining Vonoprazan (IR) and Ibuprofen (SR) achieved exceptionally well out of the nine formulation trials. At 1, 2, 4, 8, and 12 hours, respectively, the sustained-release profile of Ibuprofen reached 15.79%, 33.54%, 56.47%, 81.22%, and 99.12%, exhibiting an established release pattern. The in vitro chemical release profiles of Ibuprofen (SR) and Vonoprazan fumarate (IR) for formulation T9 are shown in Figure 5, emphasizing the ability of the medicine to satisfy both immediate and sustained release specifications.



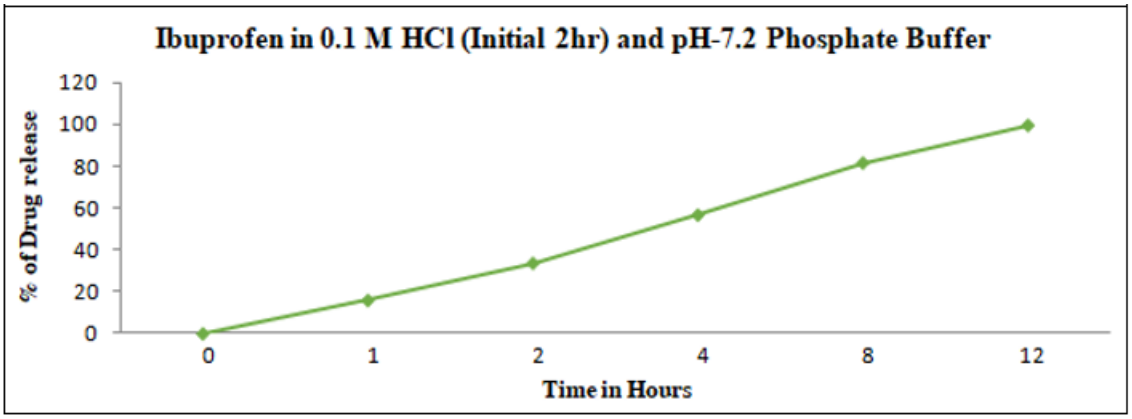


Figure 5: The finalized formula for the *in vitro* dissolution profile of formulation T9

4. Summary and Conclusion

This study involved the development and evaluation of a bilayer tablet that contained immediate-release vonoprazan and sustained-release ibuprofen. Three independent super disintegrants were incorporated into the Vonoprazan (IR) layer; the formulation containing 7.5 mg of Croscarmellose sodium exhibited the briefest duration of dissolution. Polymers with high viscosity, such as Hypromellose, have been tested to stabilise drug release for the ibuprofen (SR) layer; the most significant was Hypromellose K100M Premium CR, which is available in a 325 mg per tablet formulation. The optimized formulation met all parameters within acceptable limits, as demonstrated by comprehensive stability, chemical, and physical testing. The objective of this study was to develop a novel bilayer tablet formulation that combined sustained-release ibuprofen with immediate-release vonoprazan. The SR layer incorporated hydrophilic matrix formers (HPMC K4M, K15M, and Hypromellose K100M CR Premium) to facilitate prolonged drug release, whereas the IR layer employed superdisintegrants to expedite drug release. In a combination of Vonoprazan and Ibuprofen, this dual-action mechanism promptly suppresses stomach acid and also delivers long-lasting anti-inflammatory and analgesic effects from Ibuprofen. The enhanced formulation demonstrates excellent clinical promise by concurrently fulfilling two key therapeutic requirements: sustained pain relief and rapid acid control. This also increases patient compliance by reducing the number of doses and minimising gastrointestinal discomfort. Combination therapy offers an effective pharmacological approach to treating acid-peptic diseases and chronic inflammatory pain conditions.

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