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Formulation And In-Vitro Characterization Of Floating Tablet Of Vonoprazan Fumarate

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Abstract: A recent study aimed to develop a sustained-release floating tablet of Vonoprazan Fumarate using a direct compression method to simplify processing. The research began by screening various rate-controlling polymers, with Carbopol 934 and Chitosan evaluated for their effectiveness in modulating the drug release rate. Carbopol 934 was identified as the most effective and selected for further formulation development. Preformulation studies confirmed the compatibility of Vonoprazan Fumarate with the chosen excipients. Fifteen formulations (F1-F15) were developed and subjected to comprehensive physical and chemical evaluations. Formulation F6 demonstrated the most promising results in initial assessments. To optimize the formulation, a factorial design approach was employed, varying the concentrations of Carbopol 934 and a floating agent as independent variables. This design aimed to assess their effects on drug release at the 1-hour mark and on floating lag time. Evaluations of the factorial batches (V1-V9) indicated that all parameters, including weight variation, friability, hardness, and thickness, remained within acceptable limits, with drug content consistently ranging from 97% to 99%. The study found that increasing the concentration of Carbopol 934 resulted in a decrease in drug release, highlighting its significant role in controlling release rates. Conversely, the floating agent concentration primarily influenced the floating time of the tablet. The O1 formulation, which exhibited stable performance in a one-month stability study, was finalized as the optimized formulation. It demonstrated controlled drug release, satisfactory floating properties, and stability, making it a strong candidate for future clinical evaluation.

Key words: **Vonoprazan Fumarate, Carbopol 934, Floating tablets.**

I. INTRODUCTION

1.1 Introduction of Floating Drug Delivery System

The oral route is widely recognized as the most significant and convenient method for administering medications. However, achieving sustained drug release over extended durations remains a challenge due to variations in absorption across different parts of the gastrointestinal tract (GIT). As a result, only a limited number of drug delivery systems have been developed to specifically target regions such as the stomach, upper small intestine, or colon.

A key obstacle in designing controlled-release oral dosage forms is not only extending drug delivery beyond 12 hours but also ensuring prolonged retention of the dosage forms in the upper small intestine or stomach. The development of dosage forms with extended gastric residence times (GRT), also known as gastro-retentive or gastro-retaining dosage forms (GRDF), opens up significant new therapeutic possibilities.

Key Features of GRDDS:

The use of gastro-retentive drug delivery systems (GRDDS) offers several key advantages, including:

- Increased patient compliance through reduced dosing frequency.
- Enhanced therapeutic effectiveness for drugs with a short half-life.
- Targeted delivery of medications to specific sites.

- Sustained and controlled drug release within the stomach.

- Prolonged drug residence time at the site of absorption.

Types of GRDDS:

Non-floating drug delivery systems3

- High density (sinking) drug delivery system
- Bioadhesive or mucoadhesive drug delivery system
- Magnetic system
- Expandable System
- Floating Drug Delivery System3

Effervescent System

- Gas generating system
- Volatile liquid containing system
- Non-effervescent systems
- Hydrodynamically balanced system
- Microballoons
- Microporous compartment
- Alginate beads

Applications of GRDDS4:

- **Sustained Drug Delivery**: These systems can help address challenges related to drug delivery by staying in the stomach for extended durations. This prolonged retention allows the dosage forms to remain buoyant on the gastrointestinal (GI) contents, ensuring effective drug release and absorption.
- **Site Specific Drug Delivery Systems**: These systems are particularly advantageous for drugs that are primarily absorbed in the stomach or the proximal small intestine. By providing controlled or slow drug release within the stomach, they ensure sufficient local therapeutic levels while minimizing systemic exposure. This reduction in systemic drug levels helps to lower side effects caused by the drug in the bloodstream. Additionally, the extended gastric retention of a site-specific delivery system can decrease the need for frequent dosing.
- **Absorption Enhancement**: Drugs that are having poor bioavailability due to site specific absorption from upper part of the gastrointestinal tract are potential candidates to be formulated as FDDS(Floating Drug Delivery System), thus maximizing their absorption.
- **Reduced fluctuations of drug concentration**: Administering controlled-release gastro-retentive drug delivery systems (GRDF) allows for a steady input of the drug, resulting in blood concentrations that remain within a more consistent range compared to immediate-release dosage forms. As a result, fluctuations in drug effects are minimized, and concentration-dependent adverse effects associated with peak drug levels can be effectively prevented.

Comparison of P-CABs and PPi:

P-CABs reversibly inhibit the H+/K+-ATPase enzyme by competitively binding to its K+-binding domain, while PPIs irreversibly inhibit the same enzyme. P-CABs deliver their full therapeutic effect after the first dose, whereas PPIs require 3-5 days to achieve maximum efficacy. Compared to PPIs, P-CABs offer greater potency and a longer duration of action. Unlike PPIs, which are acid-unstable and require protective formulations such as enteric-coated tablets, P-CABs are stable in acidic environments. P-CABs provide more consistent and potent acid suppression compared to other treatments. Both P-CABs and PPIs deliver extended acid suppression, making them suitable for once-daily dosing.

Fig 1. Avantage of FDDS

Different type of Formulation used in GRDDS:

- **Controlled Release (CR) Formulations**: These are designed to gradually release the active pharmaceutical ingredient (API) over time, ensuring a consistent drug concentration in the bloodstream.
- **Enteric-Coated Formulations**: Created to withstand the acidic environment of the stomach, these formulations dissolve only when they reach the neutral pH of the intestines.
- **Extended Release (ER) Formulations**: Designed for prolonged drug release, typically maintaining effectiveness for 12-24 hours.
- **Matrix Systems:** A widely used approach for achieving controlled release of medications.
- **Floating Systems**: Engineered to remain buoyant in the gastric fluids of the stomach, enabling extended retention and targeted release.

Approaches of FDDS:

Effervescent floating systems use gas-generating compounds like sodium bicarbonate and citric acid. These react with gastric acid to release carbon dioxide, forming bubbles that reduce the dosage form's density, allowing it to float. This mechanism ensures rapid buoyancy but may lead to bloating or discomfort due to gas production.

Non-effervescent floating systems rely on low-density materials or hydrophilic polymers that swell in gastric fluids, forming a buoyant gel-like structure. These systems are ideal for sustained gastric retention without generating gas.

Swelling-based floating systems utilize materials that significantly expand upon exposure to gastric fluids. This expansion increases their volume, aiding in buoyancy, although their swelling consistency may vary.

Bioadhesive floating systems employ polymers that adhere to the gastric mucosa, improving retention time. Some incorporate floating agents for added buoyancy. While they ensure prolonged mucosal contact, they can sometimes cause irritation.

Matrix systems with floating properties combine low-density materials or polymers with floating agents. These systems offer controlled drug release and buoyancy but require intricate formulations.

Expandable floating systems enlarge after ingestion to prevent early passage through the pylorus, enhancing buoyancy. However, the expansion may occasionally cause discomfort.

Raft-forming systems create a viscous gel or "raft" that floats atop stomach contents, commonly used in managing gastroesophageal reflux disease (GERD).

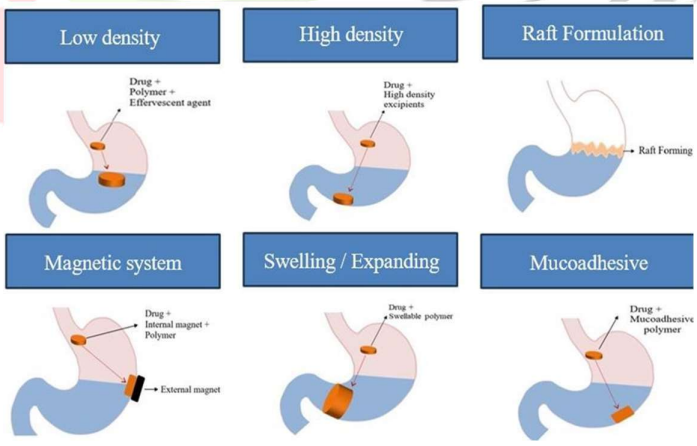


Fig 2. Approaches of FDDS

Materials and Methods:

Vonoprazan Fumarate was obtained as gift sample from Sanjar Pharma, Himatnagar, Carbopol 934 and Chitosan from ACS Chemicals, Ahemdabad, Polypropylene foam powder and lactose from Astron Research Centre, Ahemdabad, Magnesium Stearate and Talc from ACS Chemicals, Ahemdabad.

Method of preparation:

The drug, selected polymers, and lactose were weighed in appropriate quantities and individually passed through a 40 # mesh.

In a dry state, the drug was combined with the other ingredients and mixed in a mortar for 10 minutes to achieve a uniform powder mixture. This was further blended with talc and magnesium stearate for 2-3 minutes to enhance flow properties. The resulting powder was then compressed. Compression was done using rotary compression machine in 6.35 mm round punch using BB tooling. Evaluation of prepared tablets were done.

Table 1 Formulation table of trial batches of floating tablets

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Drug	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Chitosan	100	75	50	25	-	-	-	-	-	-	90	80	70	60	50
Carbopol 934	-	25	50	75	100	90	80	70	60	50	-	-	-	-	-
Polypropylene foam powder	-	-	-	-	-	20	20	20	20	20	20	20	20	20	20
Spray dried Lactose	54	54	54	54	54	44	54	44	34	24	44	54	44	34	24
Mg. Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Total	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Table 2 Layout of factorial designs

3^2 Full Factorial Designs		
Batch No.	**X1 Amount of Carbopol 934**	**X2 Amount of Polypropylene foam powder**
V1	-1	-1
V2	-1	0
V3	-1	+1
V4	0	-1
V5	0	0
V6	0	+1
V7	+1	-1
V8	+1	0
V9	+1	+1

Translation of coded level in actual limit			
Independent variables	**Real Value**		
	Low (-1)	**Medium (0)**	**High (+1)**
Amount of Carbopol 934 (mg) X1	85.0	90.0	95.0
Amount of Polypropylene foam powder (mg) X2	15.0	20.0	25.0

All 9 batches were evaluated for the % drug release at 1 hour. (Y1) and Floating Time (sec) (Y2) to find out effect of the both parameters (X1, X2)

- **Independent variables**
  - X1-Amount of Carbopol 934 (mg)
  - X2-Amount of Polypropylene foam powder (mg)

- **Dependent variables**
  - Y1- % Drug release at 1 hour
  - Y2- Floating Lag Time (sec)

Ingredient (mg)	V1	V2	V3	V4	V5	V6	V7	V8	V9
Drug	40	40	40	40	40	40	40	40	40
Carbopol 934	85	85	85	90	90	90	95	95	95
Polypropylene foam powder	15	20	25	15	20	25	15	20	25
Spray dried Lactose	54	49	44	49	44	39	44	39	35
Mg. Stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Table 3 Formulation table of factorial trial batch

EVALUATION OF FLOATING TABLETS:-

PRE COMPRESSION PARAMETERS:-

- Bulk Density And Tapped Density

A precisely weighed amount of the blend (W) was gently transferred into a graduated cylinder, and its initial volume (Vo) was recorded. The graduated cylinder, equipped with a lid, was then placed in a tapped density apparatus. The apparatus was operated for 100 taps, after which the tapped volume (Vf) was measured. The bulk density and tapped density were calculated using the respective formulas.

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}}$$

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume of the powder}}$$

- Compressibility index (CI) / Carr's index

It was obtained from bulk and tapped densities. It was calculated by using the following formula.

$$\text{CI}\ (\%) = \left(\frac{\text{TD} - \text{BD}}{\text{TD}}\right) \times 100$$

- Hausner's ratio

Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.

Hausner's ratio = (Tapped density ÷ Bulk Density)

- Angle of repose

The angle of repose for the powder was determined using the funnel method. An accurately weighed amount of the powder blend was placed into a funnel. The funnel height was adjusted so that its tip was positioned just above the apex of the powder blend. The powder was then allowed to flow freely through the funnel onto the surface.

The diameter of the resulting powder cone was measured, and the angle of repose was calculated using the corresponding formula.

$$\mathbf{Tan\ \theta = h/r}$$

POST COMPRESSION PARAMETERS:-

- Weight Variation

Twenty tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation as per IP.

USP Average weight of tablet (mg)	%Deviation	IP/BP Average weight of tablet (mg)
80 or less	10%	130 or less
From 80 to 250	7.5%	From 130 to 324
250 or more	5%	More than 324

- Thickness

Thickness Of Tablets Is Important For Uniformity Of Tablet Size. Thickness Was Measured Using Vernier Calipers On 3 Randomly Selected Samples. 35

- Hardness

The Tablet's Resistance To Damage During Storage, Transportation, Handling, And Usage Relies On Its Hardness. To Assess This, The Hardness Of Each Tablet Formulation Was Determined Using A Monsanto Hardness Tester.

- Friability

Friability Measures The Tablet's Mechanical Strength. The Roche Friabilator Was Employed To Test Friability Using The Following Method: Twenty Tablets Were Precisely Weighed And Placed In The Tumbling Apparatus, Which Operated At 25 Revolutions Per Minute (Rpm), Dropping The Tablets From A Height Of Six Inches With Each Turn. After 4 Minutes, The Tablets Were Re-Weighed, And The Percentage Weight Loss Was Calculated To Assess Friability.

- Uniformity of Content

The content of the active ingredient in randomly selected tablets was analyzed as follows: Ten tablets were weighed to determine their average weight. The tablets were then crushed, and a powder quantity equivalent to 8 mg of the active ingredient was dissolved in 250 ml of 0.1 N HCl. The mixture was shaken for 20 minutes, filtered, and appropriately diluted using 0.1 N HCl. The absorbance was measured spectrophotometrically at 254 nm against a reagent blank, and the amount of the drug in each tablet was calculated.

- Floating Lag Time

The lag time was carried out in beaker containing 100 ml of 0.1 N HCl as a testing medium maintained at 37 °C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

- Floating Time:

Floating time was the time, during which the tablet floats in 0.1 N HCL dissolution medium (including floating lag time).

- Swelling Characteristics

The swelling properties of matrix tablet containing drug were determined by placing the tablet matrices in the USP Dissolution Testing Apparatus II, in 900 ml of 0.1 N HCl at 37 ± 0.5 °C, rotated at 50 rpm. The tablets were removed periodically from dissolution medium, blotted to remove excess water and weighed. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation.

$$\% \text{ SI} = \frac{\text{Weight of the swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

- Dissolution Studies

The release rate of Vonoprazan Fumarate from floating tablets was evaluated using the USP Dissolution Testing Apparatus II (paddle type). The test was conducted with 900 ml of 0.1 N HCl at a temperature of 37 ± 0.5 °C and a speed of 50 rpm. At hourly intervals over a span of 24 hours, aliquots were withdrawn from

the dissolution apparatus, and the medium was replenished with fresh solution. After filtration and appropriate dilution, the amount of drug released was calculated using the calibration curve.

Details of Dissolution Test:

1. Apparatus : USP Type II
2. Volume of medium : 900 ml
3. Temperature : 37 ˚C
4. Paddle Speed : 50 rpm
5. Dissolution medium used : 0.1 N HCl
6. Aliquot taken at each time interval: 10 ml

- Drug Release Kinetic Study

Data obtained form in vitro drug release studies were fitted to disso calculation software. The kinetic models used are zero order, first order, Korsemeyer - Peppas, Hixon crowell, and Higuchi equation.

The rate and mechanism of release of Vonoprazan Fumarate from the prepared tablets were analyzed by fitting the dissolution data into the zero-order equation:

$$\mathbf{Q = k0t}$$

Where, Q is the amount of drug released at time t, k0 is the release rate constant.

The dissolution data fitted to the first order equation:

$$\mathbf{\ln (100–Q) = \ln 100 – K1\ t}$$

Where, k1 is the release rate constant.

The dissolution data was fitted to the Higuchi's equation:

$$\mathbf{Q = K2\ t1/2}$$

Where, k2 is the diffusion rate constant.

The dissolution data was also fitted to Korsmeyer equation, which is often used to Describe the drug release behavior from polymeric systems:

$$\mathbf{Log\ (Mt/M\infty) = log\ k + n\ log\ t}$$

Where Mt is the amount of drug released at time t, M∞ is the amount of drug release After infinite time, K is a release rate constant incorporating structural and geometric Characteristics of the tablet, n is the diffusional exponent indicative of the mechanism of drug release.

- Stability Study

Stability testing of drug products begins during drug discovery and continues until the compound or commercial product is no longer in use. To evaluate the stability of the drug and its formulation, stability studies were conducted in accordance with ICH guidelines. The studies focused on the most satisfactory formulation, which was sealed in aluminum packaging and stored in a humidity chamber maintained at 40 ± 2 °C and 75 ± 5% RH for one month. Upon completion of the study, the samples were examined for drug content, in vitro dissolution, floating behavior, and various physicochemical properties.

RESULTS & DISCUSSION

PRE FORMULATION STUDIES

Table 4. API Properties

Sr. No.	Characteristic Properties		Observation/Result
1	Organoleptic Characteristics	Colour	White to off-white solid
2		Odour	Odorless
4	Flow Properties	Bulk density (g /ml)	0.47
5		Tapped density (g /ml)	0.55
6		Carr's index (%)	10.8
7		Hausner's ratio	1.16
8		Angle of repose (θ°)	11º 97′
9	Solubility	Solubility	Slightly soluble in water Soluble in 0.1 N HCl
10	Melting Point	194 °C	

DRUG POLYMER COMPATIBILITY STUDIES

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

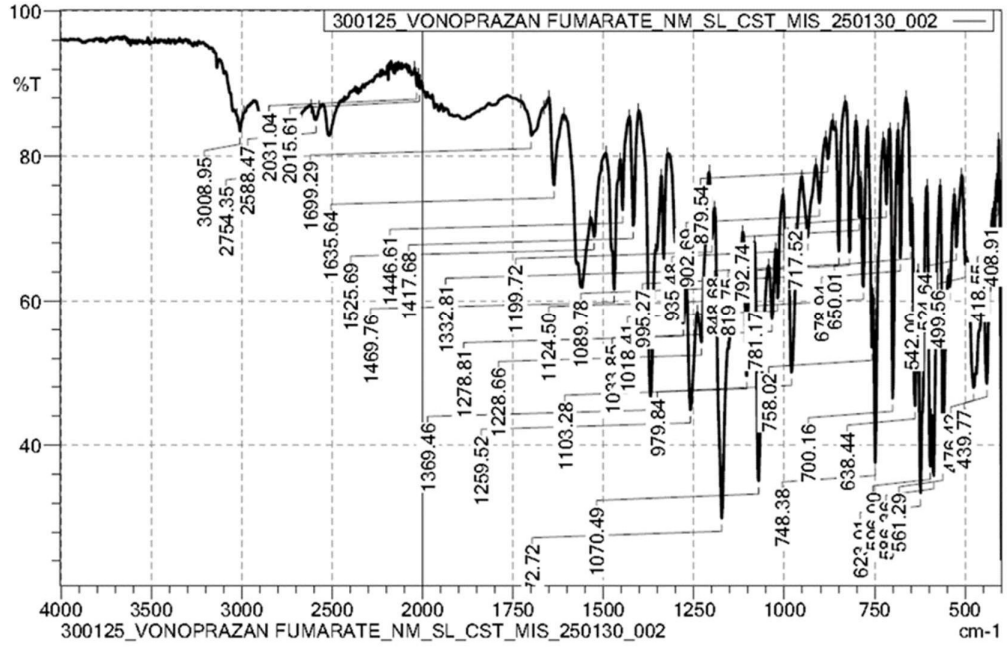


Fig 3 FTIR of Vonoprazan fumarate

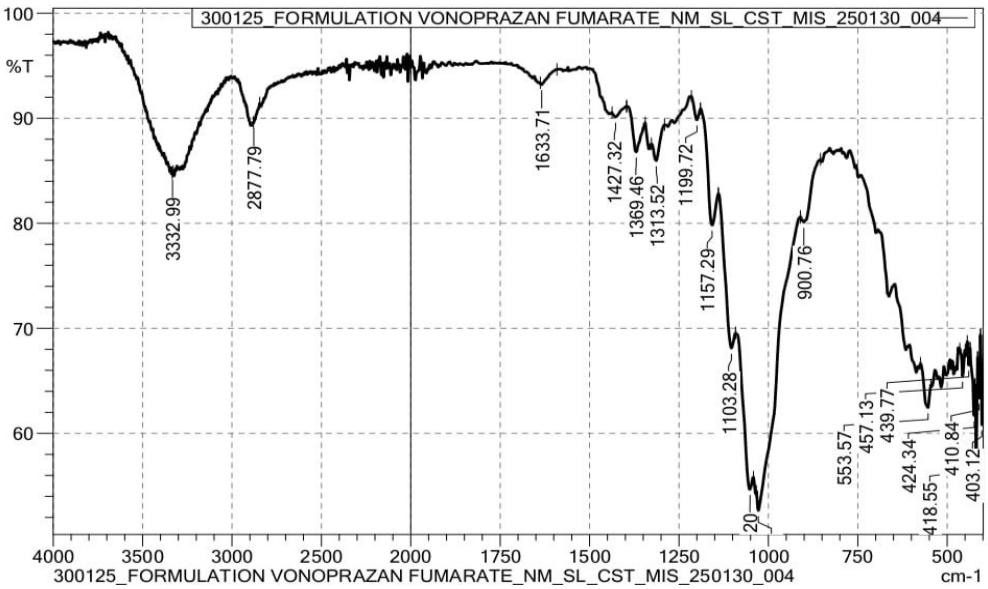


Fig 4 FTIR of mixture

Functional Groups	Peak positions in pure drug (cm^{-1})	Peak positions in formulation mixture (cm^{-1})
C=N stretch	1635.64	1633.71
C-N stretch	1332.81	1313.52
C-H stretch	2754.35	2877.79
O-H stretch	3008.95	3332.99

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

DETERMINATION OF λmax AND CALIBRATION CURVE OF DRUG

Table 5 Standard calibration curve of Vonoprazan in 0.1 N HCl

Sr. No.	Concentration (µg/ml)	Absorbance at 272 nm (mean ± SD)
1	0	0
2	4	0.166 ± 0.003
3	8	0.318 ± 0.004
4	12	0.485 ± 0.002

5	16	0.638 ± 0.004
6	20	0.799 ± 0.006

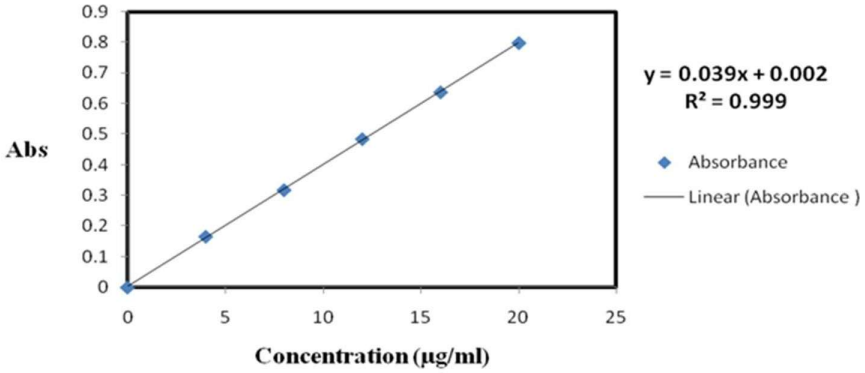


Fig 5 Standard caliberation curve of vonoprazan fumarate in 0.1N HCl

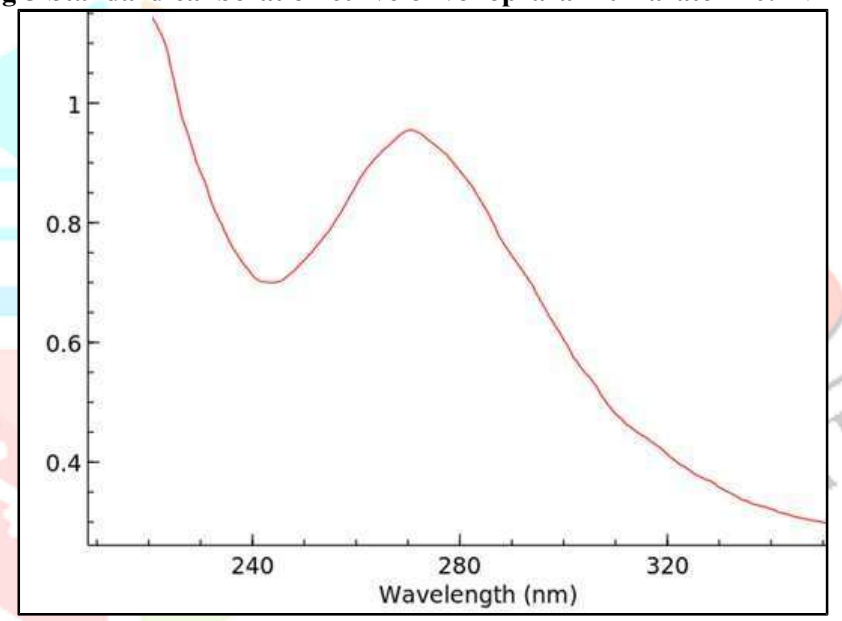


Fig 6. λmax of drug in 0.1 N HCl

Pre Compression Parameters:-

Powder blend of formulation F1-F15 checked for pre compression parameters like,

- ✓ **Bulk density**
- ✓ **Tapped density**
- ✓ **Compressibility index (CI) / Carr's index**
- ✓ **Hausner's ratio**
- ✓ **Angle of repose**

Table 5 Pre-Compression Parameters of Formulation F1-F15

Formulation	Bulk density (g/ml)(n=3)	Tapped density (g/ml)(n=3)	Carr's index(%) (n=3)	Hausner's ratio (n=3)	Angle of repose(θ°) (n=3)
F1	0.51 ± 0.08	0.56 ± 0.05	8.93 ± 0.04	1.10 ± 0.01	19.56 ± 0.04
F2	0.52 ± 0.02	0.58 ± 0.04	10.34 ± 0.05	1.12 ± 0.01	18.75 ± 0.03
F3	0.47 ± 0.04	0.54 ± 0.02	12.96 ± 0.05	1.15 ± 0.01	17.84 ± 0.03
F4	0.58 ± 0.03	0.65 ± 0.03	10.77 ± 0.02	1.12 ± 0.01	19.29 ± 0.05
F5	0.49 ± 0.04	0.58 ± 0.08	15.52 ± 0.03	1.18 ± 0.02	22.14 ± 0.08
F6	0.47 ± 0.05	0.54 ± 0.08	12.96 ± 0.04	1.15 ± 0.02	21.04 ± 0.07
F7	0.48 ± 0.06	0.59 ± 0.07	18.64 ± 0.02	1.23 ± 0.01	18.56 ± 0.05
F8	0.58 ± 0.05	0.64 ± 0.05	9.38 ± 0.03	1.10 ± 0.01	17.45 ± 0.06
F9	0.48 ± 0.04	0.53 ± 0.06	9.43 ± 0.05	1.10 ± 0.02	16.84 ± 0.04
F10	0.43 ± 0.03	0.49 ± 0.04	12.24 ± 0.06	1.14 ± 0.01	19.84 ± 0.06
F11	0.46 ± 0.07	0.52 ± 0.07	11.54 ± 0.02	1.13 ± 0.01	21.54 ± 0.04
F12	0.51 ± 0.03	0.57 ± 0.05	10.53 ± 0.04	1.12 ± 0.02	23.45 ± 0.05
F13	0.52 ± 0.02	0.59 ± 0.07	15.25 ± 0.08	1.18 ± 0.01	21.15 ± 0.02
F14	0.54 ± 0.10	0.62 ± 0.04	12.90 ± 0.07	1.15 ± 0.03	20.19 ± 0.05
F15	0.57 ± 0.06	0.65 ± 0.03	12.31 ± 0.04	1.14 ± 0.02	23.15 ± 0.03

Table 6 Post Compression Parameters of Formulation F1-F15

Formulation Code	Weight variation (mg)(n=3)	Thickness (mm)(n=3)	Hardness (kg/cm^2)(n=3)	Friability (%)(n=3)
F1	200± 1.5	2.2 ± 0.3	6.1 ± 0.28	0.23
F2	200 ± 2.3	2.3 ± 0.2	5.3 ± 0.16	0.36
F3	201 ± 3.2	2.4 ± 0.3	5.6 ± 0.17	0.12
F4	201 ± 3.3	2.5 ± 0.4	6.3 ± 0.33	0.47
F5	201 ± 2.4	2.7 ± 0.5	5.3 ± 0.16	0.31
F6	**199 ± 1.9**	**2.7 ± 0.3**	**6.3 ± 0.28**	**0.47**
F7	201 ± 3.2	2.2 ± 0.2	6.3 ± 0.28	0.38
F8	198 ± 2.5	2.6 ± 0.4	5.1 ± 0.16	0.29

F9	197 ± 3.1	2.5 ± 0.3	5.3 ± 0.16	0.14
F10	199 ± 2.4	2.4 ± 0.2	5.5 ± 0.28	0.26
F11	201 ± 3.9	2.3 ± 0.3	5.3 ± 0.16	0.39
F12	198 ± 2.6	2.3 ± 0.4	5.6 ± 0.16	0.52
F13	199 ± 2.7	2.4 ± 0.3	5.7 ± 0.28	0.31
F14	199 ± 3.9	2.3 ± 0.4	5.3 ± 0.28	0.39
F15	201 ± 2.8	2.3 ± 0.5	5.8 ± 0.16	0.28

Table 7 Post Compression Parameters of Formulation F1-F15

Formulation Code	Uniformity of content (%)	Floating lag time (sec)	Floating Time (hour)
F1	99.6 ± 1.6	No	0
F2	99.5 ± 2.3	No	0
F3	98.7 ± 2.3	No	0
F4	99.1 ± 2.9	No	0
F5	98.0 ± 1.5	No	0
F6	**98.6 ± 2.5**	**45 ± 6**	**24 ± 1**
F7	99.3 ± 2.6	49 ± 7	24 ± 1
F8	98.4 ± 2.3	48 ± 4	24 ± 1
F9	99.8 ± 2.7	51 ± 2	24 ± 1
F10	99.8 ± 2.7	55 ± 5	24 ± 1
F11	99.3 ± 3.7	48 ± 4	24 ± 1
F12	97.6 ± 1.6	51 ± 5	24 ± 1
F13	98.3 ± 2.3	55 ± 3	24 ± 1

F14	98.7 ± 1.6	56 ± 2	24 ± 1
F15	99.5 ± 2.5	58 ± 5	24 ± 1

Table 8 Swelling Characteristics of Floating Tablets F1-F15

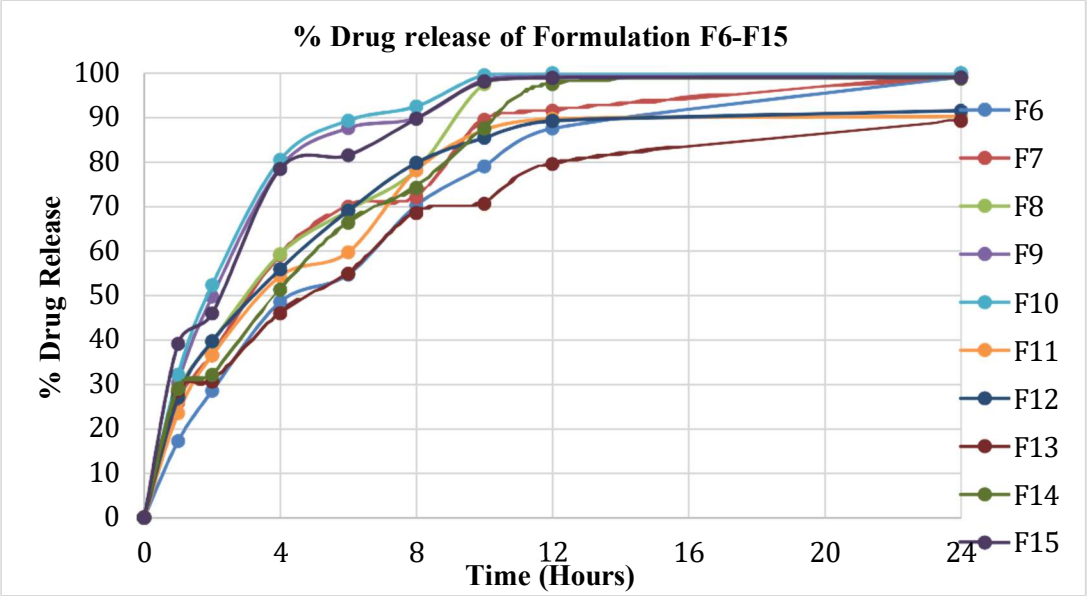
Formulation Code	% Swelling Index			
	2 hr	4 hr	12 hr	24 hr
F1	50	85	98	104
F2	57	65	87	97
F3	84	104	141	185
F4	54	94	115	140
F5	47	68	87	108
F6	**57**	**84**	**110**	**175**
F7	24	42	98	142
F8	35	48	68	147
F9	84	110	125	165
F10	65	84	113	145
F11	47	63	89	115
F12	24	51	68	95
F13	45	68	98	116
F14	24	54	87	121
F15	25	39	69	125

In-Vitro Drug Release

Table 9 % Drug release of F1 to F15 Formulations Tablets

Time (hrs.)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	59.2	40.3	14.8	15.6	16.2
2	98.3	58.2	35.9	37.1	39.7
4		79.6	54.5	46.9	59.6
6		98.9	72.3	56.3	67.3
8			96.6	62.4	79.2
10				81.3	84.6
12				95.9	86.9
24				-	95.3

Time (hrs.)	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
0	**0**	0	0	0	0	0	0	0	0	0
1	**17.2**	25.9	27.9	30.3	32.2	23.5	27.0	28.5	29.0	39.1
2	**28.5**	36.5	39.5	49.7	52.3	36.5	39.7	30.6	32.1	45.9
4	**48.5**	59.0	59.3	78.8	80.5	54.3	55.9	45.9	51.3	78.4
6	**54.7**	69.9	69.1	87.6	89.3	59.7	69.0	54.9	66.3	81.5
8	**70.2**	72.1	78.2	89.9	92.5	78.1	79.8	68.5	74.2	89.7
10	**79.0**	89.5	97.5	98.5	99.5	87.2	85.4	70.6	87.5	98.1
12	**87.5**	91.5	99.0	99.6	100.0	89.7	89.2	79.5	97.5	98.9
24	**99.1**	99.2	99.4	99.9	100.0	90.2	91.5	89.2	98.7	99.0



Evaluation of factorial batches

Powder blend of factorial batches F1-F9 checked for pre-compression parameters.

Observed results are mentioned in following table 15. From the below table it concluded that the all batches have a good flow properties.

Table 10 Precompression Parameters of factorial batches F1-F9

Batch	Bulk density (g/ml) (n=3)	Tapped density (g/ml)(n=3)	Carr's index (%) (n=3)	Hausner's ratio (n=3)	Angle of repose (θ°) (n=3)
V1	0.49 ± 0.04	0.58 ± 0.08	15.52 ± 0.03	1.18 ± 0.02	32.14 ± 0.08
V2	0.47 ± 0.05	0.54 ± 0.08	12.96 ± 0.04	1.15 ± 0.02	31.04 ± 0.07
V3	0.48 ± 0.06	0.59 ± 0.07	18.64 ± 0.02	1.23 ± 0.01	33.56 ± 0.05
V4	0.58 ± 0.05	0.64 ± 0.05	9.38 ± 0.03	1.10 ± 0.01	31.45 ± 0.06
V5	0.48 ± 0.04	0.53 ± 0.06	9.43 ± 0.05	1.10 ± 0.02	34.84 ± 0.04
V6	0.43 ± 0.03	0.49 ± 0.04	12.24 ± 0.06	1.14 ± 0.01	32.84 ± 0.06
V7	0.46 ± 0.07	0.52 ± 0.07	11.54 ± 0.02	1.13 ± 0.01	31.54 ± 0.04
V8	0.51 ± 0.03	0.57 ± 0.05	10.53 ± 0.04	1.12 ± 0.02	33.45 ± 0.05
V9	0.52 ± 0.02	0.59 ± 0.07	15.25 ± 0.08	1.18 ± 0.01	31.15 ± 0.02

Table 11 Post Compression Parameters of factorial batches F1-F9

Batch	Weight variation test (mg) (n=20)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability (%) (n=3)
V1	202 ± 2.2	4.53 ± 0.10	4.9 ± 0.3	0.82 ± 0.12
V2	201 ± 2.8	4.53 ± 0.14	5.0 ± 0.2	0.65 ± 0.08
V3	200 ± 2.9	4.52 ± 0.19	4.8 ± 0.4	0.87 ± 0.13
V4	203 ± 2.8	4.51 ± 0.09	5.1 ± 0.2	0.67 ± 0.11
V5	201 ± 2.5	4.50 ± 0.12	5.2 ± 0.5	0.60 ± 0.18
V6	200 ± 3.1	4.48 ± 0.18	5.2 ± 0.2	0.62 ± 0.17
V7	202 ± 2.8	4.47 ± 0.17	5.4 ± 0.3	0.52 ± 0.12
V8	204 ± 1.9	4.45 ± 0.12	5.6 ± 0.1	0.47 ± 0.15
V9	202 ± 2.4	4.46 ± 0.16	5.4 ± 0.4	0.51 ± 0.14

Table 12 Post Compression Parameters of factorial batches F1-F9

Batch	Drug Content (%) (n=3)	Swelling Index (24 hrs.) (%) (n=3)	Floating Lag Time (sec) (n=3)	Total Floating Time (hr.)
V1	96.8 ± 3.1	162.5 ± 1.9	53 ± 3	24
V2	98.7 ± 2.9	163.7 ± 2.5	50 ± 3	24
V3	98.6 ± 2.7	164.1 ± 2.1	47 ± 2	24
V4	99.8 ± 2.2	167.6 ± 2.6	55 ± 4	24
V5	97.5 ± 1.8	168.9 ± 2.1	48 ± 6	24
V6	99.1 ± 2.7	168.2 ± 2.9	42 ± 3	24
V7	98.3 ± 2.9	170.3 ± 3.4	59 ± 5	24
V8	99.4 ± 1.4	172.5 ± 2.7	50 ± 7	24
V9	98.6 ± 1.8	171.8 ± 3.2	48 ± 4	24

Table 13 Drug release of factorial batches F1-F9

Time in hr.	V1	V2	V3	V4	V5	V6	V7	V8	V9
0	0	0	0	0	0	0	0	0	0
1	19.2	21.9	22.3	15.8	16.9	16.5	10.9	11.3	12.6
2	30.5	32.6	33.8	26.5	26.8	27.9	23.5	24.5	25.3
4	52.1	53.9	54.6	45.8	47.5	48.1	42.8	43.9	44.8
6	58.6	60.4	62.5	56.9	55.6	57.6	50.6	51.4	53.6
8	72.3	74.9	75.8	70.2	69.3	71.3	64.8	65.9	67.9
10	85.9	86.3	88.6	78.1	79.5	80.5	75.3	76.8	77.8
12	95.2	96.4	97.1	87.2	88.2	89.7	83.6	84.2	85.9
24	99.6	99.3	99.5	98.5	98.7	99.1	92.9	93.6	94.2

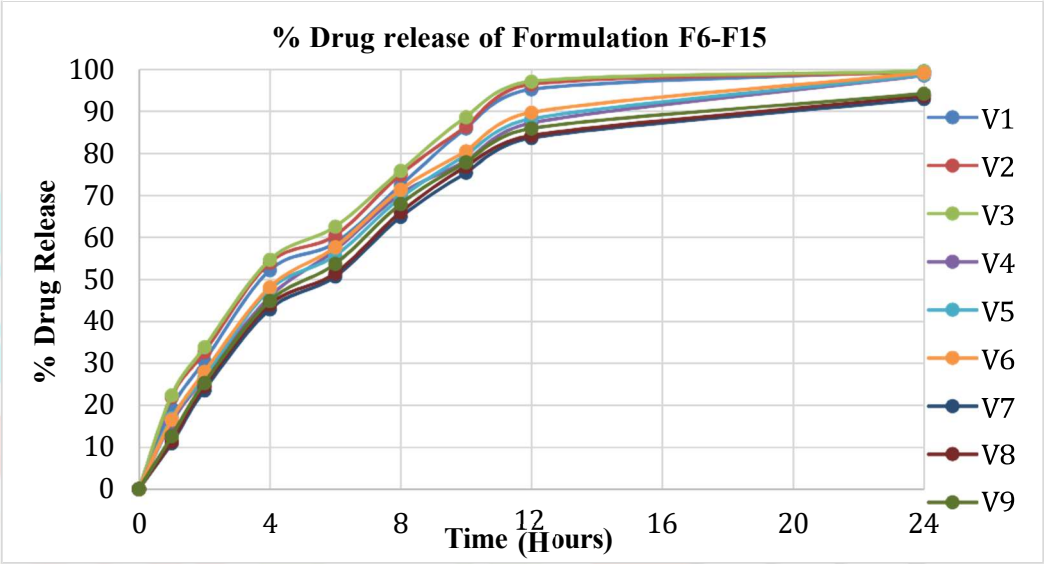


Table 14 Drug Release Kinetic Study of factorial batches V1-V9

Formulation code	Zero Order	First Order	Higuchi	Peppas- model	
	R^2	R^2	R^2	R^2	Slope n
V1	0.996	0.811	0.991	0.985	0.659
V2	0.994	0.820	0.970	0.986	0.658
V3	0.998	0.732	0.971	0.988	0.703
V4	0.998	0.698	0.972	0.987	0.722
V5	0.994	0.919	0.987	0.993	0.625
V6	0.989	0.902	0.984	0.996	0.610
V7	0.995	0.830	0.984	0.994	0.598
V8	0.998	0.870	0.987	0.954	0.602
V9	0.998	0.798	0.985	0.967	0.621

Analysis of factorial design

The compiled results were analyzed using factorial design. For this purpose, Stat Ease DoE (Design of Experiment) software was utilized. The factors and responses were input into the software, and the analysis was conducted based on the data presented in the table below.

Table 15 Factorial design layout

Batch	Independent variable		Dependent Variables	
	X_1 (Carbopol 934) mg	X_2 (Polypropylene foam powder) mg	Y_1 (% Drug release at 1 hour)	Y_2 Floating lag time (sec)
V1	85	15	19.2	53
V2	85	20	21.9	50
V3	85	25	22.3	47
V4	90	15	15.8	55
V5	90	20	16.9	48
V6	90	25	16.5	42
V7	95	15	10.9	59
V8	95	20	11.3	50
V9	95	25	12.6	48

ANOVA for Quadratic model

Response 1: % Drug Release at 1 hour

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	142.33	5	28.47	45.24	0.0050	Significant
A-Carbopol 934	136.33	1	136.33	216.65	0.0007	
B-Polypropylene Foam powder	5.04	1	5.04	8.01	0.0662	
AB	0.4900	1	0.4900	0.7787	0.4425	
A^2	0.0022	1	0.0022	0.0035	0.9563	
B^2	0.4672	1	0.4672	0.7425	0.4522	
Residual	1.89	3	0.6293			
Cor Total	144.22	8				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 45.24 implies the model is significant. There is only a 0.50% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Final Equation in Terms of Coded Factors

% Drug Release at 1 hour	=
+16.72	
-4.77	Carbopol 934
+0.9167	Polypropylene Foam Powder
-0.3500	Carbopol 934xPolypropylene Foam Powder
-0.0333	Carbopol934^2
-0.4833	Polypropylene Foam Powder^2

Y=+16.72-4.77+0.9167-0.3500-0.0333-0.4833

The equation expressed in terms of coded factors allows for predicting the response at specific levels of each factor. Typically, high factor levels are represented by +1, while low factor levels are denoted as -1. This coded equation is particularly useful for assessing the relative influence of factors by comparing their coefficients.

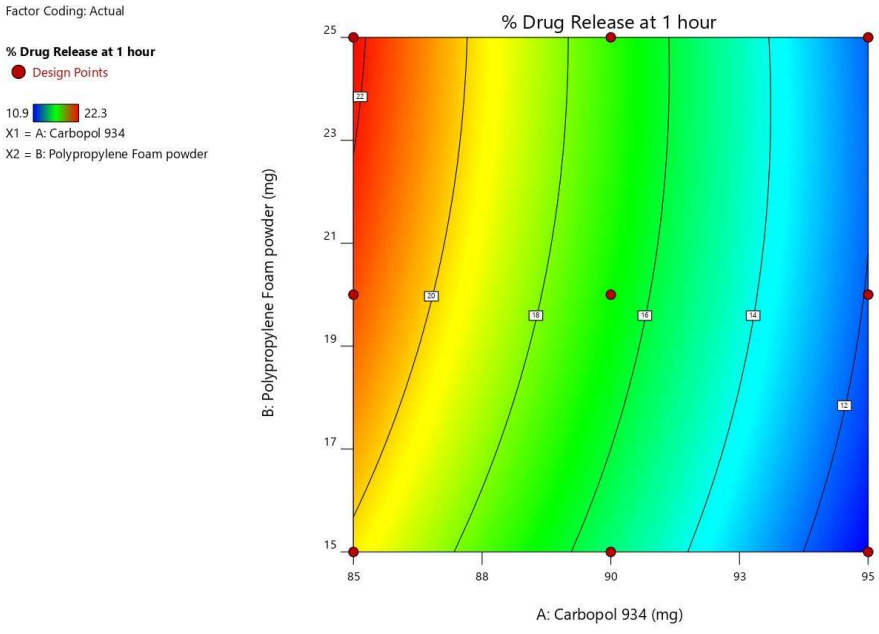


Figure 7 Contour plot for drug release

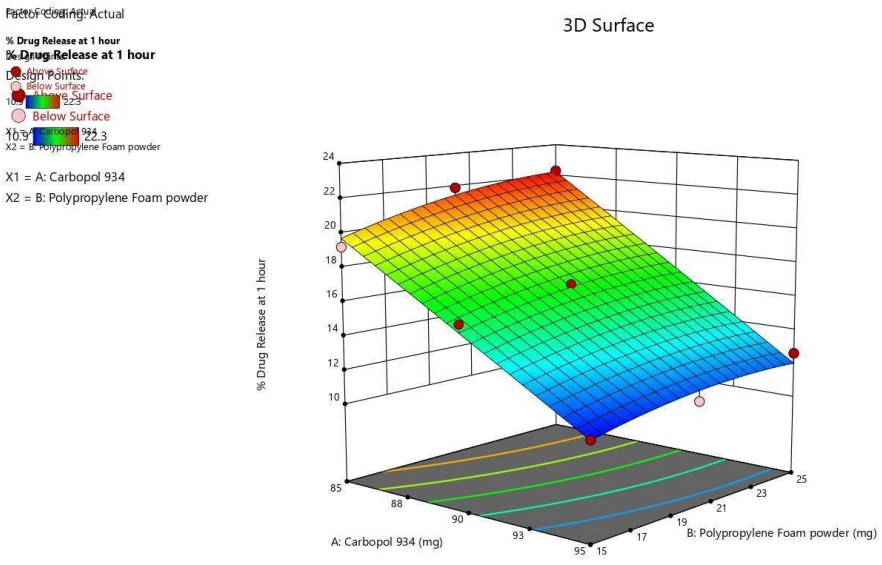


Figure 8 Surface plot for drug release

ANOVA for Quadratic model

Response 2: Floating lag time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	184.03	5	36.81	9.58	0.0460	Significant
A-Carbopol 934	8.17	1	8.17	2.13	0.2410	
B-Polypropylene Foam powder	150.00	1	150.00	39.04	0.0083	
AB	6.25	1	6.25	1.63	0.2920	
A^2	16.06	1	16.06	4.18	0.1335	
B^2	3.56	1	3.56	0.9253	0.4070	
Residual	11.53	3	3.84			
Cor Total	195.56	8				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 9.58 implies the model is significant. There is only a 4.60% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case B is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Final Equation in Terms of Coded Factors

Floating lag time	=
+47.44	
+1.17	Carbopol 934
-5.00	Polypropylene Foam Powder
-1.25	Carbopol934xPolypropylene Foam Powder
+2.83	Carbopol 934^2
+1.33	Polypropylene Foam $Powder^2$

Y=+47.44+1.17-5.00-1.25+2.83+1.33

An equation based on coded factors enables predictions about the response for specific levels of each factor. Typically, high factor levels are represented as +1, while low levels are denoted as -1. This coded equation is particularly beneficial for evaluating the relative influence of the factors by comparing their coefficients.

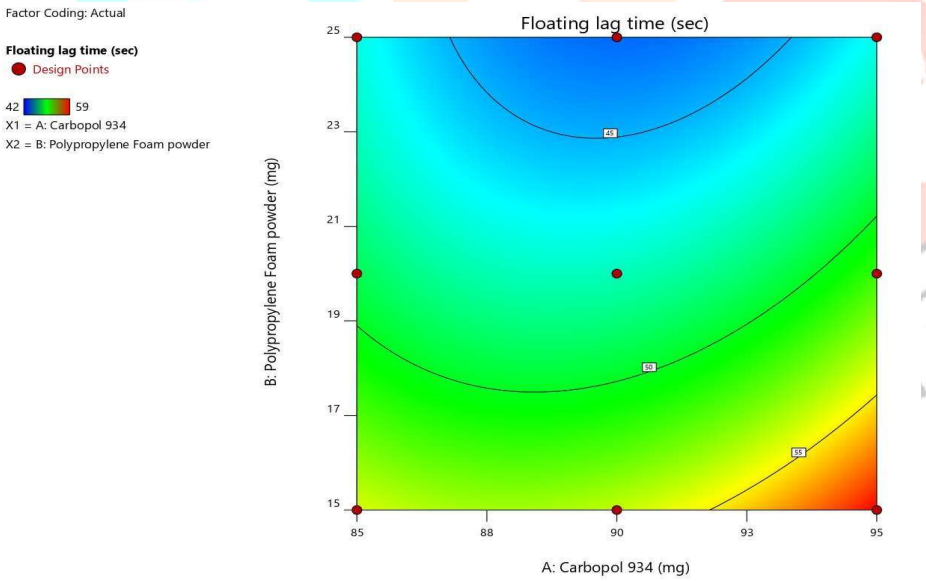


Figure 9 Contour plot for Floating lag time

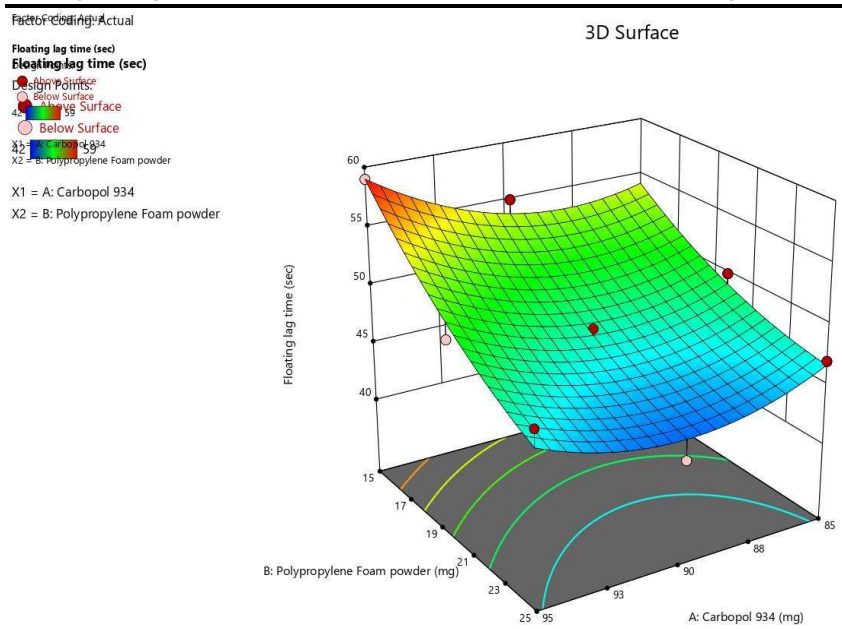


Figure 10 Surface plot for Floating lag time

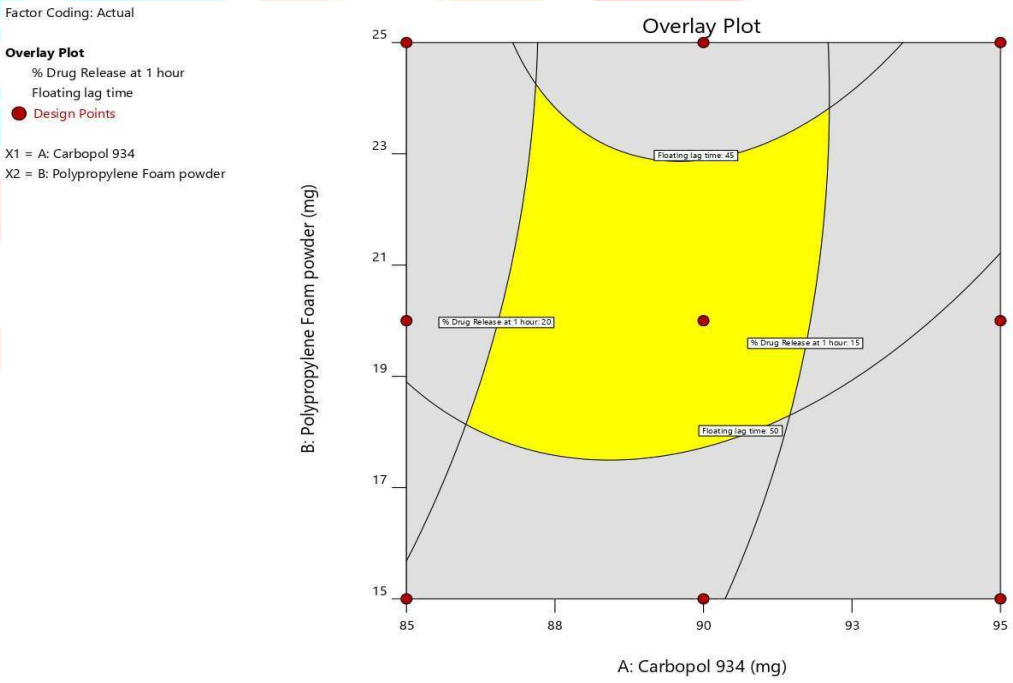


Figure 11 Overlay Plot

- **Validation of model**

A checkpoint batch was created based on the desirability function, as presented in Table 6.15. To validate the predictions, checkpoint batches C1 and C2 were prepared and tested under the same conditions as the other batches. The response data was compared against the required data. The response variables obtained from the checkpoint batches were analyzed in relation to the target response parameters, and the bias between predicted and observed responses was found to be acceptable.

Table10 Check point batch

Batch	Amount of X1 (mg)	Amount of X2 (mg)	% Drug release at 1 hour			Floating lag time (sec)		
			Predicted	Observed	% Bias	Predicted	Observed	% Bias
C1	88	21.8	18.6	18.5	1.00	45	44	1.02
C2	93	21.5	13.9	13.4	1.03	47	46	1.02

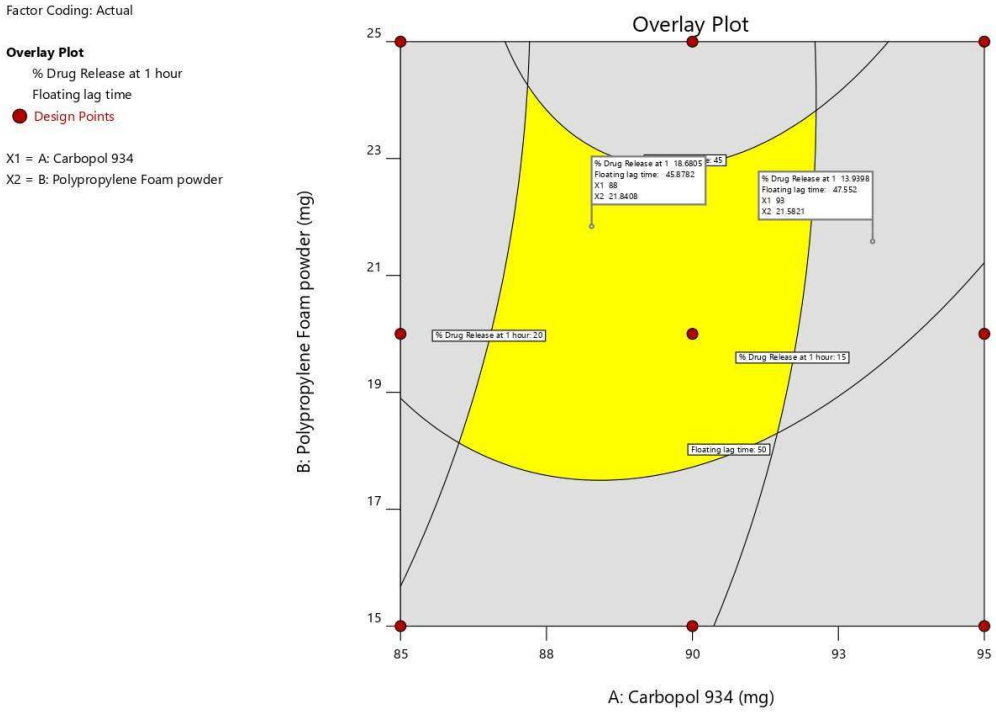


Figure 12 Overlay Plot for check point batch

- **Selection of Optimized batch**

The optimized batch was chosen from the design. According to the overlay plot, the formulation of the optimized batch closely resembled that of the V5 batch, which is already part of the factorial batches. Hence, it was designated as the optimized batch.

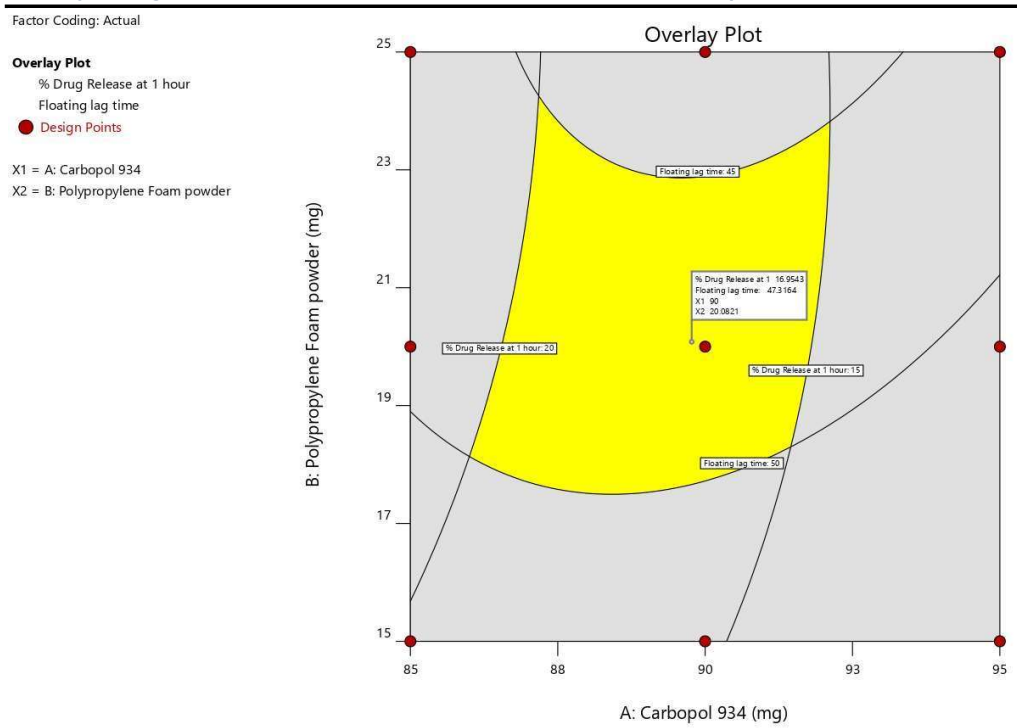


Figure 13 Overlay Plot for optimized batch

Composition of Optimized batch

Ingredients	**O1**
Vonoporazan Fumarate	40.0
Carbopol 934	90.0
Polypropylene foam powder	20.0
Spray dried Lactose	44.0
Magnesium stearate	2.0
Talc	4.0
Total Weight	**200.0**

Results of optimized batch O1

Evaluation Parameters	**Results**
Weight variation (mg)	201 ± 1.5
Thickness(mm)	4.52 ± 0.02
Hardness(kg/cm^2)	5.3 ± 0.1
Friability (%)	0.45 ± 0.03
Drug Content (%)	99.5 ± 1.8

Floating Lag Time (sec)	47 ± 5	
Total Floating Time (hr.)	24 hours	
% Drug Release	**Time (hour)**	**% Drug Release**
	0	0
	1	17.8± 3.9
	2	27.9± 3.1
	4	48.8± 2.5
	6	56.8± 2.7
	8	68.4± 1.9
	10	79.5± 1.5
	12	87.3± 0.8
	24	98.9± 0.5
Drug Release Kinetic Study	**Kinetic Model**	**R^2 value**
	Zero Order	0.984
	First Order	0.917
	Higuchi	0.988
	Peppas	**0.998**

Table 11 Results of stability study of batch O1

Batch	Time Period	Appearance	Drug Content (%) (n=3)	Floating Lag Time (sec) (n=3)	*In-vitro* drug release at 24 hrs. (n=3)
O1	Initial	White tablet	99.5 ± 1.8	47 ± 6	98.9 ± 0.5
	After 30 days	White tablet	99.2 ± 2.1	49 ± 5	98.5 ± 1.8

CONCLUSION

The study focused on developing a sustained-release floating tablet of Vonoprazan Fumarate using the direct compression method to simplify processing. Initially, various rate-controlling polymers were screened, including Carbopol 934 and Chitosan. Carbopol 934 proved effective in controlling the drug release rate and was selected for further development. Preformulation studies confirmed compatibility between the drug and the chosen excipients. Fifteen batches (F1 to F15) were developed and underwent physical and chemical analysis. Formulation F6 displayed satisfactory results and was further optimized using a factorial design approach. The quantities of Carbopol and the floating agent were chosen as independent variables to study their impact on drug release at 1 hour and floating lag time. Evaluation of the factorial batches (V1-V9) showed acceptable levels of weight variation, friability, hardness, and thickness. The drug content in all batches ranged between 97% and 99%. The results indicated that Carbopol 934 had a significant effect on drug release at 1 hour, while the floating agent influenced floating time. An increase in the Carbopol 934 concentration led to a reduction in drug release percentage. The O1 formulation, which exhibited stable performance in a one-month stability study, was finalized as the optimized formulation. It demonstrated controlled drug release, satisfactory floating properties, and stability, making it a strong candidate for future clinical evaluation.

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