Formulation And Evaluation Of Gastro Retentive Drug Delivery Systems Effective Against H Pylori

Dr. Sandip R Pawar[1]*, Miss. Utkarsha Khachane[2], Dr. Bharat V. Jain[2], Mr. Kiran D. Baviskar[3], Mr. Atul A. Sabe[4], Mr. Yogesh A. Chaudhari[5]

[1*,2,3,4,5]Department of Pharmaceutics, Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda, Maharashtra, India.

***Corresponding Author:** Dr. Sandip R Pawar
*Department of Pharmaceutics, Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda, Maharashtra, India.
E-mail address: sandip_pank1@rediffmail.com

Abstract:
Development of an efficient gastro retentive dosage form for stomach specific drug delivery is an actual challenge. Thus, to produce the preferred gastro retention several methods have been used, out of which, the floating drug delivery system has emerged as the best promising method. These systems provide the benefit of better absorption of drugs that are absorbed from upper part of stomach. Local action of drug is increased as the system rests in stomach for longer time. This leads to less frequent dosing and enhanced efficiency of the treatment. Good stability and better drug release as compared to other conventional dosage forms make such system more reliable. Drug absorption in GIT is a highly variable procedure and prolonging GI retention of the dosage form prolongs the time of drug absorption. Floating drug delivery system promises to be a potential approach for gastric retention. Though there are number of complications to be worked out to achieve extended GI retention, many companies are focusing toward commercializing this method.

Keywords: Vonoprazan, HPMC, UV Spectroscopy, FT-IR spectroscopy, Angle of repose.

INTRODUCTION:

Gastro retentive drug delivery system are one of the type of controlled release drug delivery systems they can retain in the gastro intestinal region for a long period of time and altering the gastric emptying time and motility pattern of GIT5.GRDDS are feasible for drugs that having low absorption in the lower part of GIT. Unstable, and poorly soluble at alkaline pH and the drugs having shorter half-life 6, 7.Various formulation related factors such as polymer types (non-cationic, anionic) polymer, composition, viscosity, molecular weight of polymer and drug solubility can effect the quality of the gastro retentive dosage form 8.

The stomach is a J-shaped enlargement of the GI tract directly inferior to the diaphragm in the abdomen. The stomach connects the oesophagus to the duodenum, the first part of the small intestine. **Mentis A, Lehours P 2015**

ADVANTAGES OF GRDDS

The advantages regarding gastro retentive drug delivery system includes

- It has been using in the treatment of peptic ulcer disease.
- Commonly used for drug having narrow therapeutic index. To minimize the dosing frequency.
- Improved bioavailability of drugs.
- Used for drugs which are normally unstable in intestinal fluids.
- Used to provide sustained delivery for the drugs used for maintaining maximum therapeutic drug concentration within the therapeutic withdraw.

DISADVANTAGES OF GRDDS

- Although there are advantages, this also having disadvantages 12, 13. They are
- Drugs that are unstable in high acidic environment, very low solubility in acid environment causes irritation to gastric mucosa and cannot formulated as GRDDS.
- FDDS (Floating Drug Delivery Systems) require high level of fluid in stomach for floating and working more efficiently. So more water intake has needed with such dosage form.

MATERIALS AND METHODS:

Materials

Table 1: Materials used

INGREDIENTS	SUPPLIERS
Vonoprazan	Anant Pharmaceuticals Pvt. Ltd.
Sodium Bicarbonate	Badrivishal Chemicals,pune
Citric Acid	Badrivishal Chemicals,pune
HPMC	Coloreon Asia
Polyvinyl Pyrrolidine	CDH
Microcrystaline cellulose	Hetero lab's Hyderabad
Talc	Badrivishal Chemicals,pune
Lactose	Badrivishal Chemicals,pune
Isopropyl Alcohol	Badrivishal Chemicals,pune

Methods

Standard graph of Vonoprazan in 0.1N HCl

The stock solution was freshly prepared by dissolving 100mg of Vonoprazan in 10ml of methanol in a 100mL volumetric flask and then making up the solution up to the mark using 0.1N HCl for obtaining the solution of strength 1000 micro g/mL (stock I). From this stock 0.1, 0.5, 1, 1.5, 2.0, 3.0 and 3.5mL were taken separately and made up to 10mL with distilled water, to produce 10, 50, 100, 150, 200, 300 and 350 micro g/mLrespectively. The absorbance was measured at 272nm using a UV-Visible spectrophotometer (Simadzu) against 0.1 N HCl as blank and plotted graphically to give the standard graph of Vonoprazan

Solubility study of Vonoprazan

Excess amount of Vonoprazan was placed in 0.1 N HCl in order to determine its solubility. The samples were shaken for 24 h at 37°C in a horizontal shaker. The supernatant was filtered and the filtrate was diluted with 0.1N HCl and estimated by UV/ Visible Spectrophotometer at Lamda max of 272 nm.

Tableting

The resulting uniform blends of composition per tablet were compressed on 12 stations compression machine using 8 mm flat faced tooling.

Tablet batches

The effect of glycine was studied at three levels (-1, 0, +1), amount of rest of the ingredients were fixed. At the level of (-1), glycine concentration of 2%, at level (0), Glycine concentration 4%, at level (+1), Glycine at concentration of 6% of that of the tableting mass were taken**.**

Pre-formulation studies

Pre-formulation testing is defined as investigation of physical and chemical properties of drug substances alone and when combined with excipients.

Spectroscopic studies

Fourier transform infrared (FTIR) spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). Pure Vonoprazan, individual polymers and optimized formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm−1.

UV Spectroscopy (Determination of lamda max)

The light absorption in the range 200 to 800 nm of a solution buffer it exhibits a maximum only at about 272 nm.

Particle size distribution of Vonoprazan powders

The particle size measurement of Vonoprazan micronized powder was determined by using a (Mastersizer-2000) particle size analyzer. An appropriate amount of Vonoprazan powder was added into the analyzing chamber containing deionized water as the medium. A few drops of Triton solution (1% w/w) were added to disperse the powders. Test results of the type of powder were recorded. In addition, this powder was examined under a microscope with a magnification of 400X.

Compatibility studies of Vonoprazan and Formulation components

The compatibility of drug and polymers under experimental conditions is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and not affecting the shelf life of product or any other unwanted effects on the formulation. The physical mixture of drug & polymers was used for determination of Infrared spectrums.

Formulation development

Formulation of Effervescent Vonoprazan, tablets

Required quantity of isopropyl alcohol was taken into a suitable vessel and to it Hydroxypolymethyl 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) were added slowly under continuous stirring to dissolve completely. Then Polyvinyl Pyrrolidine (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±5°C to evaporate excess solvent. The Tablets were stored in suitable air tight container**.**

Table 2: Formulation chart of Vonoprazan Tablets

INGREDIENTS	QUANTITY		
	F1	F2	F3
Vonoprazan	230	230	230
Sodium Bicarbonate	25	25	10
Citric Acid	10	10	10
HPMC	5	10	20
Polyvinyl Pyrrolidine	10	15	10
Microcrystaline cellulose	10	5	10
Talc	1	1	1
Lactose	5	2	5
Isopropyl Alcohol	4	2	4
Total Weight	300	300	300

Evaluation of Tablets blend

i. Angle of repose

The frictional forces in a loose powder or granules can be measured by the angle of repose. Angle of repose was determined by funnel method. The blend was poured through a funnel which raise vertically until a maximum cone height (h) was obtained. Radius of the heap (r) measured and angle of repose (θ) calculated by using the formula:

$h\ tan\theta$ = (-) r

Where, is the angle of repose h is the height r is the radius

Table 3: Relationship between angle of repose (θ) and flowablity

Angle of repose (θ)	Flowablity
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very Poor

ii) Bulk density

Weighed quantity of 60 gms Tablets was transferred into a 100 ml measuring cylinder without tapping, during transfer the volume occupied by pellets was measured. Bulk density was measured by using formula.

Pi = m/Vo

Where,

Pi = Bulk density,

m = Mass of the Tablets,

Vo = Untapped Volume

iii) Tapped density

Weighed quantity of 60 gms Tablets was taken into graduated cylinder, volume occupied by granules were noted down. Then cylinder was subjected to 500 taps in tapped density tester (Electro Lab USP II), the % Volume variation was calculated by following formula.

Pt = m/Vi

Where,

Pt = Tapped density,

m= Mass of the Tablets

Vi = Tapped volume

iv) Carr's compressibility index

Compressibility is the ability of Tablets to decrease in volume under pressure. Using untapped density and tapped density the percentage compressibility of pellets was determined, which is given as Carr‟s compressibility index.

Table 4: Compressibility index

Carr's index (%)	Type of Flow
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Extremely poor

v) Hausner'sratio

It is measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

Table 5: Compressibility index

Type of Flow	Hausner's Ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35-1.45

vi) Procedure for content uniformity

The content of one capsule was transferred into 200 ml volumetric flask, to it 100 ml equal volume of methanol and 0.1N HCl buffer (pH 1.2) was added. Then the solution was sonicated until then contents are dispersed and volume was made up with methanol and 0.1N HCl buffer (pH 1.2) in 1:1 ratio. This solution contains about 25 µg/ml vonoprazan

vii) Percentage yield

The yield was determined by weighing the tablets and then finding out the percentage yield with respect to the weight of the input materials.

viii) Loss on drying

It was done in Electronic Loss on Drying (LOD) apparatus (Sartorius, Germany). Weighed quantity of 1 gm sample was placed in the pan and the temperature was increased to 105oC and the loss on drying in % was noted.

ix) In-Vitro drug release studies:

In-vitro drug release studies of vonoprazan were carried by using apparatus USP test-per rotation basket method with a stirring speed 50 rpm at 37 ± 0.5°C in 750ml of 0.1N HCl (pH 1.2) buffer for 12 hours. 5 ml of sample, with drawn at interval of 0.5, 1, 2, 4, 6, 12, 24 hours with the replacement of equal volume of dissolution media.

Filtered the solution through millipore HYLP filter and these filtrate was measured at 272 nm by UV spectrophotometer (UV-1700 SHIMADZU).

Table 6: The percentages of the labeled amount of vonoprazan dissolved at the time specified acceptance table.

Type Hours	Amount Dissolved
1	Between 10% and 25%
2	Between 20% and 40%
4	Between 35% and 55%
6	Between 45% and 65%
12	Between 60% and 80%
24	Not Less than 90%

RESULT:

Calibration curve of vonoprazan 0.1N HCl

An UV- Visible Spectrophotometric method was used for estimation of vonoprazan A solution of vonoprazan (10 micro g/mL) was scanned in the wavelength range of 200-300 nm and found to have maximum absorption (Lamda max) at 272 nm. Standard stock solutions of pure drug containing 100mg of vonoprazan /100mL were prepared in 10mL of methanol and making up the volume with 0.1N HCl solution. The working standard solutions were obtained by dilution of the stock solution in 0.1N HCl.

Table 7: Calibration curve of vonoprazan in 0.1 HCL at Lamdamax272 nm.

Sr.No	Concentration	Absorbance
1	0	0
2	10	0.032
3	50	0.145
4	100	0.284
5	150	0.428
6	200	0.563
7	300	0.828
8	350	0.964

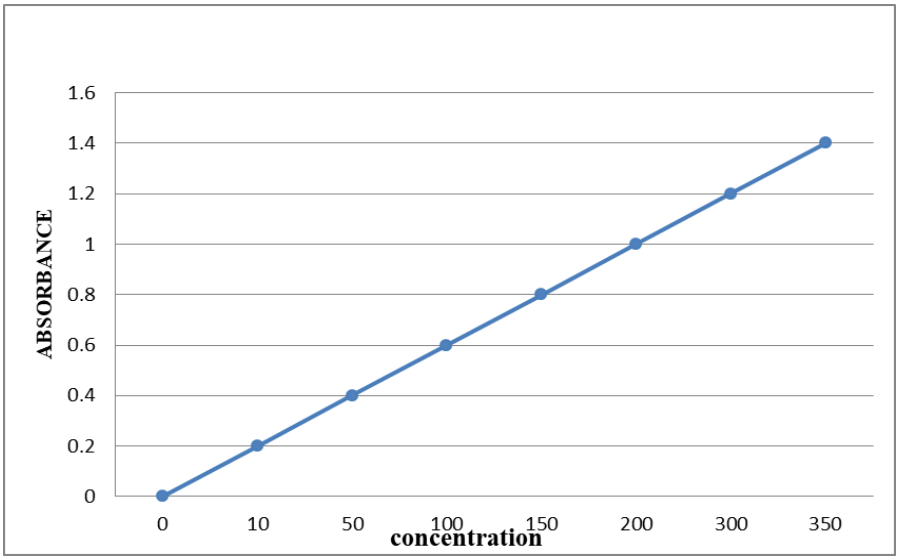

Figure 1: Standard curve for vonoprazan in 0.1 N HCl.

Solubility of vonoprazan

The solubility of vonoprazan in 0.1N HCl was carried out. AMT is highly soluble in 0.1 N HCl, having quantitative solubility 139.1 mg/mL. It shows pH dependent solubility, highly soluble in acidic pH but poorly soluble in alkaline pH.

Table 8: Solubility data of vonoprazan

Medium	Solubility mg/ml
0.1N HCL	139.1
6.8 pH Phosphate buffer	4.7
Water	3.9

8.3 Drug- Excipient compatibility study

Drug-Excipients compatibility study was carried out using various Excipients mentioned below from the pre-formulation studies, it was observed that mixtures shown have no color change.

Table 9: Physical observation

Sr.No	Composition Details	Initial Physical Description	25 C/60% RH & 48 C/75% RH		
			1st week	2nd week	3rd week
1	Vonoprazan	White to light Yellowish Powder	NCC	NCC	NCC
2	Vonoprazan + HPMC	White to light Yellowish Powder	NCC	NCC	NCC
3	Vonoprazan + Polyvinyl Pyrrolidine	White to light Yellowish Powder	NCC	NCC	NCC
4	Vonoprazan + Microcrystaline cellulose	White to light Yellowish Powder	NCC	NCC	NCC
5	Vonoprazan + Sodium Bicarbonate	White to light Yellowish Powder	NCC	NCC	NCC
6	Vonoprazan + Citric Acid	light Yellowish Powder	NCC	NCC	NCC
7	Vonoprazan + Talc	light Yellowish Powder	NCC	NCC	NCC
8	Vonoprazan + Lactose	light Yellowish Powder	NCC	NCC	NCC

Fourier transform infrared (FT-IR) spectroscopy

The thermal behaviour of pure drug and the respective excipients and the binary mixture of drug and excipients are compared in the FT-IR thermograms.

Evaluation of Tablets of Vonoprazan

Table.10: Evaluation of Tablets of Vonoprazan

Batch Code	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F1	0.837 ± 0.006	0.890 ± 0.007	6.01 ± 1.57	1.074 ± 0.017	30.11 ± 1.12
F2	0.833 ± 0.012	0.886 ± 0.015	6.012 ± 0.79	1.06 ± 0.008	29.24 ± 1.40
F3	0.845 ± 0.012	0.899 ± 0.008	6.209 ± 0.63	1.049 ± 0.030	28.31 ± 1.23

 # all the reading taken in replicate represented as mean ± SD

Content uniformity

The results for uniformity of dosage units are presented in the table given below.

Table 11: Drug Layered Tablet Content uniformity

Sr.No	Drug Layered Tablet Content uniformity
F1	100.5 ± 0.75
F2	100.9 ± 0.66
F3	100.7 ± 1.19

Weight Variation & Loss on drying

The prepared Tablets of all the batches were evaluated for their moisture content. It is observed that the range around 1%.

Table 12: Weight Variation & Loss on drying

Sr.No	Weight (mg) ± SD	Loss on Drying (%)
F1	409 ± 1.89	1.22 ± 0.02
F2	409 ± 2.63	1.20 ± 0.03
F3	415 ± 2.02	1.21 ± 0.02

In-vitro release of formulations of Vonoprazan Tablet

Table 13: Time Hours and Amount Dissolved

Time Hours	Amount Dissolved
1	Between 10% and 25%
2	Between 20% and 40%
4	Between 35% and 55%
6	Between 45% and 65%
12	Between 60% and 80%
24	Not Less than 90%

Table 14: In-vitro dissolution data of F1

Sr.No	Time Hours	Amount of Drug Release	% Drug Release	Cumulative % Drug Release
1	1	27.25	36.33	36.33
2	2	35.40	47.28	47.52
3	4	45.37	60.49	60.80
4	6	53.90	71.86	72.26
5	12	61.52	82.02	82.50
6	24	72.78	97.04	97.59

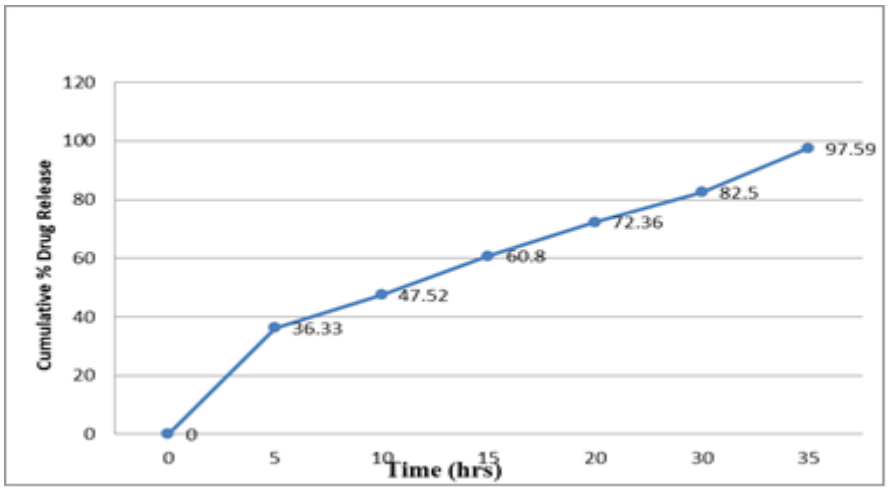

Figure 2: In-vitro dissolution data of F1

Table 15: Comparative In–VitroDrug Release Profile Before and After 1 Month and 2 Month Storage at (40°C / 75% RH.)

	INITIAL		1 MONTH		1 MONTH	
Time Hours	Amount of Drug Release	Cumulative % Drug Release	Amount of Drug Release	Cumulative % Drug Release	Amount of Drug Release	Cumulative % Drug Release
1	12.09	17.32	12.72	16.96	14.05	18.74
2	23.50	31.44	24.03	32.15	24.85	33.26
4	30.56	40.94	30.94	41.47	30.94	41.48
6	39.95	53.53	40.73	54.58	38.91	52.16
12	51.03	68.39	49.68	60.60	53.42	71.57
24	72.63	97.29	72.63	97.28	73.84	98.93

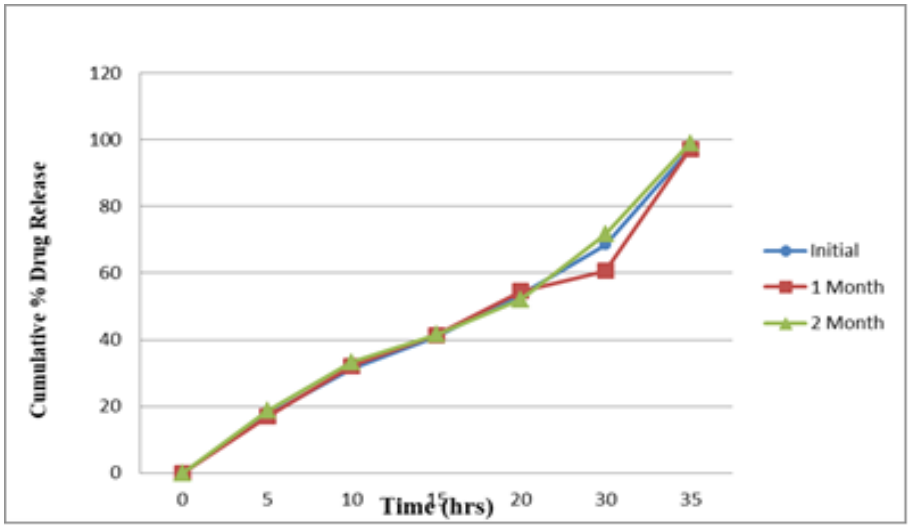

Figure 3: Comparative In–VitroDrug Release Profile Before and After 1 Month and 2 Month Storage at (40°C / 75% RH.)

Drug content

Table 16: Drug content

Time (Month)	40 C/ 75% RH
Initial	98.4 1.09
1st Month	97.5 1.05
2nd Month	97.03 0.98

CONCLUSION:

The present work was carried out to design and evaluate Vonoprazan Tablets. Vonoprazan is an antibiotic and is one of the most widely used drug for treating variety of bacterial infections. The combination of microcrystalline cellulose and other polymers the drug release rate increased due to a formation of a Tablets Formulation F-3 (containing Microcrystalline cellulose 5% w/w and hydroxypropyl methyl cellulose 9%w/w) showed better release profile i.e. very low initial drug release in the first two hrs and afterwards the rate of drug release increased with almost complete release of the drug being achieved in 97.03% at 24 hrs respectively. Hence F-3 release profile was passed all USP test-1 limits. .In the present study, it was found that incorporation of hydroxypropyl methyl cellulose in the not only helped to provide good initial retardation in the release but also helps to enhance the overall release rate of the drug after a suitable lag time and also it will act as suitable binding property. Optimized formulation F-3 was subjected to data obtained from stability studies indicate that there is no much change in the release profile and drug content of Tablets. Hence the prepared Tablet of formulation (F-3) were found to be stable..

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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