

Stability Indicating HPLC and HPTLC Method for Estimation of Letemovir

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ABSTRACT

Aim: The aim of this study is to develop and validate High-Performance Thin-Layer Chromatography (HPTLC) and High-Performance Liquid Chromatography (HPLC) techniques for the quantification of Letemovir and its degradation products under various stress conditions. **Materials and Methods:** A CAMAG system was employed using silica gel 60 F₂₅₄ plates for HPTLC. The mobile phase consisted of chloroform and methanol in a 9:1 (v/v) ratio, with detection performed at 257 nm. A Jasco Liquid Chromatographic System featuring a PU 2080 Plus pump and an MD 2010 Plus PDA detector was utilized in HPLC. The mobile phase was a mixture of methanol and water in a 90:10 (v/v) ratio, with a flow rate set at 1 mL/min. Both methodologies underwent validation for parameters including linearity, accuracy, precision, robustness, and detection/quantification limits. Forced degradation studies were carried out under acidic, alkaline, oxidative, neutral, photolytic, and thermal conditions. **Results:** The results demonstrated good linearity, with correlation coefficients of 0.9934 for HPTLC and 0.997 for HPLC. Forced degradation studies revealed that Letemovir is vulnerable to hydrolysis under acidic and basic conditions and oxidative environments. The methods proved to be sensitive, selective, accurate, and reproducible for the analysis of Letemovir and its degradation products. **Conclusion:** The HPTLC and HPLC methods developed in this study represent a significant advancement over previously established techniques for evaluating the stability and purity of Letemovir. They are dependable, sensitive, and appropriate for routine analysis in stability assessments of Letemovir within pharmaceutical formulations.

Keywords: HPLC, HPTLC, Letemovir, Stability indicating method, Validation.

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INTRODUCTION

Letemovir, a novel antiviral drug, is utilized in adult transplant recipients susceptible to Cytomegalovirus (CMV) infection and its associated ailments for preventive purposes. Chemically Letemovir is 2-[(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4H-quinazolin-4-yl] acetic acid with molecular formula C₂₉H₂₈F₄N₄O₄ and Molecular Weight 572.5 g/mol (Figure 1). Letemovir was approved by the FDA on November 8th, 2017, for the prevention of Cytomegalovirus (CMV) infection in patients undergoing allogeneic hematopoietic stem cell transplants. It is the first drug in a new class of CMV anti-infectives known as DNA terminase complex inhibitors. Letemovir functions by inhibiting CMV replication, which lowers the risk of infection in vulnerable individuals. It is generally given as a once-daily oral

tablet or an Intravenous (IV) infusion, depending on the patient's condition and particular needs.¹⁻⁵ The International Conference on Harmonization (ICH) guideline titled 'Stability Testing of New Drug Substances and Products' mandates that stress testing be conducted to determine the stability characteristics of the active substance and identify possible degradation pathways. A selective stability-indicating method can help in identifying the likely degradation products thereby helping to establish degradation pathways and stability of molecule. This process also validates the stability indicating the capability of analytical procedures employed.⁶⁻⁸

A literature review was conducted to evaluate the various analytical methods reported for quantifying Letemovir. Among reported chromatographic methods, an analytical HPLC method was published for estimation of Letemovir in bulk and its degradation studies^{9,10} and its enantiomeric purity,¹¹ Bio-analytical methods for quantifying letemovir in biological samples have utilized HPLC,¹² UPLC¹³ and LC-MS/MS.¹⁴ One HPLC method is reported for evaluating process-related impurities of letemovir, and LC-MS/MS technique was used for characterizing degradation products.¹⁵ The literature review suggests the absence of stability indicating HPTLC method for estimation of Letemovir. The percent degradation reported in



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literature is less than 10%, thus indicating the need to optimize the stress conditions to obtain % degradation in the range 5-20% as per ICH guideline. So, the present study was aimed at development and validation of stability indicating HPTLC and HPLC methods for estimation of Letermovir and comparative evaluation.

MATERIALS AND METHODS

Instrumentation and chromatographic conditions

HPTLC system included following

The CAMAG HPTLC system, featuring the Linomat 5 sample applicator from Muttenz, Switzerland, was operated with a gentle stream of nitrogen and paired with a Hamilton microliter syringe (100 μ L) from Hamilton, Switzerland. utilizing the CAMAG TLC SCANNER 3 controlled by Win CATS software version 1.4.3, spots were applied and detected. Chromatographic separation occurred on TLC aluminum plates pre-coated with silica gel 60 F₂₅₄ (10 $\times$ 10 cm), and development took place in a twin trough glass chamber using Chloroform: Methanol (9:1 v/v). Chamber saturation lasted for 20 min at room temperature. The plates were then developed and air-dried at room temperature before densitometric scanning was conducted at a wavelength of 257 nm.

HPLC system

The HPLC method was conducted on a Jasco Liquid Chromatographic System equipped with a PU 2080 Plus pump and an MD 2010 Plus Photo Diode Array (PDA) detector. The analysis used Rubitas C18 (250 $\times$ 4.6mm) 0052 Column, and detection was performed using Borwin Chromatographic Software (version 1.5). The optimized mobile phase used was Methanol: Water (90:10v/v) with flow rate of 1 mL/min and run time of 10 min.

Several instruments were utilized for the research, including a UV-visible spectrophotometer (JASCO, Model V730), Electronic balance (Shimadzu, Model ATX224R), Sonicator (PRAMA, Model SM15 US), and a Hot air oven (BIOMEDICA). The Photostability study was carried out in a photostability chamber (Make NEWTRONIC, Model NEC103RSPI).

Chemicals and reagents

Analytically pure Letermovir was obtained as a gift sample. Methanol, Chloroform, Sodium hydroxide, Hydrochloric acid, and 30% Hydrogen Peroxide of analytical reagent grade were purchased from Loba Chemie Pvt. Ltd., Mumbai India. Methanol (HPLC grade) was used for HPLC and purchased from Loba Chemie Pvt. Ltd., HPLC-grade water with a conductivity below 0.05 μ S/cm was obtained using the Extrapure Lab. Link Water Purifier System.

Preparation of standard stock solution (1000 μ g/mL)

Accurately weighed 10 mg of Letermovir was transferred in a 10 mL volumetric flask and was then dissolved in methanol and the volume was made up to mark to get a standard stock solution of 1000 μ g/mL.

Preparation of working standard solution

Standard stock solution (1000 μ g/mL) was suitably diluted to get a working solution of 50 μ g/mL for HPTLC and 10 μ g/mL for HPLC respectively.

Selection of detection wavelength

The solution of Letermovir (20 μ g/mL) was prepared using methanol and UV spectrum was recorded. It showed maximum absorbance at 257 nm. The UV spectrum of letermovir is shown in Figure 2.

Forced degradation study

The stress testing, conducted following ICH Q1A (R2) guidelines, involved subjecting the drug to various stress conditions for varying time intervals. Adjustments were made to the reagent strength and exposure time to achieve a degradation level ranging from 10% to 30%. The optimized stress conditions were applied for HPTLC and HPLC methods. The following are the optimized stress conditions:

Alkali hydrolysis

To perform alkali degradation study, 1 mL of stock solution (500 μ g/mL) was mixed with 1 mL of 1 N NaOH and diluted up to the mark with methanol to obtain a final concentration of 50 μ g/mL of Letermovir. The resultant solution was kept aside in the dark for 48 hr of reaction time. In case of HPLC, 1 mL of 100 μ g/mL was mixed 1N NaOH was added. This solution after 48 hr it was neutralized with 1N HCl and then the volume was made up to 10 mL with mobile phase to get a solution of 10 μ g/mL.

Acid hydrolysis

To check hydrolytic degradation under acidic pH, 1 mL of the working stock solution (500 μ g/mL) was treated with 1 mL of 1 N HCl and the solution was diluted to the mark with methanol to achieve a final concentration of 50 μ g/mL of Letermovir and kept for 4 hr of reaction time. For HPLC, 1 mL of 100 μ g/mL was combined with 1 mL of 1 N HCl in a 10 mL volumetric flask. The solution was placed at room temperature for about 4 hr. After 4 hr of reaction time the solution was neutralized using 1 mL of 1N NaOH and the volume was made up to 10 mL with mobile phase to obtain 10 μ g/mL.

Neutral degradation

1 mL solution of Letermovir (500 μ g/mL) was mixed with 1 mL of distilled water, and methanol was added to achieve a final volume

of 10 mL. For HPLC, Letermovir working solution (100 µg/mL), 1 mL was combined with 1 mL water and then the volume was made up with mobile phase to obtain 10 µg/mL. The resulting solution was kept for 5hr of reaction time.

Oxidative degradation

1 mL of 30% H₂O₂ was added to 1 mL of stock solution (500 µg/mL) of Letermovir and volume was made up to 10 mL with methanol to get a final concentration of 50 µg/mL and kept for 30 min reaction time. For HPLC, for sample preparation 1 mL of Letermovir working solution (100 µg/mL), was combined with 1 mL of 30% H₂O₂ v/v and then the volume was made up to 10 mL with mobile phase to obtain 10 µg/mL. The solution is kept for 30 min of reaction time.

Photolytic Degradation

Following the ICH Q1B Guidelines, a solid-state sample of Letermovir was subjected to UV light exposure until reaching 200-watt hr/square meter and to cool white fluorescent light for up to 1.2 million lux hours in a photostability chamber. Letermovir solutions of 50 µg/mL and 10 µg/mL for HPTLC and HPLC were prepared in methanol after the exposure.

Thermal Degradation

The solid-state bulk drug underwent thermal degradation by heating it in an oven at 60° for 4 hr. Following removal from the oven, the sample was cooled to room temperature, weighed, and diluted with methanol to achieve a final concentration of 50 µg/mL for HPTLC and 10 µg/mL for HPLC.

Method Validation

The developed HPTLC and HPLC method was validated in accordance with the International Conference on Harmonization (ICH) guidelines Q2 (R1).

Specificity

The specificity or selectivity of an analytical procedure can be demonstrated through absence of interference. The specificity of the method was evaluated using peak purity profile studies. This involved monitoring the correlation coefficients between the spectra extracted at the start slope and peak maximum (r_{sm}), as well as the correlation coefficient between the spectra extracted at the peak maximum and the end slope (r_{me}). The peak purity for HPTLC was established to be 0.9998 and 998 for HPLC demonstrating the absence of interference from any other degradation product, impurity, or matrix peak. The method was deemed specific.

Linearity

It is essential to assess the linear relationship between analyte concentration and response throughout the working range of the analytical method to ensure the procedure's appropriateness for its intended application. For HPTLC, standard solution of Letermovir (50 µg/mL) was utilized to spot volumes of 5, 8, 10, 12 and 15 µL onto the TLC plate, resulting in spotted quantities ranging from 250 to 750 ng/band. The calibration curve was plotted using the peak area against amount spotted. The regression equation was calculated, and the correlation coefficient was determined. For HPLC, the standard stock solution was diluted to achieve final concentrations ranging from 5 to 25 µg/mL. The calibration curve was checked by plotting peak area against concentration.

Accuracy

It was illustrated by comparing the obtained results with the anticipated value. The accuracy of the developed method was accessed by the standard addition method. The addition was done at three levels i.e. 80, 100, 120%. The percent recovery was calculated from peak areas for both HPTLC and HPLC.

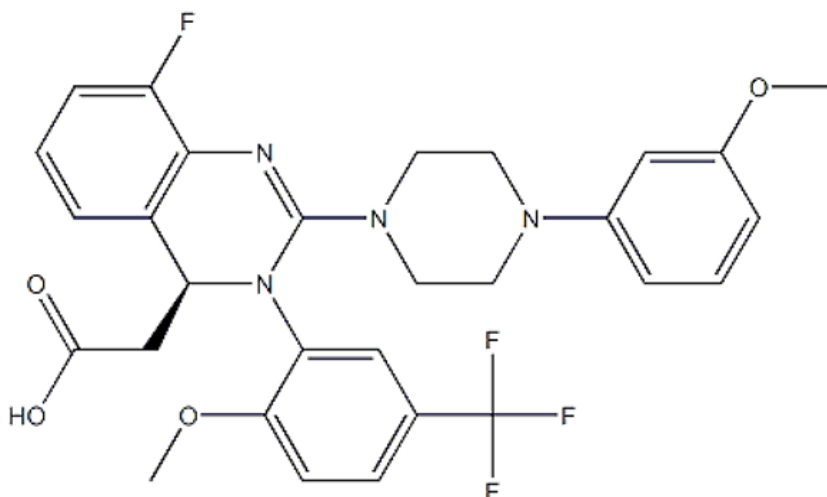


Figure 1: Chemical structure of Letermovir.

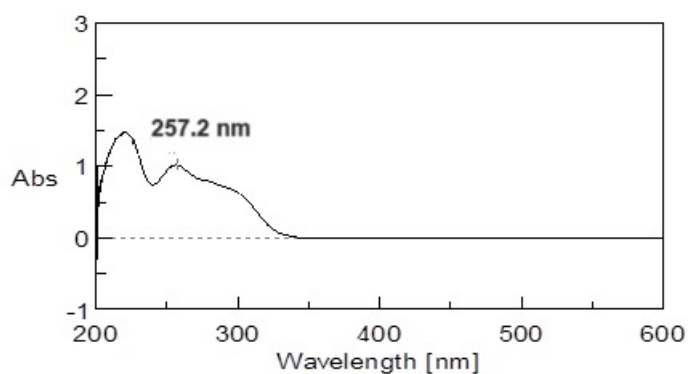


Figure 2: UV Spectrum of Letermovir (20 µg/mL).

Table 1: Summary of Stress degradation for HPTLC.

Sl. No.	Stress condition	Concentration and time	% Recovery	Peak Purity		R _f of degradation product
				Purity front	Purity tail	
1.	Acid hydrolysis	1 N HCl for 4 hr.	-	0.999	0.997	0.24
2.	Alkaline hydrolysis	1 N NaOH for 48 hr.	-	0.997	0.992	0.23
3.	Oxidative degradation	30% H ₂ O ₂ for 30 min.	-	0.998	0.999	0.20
4.	Neutral degradation	Water for 5 hr.	88.60	0.997	0.998	-
5.	Thermal Degradation	60°C for 4 hr.	86.31	0.999	0.996	-
6.	UV degradation	200Watt hr/m ² .	82.51	0.996	0.998	-
7.	Fluorescence degradation	1.2 million lux hr.	86.29	0.991	0.997	-

Precision

An examination of precision was carried out with the use of homogeneous and genuine samples, and the evaluation of repeatability was also undertaken. Precision was assessed by evaluating intermediate precision studies. For HPTLC, in repeatability precision, six replicates of a standard (250 ng/band) were spotted on a TLC plate on the same day at different time intervals. For intermediate precision, six replicates of the standard (250 ng/band) were spotted to a TLC plate over three consecutive days. In the case of HPLC method, for repeatability precision, six replicates of the standard solution of 5 µg/mL were injected six times on the same day at different time intervals. Intermediate precision was determined by injecting six replicates of a solution (5 µg/mL) on three consecutive days and then % RSD was calculated.

Assay

The examination was based on if the confidence intervals were in agreement with the corresponding assay specifications. An assay of Letermovir was done on a spiked blend due to the unavailability of its marketed preparation in the local market. For preparation of the spiked blend 5 g starch and 5 g lactose was mixed to prepare blank blend. To the 260 mg of blank blend 240 mg of standard Letermovir drug was added and then 500 mg of blend equivalent to 10 mg of drug was accurately weighed and diluted to 10 mL

with methanol to obtain a solution (1000 µg/mL). The solution was sonicated and then filtered using Whatman filter paper. Appropriate dilutions were prepared for both HPTLC and HPLC and then the peak area was recorded followed by calculating the percent recovery.

Detection Limit and Quantification Limit

Based on the standard deviation of the response and the slope of the calibration curve, the LOD and LOQ of the developed HPTLC and HPLC methods were calculated according to ICH guidelines. These calculations were made using the standard deviation of the response at the lowest concentration and the slope of the calibration curve, as per the following equations:

$$\text{Limit of detection (LOD)} = 3.3 \times \sigma S$$

$$\text{Limit of quantification (LOQ)} = 10 \times \sigma S$$

Where σ is the standard deviation of response, S is the slope of the calibration curve.

Robustness

To ascertain the reliability of the analytical procedure, robustness testing was performed, focusing on its response to intentional alterations in various parameters. The small deliberate changes include changes in the mobile phase ratio, saturation time, and

Table 2: Summary of Stress degradation for HPLC.

Sl. No.	Stress condition	Concentration and time	% Recovery	Peak purity		RT of degradation product (min)
				Purity front	Purity tail	
1.	Acid hydrolysis	1 N HCl for 4 hr.	-	998.03	986.44	3.473
2.	Alkalinehydrolysis	1 N NaOH for 48 hr.	-	964.46	951.90	3.349
3.	Oxidative degradation	30% H ₂ O ₂ for 30 min.	-	999.03	995.00	2.326
4.	Neutral degradation	Water for 4 hr.	87.83	998.23	997.25	
5.	Thermal degradation	60°C for 4 hr.	88.32	999.67	999.01	
6.	UV degradation	200watt hr/m ² .	81.02	999.06	998.76	
7.	Fluorescence degradation	1.2 million lux hr.	88.23	999.29	997.59	

Table 3: System suitability parameters for HPLC.

Parameter	Obtained values
Concentration (µg/mL)	20 µg/mL
RT (min)	2.5±0.02
Area	953731.93±17.518
Asymmetry	1.24
Theoretical Plates (N)	3190.32

detection wavelength in case of HPTLC. The mean and % RSD values of the peak areas were calculated. For HPLC, the developed method was tested for robustness by small but deliberate changes in the mobile phase ratio, flow rate, and detection wavelength. The mean and % RSD was calculated.

RESULTS

The stress degradation samples were studied by both the developed methods. Under alkaline hydrolytic condition, the drug was found to be completely converted to a degradation product with R_f 0.23 and in the case of HPLC, degradation product after complete degradation was observed at a Retention time of 3.36 min. For Acid induced degradation the product was well resolved with R_f 0.24 in HPTLC and retention time 3.47 min in HPLC. The oxidative degradation product was also resolved. The photolytic, thermal, and neutral degradation study resulted in degradation within a range of 10-30% with no degradation product observed.

DISCUSSION

There are stability-indicating HPLC methods for estimation of letermovir available in literature in which a very low percent degradation of less than 10% was observed and till now no HPTLC method has been reported. It is noteworthy that degradation was not observed under hydrolytic and oxidative conditions. Additionally, the work cited in another literature source also fails to include a photolytic study involving fluorescent light exposure. While they employed milder hydrolytic and oxidative conditions and reported degradation products under these circumstances,

they did not conduct hydrolysis at neutral pH. So, our prime objective was to develop and validate stability-indicating methods and their comparative evaluation. The degradation study indicated that the drug was highly susceptible to acidic, basic, and oxidative stress conditions, with degradation products obtained as there is complete conversion of the drug under these conditions. The complete conversion of the drug to degradation product was observed even upon reducing the time of exposure to hydrolytic and oxidative conditions. Further, the UV spectrum of degradation products was analyzed to compare the spectrum of degradation products observed under acidic and basic conditions. It was found that the retention time of degradation product (3.36 min for Basic and 3.37 min for Acidic condition) and wavelength (257 nm) were similar for both conditions, but the intensity of absorption was different, so the degradation products observed under hydrolytic conditions could be the same. The probable reaction that can be predicted as per reference¹⁶ for acidic conditions is the reaction of the ether linkage of the drug by cleavage with acid, which forms alkyl halide and alcohol. There is scope for further LC/MS studies for the characterization of degradation product.

The densitogram for Acid, Alkali, and oxidative stress conditions is shown in Figure 3.

The summary of stress degradation is shown in Tables 1 and 2.

METHOD VALIDATION

Specificity

Evaluation of the drug peaks, and peak purity under stress conditions using BORWIN and winCATS software revealed that it falls within the specified limits for both methods. This indicates that there are no interferences from degradation products, impurities, or matrix components leading to additional peaks.

Linearity

For HPTLC, the method was determined to be linear within a concentration range of 250 to 750 ng/band for Letermovir.

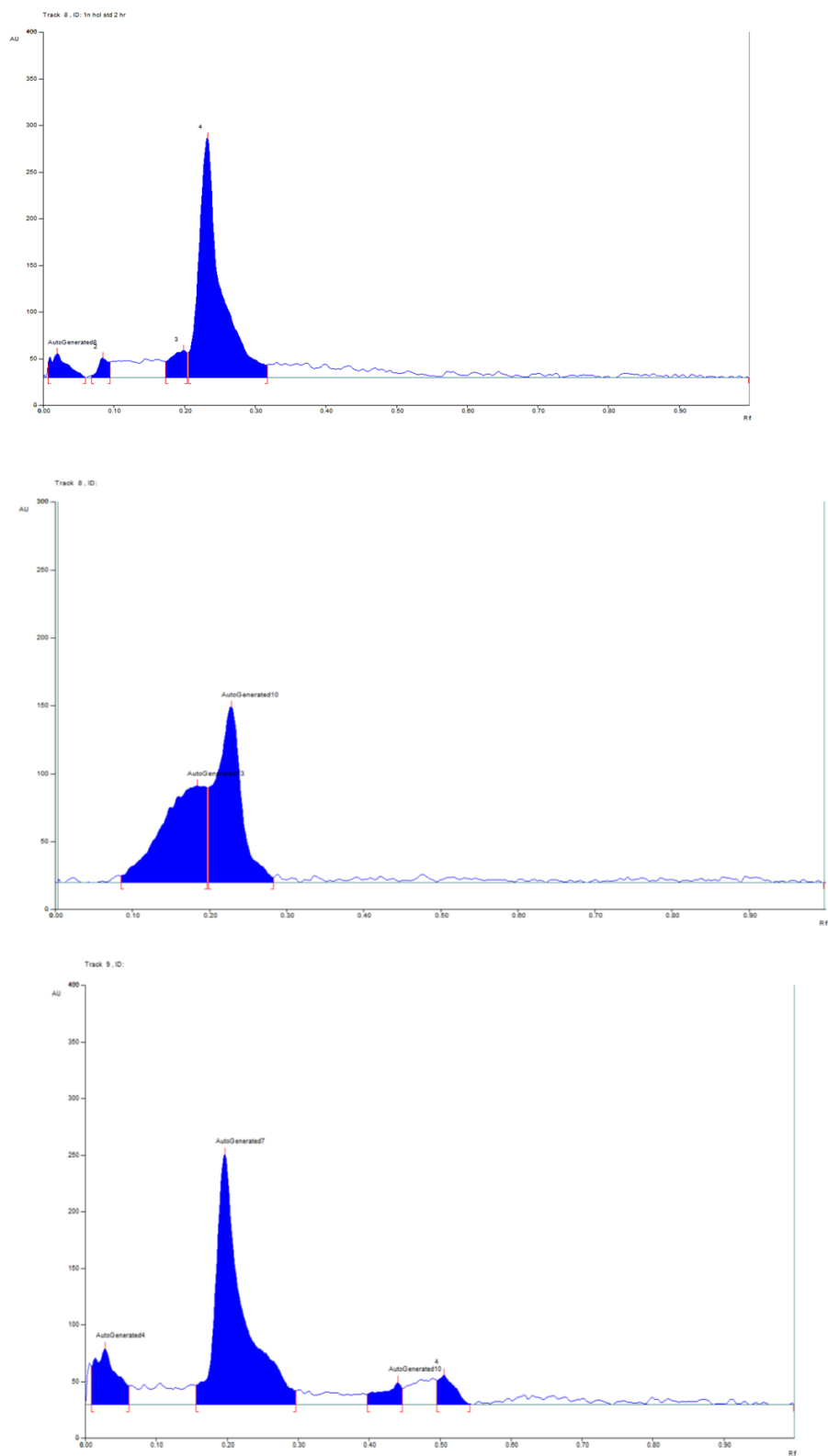


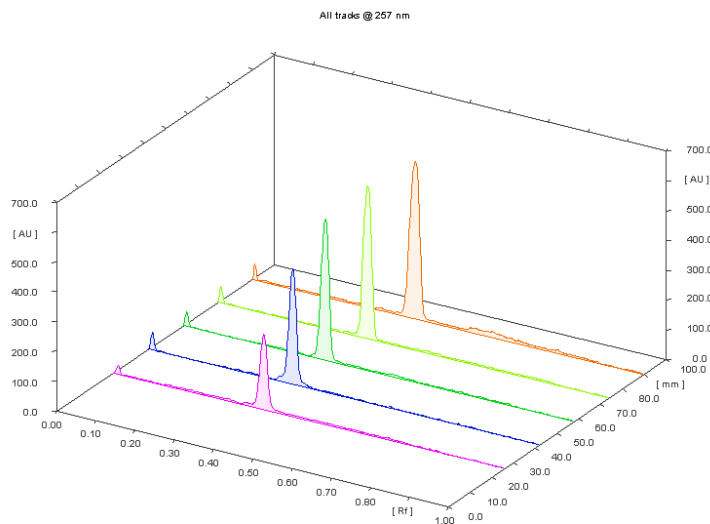
Figure 3: Densitograms for forced degraded samples a) 1N HCl treated Letermovir for 4 hr showing DP at R_f 0.24 (b) 1N NaOH treated Letermovir for 48 hr showing DP at R_f 0.23 (c) 30% H_2O_2 treated Letermovir for 30 min showing DP at R_f 0.20.

Table 4: Accuracy studies.

Sl. No.	Amount of Blend (mg)	Amount of API Added (mg)	Total amount of spiked blend (mg)	% Recovery HPTLC	% Recovery HPLC
1.	308	192	500	101.97	101.21
2.	260	240	500	101.99	99.95
3.	212	288	500	101.13	102.0

Table 5: Summary of Validation parameters.

Sl. No.	Validation Parameter	HPTLC	HPLC
1.	Linearity Range	$y=8.6759x+1489.7$ $R^2=0.9934$ 250-750 ng/band	$y= 46271x-1822.3$ $R^2=0.997$ 5-25 ($\mu\text{g/mL}$)
2.	Intraday Precision Interday Precision	% RSD-0.98 % RSD-1.14	%RSD-1.90 %RSD-1.73
3.	Assay	101.99	100.71
4.	Accuracy Level 80% Level 100% Level 120%	101.97 101.99 101.13	101.21 99.95 102.0
5.	LOD LOQ	12.41 ng/band 37.61 ng/band	0.24 $\mu\text{g/mL}$ 0.74 $\mu\text{g/mL}$
6.	Robustness	Robust	Robust
7.	Specificity	Specific	Specific

**Figure 4:** 3D Densitogram of Letermovir Linearity (250-750 ng/band) $R^2=0.9934$.

The regression equation with correlation coefficient, $r^2=0.9934$ indicate a strong linear relationship over the studied concentration range, confirming the method's suitability for analysis. The 3D Densitogram obtained in HPTLC is shown in Figure 4. For HPLC, the method was found to be linear in the concentration range of 5-25 $\mu\text{g/mL}$ for Letermovir. The regression equation was

found to be $y=46271x-1822.3$ with a correlation coefficient of $R^2=0.997$. The optimized chromatographic conditions for HPLC are shown in Table 3.

Accuracy

Recovery studies were conducted at 80%, 100%, and 120% of the test concentration per ICH guidelines for both HPTLC and

HPLC. The values indicated in Table 4 show that the method is accurate.

Precision

For HPTLC, the % RSD for both Interday and Intraday precision was found to be 1.14 and 0.98 which indicates that the method is precise. For HPLC, the % RSD for Intraday and Interday precision was found to be 1.73 and 1.90 which confirms that method is precise.

Limit of detection and limit of quantification

In case of HPTLC, the LOD and LOQ for Letemovir were found to be 12.41 ng/band and 37.61 ng/band and for HPLC it was found to be 0.24 µg/mL and 0.74 µg/mL which indicates sensitivity of the developed method.

Robustness

The robustness of the developed method was evaluated by making small deliberate changes in parameters of developed HPTLC and HPLC method and the % RSD was found to be less than 2 % confirming that the developed method is robust.

Summary of Validation parameters are shown in Table 5.

CONCLUSION

The proposed methods offer reproducible approach for determining Letemovir in the presence of its degradation products using the HPTLC densitometric technique and HPLC method. As per literature search there was no reported HPTLC method for estimation of Letemovir and in the reported HPLC method, reported degradation was less than 10%, except under oxidative conditions. The developed HPTLC method has an advantage of simple mobile phase, rapid analysis and high-throughput benefit. Our literature search showed only two stability-indicating HPLC methods (Ref. No. 10 and 15). This method reported in reference 10 has some drawbacks viz. the stress conditions were not optimized to get 10-30% degradation. Surprisingly, they did not find degradation under hydrolytic and oxidation conditions. They have not performed photostability test as per ICH guidelines. We have followed the exposure to UV light as well as Cool white fluorescent light. The work reported in the other literature method (Ref. No. 15), also lacks photolytic study based on exposure to fluorescent light. They have used milder conditions of hydrolysis and oxidation and also reported degradation product under these conditions. They have not performed hydrolysis under neutral pH.

We have worked on all stress conditions. The proposed methods also included studies on neutral and fluorescent degradation conditions. Consequently, an improved stability-indicating approach was developed using HPLC, achieving a forced degradation of 10-30% under each condition except for Acidic, Basic and Oxidative conditions, wherein complete degradation

was observed. The results obtained by both HPLC and HPTLC methods are comparable.

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CONFLICT OF INTEREST

The authors have no competing interests to declare that are relevant to the content of this article.

ABBREVIATIONS

HPLC: High Performance Liquid Chromatography; **HPTLC:** High Performance Thin Layer chromatography; **UPLC:** Ultra Performance Liquid Chromatography; **UV:** Ultraviolet; **CMV:** Cytomegalovirus; **PDA:** Photo Diode Array; **RSD:** Relative Standard Deviation; **SD:** Standard Deviation; **Hr:** Hours; **QL:** Quantification Limit; **LOD:** Limit of Detection; **LOQ:** Limit of quantification; **ICH:** Conference on Harmonization; **mg:** Milligram; **v/v:** Volume by volume; **ppm:** Part per million; **r²:** Co-relation coefficient; **nm:** Nanometer; **NaOH:** Sodium Hydroxide; **HCl:** Hydrochloric acid; **min:** minutes; **H₂O₂:** Hydrogen peroxide.

SUMMARY

Stability-indicating chromatographic methods were developed and validated for Letemovir which may be used for routine quality control purposes.

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