A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

Section A-Research paper

A NOVEL RP-UPLC METHOD DEVELOPMENT AND VALIDATION FOR THE SIMULTANEOUS DETERMINATION OF VONOPRAZAN AND AMOXICILLIN IN FIXED DOSAGE COMBINATION

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Abstract

Background and Aim: The present day scenario, the dualdrug therapy is more effective than single-dose therapy due to reduction of side effects at minimum dosage. Hence, The present research aims to create a novel, fast, easy, sensitive, and one-of-a-kind ultra-performance liquid chromatographic (UPLC) stability-indicating approach for the dosage-simultaneous assessment of amoxicillin and vonoprazan.

Materials and Methods: An efficient chromatographic separation was accomplished with a flow rate of 0.5 ml/min, a BEH-C18 column, and a mobile phase consisting of 0.1% H_3PO_4 and CH_3CN (50:50 v/v). The adapted elution process was isocratic and separation was completed within 6 minutes of run time under ambient temperature conditions at 230nm. Forced degradation studies and method validation were undertaken in accordance with the norms of the ICH.

Results and Discussion: The linearity of Amoxicillin and Vonoprazan was studied at concentrations of 62.5–375µg/ml and 2.5–15µg/ml, and the correlation coefficient (r^2) for both drug were found to be greater than 0.99. LOD values of Amoxicillin and Vonoprazan were determined at 0.75µg/ml and 2.5µg/ml as well as 0.03µg/ml and 0.1µg/ml being the LOQ values. For Amoxicillin, the obtained percentage recovery values lay between 99.7% and 100.7%, and for Vonoprazan, between 100.1% and 100.4%. Studies on forced degradation revealed a clear resolution of the analyte peaks.

Conclusion: Using a new, rapid, sensitive, and affordable RP-UPLC approach, the simultaneity of Vonoprazan and Amoxicillin determination in Fixed Dose combination was effectively developed and validated.

Keywords: Development, Validation, Vonoprazan, Amoxicillin, UPLC,P-CAB.

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A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

Section A-Research paper

1. INTRODUCTION

Vonoprazan (VAN): P-CAB (potassium-competitive acid blocker) is prescribed to treat illnesses associated with acid-related disorders in the body [1-6],as well as VAN (Figure1) is 350-times more potent than Lansoprazole.
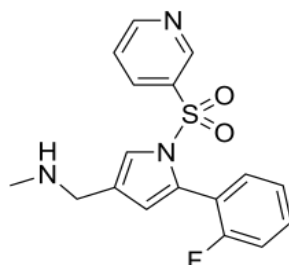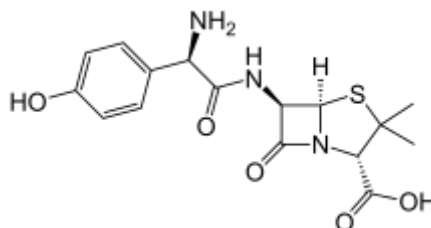

Figure 1: Structure of Vonoprazan

Figure 2: Structure of Amoxicillin

Amoxicillin trihydrate(Figure.2) belongs to the penicillin class of antibiotics and is an effective medicine for the treatment of pneumonia[7-11], controlling a middle ear infection, skin infections, strep throat, urinary tract infections, etc.Government regulatory agencies generally try to employ combo medications. Combination therapy is more effective than single-drug therapy; additionally, combination therapy is frequently associated with less side effects than high-dose monotherapy; as a result, patient adherence may be improved. Fixed-dosage combination (FDC) medications are necessary to treat other diseases and reach glycaemic targets because they have the following advantages over higher dose monotherapy: greater efficacy, decreased risk of adverse effects, increased compliance, synergism, and lower total costs [12-13].The dual therapy of Amoxicillin (AMX) and Vonoprazan would provide an effective eradication rate for Helicobacter infections[14]. In this context, a literature survey has been carried out to learn more about dual therapy and explore the different published analytical methods for the determination of Amoxicillin and Vonoprazan. With the different drug materials, and at the same time, development of a rapid and accurate UPLC method that could also be employed for force degradation is an important prime concern.

The simultaneous determination of Vonoprazan and Amoxicillin cannot be done analytically, according to the literature. However, there are a lot of research papers in the literature that can be used to determine how Vonoprazan and Amoxicillin work individually. There aren't many publications available about getting to find Vonoprazan in human plasma and active pharmaceutical ingredients. Vonoprazan has been determined by using HPLC [15-16] and LC-MS [17] methods.Utilizing these techniques, HPLC [18–20] HPLC-MS [21], and UPLC-MS [22] regarding the assessment of amoxicillin in API, biological samples, and porcine tissues have been identified. The UPLC

Eur. Chem. Bull. 2023, 12 (S3), 3571 – 3583

3572

A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

Section A-Research paper

method offers some major benefits with improvements in technology, including speed while maintaining excellent resolution and sensitivity when comparable to the HPLC methods. These benefits may help producers minimise expenses when conducting analysis. Because the analysis from UPLC takes short runtime, the analysts' time is used more effectively[23]. Various analytical method of HPLC [24], LC-MS[25],UPLC[26-27] have been conveyed for the study of amoxicillin combinations with other drugs. The literature on Vonoprazan is only available in its therapeutic activity process, which was the eradication and remedies for adult patients with Helicobacter pylori infections using the combination drugs, i.e., VOQUEZNA DUAL PAK. Several approaches for the spectral analysis of Vonoprazan combination with other drugs were not disclosed in the literature [28].

However, there hasn't been a published UPLC approach for the detection of Amoxicillin and Vonoprazan. A novel RP-UPLC method for the simultaneous determination of Amoxicillin and Vonoprazan is thus being developed and validated as the main goal of the current research work, in addition to the above, the force degradation study was evaluated.

2. MATERIAL AND METHODS

Chemicals and reagents:
The working standards of Vonoprazan and Amoxicillin were procured from Glenmark Pharmaceuticals Ltd., Hyderabad. HPLC-grade acetonitrile, orthophosphoric acid, water, and chemicals such as HCl, H_2O_2, and NaOH were procured from E. Merck Ltd, Mumbai. The Borosil double distillation device was used for making purified water.

Apparatus and instrumentation:

An Agilent 1290 Infinity II LC System with quaternary pump, photodiode array (PDA-2998) detector, and auto sample injector was employed in the studyThe output signals were integrated and monitored using the Waters Empower 2 software. The Metler Toledo ME204 analytical balance, the Hover Labs LMPH-9 pH metre, the Remiultra sonicator, the Borosil double distillation device, the Millipore vacuum filtering unit, and the Kemi hot air oven were among the additional tools and equipment used.

Chromatographic conditions:
On a BEH-C18 column with dimensions of 100×2.1mm, 1.7μm, column, analysis was undertaken using acetonitrile (ACN) and 0.1% H_3PO_4 buffer (50:50, v/v) as the mobile phase. The entire investigation were carried out with a flow rate 0.5 ml/min., isocratically at 25 °C, with run time of 6 min. At 230 nm, analytical outputs were monitored.

Preparation of buffer:
Dissolve 1ml of H_3PO_4 in 1000ml of HPLC-grade water and filter through 0.45μm filter paper.

Preparation of mobile phase:
Acetonitrile and buffer combined in a 50:50 v/v volume ratio, later sonicated for half an hour. Next, filter it through 0.45μm membrane filter paper.

Diluent:
Mobile phase was used as diluent.
Development of the St. Sol.:
Standard stock solutions of Vonoprazan and Amoxicillin were made by precisely calculating 10 mg and 250 mg of the medicines in a 100 ml volumetric flask. After being dissolved in a solvent, the drug was run through a 0.45-m filter. Additional 5 ml of the aforementioned

Eur. Chem. Bull. 2023, 12 (S3), 3571 – 3583

3573

A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

Section A-Research paper

solution were diluted with diluent to make a 50 ml volumetric flask.

Solution preparation for samples:

Ten pills of Vonoprazan and Amoxicillin were precisely weighed and fine powdered. In a 100ml volumetric flask, an equivalent weight of 10 mg Vonoprazan tablet powder and 250 mg Amoxicillin capsule powder were added before being dissolved in diluent. The solution was ultrasonically diluted with diluent for a period of ten minutes. Then, 5 ml of the aforementioned solution were diluted with diluent to make a 50 ml volumetric flask. The sample solution was then used to prepare sample solution for the assay of vonoprazan and amoxicillin after being filtered with a 0.45 micron syringe filter.

Procedure for validation:

In accordance with ICH Q2 (R1) standards, the appropriateness, precision, specificity, accuracy, linearity, robustness, LOD, LOQ, and forced degradation of the analytical system were verified.

Optimization of chromatographic conditions:

Regarding resolution, theoretical plate count, tailing, and other system suitability criteria, several combinations of mobile phases were screened. Finally, the most effective separation was achieved with freshly prepared mobile phase. All of the chromatographic conditions that were optimized are shown in Table 1, and the analysis process was completed with the ambient temperature being maintained throughout the process to produce a symmetric peak of Amoxicillin and Vonoprazan.

Table 1: The optimized chromatographic condition

Parameters	Values
Column	BEH -C18 column of dimensions 100×2.1mm, 1.7μm
Mobile Phase	H_3PO_4 Buffer: CH_3CN (50:50% v/v)
Flow Rate	0.5ml/min.
Wave length of detection	230nm
Injection volume	5μl
Run time	6 min
Column Temp.	Ambient
Elution Mode	Isocratic

Amoxicillin and Vonoprazan showed retention times of 1.778 and 3.171 minutes, respectively. The suggested technique has been verified as being within the limits of the most recent ICH suggestions.

Suitability of the System to VAN & AMX:

A system appropriateness test must be carried out to ensure the analytical system is operating properly before the start of laboratory research to establish method validity. Six replicates of the Vonoprazan and Amoxicillin standard solutions were made and examined by UPLC for this and the peak area of VAN & AMX have been computed.

Linearity and Range:

To check the linearity, many concentrations were prepared from the stock solution. After each solution underwent UPLC analysis, the filtrate was degassed in an ultrasonic bath and diluted with the mobile phase to produce a working test solution with 10 mg/ml of vonoprazan and 250 mg/ml of amoxicillin.

Accuracy:

Recovery studies, in which three distinct concentrations (50%, 100%, and 150% of

Eur. Chem. Bull. 2023, 12 (S3), 3571 – 3583

3574

the standard solution containing 10µg/mlof Vonoprazan and 250µg/mlof amoxicillin) were assessed by UPLC in three replications, were used to assess the accuracy of this new approach. The amount recovered was calculated employing the linear regression equation (calibration curve -percentage recovery value).

VAN & AMX Precision Study (Intermediate Precision and Repeatability)

VAN & AMX - Repeatability:

The reference solution of 250µg/ml of Amoxicillin and 10µg/ml of Vonoprazan was divided into six replicates and subjected to UPLC analysis. Each trial's results were recorded as well as calculations were made for the observations' SD and percentage of RSD.

VAN & AMX - Intermediate precision:

The capability to reliably replicate data from one day to the next is assessed using the Intermediate precision test. As part of the intra-day procedure, the working standard solution was injected repeatedly throughout the day. During the inter-day process, the working standard solution was injected on a number of days. The SD and%of RSD figures reflect the variation seen in the results obtained.

Method robustness:

By purposefully altering the significant chromatographic parameters to a small level, the robustness of the new approach was evaluated. A 0.1ml/min flow rate altered, and a 5% changed in the quantity of ACN in the mobile phase were all made. All of the observed, expressed variation in the results was % RSD.

Limit of detection (LOD) and limit of quantitation (LOQ):

Using the formulas LOD=3.3 σ /s and LOQ=10 σ /s, the LOD and LOQ were determined from the slope (s) of the calibration plot and the SD (σ) of the peak areas.

Forced degradation studies:

To determine the forced degradation study (stress testing), assess the stability of pharmaceutical drugs, and solve stability-related issues, stress tests are conducted. It is carried out early in the medication development cycle and aids in selecting appropriate dose forms and storage settings. By subjecting the product to physical stress stability research was carried out.

Acid hydrolysis:

30ml of HCl (0.1N), 10mg of Vonoprazan, and 250mg of Amoxicillin were added to a round-bottom flask and refluxed at 60°C in a water bath for four hours. Once it reached room temperature, a NaOH (0.1N) solution was used to neutralise it. Prior to UPLC analysis, it was diluted with the mobile phase to a concentration of 10 g/ml. Three rounds of this experiment were conducted with the aim to examine the degradation profile in an acidic medium.

Base hydrolysis:

In a round bottom flask filled with 30ml of NaOH (0.1N), 10mg of Vonoprazan and 250mg of Amoxicillin were combined, and the mixture of VAN & AMX was refluxed at 60°C for four hours. Once it reached room temperature, HCl (0.1N) solution was used to neutralize it. Prior to UPLC analysis, it was diluted to a concentration of 5µg/ml using the mobile phase. To investigate the degradation profile in an acidic media, this experiment was done three times.

Thermal degradation:

With 30ml of UPLC grade water, 10mg of Vonoprazan and 250mg of Amoxicillin were administered before being refluxed at 60°C in a water bath for four hours. After reaching room temperature, with the mobile phase, prepared as a concentration of 10 µg/ml solution, and three repetitions of the UPLC analysis were performed.

Photolytic degradation:

For 24 hours, 10 mg of Vonoprazan and 250 mg of Amoxicillin were exposed to

UV light with a wavelength of 230 nm. The mobile phase was used to create a 10μg/ml concentration of the UV-exposed medication, which was then examined three times by UPLC.

Oxidation with (3%) H_2O_2

A accurate amount of 10 mg of Vonoprazan and 250 mg of amoxicillin were taken in 30 ml of H_2O_2 (3%) and a small amount of mobile phase was added to make it soluble. This mixture was then left as is for 24 hours in the dark. A suitable dilution with the mobile phase was created to create a concentration of 10 μg/ml, which was then examined by UPLC in three duplicates.
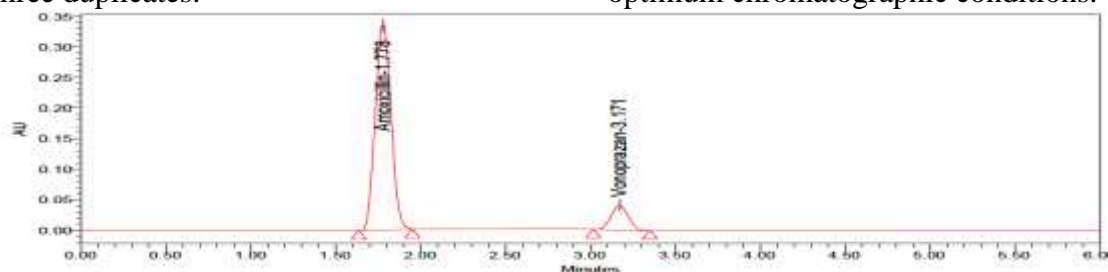
3. RESULTS AND DISCUSSION:

It was attempted to establish an easy method for simultaneously estimating Vonoprazan and Amoxicillin in API. Following ICH recommendations, forced degradation studies were used to verify the stability research. The developed stability-indicating approach was approved and discovered to be suitable for Vonoprazan and Amoxicillin qualitative and quantitative assessment. Figure 3 shows a sample chromatogram of Vonoprazan and Amoxicillin that was recorded under optimum chromatographic conditions.

Figure3:
A sample chromatogram of Amoxicillin and Vonoprazan in the optimized chromatographic conditions

System suitability:

By injecting a normal solution comprising 10 μg/ml of vonoprazan and 250 μg/ml of amoxicillin in six duplicates, system the suitability was obtained. The results indicate that the system the suitability criterion was within limits (Table 2).

Table 2: Results of system suitability

System suitability parameter	Amoxicillin			Vonoprazan		
	Mean	Std. Dev.	% RSD	Mean	Std. Dev.	% RSD
USP Plate count	8455	0.623	1.12	3874	1.204	0.82
USP Tailing	0.98	0.754	0.48	1.11	0.547	0.57
USP Resolution	-	-	-	6.43	0.248	0.64
Retention time	1.765	1.241	0.33	3.169	0.652	0.49

Specificity:

According to the specificity chromatograms of the placebo and blank shown in Figures 4 and 5, respectively, no interfering peaks were seen at the retention times of Amoxicillin and Vonoprazan.
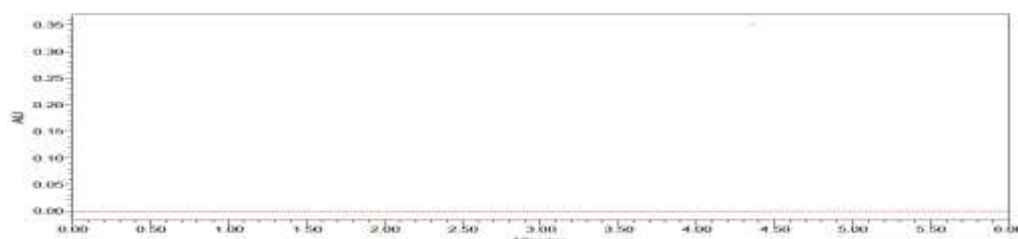
A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

Section A-Research paper
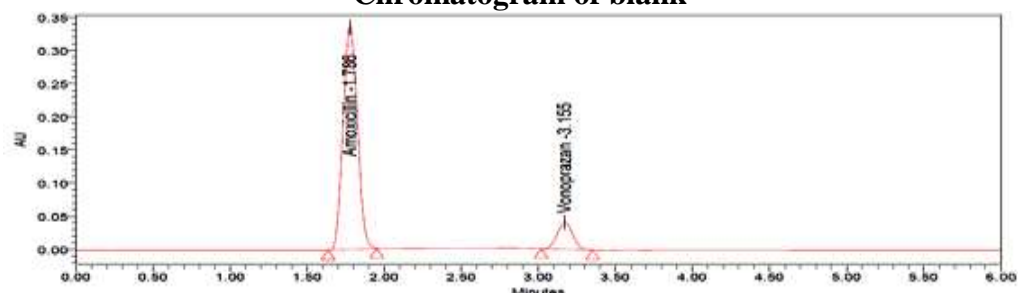
Figure4:
Chromatogram of blank

Figure 5:
Standardchromatogram of Amoxicillin and Vonoprazan

Linearity:

By constructing a curve between peak areas and the corresponding concentrations, linearity was confirmed. From this calibration curve, it was observed that the curve was linear over the concentration ranges of 2.5–15 µg/ml Vonoprazan and 62.5–375 µg/ml Amoxicillin. The calibration curve regression equations were Y= 28129.7x + 2578.96 (r^2 =0.999) for Vonoprazan and Y=16858.91x + 29808.5 (r^2 = 0.999) for Amoxicillin (Table 3, Figures 6&7).

Table 3: Linearity data

Linearity level	Vonoprazan		Amoxicillin	
	Conc. (µg/ml)	Peak area	Conc. (µg/ml)	Peak area
Level-1	2.50	74638	62.50	1061110
Level-2	5.00	146882	125.00	2134159
Level-3	7.50	214383	187.50	3307769
Level-4	10.00	280360	250.00	4258351
Level-5	12.50	350920	312.50	5222646
Level-6	15.00	427679	375.00	6351942
Slope	28129.70		16858.91	
Intercept	2578.96		29808.50	
CC	0.9998		0.99966	

Eur. Chem. Bull. 2023, 12 (S3), 3571 – 3583

3577

A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

Section A-Research paper
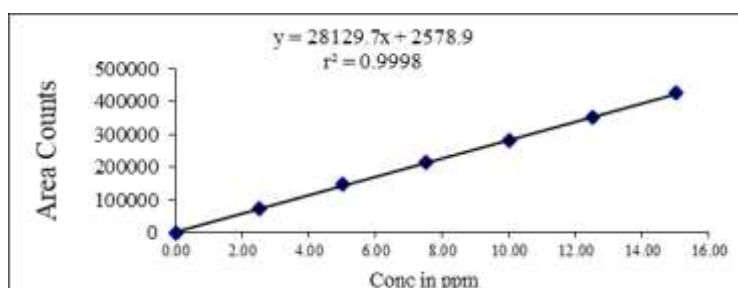
Figure6:
Linear graph of Vonoprazan

$$y = 16858.9x + 29808.5$$
$$r^2 = 0.9996$$

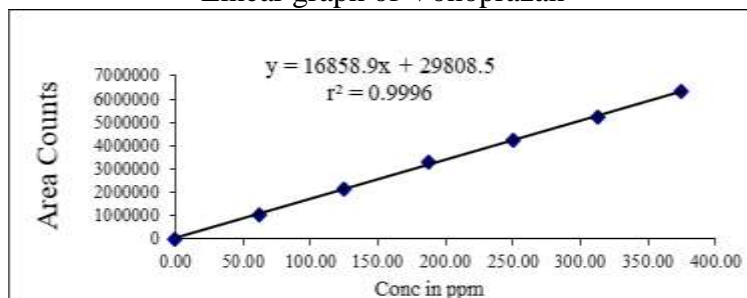**Figure7:**
Linear graph of Amoxicillin

Precision:

This method's precision was evaluated in terms of intraday and Inter-day precision. Six times the sample solutions of Vonoprazan and amoxicillin were tested under identical conditions on the same day to calculate the intraday studies. The intermediate precision of this method was tested in the same laboratory by studying the analysis using several analysts and various tools. The approach is quite precise because the % RSD values were found to be 2%. The drug recovered well with every added concentration, It was meant to indicate that the procedure succeeded. Table 4 displays the results of the precision study.

Table 4: Results of precision

Parameter	Vonoprazan				Amoxicillin			
	Mean % Recovery	Std. Dev.	% RSD	Conc. (µg/ml)	Mean % Recovery	Std. Dev.	% RSD	Conc. (µg/ml)
Method precision	100.5	0.629	0.96	10	99.7	0.97	0.97	250
Intermediate precision	101	0.724	0.72	10	100.1	1.063	1.06	250

Accuracy:

The precise method was carried out by monitoring the recovery tests at three points (50 percent, 100 percent, and 150 percent). 5µg/ml, 10µg/ml, 15 µg/ml of Vonoprazan and 125µg/ml, 250µg/ml, and 375µg/ml of amoxicillin were used to make APls. The test solution was administered three times for each spike level, the assay was carried out in accordance with the test procedure, and the RSD values were less than 2%. The mean, relative standard deviation, and recovery % have all been established. Recovery values demonstrated that the technique was specific within the targeted range (Table 5).

Table 5: Results of accuracy

Accuracy level	Vonoprazan			Amoxicillin		
	% Recovery	Std. Dev.	% RSD	% Recovery	Std. Dev.	% RSD
50%	100.1	0.61	0.61	100.7	1.25	1.24

Eur. Chem. Bull. 2023, 12 (S3), 3571 – 3583

3578

A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

Section A-Research paper

100%	100.3	0.31	0.31	100.5	0.1	0.1
150%	100.4	0.74	0.74	99.7	0.41	0.42

Robustness:
Studies were made to assess the robustness of the chromatographic process by adjusting the flow rate and mobile phase's makeup. The method used was determined to be robust as the % RSD was found to be within the acceptable range (Table 6).

Table 6: Results of robustness

Change in parameter	Vonoprazan	Amoxicillin
	% RSD	
Flow plus (0.55ml/min.)	1.58	0.64
Flow minus (0.45ml/min.)	0.42	1.21
Organic plus (55:45)	0.42	1.58
Organic minus (45:55)	0.44	0.43

LOD and LOQ:
Limit of detection (LOD) and limit of quantification (LOQ):
To examine the sensitivity of the process, the limits of detection (LOD) and limit of quantification (LOQ) were evaluated. Due to the test method for the LOD and LOQ studies, three duplicates of each analyte at the lowest concentration have been generated and injected into the UPLC machine. LOD was found by identifying the concentration, which produced a signal-to-noise (S/N) ratio of 3, as opposed to LOQ, which was obtained by recognising the concentration, which produced a S/N ratio of 10. Table 7's display of the LOD and LOQ results indicates that the suggested approach was quite sensitive.

Table 7: LOD and LOQ observed for Amoxicillin and Vonoprazan

Standard drug solution	#LOD (µg/ml)	#LOQ (µg/ml)
Amoxicillin	0.75	2.5
Vonoprazan	0.03	0.10

Forced degradation:
The acid, base, peroxide, reduction, heat, light, and hydrolysis degradation processes were all included in the forced degradation study, which was conducted in accordance with ICH rules. Although degradation peaks were found, it is clear from the data that selected drugs were stable under the stress conditions used. Table 8 provides a summary of the results obtained.

Acid degradation:
The acid degradation of both Amoxicillin and Vonoprazan was studied in 1N HCl- 13.5% of Vonoprazan and 14.3% of Amoxicillin degradation were observed in UPLC.

Alkali degradation:
In 1N NaOH, it was investigated how Vonoprazan and Amoxicillin degraded in the presence of alkalis. In the UPLC, degradation of Vonoprazan (14.9%), and Amoxicillin (13.5%), were observed.

Peroxide degradation:
Amoxicillin and Vonoprazan's peroxide degradation was examined in 30% hydrogen peroxide. Degradation of Vonoprazan (15.3%) and Amoxicillin

Eur. Chem. Bull. 2023, 12 (S3), 3571 – 3583

3579

A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

Section A-Research paper

(15.8%) had been observed in UPLC.

Thermal degradation:
Degradation of Vonoprazan and Amoxicillin was seen after the sample was subjected to 105°C for 6 hours. As a result, 4.3% of Vonoprazan and 4.4% of Amoxicillin degradation were observed.

Photo degradation:
When being exposed to the sun for 24 hours, the sample showed degradation of 3.3% of Vonoprazan and 3.7% of Amoxicillin.

Table 8: Results of Stress Study

Stress condition	Hours	Vonoprazan		Amoxicillin	
		% Degradation	% Assay	% Degradation	% Assay
Control degradation	-	0	100	0	100
Acid degradation	4	13.5	86.5	14.3	85.7
Alkali degradation	4	14.9	85.1	13.5	86.5
Peroxide degradation	24	15.3	84.7	15.8	84.7
Photo degradation	24	3.3	96.7	3.7	96.3
Thermal degradation	6	4.3	95.7	4.4	95.6

4. CONCLUSION

The acquired results led to the conclusion that the established assay method for Vonoprazan and Amoxicillin was validated with the following objectives in accordance with ICH recommendations:

a) An easy, accurate, precise and very effective analytical assay method was developed for the quantification of Vonoprazan and Amoxicillin by using RP-UPLC technique in VOQUEZNA DUAL PAK a fixed dosage form. (This method requires a shorter run time (6 minutes) and enables rapid determination of Vonoprazan and Amoxicillin having a symmetrical peak and complying with the system's suitable conditions).

b) The developed approach has been validated in accord with ICH recommendations and meets all of the established criteria stated in ICH guidelines. (From the experimental result the data: For the sensitivity study LOD for Vonoprazan and Amoxicillin as 2.5µg/ml and 0.75µg/ml and LOQ were estimated as 0.03µg/ml and 0.1µg/ml, in the precision % RSD was found to be < 2, for linearity study Correlation co-efficient was 0.999, for Robustness study, % of recovery were <2.0%.)

c) According to the results of forced degradation study it is proved that no degradation peak was merged with that of the drugs. (Stress testing results show that the procedure is stability-indicating. The suggested approach can separate Vonoprazan and Amoxicillin from the degradation products that are present in Fixed Dosage Forms.)

As a result, a stability-indicating analytical method was developed and validated with the help of the RP-UPLC technique. This method may now be easily implemented for routine quality control analysis of both Vonoprazan and Amoxicillin in VOQUEZNA DUAL PAK, bulk, and dosage forms.

5. REFERENCES

Eur. Chem. Bull. 2023, 12 (S3), 3571 – 3583

3580

A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

Section A-Research paper

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Eur. Chem. Bull. 2023, 12 (S3), 3571 – 3583

3581

A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

Section A-Research paper

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3582

A Novel Rp-Uplc Method Development and Validation for the Simultaneous Determination of Vonoprazan and Amoxicillin in Fixed Dosage Combination

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3583