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# Integrated RP-HPLC Approach Development and Validation For Quantification of Pidotimod with in Silico Evaluation

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**Abstract:** *The intent of this investigation was to devise and verify a straightforward, dependable, and cost-efficacious reverse-phase high-performance liquid chromatography (RP-HPLC) approach for the quantitative assessment of Pidotimod in pharmaceutical formulations, as well as to conduct an In-Silico evaluation. A Cosmosil C18 column (250 mm × 4.6 mm, 5 µm) with a mobile phase made of methanol and water (75:25, v/v) at a flow rate of 1.0 mL/min was employed to accomplish chromatographic isolation. Pidotimod illustrated a retention time of around 4.44 minutes when screening was done at 203 nm. With a correlation coefficient ($R^2$) of 0.9983, the technique showed excellent linearity over the concentration range of 10–50 µg/mL. The method's correctness was confirmed by the assay results, which revealed a drug content of 100.01%. Values within the permissible range of 98–102% were retrieved from recovery studies conducted at various concentration levels. High repeatability and reproducibility were demonstrated by precision studies, which showed low variability with intra-day and inter-day %RSD values below 0.3%. Robustness testing showed negligible effects from minor changes in chromatographic conditions. The method also exhibited satisfactory sensitivity, with low detection and quantification limits.*

*Studies of forced degradation in acidic, alkaline, oxidative, thermal, and photolytic circumstances proved the approach's capacity to indicate stability. Overall, it was demonstrated that the validated RP-HPLC approach was trustworthy, accurate, and valid for patron quality control analysis of Pidotimod in tablet formulations.*

**Keywords:** *Pidotimod, RP-HPLC, Validation, Stability study, ICH*

## I. INTRODUCTION

**Pidotimod**

The dipeptide-structured biological response modulator pidotimod (PDM), (R)-3-[(S)-(5-oxo-2-pyrrolidinyl) carbonyl]-thiazolidine-4-carboxylic acid (Figure 1), can strengthen both adventitious and innate immune responses against pathogenic microbes and viruses [1,2]. According to research, PDM has little antibacterial activity on its own, but when taken with other antibacterial medications, it can reduce clinical complaints, promote healing, and decrease hospital stays. Pervasive infections of the respiratory, pelvic, ocular, nostrils, and lingual systems are frequently remedied wide it. Kids who frequently get respiratory ailments can be treated using PDM regimen, which is dependable, straightforward, and safeguarding. It has scanted hostile effects and good assurance and tolerance. [3] A thorough review of the literature showed that only a few analytical techniques, such as HILIC-MS/MS [7], HPLC-UV [4], HPLC-MS [5], and HPLC-MS/MS [6], have been described for the measurement of PDM. There is one disclosed report apropos the

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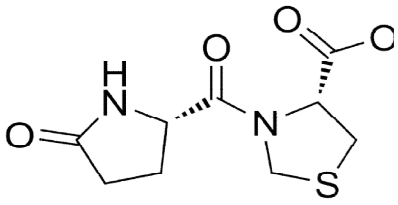
execution of GC to identify any lingering organic solvents in PDM. [8]. The goal of the current investigation was to separate the R and S enantiomers of Pidotimod on a beta cyclodextrin-based chiral stationary phase as Zhang Lu Xing [9] described chiral separation of PDM by polysaccharide stationary phase.



[Fig-1] – Structure of Pidotimod

[Table-1]- Drug Profile

| | |
|---|---|
| Category | Immunostimulant |
| Chemical Name | Oxopyrolidine-2-carbonyl (R)-3-((S)-5-Thiazolidine-4-carboxylic acid |
| Mol. Formula | $C_9H_{12}N_2O_4S$ |
| Mol. Weight | 244.27g/mol |
| Description | White powder |
| Solubility | Soluble in Water and Methanol. |
| Storage | Store at 2° to 8°C |
| Melting point | 192°c -198°c |

**1.1] Mechanism of Action [10]:**

Pidotimod prevents increases in extracellular signal-related kinase (ERK) phosphorylation caused by tumor necrosis factor α (TNF-α). Additionally, it enhances the expression and translocation of nuclear factor κB (NFκB) to the nucleus. The increase in toll-like receptor expression observed with pidotimod is believed to be caused by these modulatory effects on ERK and NFκB signaling. Pidotimod promotes the development of dendritic cells, which are in charge of exposing naive Th-cells to antigens. Additionally, it seems to increase the number of these cells developing into Th1 cells, which are thought to mediate the immune response to pathogens including bacteria and viruses. Finally, pidotimod seems to enhance the cytotoxic response and antigen-specific antibody titer upon antigen exposure. Uncertainty surrounds the exact process and sequence of events that led to these impacts.

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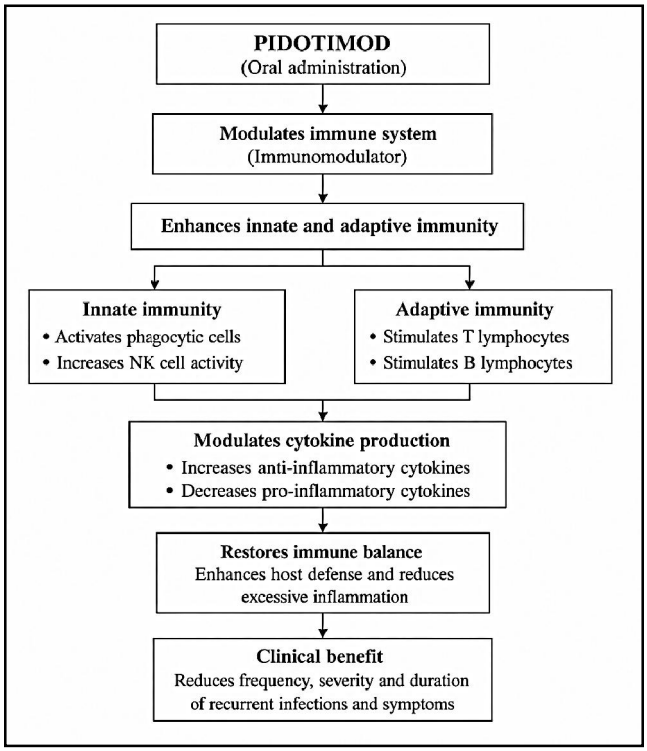


[Fig-2] - Mechanism of Action

**2] Test Work**

**2.1] Resources and Approaches:**

**Resources:**

**A) Sample:**

[Table-2]- Drug and drug product samples suppliers and manufacturers

| Sample | Victualler and Mfg. By |
|---|---|
| Pidotimod Drug | Wockhardt Ltd. |
| Pidotimod tablet. | Immulina 400mg Wockhardt Ltd |

**B) Reagents:**

**[Table-3]-List of Reagent**

| Sr. No | Chemical | Make |
|---|---|---|
| 1 | Water | Thermo Fischer |
| 2 | Methanol | Thermo Fischer |
| 3 | HCL | Thermo Fischer |
| 4 | NAOH | Thermo Fischer |

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| | | |
|---|---|---|
| 5 | H2O2 | Thermo Fischer |

**C) Instruments: HPLC:**

[Table 4]-Instrumentation

| | |
|---|---|
| Make | Analytical Technologies LTD (3000 Series) |
| Pump | P-3000-M Reciprocating (40MPa) |
| Detector | UV-3000-M |
| Software | HPLC- Workstation |
| Column | CosmosilC18(250MM×4.6ID Particle size 5µ |
| Digital analytical balance | Wenser High Precision Balance. PGB-100 |
| Sonicator | Wenser Ultra Sonicator WUC-4L |

**2.2] Method Development & Validation:**

After reviewing the literature and doing a solubility test, it was discovered that standard pidotimod was soluble in methanol. With a wavelength of 203 nm and a methanol water ratio (mobile phase) of 75:25 v/v, experiments employing methanol water as the mobile phase produced superior results.

The ICH Guidelines were followed in the validation of the devised approach.

2.2.1] Mobile phase preparation: Consider a 75:25 v/v mixture of methanol and water. Mix it well, sonicate it to degas.

2.2.2] Diluent Preparation: Make a 75:25 v/v combination of methanol and water.

2.2.3] Blank Preparation: The blank is diluent.

2.2.4] Pidotimod Standard stock solution preparation: weigh precisely 10 mg of pure medication diluted in 10 ml of solvent (solvent was employed as our mobile phase only); this yields a 1000 ppm solution.

2.2.5] Pidotimod Sample solution preparation: Dilute 0.1, 0.2, 0.3, 0.4, and 0.5 ml of this solution separately in 10 ml of diluent solution to create dilutions of 10, 20, 30, 40, and 50 ppm, respectively.

2.3] Development of Chromatographic Parameters:

Finding a set of conditions that sufficiently discriminate and permit the quantification of the aforementioned molecule from the endogenous material with acceptable accuracy, sensitivity, precision, cost, specificity, ease, and speed is the process of HPLC invention.

[Table-5]-Final RP-HPLC Conditions With Gradient Elution

| | |
|---|---|
| Column | Cosmosil$C_{18}$(250MM×4.6ID Particle size 5µ |
| Flow velocity | 1.0 ml/min |
| Std. Injection Volume | 20µl |
| λ | 203 nm |
| RT | 7.4 minutes |
| RT | 4.443 minutes |

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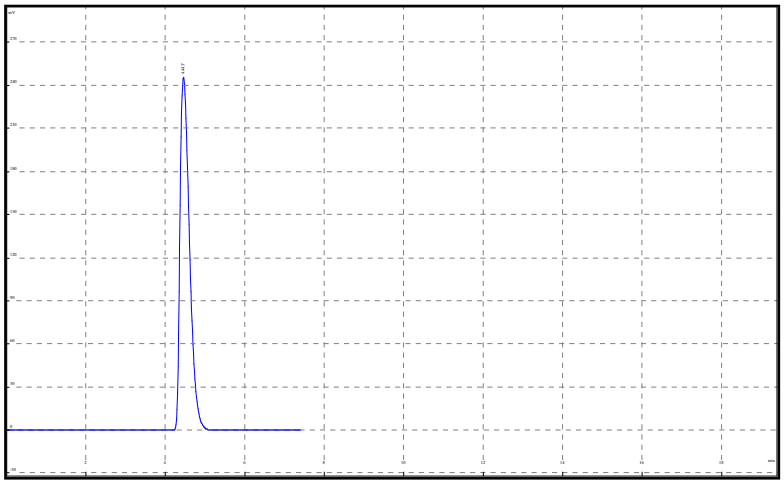
## III. RESULTS AND DISCUSSION

### 3.1 Optimization of chromatic state:

The preferred chromatographic circumstances for Pidotimod are as aforementioned, owing to the choice of mobile phase.

[Table-6]- Data of Pidotimod For Optimization of Chromatographic Condition.

| Sr. No. | Mobile phase | Flow rate | Wavelength | Injection volume | Observation | Conclusion |
|---|---|---|---|---|---|---|
| 1 | Methanol: water 70:30 | 1.0ml/min | 203 | 20µl | Poor resolution | Method is rejected |
| 2 | Methanol: water 75:25 | 1.0ml/min | 203 | 20µl | Peak shape is proper | Method is selected for further validation. |



[Fig-3]-Chromatogram for Pidotimod trial 2

[Table-7]- The Optimized Chromatographic Conditions For Pidotimod

| Sr. No. | Parameters | Optimized condition |
|---|---|---|
| 1 | Mobile phase | Methanol: Water |
| 2 | Flow velocity | 1.0 ml/min |
| 3 | Std. Injection Volume | 203 |
| 4 | λ | 20µl |
| 5 | Column | Cosmosil C18 (250 x 4.6 ID) 5µ particle size |

### 3.2. VALIDATION PARAMETERS

Validation was performed as per ICH Q2(R1) guidelines.

3.2.1] Linearity: The linearity of the approach was evaluated by gauging the absorbance of distinct Pidotimod concentrations spanning a threshold range of 10–50µg/ml.

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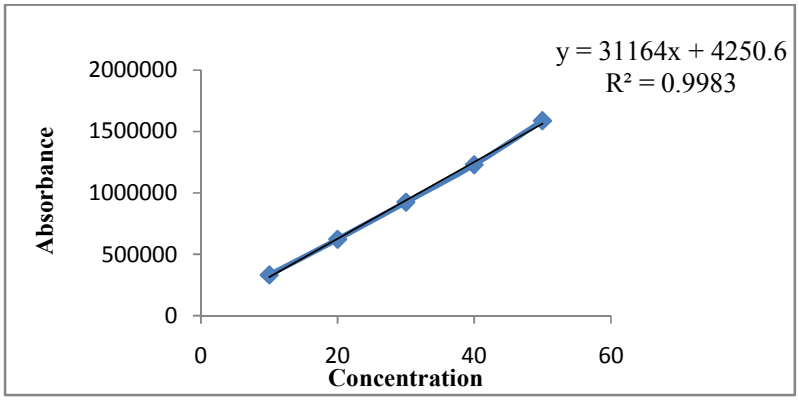
[Table-8]- Linearity of Pidotimod

| Concentration | Area |
|---|---|
| 10 | 332433 |
| 20 | 622775 |
| 30 | 924162 |
| 40 | 1228909 |
| 50 | 1587562 |




[Fig-4] Calibration curve of drug sample

[3.2.2] Assay: To test a commercially available formulation, a sample of equivalent weight was injected into an HPLC system, and recovery tests were conducted.

[Table-9]- Data of assay

| Sr. No. | Name of Sample | Region of Standard | Area of Sample | % Assay |
|---|---|---|---|---|
| 1 | Pidotimod | 924162 | 924243 | 100.009 |

3.2.3] Accuracy: To verify the accuracy of the advisable approach, recovery tests were accomplished by peering at the samples, which were carried out by analyzing the measured concentration and the administered concentration of the drug. Every sample received three injections. The following is an estimate of the percentage of drug recoveries.

[Table-10]-Accuracy data of Pidotimod

| Sr. No | % Composition | Sample Amount | | Area of Sample | Amount Recovered in ppm | % Mean Recovery | % SD |
|---|---|---|---|---|---|---|---|
| | | Sample Amount in ppm | Amount Added in ppm | | | | |
| 1 | 50% Recovery | 20 | 10 | 922080 | 29.93 | 99.91 | 0.107 |
| | | 20 | 10 | 924126 | 29.99 | | |
| | | 20 | 10 | 924223 | 29.99 | | |
| 2 | 100% Recovery | 20 | 20 | 1224706 | 39.86 | 99.81 | 0.0048 |

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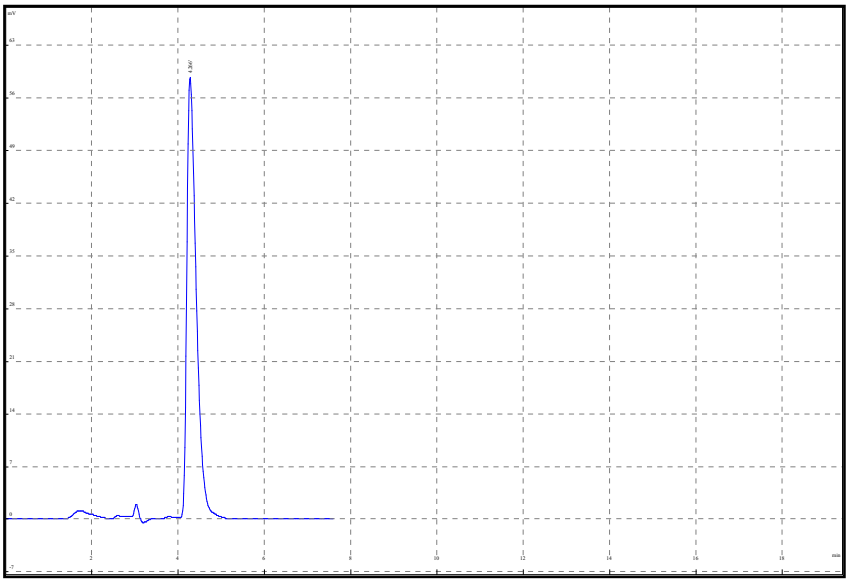
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | 20 | 20 | 1227814 | 39.96 | | |
| | | 20 | 20 | 1227676 | 39.95 | | |
| 3 | 150% Recovery | 20 | 30 | 1582977 | 49.85 | 99.88 | 0.117 |
| | | 20 | 30 | 1587320 | 49.99 | | |
| | | 20 | 30 | 1586312 | 49.99 | | |



[Fig-6]- Chromatogram for Pidotimod for accuracy at 50%

3.2.4] Precision: One of the key elements that determine an analytical method's dependability is precision. Pidotimod was investigated for the intraday and Interday precision studies; the table below displays the findings.

[Table-11]-Interday & Intraday Precision Values of Pidotimod

| Interday Precision | | Intra-day Precision | |
|---|---|---|---|
| Day 1 | Area | Morning | Area |
| | 924162 | | 924162 |
| | 925947 | | 925947 |
| | 926278 | | 926278 |
| Day 2 | 922530 | Evening | 926348 |
| | 922865 | | 931882 |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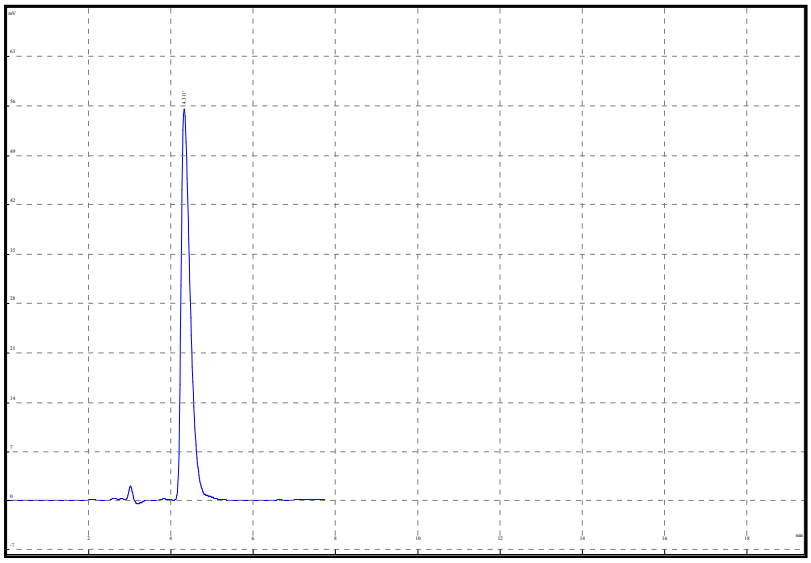
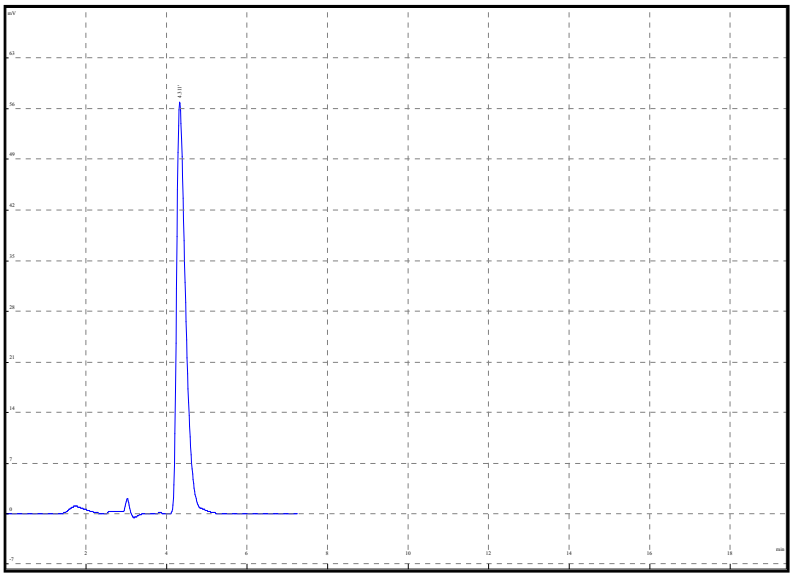
| | | | |
|---|---|---|---|
| | 923867 | | 929599 |
| Mean | 924274.83 | Mean | 927369.33 |
| SD | 1415.3887 | SD | 2578.1041 |
| % RSD | 0.15% | %RSD | 0.28% |



[Fig-7.1]- Chromatogram for Pidotimod for Interday precision at Day1 Trial 1.



[Fig-7.2]- Chromatogram for Pidotimod for Interday precision at Day 2 Trial 1.

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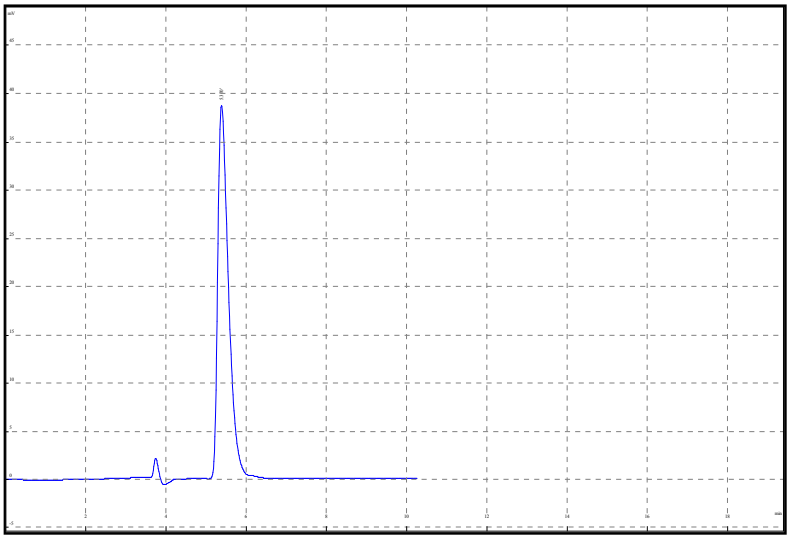
3.2.5] Robustness:

By analyzing samples from homogenous sets using different physical parameters, such as changes in flowrate and wavelength, which may differ but the responses were still within the assay's bounds, the planned method's robustness was determined.

[Table-12]- Robustness data of Pidotimod

| Level | Pidotimod | | Area |
|---|---|---|---|
| | Retention time | Tailing factor | |
| Entitize in | Flow Velocity (ml/min) | | |
| -0.2(0.8ml) | 5.37 | 1.24 | 621636 |
| 0(1.0ml) | 5.37 | 1.24 | 622775 |
| +0.2(1.2ml) | 3.613 | 1.29 | 625725 |
| Change in | Wavelength (nm) | | %RSD 0.276403 |
| -2(201nm) | 4.299 | 1.21 | 621032 |
| 0(203nm) | 4.301 | 1.2 | 622775 |
| +2(205nm) | 4.343 | 1.21 | 625002 |
| --- | --- | --- | %RSD 0.260822 |



[Fig-8.1]- Chromatogram for Pidotimod of variation in flow rate at -0.2 ml (0.8ml).

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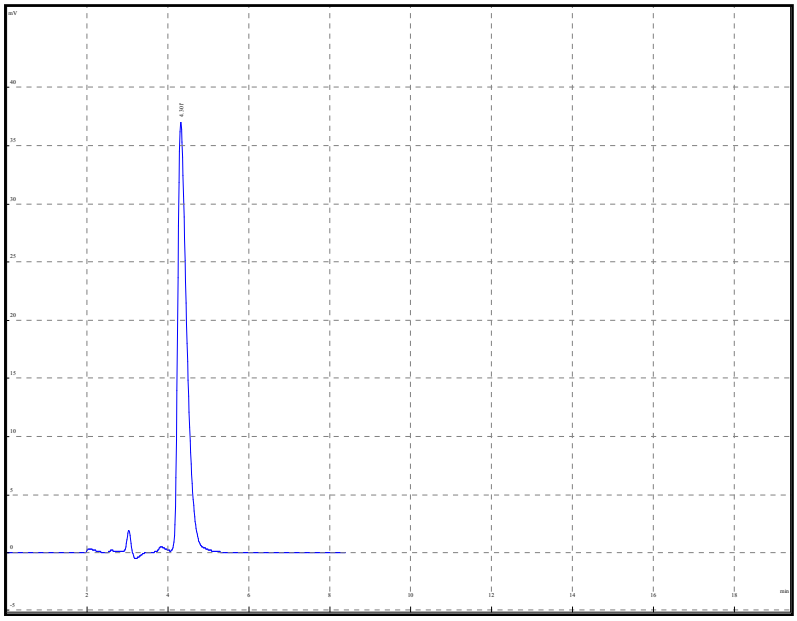

[Fig-8.2]- Chromatogram for Pidotimod of variation of wavelength at 0 nm (203nm).

**3.2.6] Limit of Detection and Limit of Quantification:**

The susceptibility of the invented approach was assessed by determining the Limit of Detection (LOD) and Limit of Quantification (LOQ) in conformity with ICH recommendations. These values were derived from the ratio of the standard variance of the response to the tilt of the calibration plot. LOD and LOQ, which reflect the lowest detectable and quantifiable quantities of the analyte, were assessed using multiplication indices of 3.3 and 10, respectively.

Where,

$LOD = 3.3 \times (SD / S)$

$LOQ = 10 \times (SD / S)$

SD = Standard variance of the response

S = Slope of the calibration arc

The LOD implies the lowest concentration

[Table-13]- Data of LOD and LOQ

| Sample | Pidotimod |
|---|---|
| LOD | 0.918968 |
| LOQ | 2.784753 |

**3.3] STABILITY STUDY:**

Stability is a measure of how well a new medication works in conditions that are more serious than accelerated conditions. This study is useful for clarifying the structure involved in product degradation. Analyzing a molecule's chemical behavior aids in formulation and packaging creation. The type of drug product and the specific pharmacological substance involved will determine the nature of the stress test.

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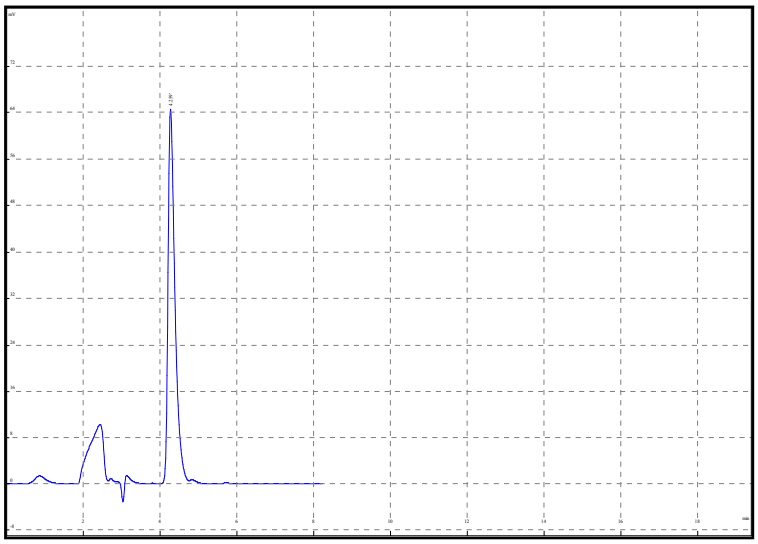
[Table-10]-Stability Study of Pidotimod

| Sr. No. | Deterioration | Area of Standard | Area of Deterioration Sample | Deterioration up to % | Actual % Deterioration |
|---|---|---|---|---|---|
| 1 | Acid Deterioration | 1587562 | 1365562 | 86.01629417 | 13.98370583 |
| 2 | Basic Deterioration | 1587562 | 1403076 | 88.37928849 | 11.62071151 |
| 3 | H2O2 Deterioration | 1587562 | 1477649 | 93.07661685 | 6.92338315 |
| 4 | Thermal Deterioration | 1587562 | 1543941 | 97.25232778 | 2.747672217 |
| 5 | Photolytic Deterioration | 1587562 | 1553771 | 97.8715162 | 2.128483801 |



[Fig-9.1]-Chromatogram for degradation study of Pidotimod after exposing to acid 0.1 N HCL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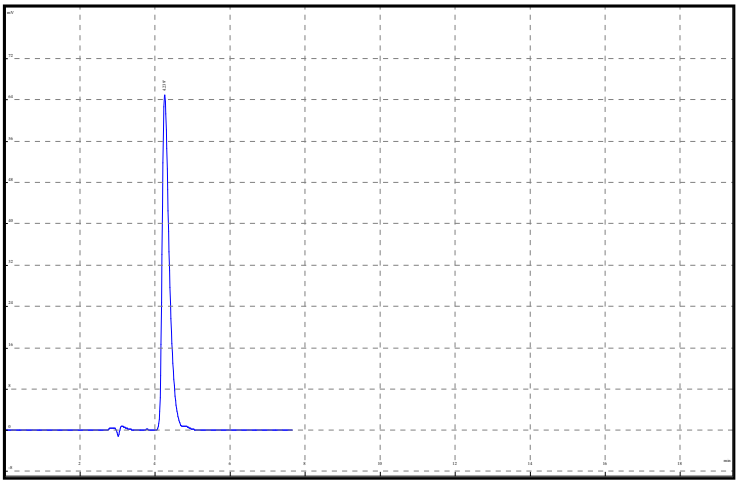
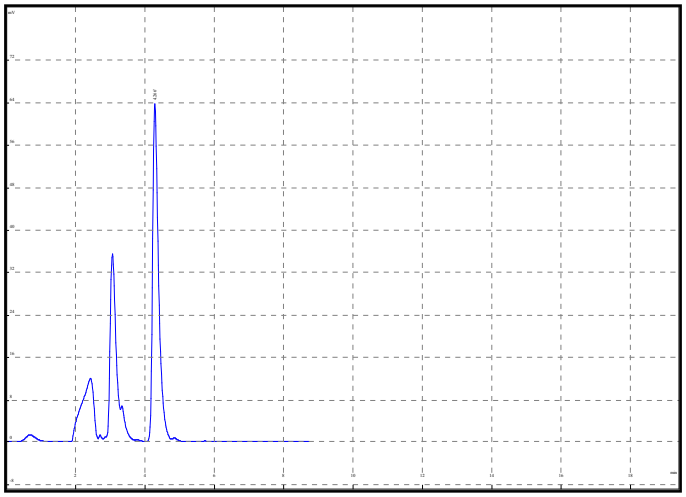
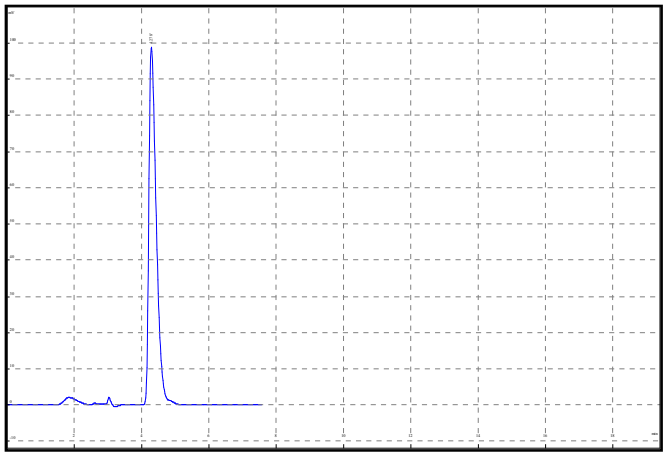


[Fig-9.2]-Chromatogram for degradation study of Pidotimod after exposing to Base 0.1 N NAOH.



[Fig-9.3]-Chromatogram for degradation study of Pidotimod after exposing to H2O2.



[Fig-9.4]- Chromatogram for degradation study of Pidotimod after exposing to Thermal / dry heat.

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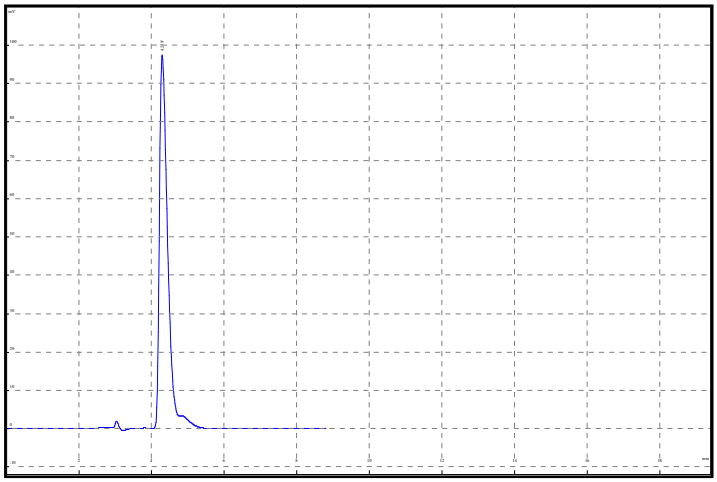

[Fig-9.4]-Chromatogram for degradation study of Pidotimod after exposing to UV-Radiation

## IV. SUMMARY & CONCLUSION

[Table-11]- Summary of Observed Validated Parameters For Pidotimod.

| Sr. No. | Validation parameters | Acceptance criteria | | | Reported observation |
|---|---|---|---|---|---|
| | Assay | Assay data for Pidotimod | | | 100.009% |
| 1 | System suitability | Retention time | Pidotimod | | 4.443 min |
| | | Resolution should be Zero | Pidotimod | | 0.00 |
| | | Theoretical plates NLT 2000 | Pidotimod | | 7629 |
| | | Tailing/Asymmetry factor NMT 2 | Pidotimod | | 1.26 |
| 2 | Linearity | Correlation coefficient | Pidotimod | | 0.9983 |
| | | Retention time | Pidotimod | | 4.443 |
| 3 | Accuracy and % recovery | Acceptable limit is 98-102%<br>Mean sample recovered for that three sample were prepared at different level RSD-NMT 2% | | | |
| | | | 50% | 100% | 150% |
| | | Pidotimod | 99.91 | 99.81 | 99.88 |
| 4 | Precision | | | | |
| | Interday precision | RSD-NMT 2% | Pidotimod | | 0.15% |
| | Intraday precision | RSD-NMT 2% | Pidotimod | | 0.27% |

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| | | | | |
|---|---|---|---|---|
| 5 | Robustness | Critical Factors | | |
| | | | | %RSD |
| | | Entitize in flow rate (± 0.2 ml/min) | Pidotimod | 0.27 |
| | | Change in wavelength (± 2 nm) | Pidotimod | 0.26 |
| 6 | LOD | Limit of detection | Pidotimod | 0.918968 |
| 7 | LOQ | Limit of quantitation | Pidotimod | 2.784753 |
| 8 | Forced degradation | Degradation NMT 20% | | |
| | | Acidic (0.1N HCL) | Pidotimod | 13.98% |
| | | Alkaline/Base (0.1N NaOH) | Pidotimod | 11.62% |
| | | Oxidative (3% $H_2O_2$) | Pidotimod | 06.92% |
| | | Photolytic | Pidotimod | 2.12% |
| | | Thermal | Pidotimod | 2.74% |

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