

FORMULATION AND EVALUATION OF VONOPRAZAN FUMARATE GASTRO RETENTIVE TABLETS

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ABSTRACT:

Potassium-competitive acid blockers (P-CABs), such as Vonoprazan, are a novel class of agents that competitively inhibit the potassium-binding site of the gastric H⁺/K⁺ ATPase, potentially overcoming the limitations of proton pump inhibitors (PPIs). Studies suggest Vonoprazan is superior or equivalent to PPIs in treating acid-related diseases including GERD, gastric and duodenal ulcers, NSAID-related ulcers, upper GI bleeding, and Helicobacter pylori eradication. This review evaluates the efficacy of Vonoprazan in peptic ulcer disease (PUD) and post-endoscopic submucosal dissection (ESD) gastric ulcers. Vonoprazan (10–20 mg) offers faster pain relief and healing compared to PPIs, with fewer adverse events. However, more prospective, randomized trials beyond Japanese populations are needed to strengthen clinical evidence.

KEYWORDS: Gastric ulcers, peptic ulcers Potassium Competitive Acid Blocker, acid-related disease, fast-release tablets.

1. INTRODUCTION:

Vonoprazan fumarate, a prominent pyrrole derivative, represents a significant advancement in the management of acid-related gastrointestinal disorders. This compound functions as a reversible potassium-competitive acid blocker (P-CAB), exhibiting potent antacid activity by precisely targeting the gastric parietal cell H⁺/K⁺ATPase pump. Unlike traditional proton pump inhibitors (PPIs) that irreversibly bind to the pump and require acid activation, Vonoprazan's competitive and reversible binding to the potassium site allows for rapid, potent, and sustained inhibition of gastric acid secretion, independent of the pump's active state. This distinct mechanism of action provides several clinical advantages, including a quicker onset of action and less variability in acid suppression due to genetic polymorphisms of metabolizing enzymes. The formulation of Vonoprazan primarily as tablets is a strategic choice in pharmaceutical development, attributed to their inherent ease of use for patients, excellent chemical and physical stability, and cost-effectiveness in large-scale production. Moreover, the versatility of tablet formulations allows for the incorporation of advanced drug delivery systems, such as sustained-release technologies, which can optimize therapeutic profiles and enhance patient compliance by reducing dosing frequency.

2. DRUG PROFILE: VONOPRAZAN FUMARATE

Synonyms:

- 1-(5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl)-N-methylmethanamine.
- TAK-438
- Vonoprazan

Salts: Fumarate.

Categories:

- Antiulcer agent
- Potassium-competitive acid blocker[P-CAB]
- Proton pump inhibitor alternative
- Gastric acid secretion inhibitor

Chemical Name: 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine (2E)-2-butenedioate

Molecular Formula: C₂₁H₂₇F₁N₃O₆S Molecular Weight: Average: 461.5 g/mol; Monoisotopic: 461.105685 Da.

Mechanism of action: Vonoprazan is a potassium-competitive acid blocker (PCAB) that inhibits the H⁺, K⁺-ATPase enzyme system in a potassium-competitive manner. Through this mechanism, Vonoprazan suppresses basal and stimulated gastric acid secretion at the secretory surface of gastric parietal cells. Although both classes of drugs inhibit the H⁺, K⁺-ATPase, the mechanism of action of PCABs differs from that of proton-pump inhibitors (PPIs). PPIs form a covalent disulphide via liver.

3. MATERIALS AND METHODS:

Materials: Vonoprazan fumarate, Lactose, Sodium bicarbonate, Hydroxy propyl methyl cellulose, Polyvinylpyrrolidone, Talc, Citric acid, Microcrystalline cellulose.

Equipment:

- Shimadzu UV-Visible Spectrophotometer
- Digital balance
- Tablet punching machine.
- Digital dissolution apparatus USP paddle.

OTHER INSTRUMENTS:

All testing facilities and equipment like Analytical Weighing Balance, FTIR Spectrophotometer, Digital Vernier Caliper, Digital Hardness Tester, Friabilator, Disintegration Testing Apparatus, Automatic Dissolution Test Apparatus.

PREFORMULATION STUDIES:

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms. The overall objective of Pre-formulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage form.

The following Pre-formulation studies are carried out:

Appearance: The color, odor, and other physical parameters were observed by visual inspection only.

Solubility: The solubility of Vonoprazan fumarate is determined by using different solvents. 10ml of each solvent (water, ethanol, methanol) were taken in a beaker. Excess of drug was dissolved in the solvents and shaken for 72hrs and filtered. The solubility was determined by UV spectrometer.

Melting point: it was determined by melting point apparatus.

Procedure for Standard graph of Vonoprazan fumarate:

100 mg of crude drug (Vonoprazan fumarate) is weighed and dissolve in 100ml of 0.1N HCl and concentration of the stock solution was found to be 1mg/ml i.e, 1000 µg/ml, from the stock solution 10ml is taken and diluted 100ml with 0.1N HCl and the concentration of second stock solution was found to be 100 µg/ml. From the second stock solution 2ml,4ml,6ml,8ml&10ml are take and diluted to 10ml respectively with 0.1N HCl and concentration of the solution was found to be 20,40,60,80,100 respectively and the standard graph was plotted by taking concentration on X-axis and absorbance on Y-axis at 272nm.

Flow properties of drug and granules

Bulk Density: - It was determined by taking 50 gm of the powder. It was poured into a graduated measuring cylinder. The bulk volume was determined.

$$\text{Bulk Density (gm/cm}^3\text{)} = \text{Mass/Bulk Volume}$$

Tapped Density: - It was determined by taking 50 gm of the powder. It was poured into a graduated measuring cylinder. Tap the measuring cylinder about 100 times. Then determine the tapped volume.

$$\text{Tapped Density (gm/cm}^3\text{)} = \text{Mass/Tapped Volume}$$

Hausner's Ratio: -It is defined as the ratio as the ratio of tapped density to that of bulk density.

$$\text{Hausner ratio} = \text{Tapped density/Bulk Density}$$

Angle of repose: -It is defined as the maximum possible between the surface of the pile of the powder and the horizontal plane.

$$\tan \Theta = h/r$$

where Θ = angle of repose

h and r are the height and radius of base of pile of powder.

Loss on drying: -

Weigh accurately a weighing bottle that has been dried for 30 minutes.

Take about 1-2 gm of powder and pour it into the weighing bottle. Place the bottle in hot air oven at 105°C for 4 hours. After 4 hours, determine the loss in weight.

$$\text{Loss on drying (\%)} = (w_1 - w_2) / w_1 \times 100$$

Where, w_1 and w_2 are the initial and final weights of powder.

Fourier transform infrared spectroscopy:

FTIR studies are carried out for pure drug as well as drug and polymer combination to see whether there are any interactions between drug and the polymer.

PREPARATION METHOD OF TABLETS:

Required quantity of isopropyl alcohol was taken into a suitable vessel and to it. Hydroxy propyl methyl cellulose (HPMC) was added and stirred well to get clear solution. This process was done at room temperature. To the above solution Sodium bicarbonate, Citric acid, Microcrystalline cellulose (Avicel-PH102) was added slowly under continuous stirring to dissolve completely. Then Polyvinyl Pyrrolidone (K-30), Lactose were added into the above mixture. Then Vonoprazan were added slowly under continuous stirring to get a uniform dispersion. After attaining uniform dispersion talc were added immediately with continuous stirring for not less than 30 min. The above dispersion was passed through #18 sieves and complete dispersion was passed. The drug Tablets were dried for not less than 2 hours at temperature of $40 \pm 5^\circ\text{C}$ to evaporate excess solvent. The Tablets were stored in suitable air tight container.

FORMULATION OF DOSAGE FORMS:

S.NO	INGREDIENTS	F ₁	F ₂	F ₃
1	VONOPRAZAN FUMARATE	20mg	20mg	20mg
2	SODIUM BICARBONATE	25mg	25mg	10mg
3	CITRIC ACID	10mg	10mg	10mg
4	HPMC	5mg	10mg	20mg
5	POLYVINYL PYRROLIDINE	10mg	15mg	20mg
6	MICROCRYSTALLINE CELLULOSE	10mg	5mg	10mg
7	TALC	1mg	1mg	1mg
8	ISOPROPYL ALCOHOL	4ml	4ml	4ml
9	LACTOSE	15mg	10mg	5mg

Table:1 Formulation of Dosage forms.**EVALUATION OF TABLETS:⁴⁶**

- a) Weight variation:** - Twenty tablets were weighed. Average weight was determined. Individual tablets were weighed and their % deviation from average weight was determined.
- b) Hardness:** - It was determined by hardness tester.
- c) Friability:** - It was determined by Roche friabilator. 10 tablets were taken and their initial weight (w₁) was determined. The friabilator was operated at 100 rpm. Then final weight (w₂) was determined.

$$\% \text{Friability} = [(w_1) - (w_2)] / (w_2) * 100]$$

- d) Thickness:** It was determined by vernier caliper's scale.

e) Disintegration: -

It was determined by disintegration apparatus. 6 tablets were taken in apparatus with 0.1N HCl as the medium. The disintegration time was determined for all the tablets.

f) In-vitro Drug release studies:¹²

The release rate of Vonoprazan fumarate from floating tablets was determined using USP Dissolution Testing Apparatus type-II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at $37 \pm 0.5^\circ\text{C}$ and 100 rpm. The samples were withdrawn and replaced with fresh medium at specific time intervals. The samples withdrawn were diluted and the amount of drug released was estimated using UV Spectrophotometer.

g) Buoyancy time:¹⁴

The time taken for tablet to emerge on the surface of the medium is called the floating lag time or buoyancy time and duration of time the dosage form constantly remains on the surface of the medium is called total floating time. The buoyancy of the tablets was performed by using 0.1 N HCl. The time of duration of floatation was observed visually.

4. RESULTS AND DISCUSSION:

We intended to develop non-floating tablets of Vonoprazan fumarate. The main aim is to enhance the retention time of the drugs by increasing the buoyancy time of the drugs. The results have shown that tablets were found to have good properties as well as enhanced buoyancy time which provides good retention time of the drug in the body.

PREFORMULATION STUDIES:**Appearance:**

COLOUR	White to off-white crystalline powder
ODOUR	Odorless
TASTE	Bitter

Table 2: Drug appearance**Solubility:**

SOLVENTS	SOLUBILITY
WATER	+
ETHANOL	+
METHANOL	+
0.1 HCL	++

Table 3: Solubility of Vonoprazan fumarate

+ = very slightly soluble

++ = slightly soluble

Melting point: The Melting point was found to be 194.8°C.

CONSTRUCTION OF CALIBRATION CURVE:

The calibration curve of Vonoprazan fumarate was prepared in 0.1 N HCl. at 272 nm and the absorbance values of different concentrations are shown in the Table.

S.NO	CONCENTRATION	ABSORBANCE
1	0	0
2	20	0.15
3	40	0.30
4	60	0.44
5	80	0.58
6	100	0.72

Table 4: Calibration curve Vonoprazan fumarate

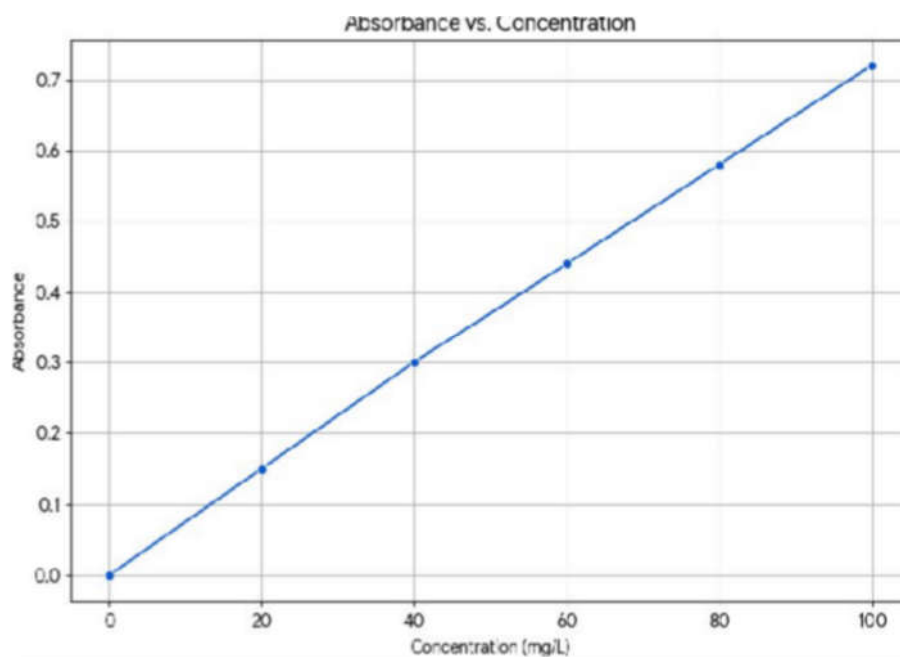


Fig1: Standard calibration curve of Vonoprazan fumarate in 0.1N HCl

FLOW PROPERTY:

INGREDIENT	BULK DENSITY	TAPPED DENSITY	CARRS INDEX	HAUSNER'S RATIO	ANGLE OF REPOSE	FLOW BEHAVIOUR
VONOPRAZAN FUMARATE	0.301	0.364	16	1.2	25	Good

Table 5: Flow property of Drug

From the flow properties of Vonoprazan fumarate, it was found that Vonoprazan fumarate has good flow properties.

<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Table 6: Angle of repose values**CARR'S INDEX:**

COMPRESSIBILITY INDEX	PERCENTAGE FLOWABILITY
5-15	free-flowing to excellent flow
12-16	free-flowing to good flow — powders
18-21	fair to passable powdered granule flow
23-28	easily fluidizable powders — poor flow
28-35	cohesive powders — poor flow
33-38	cohesive powders — very poor flow
>40	cohesive powders — very very poor flow

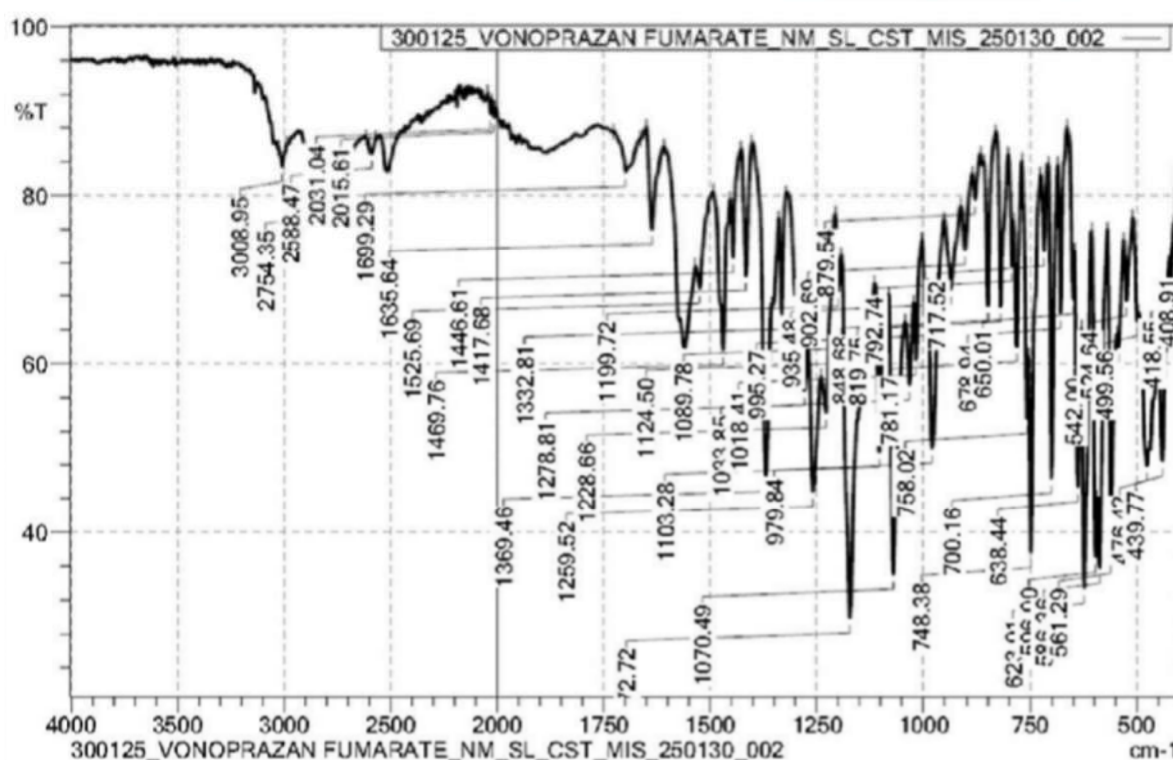
TABLE 7: Carr's index values

EVALUATION OF GRANULES:

S.NO	EVALUATION PARAMETERS	FORMULATIONS		
		F3	F2	F1
1	*Carr's index	10	11	14
2	*Hausner ratio	1.11	1.12	1.14
3	*Angle of repose	16	19	17
4	*Flow behavior	Excellent	Good	Good

Table 8: Evaluation of granules**FTIR STUDIES:**

The FTIR spectra of both pure drug and optimized formulation are depicted in figures below. Upon examination of these figures, it was determined that there is no interaction between drug and excipients.

**Fig:2 FTIR of Vonoprazan fumarate**

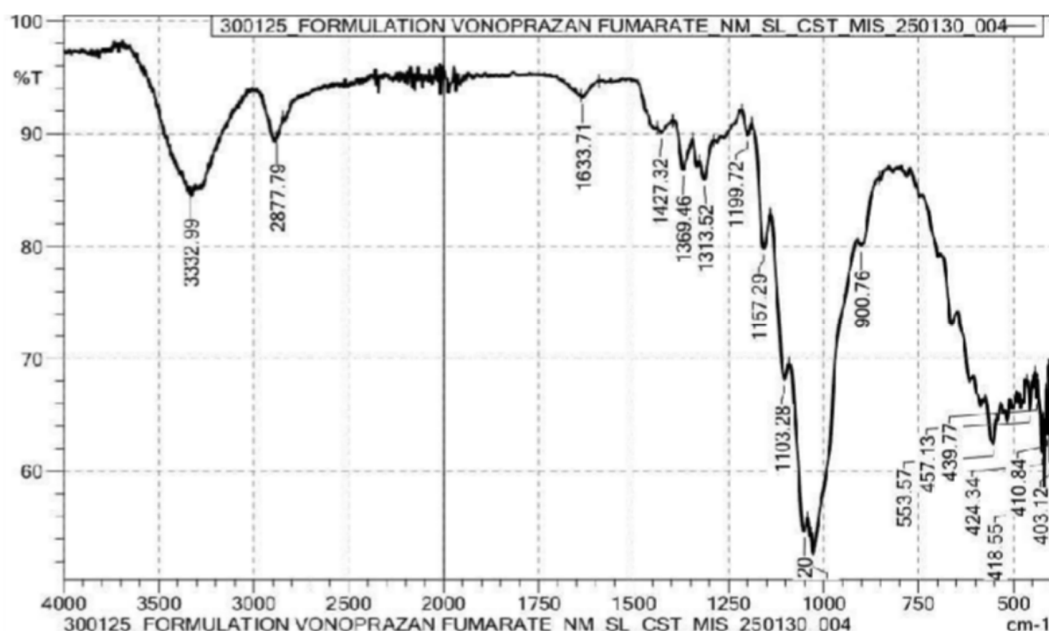


Fig.3: FTIR of Vonoprazan fumarate

Conclusion: Based on the FTIR study findings presented above, it was concluded that there were no notable interactions observed between the drug and excipients. Therefore, the drug and other excipients are deemed compatible with each other.

EVALUATION PARAMETERS OF TABLETS:

FORMULATION	HARDNESS (kg/cm)	THICKNESS (mm)	FRIABILITY (%)	AVERAGE WEIGHT (mg)
F1	4.0-5.0	3.5-4.0	<1.0	150+/-5 mg
F2	5.0-6.0	3.8-4.2	<0.8	155+/-5mg
F3	4.5-5.5	3.6-4.1	<0.9	152+/-5mg

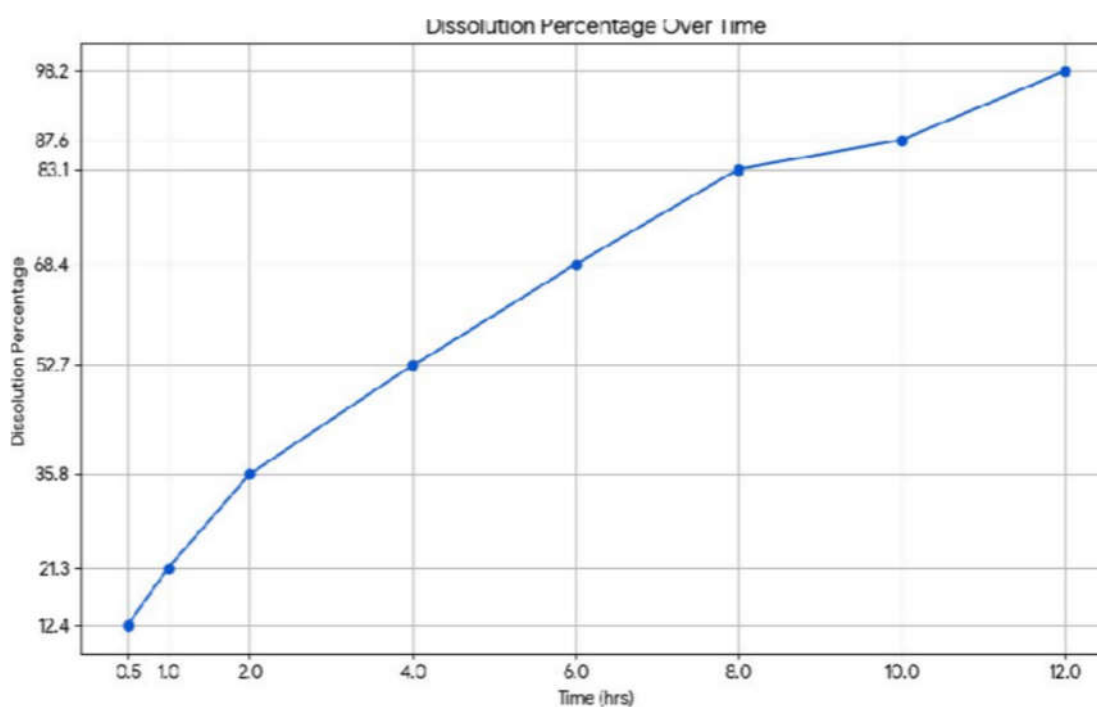
Table .9: Evaluation of tablets.

FORMULATION	FLOATING LAG TIME (sec)	TOTAL FLOATING TIME (hrs.)	DRUG CONTENT	DISINTEGRATION TIME
F1	34	24	98.25	3:45
F2	50	24	98.64	2:30
F3	72	24	99.94	4:10

Table.10: Evaluation of tablets

Invitro Dissolution studies:

Time (hrs)	F1	F2	F3
0.5	12.4	11.2	10.8
1	21.3	21	20.7
2	35.8	34.5	34
4	52.7	50.3	50
6	68.4	67.2	65.1
8	83.1	81.7	80.3
10	87.6	84.9	82.5
12	98.2	88.5	85.2
14	-	98.7	92.6
16	-		98.3

Table.11: *Invitro* drug release studies of table**Fig 4: *Invitro* Dissolution study of F1 formulation**

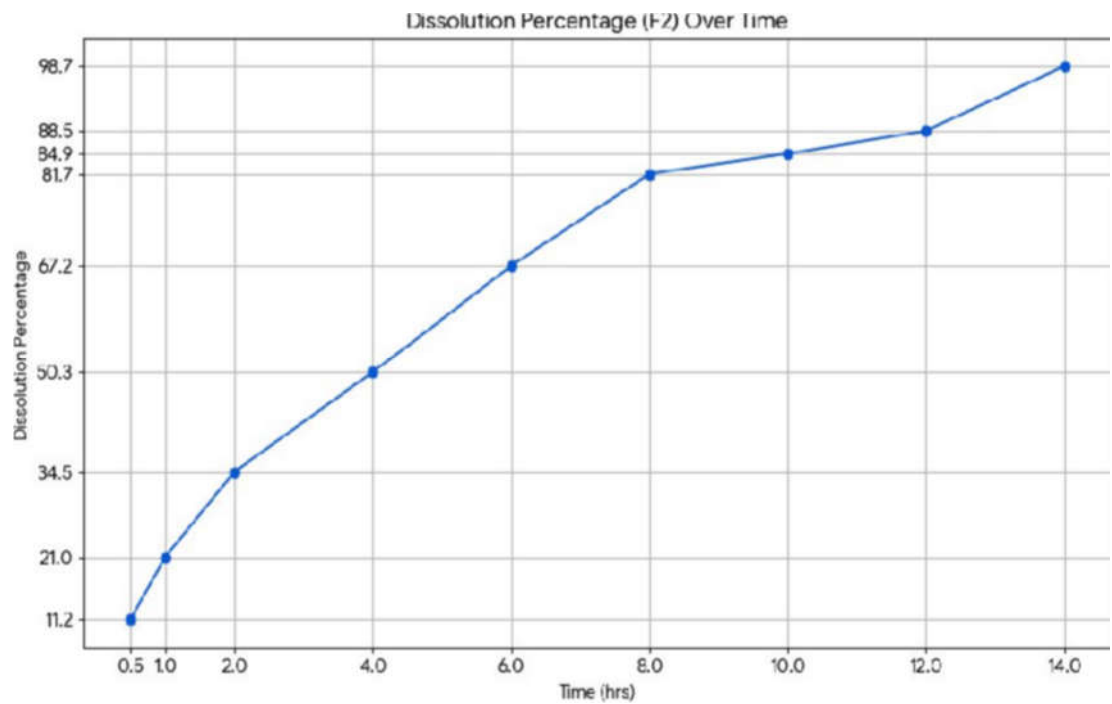


Fig 5: *Invitro* Dissolution study of F2 formulation

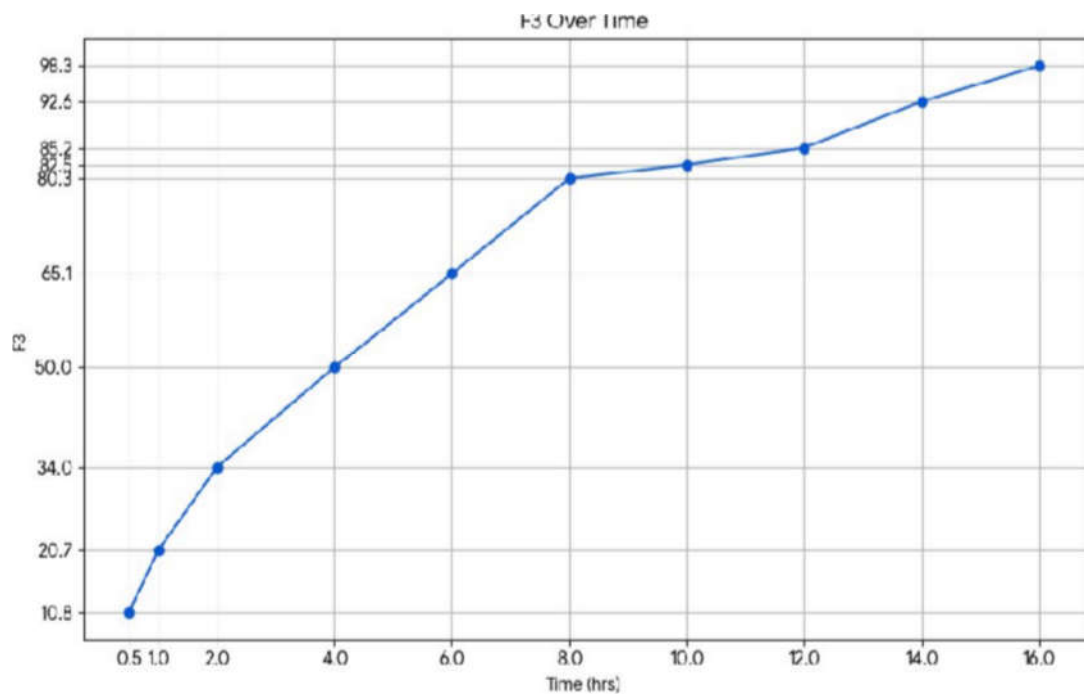


Fig 6: *Invitro* Dissolution study of F3 formulation

5. CONCLUSION:

Vonoprazan fumarate is a novel potassium-competitive acid blocker (P-CAB) that delivers rapid, potent, and sustained acid suppression—outperforming traditional PPIs in managing GERD, H. pylori eradication, and peptic ulcers, thanks to its excellent stability in acidic environments, high bioavailability, favorable safety profile, and the convenience of once-daily dosing. Among the formulations evaluated in this study, the **F3 formulation** distinguished itself as the superior extended-release gastric drug delivery system (GRDDS), demonstrating an impressive 16-hour sustained release profile. This was achieved through a carefully optimized matrix of hydrophilic polymers and effervescent agents that ensured buoyancy and controlled drug diffusion in the gastric environment, perfectly matching Vonoprazan acid-dependent solubility and its narrow absorption window. In vitro dissolution studies confirmed a consistent, prolonged release up to 16 hours, correlating with enhanced therapeutic coverage and predictable pharmacokinetics. Further, F3 maintained excellent tablet hardness, low friability, and uniform content—attributes essential for robust manufacturing and patient consistency. Stability testing also showed it retained its floating properties, structural integrity, and drug potency over time. In summary, the F3 formulation not only leverages the inherent pharmacological advantages of Vonoprazan fumarate but also elevates them into a controlled, gastric-retentive platform that promises improved compliance, efficacy, and manufacturability.

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