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INNOVATIVE BILAYER TABLETS FOR GERD: A STUDY OF VONOPRAZAN IR AND DOMPERIDONE SR COMBINATION

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ABSTARCT

This study aims to develop and evaluate a bilayer tablet containing Vonoprazan in the IR and Domperidone in the SR layer. The immediate-release layer of Vonoprazan was created using three super-disintegrants such as starch sodium glycolate, crospovidone XL 10 and crosscaramellose sodium in different concentrations (3, 6 and 9mg) for each formulation. In contrast, the domperiodone sustained release layer was formulated by using three different grades of hydrophilic matrix former HPMC (K4M, K15M, and K 100 M premium CR) with 18 and 27mg concentration for each of the formulation. The prepared bilayer tablet was evaluated for physical appearance, weight variation, thickness, hardness, friability, assay and *in-vitro* dissolution studies. The results revealed that F9 formulation of vonoprazone layer with crosscaramellose sodium of 9mg has better release (99.17±0.27 at 1hr) whereas domperidone layer shows the drug release of 98.4 at 24hrs while using 27mg of Hypromellose K-100 M Premium CRwhen compared to all other formulations.

KEYWORDS: Bilayer tablet, Vonoprazan Immediate release, Sustained release, Gastroesophageal reflux disease.

INTRODUCTION

A bilayer tablet consists of two layers, typically with different APIs, designed to modulate drug release. For quick therapy, the immediate-release layer packs while the sustained-release layer maintains dose. This tablet may use incompatible, moisture- or heat-sensitive components. Active compounds and excipients enhance tablet quality, stability, bioavailability, and production. Binders, antioxidants, disintegrants, tastes, and colours improve formulation, release, and patient acceptability.[1] Continuous release medicine

delivery systems gradually release drugs to maintain drug levels and prevent adverse effects after an initial therapeutic dose. Better medication usage, lowest dosage frequency, patient compliance, less side effects, and longer therapeutic advantages than immediate-release medicines increase pharmaceutical efficacy or reduces negative effects. Domperidone blocks D2 receptors to increase GI motility. Coordination and enhancement of esophageal and stomach contractions help GERD sufferers move food.[2] High motility prevents heartburn by preventing stomach acid from entering the oesophagus. Domperidone reduces acid reflux by strengthening LES (lower oesophagus sphinter). Vonoprazan inhibits stomach H+/K+-ATPase, acid generation by preventing potassium binding in this enzyme, reduces GERD and stomach acid faster and longer than PPIs.[3]

Vonoprazan and Domperidone are indicated for GERD treatment. The LES pressure tone diminishes with GERD, leading stomach acid to overflow into the oesophagus and induce heartburn and esophageal damage. Vonoprazan is taken with Domperidone, an anti-emetic, to enhance LES pressure and prevent stomach outflow.

MATERIALS AND METHODS

Materials

Vonoprazan fumarate (Ami Lifesciences Pvt. Ltd.), Domperidone IP (Vasudha Pharma chem limited), Micro crystallinecellulose Ph 102 and Ph 101, Pearlitol 100 SD, HPMC K4m, HPMC K15M, HPMC K100M Premium CR, Povidone K 30, Sodium starch glycolate, Crospovidone XL 10,Croscarmellose sodium, Colloidal anhydrous silica and Magnesium stearate are used.

METHODOLOGY

The composition of bilayer tablets prepared using Vonoprazan and Domperidone

Table No. 01: Formulation table of Vonoprazan fumarate IR Layer.

S. No	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
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	88.041	85.041	82.041	88.041	85.041	82.041	88.041	85.041	82.041
3.	Pearlitol 100 SD	55.000	55.000	55.000	55.000	55.000	55.000	55.000	55.000	55.000
4.	Hydroxy propyl cellulose	4.500	4.500	4.500	4.500	4.500	4.500	4.500	4.500	4.500
5.	Fumaric acid	0.036	0.036	0.036	0.036	0.036	0.036	0.036	0.036	0.036
6.	Iron oxide red	0.900	0.900	0.900	0.900	0.900	0.900	0.900	0.900	0.900
7.	Sodium starch	3.000	6.000	9.000	NA	NA	NA	NA	NA	NA

	glycolate									
8.	Crospovidone XL 10	NA	NA	NA	3.000	6.000	9.000	NA	NA	NA
9.	Croscarmelose sodium	NA	NA	NA	NA	NA	NA	3.000	6.000	9.000
10.	Magnesium stearate	1.800	1.800	1.800	1.800	1.800	1.800	1.800	1.800	1.800
Total weight of tablet (mg)		180.00	180.00	180.00	180.00	180.00	180.00	180.00	180.00	180.00

Table No. 02: Formulation table of Domperidone SR Layer.

S. No	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1.	Domperidone IP	30.000	30.000	30.000	30.000	30.000	30.000	30.000	30.000	30.000
2.	MCC 101	112.000	103.000	94.000	112.000	103.000	94.000	112.000	103.000	94.000
3.	HPMC K4M	9.000	18.000	27.000	NA	NA	NA	NA	NA	NA
4.	HPMC K15M	NA	NA	NA	9.000	18.000	27.000	NA	NA	NA
5.	Hypromellose K-100 MPremium CR	NA	NA	NA	NA	NA	NA	9.000	18.000	27.000
6.	Acrypol 974 P	10.000	10.000	10.000	10.000	10.000	10.000	10.000	10.000	10.000
7.	Povidone K 30	10.000	10.000	10.000	10.000	10.000	10.000	10.000	10.000	10.000
8.	Isopropyl alcohol	40.000	40.000	40.000	40.000	40.000	40.000	40.000	40.000	40.000
9.	Croscarmelose sodium	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000
10.	Aerosil	2.000	2.000	2.000	2.000	2.000	2.000	2.000	2.000	2.000
11.	Magnesium stearate	2.000	2.000	2.000	2.000	2.000	2.000	2.000	2.000	2.000
Total weight of tablet (mg)		180.00	180.00	180.00	180.00	180.00	180.00	180.00	180.00	180.00

Preparation of vonoprazan granules

Sift Vonoprazan Fumarate, Microcrystalline Cellulose PH 102, Pearlitol 100 SD, and Hydroxy propyl cellulose into two polythene bags using a 40# stainless steel sieve. Sift Fumaric Acid, Iron Oxide Red, Sodium Starch Glycolate, Crospovidone XL 10, and Croscarmellose Sodiumand magnesium stearate using60# mesh. Blend the dry mix with pre-lubrication components in a double cone mixer for 10 minutes, then lubricate with Magnesium Stearate for 5 minutes.

Preparation of domperidone granules

By using wet granulation method, sift domperidone and microcrystalline cellulose Ph101 with the help of #24 mesh, then it was loaded into Rapid Mixer Granulator (RMG) for 5 mins. Povidone K-30 is dissolved in isopropyl alcohol to form a transparent solution, then add binder solution slowly into the RMG. If needed, add isopropyl alcohol and stir for 2 minutes. Put wet material in the Fluid Bed Drier (FBD) basin and air-dry for 10 minutes without heat. Sift dried granules in #24 mesh, the retained particles are milled in 1.0mm multi mill then again pass the granules in #24 mesh. Wet grains dry to 2.0-3.0% W/W LOD in 15

minutes at 40-50°C (45°C) using the FBD. HPMC K 100 M premium CR, Acrypol 974 P, Croscarmellose Sodium, Aerosil were passed into #30 sieve. Dried granules and sifted excipients are mixed for 10 minutes in a Double Cone Blender before adding magnesium stearate BP for 3 minutes which is passed through #60 mesh.

Content uniformity

Ten of 30 random tablet are tested. Medicine content must be >85% and <115 in 9/10 tablets. Tablet 10 must have <75% and >125% of the required content. The remaining 20 tablet must not exceed 85%-115% if these conditions are not met.[4]

Assay procedure

Chromatographic condition

Pump Mode	:	Gradient
Column	:	Phenomenex C18 (250x4.6 i.d., 5µm particle size)
Flow Rate	:	1.5mL
UV Wave Length	:	284nm
Injection Volume	:	100 µ L
Temperature	:	25˚C+2˚C
Run Time	:	20 minutes
Diluent	:	Acetonitrile: Water [50 :50]

Preparation of mobile phase

Mobile Phase A (70 %)

Buffer preparation

Dissolve 4.14g of sodium dihydrogen orthophosphate in 1000mL of water adjust Ph to 6.5 with sodium hydroxide.

Mobile Phase B (30 %): Acetonitrile

Preparation of solutions

Standard preparation

Properly weigh and dissolve 27.0 mg Vonoprazan fumarate, 30.0 mg Domperidone in 100 mL volumetric flask, diluent, 10 minutes sonication, cool. Filter the solution after diluting 5 ml to 50 ml. Direct infusion of filtered solution.

Test preparation

20 pills were weighed, averaged, and crushed to powder. In 100 ml volumetric flask, Vonoprazan 20 mg and Domperidone 30 mg equivalents were taken. Add 25ml diluents and sonicate for 15 minutes. For volume, 100ml diluent was filtered. Dilute 5 ml of this solution to 50 mL and filter. Direct injection of filtered solution.

Procedure

Separately inject equal volumes of Diluent (blank), standard, and test preparations, record chromatograms, and measure Vonoprazan and Domperidone areas. Determine Vonoprazan and Domperidone quantities.

Procedure for dissolution testing: Method of analysis

Dissolution medium	:	900 mL of 0.1MHCl (0.1M HCl: 85mL with 10L with water)
Apparatus	:	USP Type-2 (Paddle)
Speed	:	5 RPM
Temperature	:	37+ 0.5° C
Time intervals		
For Vonoprazan	:	5, 10, 15, 20, 30, 45 & 60 minutes or until saturation complete release.
For Domperidone	:	1^{st},3^{rd}, 8^{th}, 12^{th}, $16^{th}$and 24^{th}Hours or until saturation or complete release.

Sample preparation

Put 6 tablets individually in six dissolution flasks containing the specified quantity of dissolution medium that has been equilibrated to 37°C ± 0.5°C. Take care to exclude air bubbles from the surface of the tablets, start the apparatus immediately. Collect the sample after the required time intervals. Withdraw sample from a zone midway between the surface of the medium and top of the rotating blade and not less than 1 cm from the vessel wall and filter through Whatman No.1 filter paper by discarding first 5 mL.

Standard preparation

Weigh accurately about 27 mg of Vonoprazan fumarate working reference standard and 18 mg of Domperidone working reference standard into a 100 mL volumetric flask. Dissolve in

about 30 mL medium and dilute to volume with dissolution medium and further dilute 5mL into 50mL with medium.

Chromatographic conditions

Mobile phase	:	Buffer: Acetonitrile (70:30)
Buffer	:	4.14g of sodium dihydrogen orthophosphate in1000 mL with water adjust pH 6.5 with sodium hydroxide.
Detector	:	UV at 284 nm
Column	:	C18, 250 mm × 4.6mm,5µ
Flow rate	:	1.5 mL/min
Injection volume	:	100 µL

Procedure: Inject the standard solution in 6 replicates followed by sample solutions and blank.

System suitability: The relative standard deviation of replicate injections of standard preparation is not more than 2% and the resolution between the two peaks is not less than 3.0[5]

RESULTS AND DISSCUSION

Pre-Compression parameters

Table No. 03: Pre-compression parameters for vonoprazan layer blend.

Formulation code	Bulk density (g/mL)	Tapped density (g/mL)	Hausner's ratio	Compressibility index (%)	Angle of repose (Ɵ)	Flow property
F1	0.493	0.652	1.32	24.38	43º 20'	Passable
F2	0.541	0.655	1.21	17.40	38º 09'	Fair
F3	0.527	0.635	1.20	17.0	37º 18'	Fair
F4	0.511	0.612	1.19	16.50	38º 25'	Fair
F5	0.512	0.609	1.18	15.92	32º 45'	Good
F6	0.561	0.662	1.18	15.2	33º 36'	Good
F7	0.517	0.609	1.17	15.10	34º 18'	Good
F8	0.550	0.632	1.14	12.97	33º 12'	Good
F9	0.612	0.715	1.16	14.4	32º 42'	Good

*Mean± SD (n = 3)

Table No. 4: Pre-compression parameters for domperidone layer blend.

Formulation code	Bulk density (g/mL)	Tapped density (g/mL)	Hausner's ratio	Compressibility index (%)	Angle of repose (Ɵ)	Flow property
F1	0.421	0.589	1.39	28.52	47 º 12'	Poor
F2	0.478	0.660	1.38	27.57	46º 75'	Poor
F3	0.493	0.652	1.32	24.38	41º 20'	Passable
F4	0.578	0.687	1.18	23.56	35º 35'	Good
F5	0.556	0.663	1.19	16.13	37º 45'	Good
F6	0.559	0.682	1.22	18.03	36º 70'	Good
F7	0.573	0.687	1.19	15.29	34º 46'	Good
F8	0.556	0.695	1.23	18.97	35º 75'	Good
F9	0.550	0.684	1.24	19.59	34º 25'	Good

Drugs and Excipient compatibility studies using ftir

Drug-excipient compatibility IR investigations include excipients and active compounds. KBr hydraulically presses crushed materials into pellets. Before sampling and scanning at 400cm-1 to 4000cm-1 ambient temperature, spectral smoothening and baseline changes are done. Vonoprazone fumarate fast and Domperidone sustain release layers were studied for excipient physical and chemical interactions.

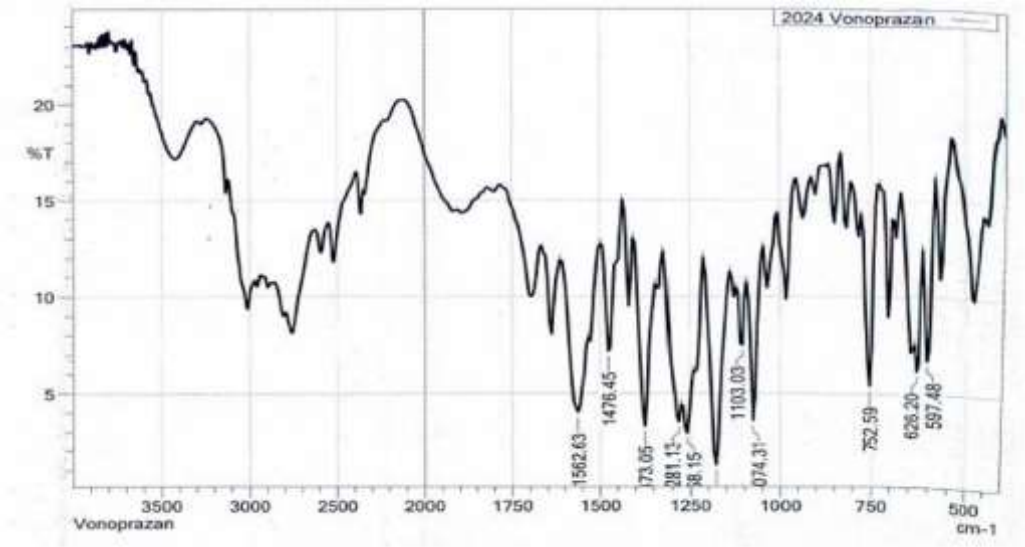


Fig. No. 1: FTIR Spectra of pure Vonoprazan fumarate.

The FTIR Spectra of Vonoprazan and the combination of drug and excepients shows nosignificant interaction between drug and excepients.

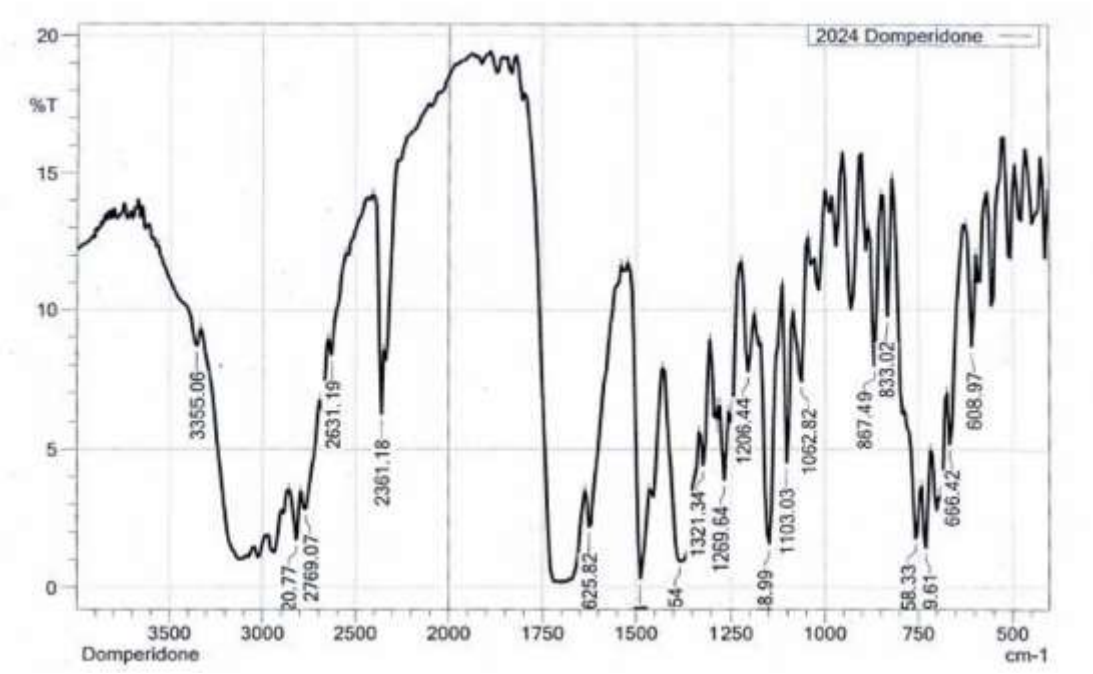


Fig No. 2: FTIR Spectra of pure domperidone.

The FTIR Spectra of Domperidone and the combination of drug and excepients shows nosignificant interaction between drug and excepients.

Post compression parameters

Table No. 5: Evaluation of Bilayer tablets of Vonoprazan IR and Domperidone SR (F1 to F5).

S. No	Tests	Specifications	F1	F2	F3	F4	F5
1.	Description	Red / White colored Capsule shaped uncoated Bilayer tablet	Complies	Complies	Complies	Complies	Complies
2.	Average weight (mg)	360mg ±3%	362	361	361	360	360
3.	Thickness* (mm)	5.00±0.2	5.05	5.07	5.02	5.07	5.01
4.	Hardness* (kg/cm2)	NLT 3.0	8.50	8.00	8.75	8.25	8.95
5.	Friability* (%w/w)	NMT 1%	0.07	0.10	0.10	0.13	0.15
6.	Weight variation (n=20)	±5% from the average weight	-2.5 to +3.1	-2.7 to +2.9	-2.7 to +2.5	-3.0 to +2.7	-2.3 to +2.9
7.	**Assay** Vonoprazan Fumarate equivalent	90 – 110%	96.9%	98.2%	97.1%	98.7%	98.1%

	toVonoprazan						
8.	**Assay** Domperid one	90 – 110%	98.1%	97.5%	98.2%	96.3%	97.5%

*All the values are mean ±SD, n=6.

Table No. 6: Evaluation of Bilayer tablets of Vonoprazan IR and Domperidone SR (F6 to F9).

S. No	Tests	Specifications	F6	F7	F8	F9
1.	Description	Red / White colored Capsule shaped uncoated Bilayer tablet	362	363	361	361
2.	Average weight (mg)	360mg ±3%	5.07	5.03	5.01	5.03
3.	Thickness* (mm)	5.00±0.2	8.00	8.45	8.35	8.75
4.	Hardness* (kg/cm2)	NLT 3.0	0.10	0.10	0.13	0.11
5.	Friability* (%w/w)	NMT 1%	-2.7 to +2.9	-2.7 to +2.5	-3.0 to +2.7	-2.3 to +2.9
6.	Weight variation (n=20)	±5% from the average weight	97.2%	98.1%	98.7%	98.1%
7.	**Assay** Vonoprazan Fumarate equivalent toVonoprazan	90 – 110%	97.5%	98.2%	97.3%	98.5%
8.	**Assay** Domperidone	90 – 110%	362	363	361	361

*All the values are mean ±SD, n=6.

Dissolution studies

According to the USP, the amount of Vonoprazan fumarate and Domperidone release at different time points is given below.

Table No. 7: Drug release criteria according to USP.

Vonoprazan fumarate immediate release		
S. No.	**Time (hours)**	**Amount released**
1.	1.0	NLT 85%
Domperidone sustained release		
1.	1	NMT 25%
2.	3	20-30
3.	8	40-50
4.	12	60-75

5.	16	75-85
6.	24	NLT 80%

Immediate release layer of vonoprazan fumarate

Table No. 8: Comparative Invitro release data for Vonoprazan fumarate F1 to F9 formulations.

S. No	Formulation	Time (hr)	Amount of drug release (mg)	Cumulative % drug release*
1.	F1	1.0	17.92	89.61±0.15
2.	F2	1.0	18.76	93.81±0.28
3.	F3	1.0	18.89	94.43±0.58
4.	F4	1.0	17.92	89.61±0.41
5.	F5	1.0	18.90	94.50±0.35
6.	F6	1.0	19.18	95.88±0.35
7.	F7	1.0	18.47	92.34±0.27
8.	F8	1.0	19.29	96.44±0.31
9.	F9	1.0	19.83	99.17±0.27

Sustained release layer of domperidone

Table No. 8: Comparative Invitro release data for Domperidone F1 to F9 formulations.

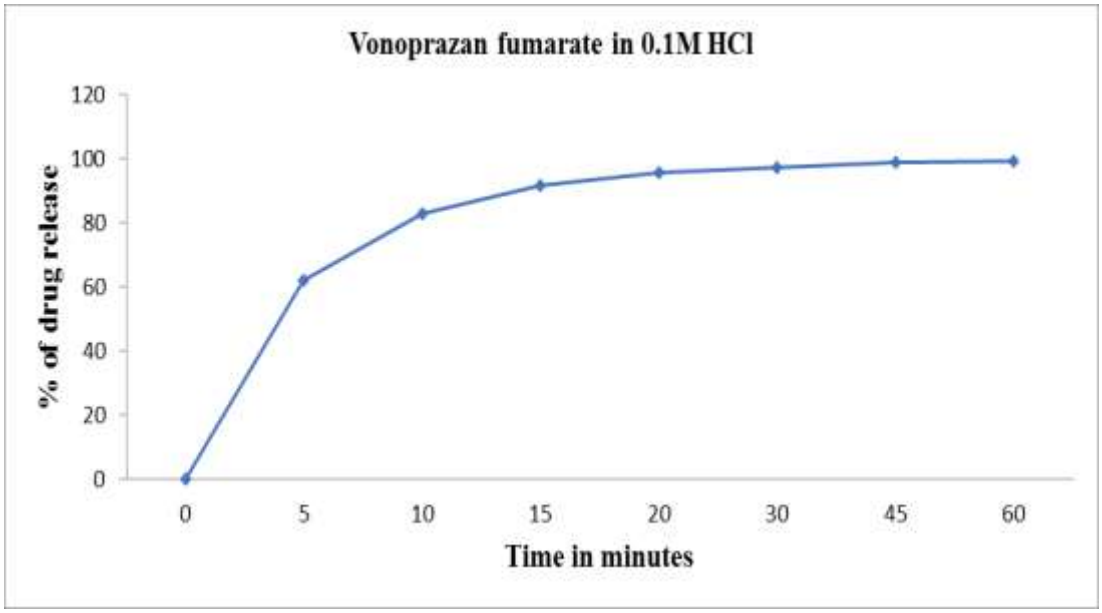
S. No	Formulation	Amount of drug release (mg)						Cumulative % drug release*					
		1hr	3hr	8hr	12hr	16hr	24hr	1hr	3hr	8hr	12hr	16hr	24hr
1.	F1	14.48	20.13	24.00	29.3	29.8	29.8	48.2	67.1	80	97.6	99.3	99.3
2.	F2	11.51	15.6	21	24.5	29.0	29.5	38.3	52	70	81.6	96.6	98.3
3.	F3	4.67	11.14	15.2	17.8	27	29.9	15.5	37.1	50.6	59.3	90	99.6
4.	F4	5.17	9.79	17.0	21.1	26.3	29.5	17.2	32.6	56.6	70.3	87.6	98.3
5.	F5	4.80	7.52	14.10	22.1	25.1	29.8	16.0	25.0	47.1	73.6	83.6	99.3
6.	F6	4.80	6.99	13.39	26.72	28.0	29.5	15.1	23.3	44.6	89.0	93.3	98.3
7.	F7	5.13	7.83	14.94	24.45	27.2	29.7	17.1	26.1	49.8	81.4	90.6	99
8.	F8	5.14	7.82	14.54	22.42	28.9	29.9	17.1	26.0	48.4	74.7	96.6	99.6
9.	F9	3.66	8.65	14.74	19.69	24.6	29.54	12.2	28.8	49.1	65.6	82.2	98.4

Among all 9 formulation trials, the combination of Vonoprazan IR and Domperidone SR demonstrated the most effective results in F9.

The release of Vonoprazan fumarate at 1st hour was found to be 99.17%.

The drug release at 1^{st}, 3^{rd}, 8^{th}, 12^{th}, 16^{th} and 24^{th} hour was found to be 12.2%, 28.83%, 49.13%, 65.64%, 82.21% and 98.47% respectively.

In below Fig. 03 shows the graph of in vitro drug release profile of Vonoprazan fumarate immediate release and Domperidone sustained release tablet for the formulation F9.



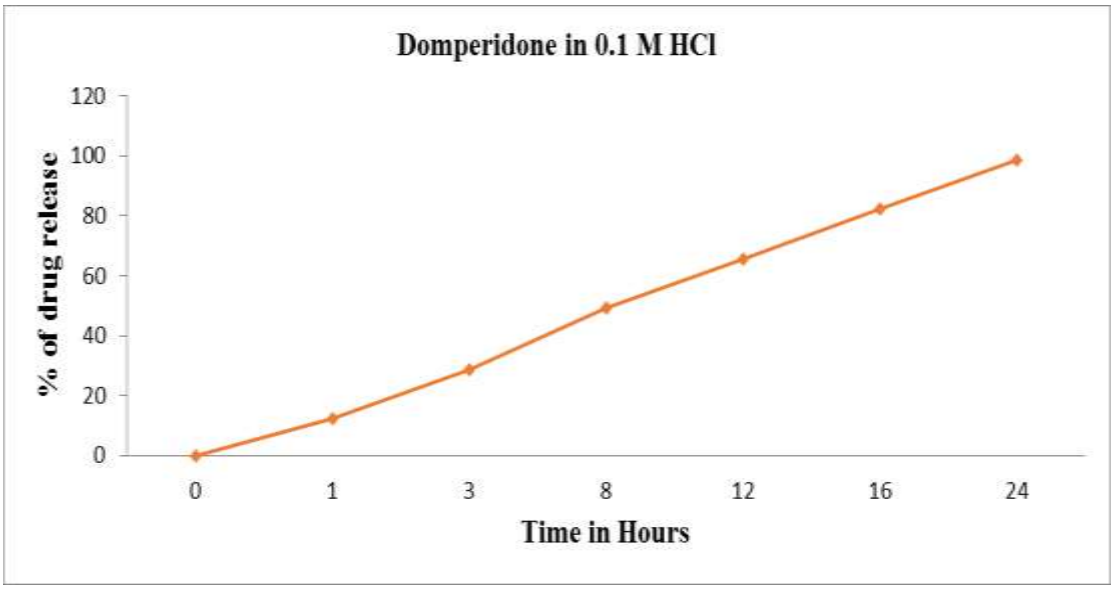


Fig. 03: In*vitro* dissolution profile of formulation F9.

SUMMARY AND CONCLUSION

Summary

This study constructed and tested immediate release Vonoprazan and sustained release Domperidone. Three Super disintegrants with different propagation combinations are in Vonoprazan layer. Croscarmellose sodium 9mg tablets dissolved best. Domperidone's prolonged release layer modulates release using viscous polymers like Hypromellose. At 27mg per tablet, HPMC K 100 M premium CR dominated tastes. Physical, chemical, and stability tests were performed on the final formula. All parameters met expectations.

CONCLUSION

This study developed a bilayer tablet of super disintegrants for instant release of Vonoprazan and Domperidone employing hydrophilic matrix formers such HPMC k4M, HPMC K15M, and HPMC K 100 M premium CR for sustained release.

Vonoprazan fumarate and Domperidone release from bilayered tablets was shown as cumulative percent drug release v/s time. Initial high Vonoprazan fumarate release is due to the quick release layer of the formulations, whereas Domperidone formulations have delayed drug release. The optimized formulation (F9) of the bilayer tablet may be a promising strategy to treat GERD, as the addition of immediate-release Vonoprazan addresses the condition, while the sustained-release portion of Domperidone willhelp to control vomiting associated with GERD.

REFERENCE

1. Aggarwal S, Syan N, Mathur P. Bi-layer tablet technology—opening new ways in drug delivery systems: an overview. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2013; 4(1): 8-16. n.d.
2. Zalte HD, Saudagar RB. Review on sustained release matrix tablet. International journal of pharmacy and biological sciences, 2013; 3(4): 17-29. n.d.
3. Gopinath C, Bindu VH, Nischala M. An overview on bilayered tablet technology. Journal of global trends in pharmaceutical sciences, 2013; 4(2): 1077-85. n.d.
4. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Official journal of the American College of Gastroenterology| ACG, 2005; 1, 100(1): 190-200. n.d.
5. Chen X, Chen T, Huang Y, Wang M, Wang Y, Wu P, et al. LC–MS/MS method for quick detection of vonoprazan fumarate in human plasma: Development, validation and its application to a bioequivalence study. Biomedical Chromatography, 2024; 38. https://doi.org/10.1002/bmc.5860.