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SIMULTANEOUS ESTIMATION OF VELPATASVIR AND SOFOSBUVIR IN BULK AND COMBINED TABLET DOSAGE FORM BY A SIMPLE VALIDATED STABILITY INDICATING RP-HPLC METHOD

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Keywords:

Velpatasvir, Sofosbuvir, Sensitive, Isocratic elution, Stability indicating method

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ABSTRACT: A Simple, sensitive, specific and stability indicating RP-HPLC method was developed for the simultaneous estimation of velpatasvir and sofosbuvir in bulk and tablet dosage form. Effective separation attained by injecting 10 µL of the standard solution containing velpatasvir and sofosbuvir into Xbrdige Phenyl (250 × 4.6 mm, 5 µ, 100 A^0) column, with a mobile phase containing methanol, buffer (0.1% formic acid in water) and acetonitrile in 40:30:30 v/v ratio, at a flow rate of 1ml/min. The eluted analytes were effectively responded qualitatively and quantitatively at 273 nm wavelength. The drugs were experienced in stress conditions such as oxidative, acid, base, photolytic, and thermal degradation. The retention times of sofosbuvir and velpatasvir were observed at 3.4 and 5.1 min, respectively. The method has a good linear response in the concentration range of 10-30 µg/ml and 40-120 µg/ml for velpatasvir and sofosbuvir respectively. LOD and LOQ were calculated as 1 µg/ml and 4 µg/ml for velpatasvir, 4 µg/ml, and 13 µg/ml for sofosbuvir. All the obtained validation parameters have been satisfied the acceptance limits of ICH guidelines. The degradants peaks were resolved significantly from sofosbuvir and velpatasvir peaks. The developed method was sensitive, specific, accurate, and stability-indicating. Thus, this method can be useful in the quality control department to estimate velpatasvir and sofosbuvir perfectly.

INTRODUCTION: Hepatitis C virus (HCV) infection is caused by a single standard RNA virus that can replicate in the liver causes cirrhosis and hepatocellular carcinoma [1]. The combination of velpatasvir and sofosbuvir termed as direct-acting antivirals (DAAs) can be used to treat HCV patients safely and successfully [1].

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Chemically, sofosbuvir is propan-2-yl (2S)-2-{[(S)-{[(2R,3R,4R,5R)- 5- (2,4-dioxo-1,2,3,4-tetrahydro pyrimidin-1-yl)- 4- fluoro-3-hydroxy-4-methyloxo-lan-2yl] methoxy} (phenoxy) phosphoryl] amino} propanoate with molecular formula $C_{22}H_{29}FN_3O_9P$ [2]. Sofosbuvir is a prodrug metabolized into its active form 2'- deoxy- 2'- α- fluoro- β- C-methyl-uridine-5'-triphosphate.

Sofosbuvir competitively blocks the nonstructural protein 5B (NS5B) polymerase, therefore, inhibiting the chain termination reaction in the HCV-RNA synthesis [3, 4]. Chemically, velpatasvir is Methyl {(2s)- 1- [(2s, 5s)- 2- 2- (9-{2[(2s,4s)-1-{(2R)-2-2 [methoxycarbonyl) amino]- 2- phenylacetyl}- 4-

(methoxymethyl)- 2- pyrrolidinyl]- 1H- imidazol-4-yl}-1,11-dihydroisochromeno[4,3:6,7]naptho[1,2d] imidazol-2-yl)- 5- mthyl-1-pyrrolydinyl]-3-methyl-1-oxo-2-butanyl}carbamate with molecular formula $C_{49}H_{54}N_8O_8$ [5]. It inhibits the Nonstructural protein 5A (NS5A), which involves in HCV-RNA replication. Chemical structures of velpatasvir and sofosbuvir were shown in **Fig. 1**.

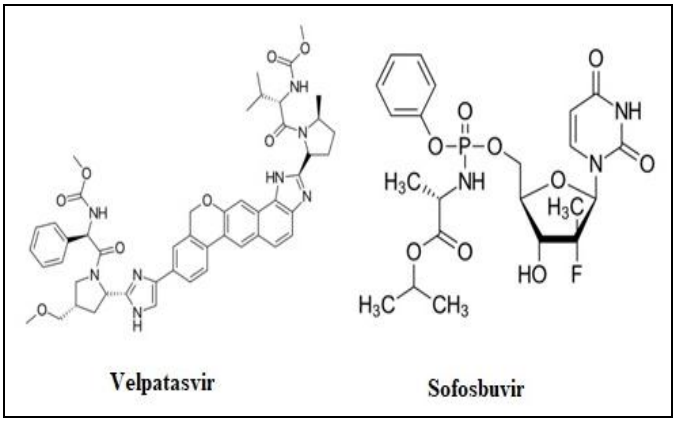


FIG. 1: CHEMICAL STRUCTURES OF VELPATASVIR AND SOFOSBUVIR

The requirement of an effective, simple, and economical analytical method in the pharmaceutical industry is essential to analyze the drugs individually or simultaneously in combination with other drugs. RP-HPLC method is one of the prominent analytical methods to determine the API in bulk and formulation qualitatively and quantitatively with accuracy and precision. Ample literature review of velpatasvir and sofosbuvir unveiled that different analytical methods such as UV and RP-HPLC methods were available for estimation of velpatasvir and sofosbuvir individually [6, 7, 8]. In addition to those there are few RP-HPLC methods were reported for measurement of velpatasvir, sofosbuvir and voxilaprevir simultaneously in bulk and combined dosage form [9]. Only few UV and RP-HPLC methods were reported for estimation of velpatasvir and sofosbuvir [10, 11, 12, 13]. Till date a single method was not reported with good sensitive, economical and stability indicating RP-HPLC method in literature for the estimation of velpatasvir and sofosbuvir simultaneously in bulk and tablet dosage form. Hence, we have undertaken current research work to develop an effective, sensitive, economical and stability indicating RP-HPLC method for analysis of velpatasvir and sofosbuvir in the drug substance and tablet dosage form. The developed method was validated as per the Q2 specification of ICH guidelines, and forced degradation conditions in stability studies were maintained as per Q1A specification of ICH recommendations.

MATERIALS AND METHODS: Active pharmaceutical ingredients of velpatasvir and sofosbuvir were provided by hetero drugs private limited, Hyderabad as gift sample. HPLC grade methanol, acetonitrile, and water were procured from Finar chemicals, Ahmedabad, India.

Chromatographic Conditions: RP-HPLC method was done on WATERS 2695 with PDA detector and auto sampling system; data-processing and data computation were assessed by Empower 2 software. Effective separation attained by injecting 10µL of the standard solution containing velpatasvir and sofosbuvir into Xbrdige Phenyl (250 × 4.6 mm, 5 µ, 100 A^0) column, with a mobile phase containing methanol, buffer (0.1% formic acid in water) and acetonitrile in 40:30:30 v/v ratio, at a flow rate of 1ml/min. The eluted analytes were effectively responded qualitatively and quantitatively at 273 nm wavelength. Ambient temperature was maintained in the injection port and in the analytical column. The 0.45 µm nylon filters were used to filter all the solutions before introducing them into HPLC system.

Preparation of Standard Solution: 20 mg of velpatasvir and 80 mg of sofosbuvir pure bulk powders were weighed and transferred into 100 ml volumetric flask, diluted to 100 ml with diluent (acetonitrile and water (50:50)). The resultant solution was further diluted with the same diluent to obtain a solution containing 20 µg/ml and 80 µg/ml concentration of velpatasvir and sofosbuvir, respectively, which is considered as 100% level concentration.

Preparation of Sample Solution: The tablet (VELASOF) powder equivalent to 20 mg velpatasvir of and 80 mg of sofosbuvir was transferred into 100 ml volumetric flask, diluted to 100ml with diluents. The resultant solution was further diluted with the same diluent to obtain a solution containing 20 µg/ml and 80 µg/ml concentration of velpatasvir and sofosbuvir, respectively. The sample solution was filtered through the 0.25 µm Nylon filter.

Method Validation: The developed method was validated as per Q2 specifications of ICH guidelines

System Suitability Test: System suitability test was accomplished by injecting a standard solution of velpatasvir and sofosbuvir in 5 replicates. System suitability parameters like theoretical plate count (N), tailing factor (T) and percentage relative standard deviation (%RSD) values were computed.

Linearity: The linearity of an analytical method represents that the obtained test outcomes are directly proportional to test concentrations. The linearity of the present method was done by injecting the concentrations ranges from 10 µg/ml to 30 µg/ml of velpatasvir and 40 µg/m to 120 µg/ml of sofosbuvir into HPLC system with optimized chromatographic conditions. The calibration curve was plotted for both drugs over concentration *vs*. peak area, and the regression coefficient (r^2) value was reckoned.

Precision: The closeness agreement among observed results of multiple sampling of homogenous analyte referred to as precision. Generally, it has to do on the same day (Intraday or repeatability) and in three different days (inter-day or reproducibility). The repeatability and reproducibility of the current method were performed by injecting standard solution for 5 times in a day and 3 times per day for three continuous days, % RSD was reckoned for peak areas thus obtained.

Accuracy: The accuracy of the method was accomplished by recovery studies in which the known amount of sample solution spiked at three different standard concentration levels about 50, 100, and 150%, each level of solution injected in triplicate. The mean percentage recovery at three different levels of the drug solution was calculated.

Specificity: The ability of the method to assess the intended analyte qualitatively and quantitatively in the presence of other substances like impurities and placebo without interferences said as the specificity of the method. It can be performed by sequence injecting a volume of 10 µL blank solution, standard solution, and standard solution with placebo in sequence manner. The retention time (RT) of analytes in the chromatogram of the standard solution alone and standard solution with placebo was observed and interference of any other peak with the peaks of velpatasvir and sofosbuvir in the obtained chromatograms.

Sensitivity: Standard deviation method used to calculate the LOD and LOQ by using the following formulae.

$$LOD = 3\sigma/S$$

$$LOQ = 10\ \sigma/S$$

Where σ is the standard deviation of the peak areas, *S* is the slope of the linearity curve

Robustness: The robustness of the method was checked by slight changes that have been made to the flow rate, and wavelength of maximum absorption. It was performed and confirmed by evaluating the system suitability parameters such as theoretical plates (N), tailing factor (T) after changing the flow rate of mobile phase (± 0.1 ml/min), and wavelength of maximum absorption (± 2nm).

Forced Degradation Studies: In the forced degradation studies, intentionally drug substance is exposed to stress conditions more intense than accelerated conditions. Forced degradation studies help to determine the chemical stability of the drug molecule. These studies were highly considered in the development of stable formulation. As per ICH Q1A, QIB, and Q2B guidelines, the forced degradation studies were performed [14].

Acid Hydrolysis: 10 ml of standard stock solution mixed with 2 ml of 0.1N HCl and reflux on the heating mantle at 70 °C for 2 h, kept the above solution in temperature controlling unit for 1 day at 70 °C temperature, cool and neutralize resultant solution with 0.1N NaOH and further diluted with diluent to obtain a solution containing 20 µg/ml and 80 µg/ml concentration of velpatasvir and sofosbuvir respectively.

Base Hydrolysis: 10 ml of standard stock solution mixed with 2 ml of 0.1N NaOH and reflux on the heating mantle at 70 °C for 2 h, kept the above solution in temperature controlling unit for 1 day at 70 °C temperature, cool and neutralize resultant solution with 0.1N HCl and further diluted with diluent to obtain a solution containing 20 µg/ml and 80 µg/ml concentration of velpatasvir and sofosbuvir respectively.

Oxidative Degradation: 10 ml of standard stock solution mixed with 2 ml of 3% hydrogen peroxide and reflux on the heating mantle at 70 °C for 2 h, kept the above solution in temperature controlling unit for 1 day at 70 °C temperature, the resultant solution further diluted with diluent to obtain a solution containing 20 µg/ml and 80 µg/ml concentration of velpatasvir and sofosbuvir respectively.

Thermal Degradation: 10 ml of standard stock solution was placed in the heating chamber at 80 °C / 75% RH for 1 day. The resultant solution further diluted with diluent to obtain a solution containing 20 µg/ml and 80 µg/ml concentration of velpatasvir and sofosbuvir, respectively.

Photodegradation: 10 ml of standard stock solution was exposed to UV light in the UV chamber for a 1-day resultant solution further diluted with diluent to obtain a solution containing 20 µg/ml and 80 µg/ml concentration of velpatasvir and sofosbuvir respectively.

Assay: The assay was done by injecting standard solution and sample solution having a concentration of about 20 µg/ml and 80 µg/ml of velpatasvir and sofosbuvir, respectively. The percentage of purity was estimated by using a method described elsewhere [15].

RESULTS AND DISCUSSION: The first step in the analytical method is the selection of mobile phase and diluents, which depend upon the solubility of the drug in different solvents. Hence, the solubility of both drugs was checked in different solvents and came to a conclusion that sofosbuvir was slightly soluble in acetonitrile (ACN) and methanol, freely soluble in water and velpatasvir was freely soluble in water and methanol. Based on the solubility studies, ACN and water in (50:50) ratio selected as diluents to make the standard and sample solutions.

Method Optimization: The optimized method was selected by performing trial and error method, in which different mobile phase compositions with different ratios, different types of columns and variation in the flow rate were used to get chromatogram with acceptable system suitability parameter values. Finally, the method using Xbrdige Phenyl (250 × 4.6 mm, 5 µ, 100 A^0) column, with a mobile phase containing methanol, buffer (0.1% formic acid in water) and acetonitrile in 40:30:30 v/v ratio, at a flow rate of 1ml/min was confirmed as the optimized method. The trial and error method results were stated in **Table 1**, trial 4 chosen as optimized chromatographic conditions elutes the sofosbuvir and velpatasvir at 3.4 min and 5.1 min, respectively, and the obtained chromatogram of the optimized method shown in **Fig. 2**.

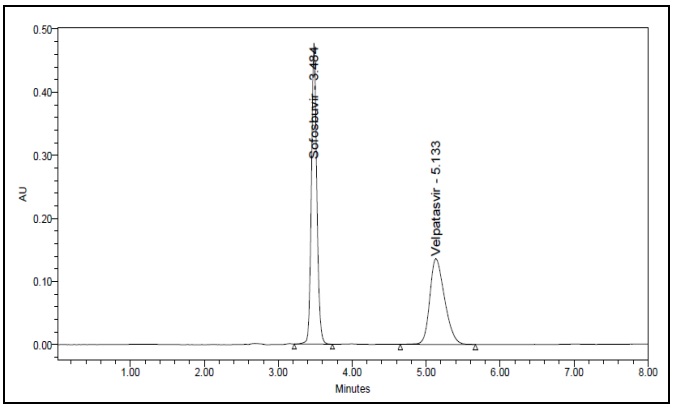


FIG. 2: OPTIMIZED CHROMATOGRAM OF THE METHOD

Method Validation:

System Suitability: The parameters such as % RSD, USP tailing factor, and USP plate count values showed in **Table 2** have not deviated from the acceptance limits **Table 3** of ICH Q2 specifications.

TABLE 1: DIFFERENT TRIALS

Trail	Column	Buffer	Mobile Phase	Flow rate ml/min	Observation
1	Intersil ODS (150 × 4.6mm, 5µm)	0.1% Formic acid in Water	Buffer: ACN : Methanol (40:60)	1	Only sofosbuvir peak eluted
2	Intersil ODS (150 × 4.6mm, 5µm)	0.1% Formic acid in Water	Buffer: ACN : Methanol (35:15:50)	1	Broad velpatasvir peak was very Broad
3	Intersil ODS (150 × 4.6mm, 5µm)	0.1% Formic acid in Water	Buffer: ACN : Methanol (40:25:35)	1	Very low resolution between peaks seems as one peak
4	Phenyl XDB (250 × 4.6mm, 5µm)	0.1% Formic acid in Water	Buffer: ACN : Methanol (30:30:40)	1	The resolution between peaks and the efficiency of the peaks was good

TABLE 2: RESULTS OF SYSTEM SUITABILITY TEST FOR SOFOSBUVIR AND VELPATASVIR

	Sofosbuvir				Velpatasvir			
Injection	**RT**	**Peak area**	**USP Plate count**	**USP tailing**	**RT**	**Peak area**	**USP plate count**	**USP tailing**
1	3.484	2404024	10672	1.12	5.133	1889947	3095	1.28
2	3.49	2452816	11266	1.14	5.232	1900427	3264	1.3
3	3.415	2429435	10733	1.12	5.111	1893444	3088	1.29
4	3.484	2328815	12791	1.12	5.245	1819389	3216	1.3
5	3.483	2383147	11245	1.15	5.254	1825555	3251	1.29
6	3.484	2404024	10672	1.12	5.133	1889947	3095	1.28
MEAN		2400377				1869785		
SD		42517.78				36899.17		
%RSD		1.78				1.98		

Linearity: The regression coefficient (r^2) values for the concentration range from 40 to 120 µg/ml of sofosbuvir and 10 to 30 µg/ml of velpatasvir were 0.998 and 0.998 for sofosbuvir, and velpatasvir respectively states that the method has good linearity for the given concentration ranges. The results of the linearity mentioned in **Table 4** and **Fig. 3**.

TABLE 3: ACCEPTANCE LIMITS OF SYSTEM SUITABILITY PARAMETERS

Parameter	Acceptance limit
USP Plate count	>2000
USP tailing	≤2
%RSD	≤2
Resolution	>2

TABLE 4: LINEARITY CURVE OF SOFOSBUVIR AND VELPATASVIR

S. no.	% level	Velpatasvir		Sofosbuvir	
		Concentration (µg/ml)	**Peak area**	**Concentration (µg/ml)**	**Peak area**
1	50	10.0	952220	40	1135443
2	75	15.0	1457282	60	1817470
3	100	20.0	1889947	80	2404024
4	125	25.0	2344309	100	2957034
5	150	30.0	2888340	120	3575122
Correlation coefficient (r^2)			0.998		0.998

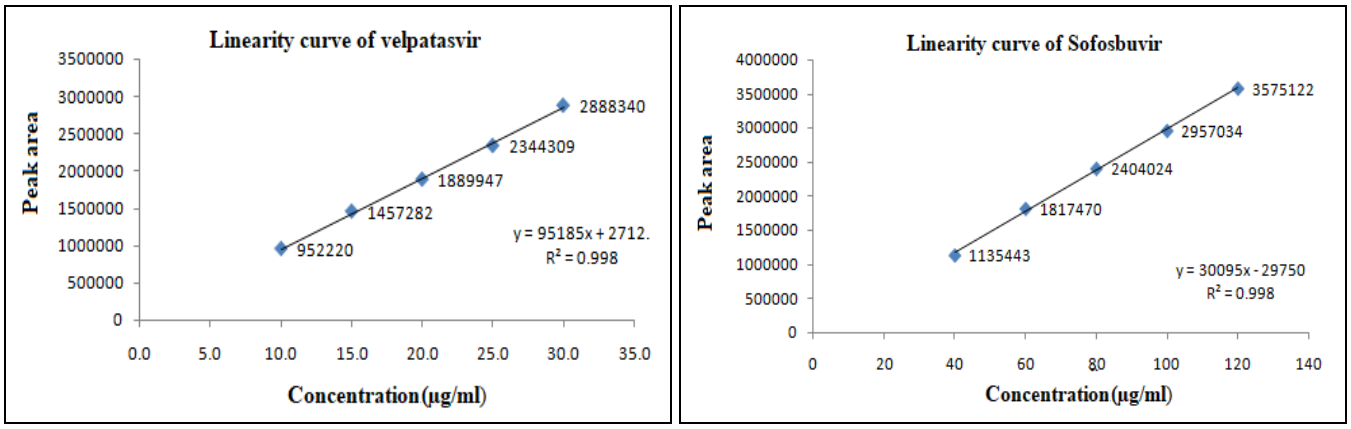


FIG. 3: CALIBRATION CURVE OF VELPATASVIR AND SOFOSBUVIR

Accuracy: The Percentage mean recovery at three different levels of concentration for sofosbuvir and velpatasvir with in the ICH acceptance limits (100% ± 2) were shown in **Table 5**.

TABLE 5: RESULTS OF PERCENTAGE RECOVERY

Drug name	% Level	Amount added (µg/ml)	Amount recovered (µg/ml)	% recovery
Velpatasvir	50	10	9.89	98.9
		10	9.84	98.4
		10	9.93	99.3
	100	20	19.78	98.9
		20	19.68	98.4

		20	19.86	99.3
	150	30	30	100
		30	29.46	98.2
		30	30.09	100.3
Sofosbuvir	50	40	40	100
		40	39.92	99.8
		40	40	100
	100	80	79.04	98.8
		80	79.92	99.9
		80	78.64	98.3
	150	120	118.56	98.8
		120	118.08	98.4
		120	121.08	100.9

Precision: The % RSD of the injected standard solution of velpatasvir and sofosbuvir was ≤ 2, and results were mentioned in **Table 6** depicts the method with good precision.

Sensitivity: The LOD and LOQ of the velpetasvir were 1 µg/ml and 4 µg/ml, and sofosbuvir was 4 µg/ml, and 13 µg/ml represents good sensitivity of the method.

TABLE 6: RESULTS OF INTRADAY AND INTER-DAY PRECISION OF 100% LEVEL SOLUTION

Precision		**Velpatasvir (20 µg/ml)**		**Sofosbuvir (80 µg/ml)**	
Intra day	**Sample name**	**RT**	**Peak area**	**RT**	**Peak area**
	Injection 1	5.264	1994422	3.5	2434193
	injection 2	5.106	1997574	3.403	2429614
	injection 3	5.106	1999319	3.403	2429614
	injection 4	5.232	2020427	3.49	2452816
	injection 5	5.111	2003444	3.415	2429435
	MEAN	5.164	10015186	3.442	2435134.4
	SD	0.07772	10252.608	0.04858	10086.6
	%RSD	1.50507	0.1023706	1.41121	0.4142112
Inter Day	**Sample name**	**RT**	**Peak area**	**RT**	**Peak area**
day-1	Injection 1	5.257	1808711	3.49	2290604
	Injection 2	5.254	1841158	3.487	2293687
	Injection 3	5.26	1819389	3.486	2265940
day-2	Injection 1	5.312	1828679	3.506	2307972
	Injection 2	5.245	1819389	3.484	2328815
	Injection 3	5.254	1825555	3.483	2283147
day-2	Injection 1	5.264	1904422	3.5	2434193
	injection 2	5.106	1817574	3.403	2429614
	injection 3	5.106	1899319	3.403	2429614
	MEAN	5.22	1840466.2	3.471	2340398.44
	SD	0.072	35945.61	0.04	70165.1
	%RSD	1.37	1.95	1.14	1.134

Robustness: Deliberately small variations in flow rate and detection wavelength or absorption maximum of the method consistently produced values of system suitability parameter in the acceptable range **Table 7** was the strong evidence for the robustness of the method.

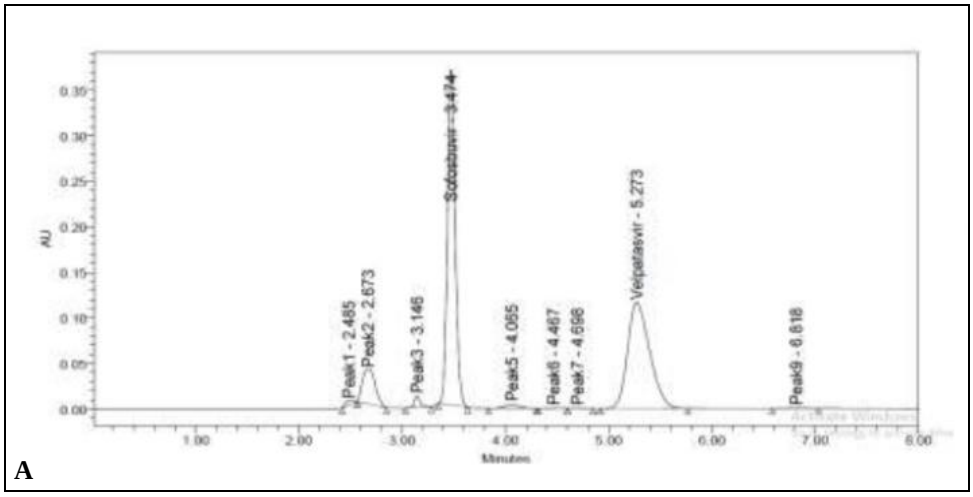
TABLE 7: RESULTS OF THE ROBUSTNESS OF 100% LEVEL SOLUTION

Variation in parameter		**Velpetasvir**				**Sofosbuvir**			
		RT	**Peak area**	**Plate count**	**Tailing factor**	**RT**	**Peak area**	**Plate count**	**Tailing factor**
Flow rate	0.9	5.106	1836541	3162	1.29	3.403	2406489	13618	1.13
(±0.1ml)	1	5.254	1845944	3251	1.31	3.487	2393897	13970	1.16
	1.1	5.245	1861132	3210	1.3	3.484	2328815	12861	1.1
Maximum	271	5.254	1836912	3301	1.29	3.483	2365613	11235	1.15
wavelength	273	5.254	1849478	3218	1.31	3.487	2395123	12928	1.14
(±2nm)	275	5.106	1835643	3093	1.28	3.403	2403291	13416	1.19

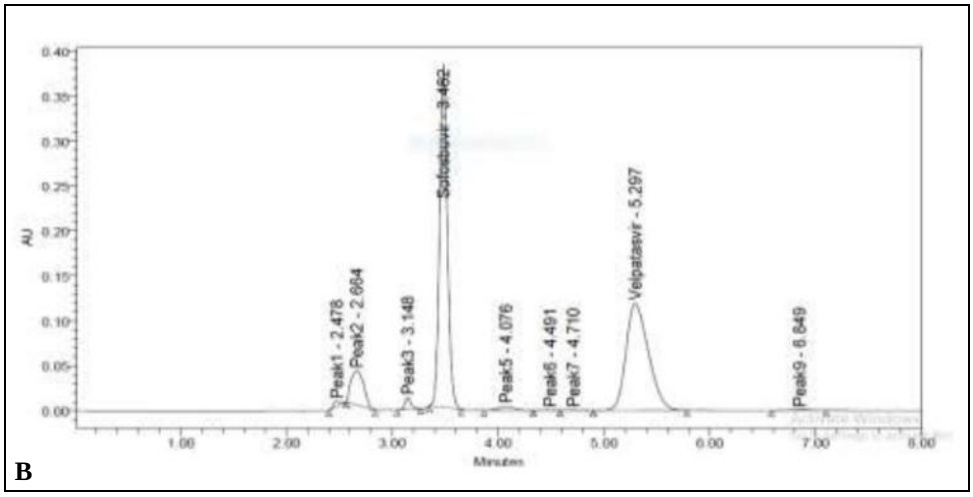
Forced Degradation: The forced degradation conditions mentioned in the method was appropriate to cause the degradation of the sofosbuvir and velpatasvir. At mentioned thermal photolytic stress condition, percentage degradation was very negligible, consider as drug substance was stable at these conditions. The results were shown in **Table 8** and **Fig. 4**.

TABLE 8: RESULTS OF FORCED DEGRADATION STUDIES

Stress conditions	% Degradation	
	Vepatasvir	Sofosbuvir
Acidic/0.1N HCl/reflux at 70 °C/24 h	13.6	22.0
Basic/0.1N NaOH/ reflux at 70°C /24 h	12.7	18.4
Oxidation/3%H_2O_2/70°C /24 h	12.7	19.5
Thermal/80°C/75% RH for 24h	4.2	0.85
Photolytic/UV light/24h	0.21	0.45



A



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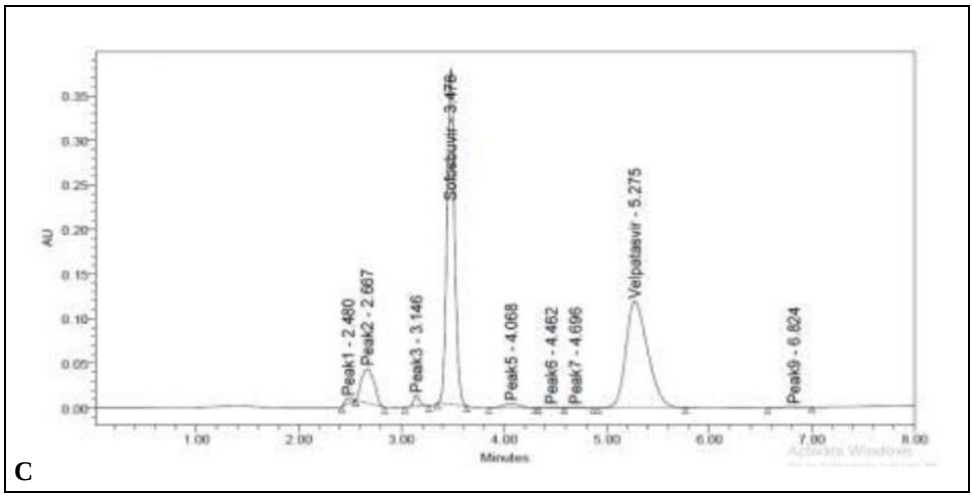


C

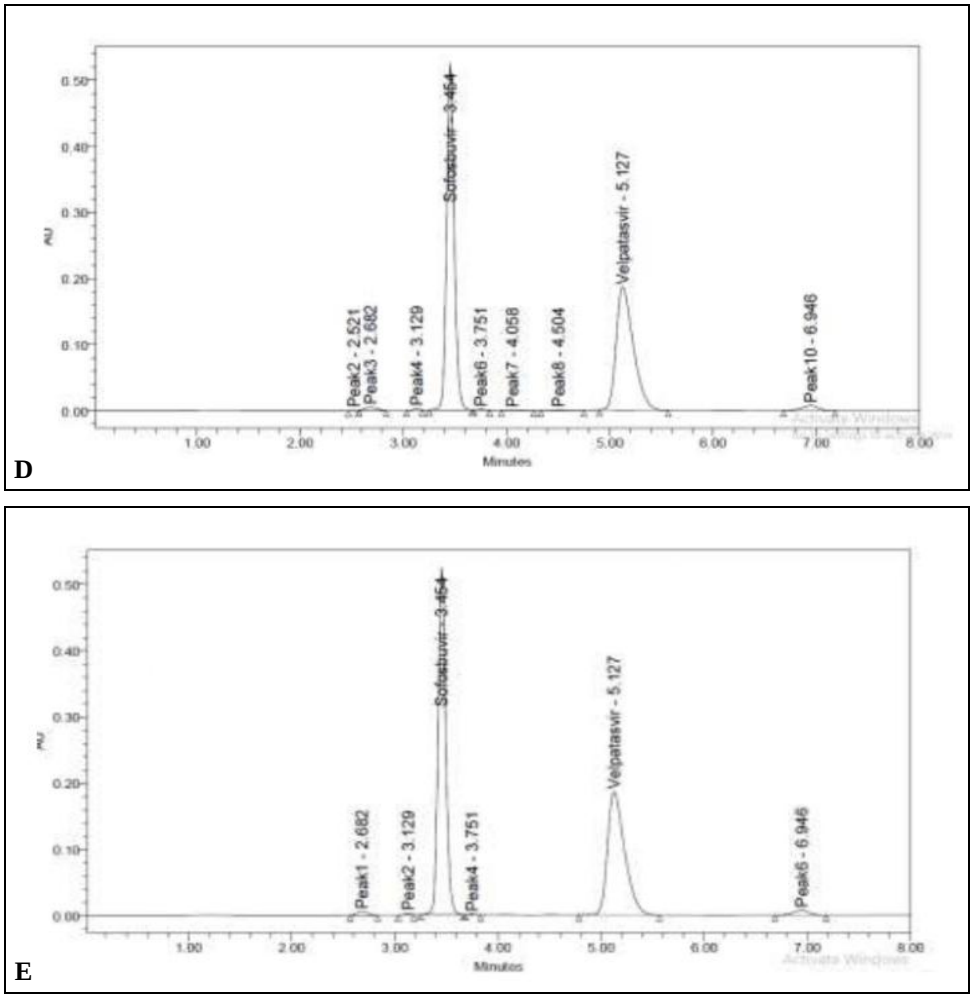
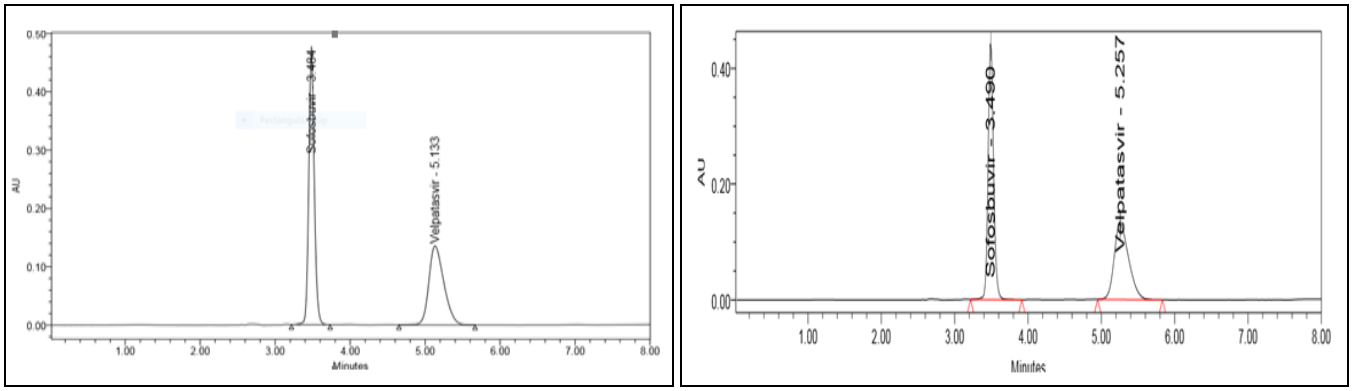


FIG. 4: CHROMATOGRAM OF BASE DEGRADATION. CHROMATOGRAMS A TO E- A. ACID HYDROLYSIS, B. BASIC HYDROLYSIS, C. PEROXIDE OXIDATION, D. THERMAL DEGRADATION, E. PHOTOLYTIC DEGRADATION

Assay: Percentage purity of the sofosbuvir and velpatasvir in commercially available tablets were in the range of 98% to 102%. The results were shown in **Table 9** and **Fig. 5**.

TABLE 9: RESULTS OF % ASSAY OF THE TABLET DOSAGE FORM

Drug	Peak name	Retention time	Peak Area	USP Tailing	USP Plate count	%Assay
Velpatasvir	Standard	3.48	1885479	1.29	3058	98.2%
	Test	3.49	1852184	1.31	3201	
Sofosbuvir	Standard	5.13	2415221	1.12	14201	98.8%
	Test	5.25	2386340	1.15	13961	
Acceptance limit				≤2	>2000	100±2



STANDARD SOLUTION CHROMATOGRAM **SAMPLE SOLUTION CHROMATOGRAM**

FIG. 5: CHROMATOGRAMS OF STANDARD AND SAMPLE SOLUTION

In general, stability indicating RP-HPLC method has a significant role in both qualitative and quantitative determination of the drugs. As of now, no single stability-indicating RP-HPLC method with good sensitivity and retention time was not developed. In reported methods, sensitivity and linear concentration range were too high. And also, the resolution between drug peak and degradants was very low. Hence attempts were done to develop an effective, sensitive stability-indicating RP-HPLC method. The retention time in the currently developed method was 5.1 min for velpatasvir, and 3.4 min for sofosbuvir depicts the method with good retention time, which can be said as an economical method. The computed and statistical results of the validation parameters of the analytical method were within the acceptance limits ICH guidelines.

CONCLUSION: An effective, sensitive, simple and specific RP-HPLC method with isocratic elution was developed to estimate velpatasvir and sofosbuvir simultaneously in bulk and its tablet dosage form. Different stress conditions have been applied to the drug solution to assess the stability-indicating property of the method. The proposed method was successfully separate velpatasvir, sofosbuvir, and degradants with good resolution and quantified the active contents at minute concentration levels. Hence, the proposed method is expected as a revival to regular analysis of combined dosage in the pharmaceutical industry.

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