A SYSTEMATIC REVIEW OF ANALYTICAL METHODS FOR THE ESTIMATION OF ANTI-HYPERTENSIVE DRUGS CILNIDIPINE AND TELMISARTAN IN BULK AND PHARMACEUTICAL DOSAGE FORM

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A SYSTEMATIC REVIEW OF ANALYTICAL METHODS FOR THE ESTIMATION OF ANTI-HYPERTENSIVE DRUGS: CILNIDIPINE AND TELMISARTAN IN BULK AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT: Cilnidipine and Telmisartan are widely marketed in oral dosage forms for the efficient control of high blood pressure. The concurrent therapy integrates a calcium channel blocker (CCB) with an angiotensin II receptor antagonist, providing enhanced antihypertensive efficacy and additional reno-protective benefits. This review article summarises and critically discusses the analytical methods reported for the concurrent analysis of cilnidipine and telmisartan, as well as methods developed for their individual determination. Various analytical techniques, including UV spectrophotometric methods, Liquid Chromatographic techniques, and stability-indicating methods under forced degradation conditions, are reviewed, with emphasis on their validation parameters and applicability for routine quality control analysis.

KEYWORDS: Cilnidipine, Telmisartan, Anti-Hypertensive drugs, Analytical method validation

1. INTRODUCTION

An increase in circulatory pressure above the standard reference value is referred to as hypertension. According to the American Heart Association as arterial blood pressure more than 130/80 mmHg. (According to three readings measured over time).

Table 1: classification of high BP in adults on the guidelines recommended by the AHA

Stage of hypertension	Arterial pressure (mm/Hg)	
	Systolic	Diastolic
Regular	Less than 120	Less than 80
Prehypertensive state	Between 120 and 139	Between 80 and 89
Hypertensive phase 1	Between 140 and 159	Between 90 and 99
Hypertensive phase 2	In excess of 160	In excess of 100
Severe hypertension	In excess of 180	In excess of 110

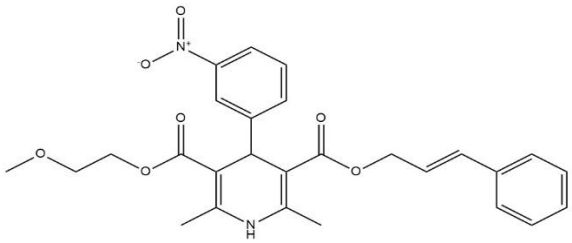
Although standardized diagnostic thresholds live, the blood pressure considered hypertensive may vary depending on individual patient characteristics such as age, gender, and life factors. The pharmacotherapy of uncomplicated blood pressure can approach in three broad ways. First, diuretics are used to lower blood volume [1]. A decrease in systemic vascular resistance can be accomplished directly by relaxing vascular smooth muscle with medications known as vasodilators or indirectly by altering the sympathetic nervous system's movement. The second uses medications that interfere with the renin–angiotensin system. The third is intended to reduce systemic vascular resistance, myocardial output, or both [2].

2. DRUG INTRODUCTION

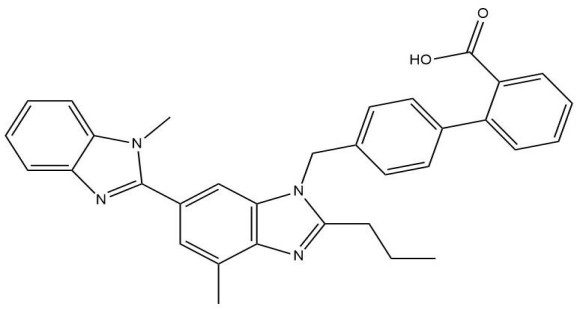
A newer generation dihydropyridine class calcium channel antagonist that's highly lipophilic, cilnidipine is authorised to treat hypertension. Essential hypertension is its main application. In contrast to amlodipine and nifedipine, which mainly target L-type channels, cilnidipine blocks N-type channels to reduce the release of norepinephrine, a sympathetic neurotransmitter. IUPAC name for cilnidipine is 3-0-(2-methoxyethyl) 5-0-[(E)-3-phenylprop-2-enyl] 2,6-dimethy-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [3].

As a cardiometabolic sartan, Telmisartan is a partial agonist of PPAR-γ receptor and a long-acting angiotensin II receptor antagonist. Telmisartan' IUPAC name is 4'-{[4-methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl]methyl}-[1'-biphenyl]-2-carboxylic acid [4].

The combination of Cilnidipine and Telmisartan was approved in 2014 by the Central Drugs Standard Control Organisation (CDSCO).



Cilnidipine



Telmisartan

Table 2 : Clinically available combination therapy of Cilnidipine with Telmisartan

Brand name	Strength	Manufacturers
DILNIP-T	10 mg + 40 mg	Lupin Ltd.
Telista CL	10 mg + 40 mg	Lupin Ltd.
Cilacar-T	10 mg + 80 mg	J.B. Chemicals & Pharmaceuticals Ltd.
Cildip-T	10 mg + 40 mg	Medley Pharmaceuticals Ltd.
Telbovil-LN-40	10 mg + 40 mg	Fibovil Pharmaceuticals (India)
Telsicap-CL	10 mg + 40 mg	Biofield Pharma
Telitoss-CL	10 mg + 40 mg	Novalab Healthcare
Cilidax-T 80	10 mg + 80 mg	Daxia Healthcare
Eritel LN	20 mg + 40 mg	Eris Lifesciences Ltd.
Telma-LN	10 mg + 80 mg	Glenmark Pharmaceuticals Ltd.
Sartel-LN	10 mg + 40 mg	Intas Pharmaceuticals Ltd.
Torcilin-T	10 mg + 40 mg	Torrent Pharmaceuticals Ltd.
Ranci T	10 mg + 40 mg	Sun Pharmaceutical Industries Ltd.
Macsart CL	10 mg + 40 mg	Macleods Pharmaceuticals Pvt Ltd.
Cilnidipine + Telmisartan (generic)	10 mg + 80 mg	Taj Pharma Ltd.

3. NEED FOR ANALYTICAL METHOD DEVELOPMENT

Developing and validating analytical techniques is an essential part of the drug discovery process. The procedure used to confirm that a testing method is appropriate for figuring out an APIs concentration in a particular formulated dosage form is development. This makes it possible to verify that an analytical process will consistently and precisely yield a measurement of an active ingredient in a compounded preparation by using reduced processes. Analytical method development and validation must comply with regulatory guidelines such as ICH harmonized guideline Q2(R1), which defines validation parameters including reliability, accuracy, linearity, precision, range, LOD, LOQ, robustness, and system suitability[5] .

Chemical analysis focus on techniques for assessing, isolating and analysing the chemical constituents of a variety of materials. Numerous factors influence the choice of analytical

methodology, including the target compound's chemical characteristics and quantity of test sample background material, the processing time and economic requirement, the nature of detections (qualitative or quantitative), and the quantity of samples[6]. The chemical identity of the species in the sample can be determined using a qualitative approach. Numerical data about the proportions of one or more analytes in the sample are provided via a quantitative approach[7].

A well-designed approach should be simple to verify. Rapid testing of non-clinical specimens, experimental formulations, and finished pharmaceutical products should be aim of any method that is created.

While the four assay tests are universal, certain procedures, such as X-ray diffraction and particle size analysis, are employed to regulate particular characteristics of the medication product or active pharmaceutical ingredient (API). The most popular techniques for determining medicament and metabolism in body fluids are gas chromatography, liquid chromatographic method such as HPLC, HPTLC, Liquid Chromatographic with Mass spectroscopy, Gas Chromatography with Mass Spectroscopy and structure identification like NMR[8].

4. ANALYTICAL METHOD FOR CILNIDIPINE AND TELMISARTAN

4.1 .OFFICIAL METHODS OF CILNIDIPINE :

S.no	Official in	Methods	Description
1)	Indian pharmacopeia (IP-2016)	Liquid chromatography	**Column:** Phenomenex-prodigy Octadecyl silane (25cm × 4.6mm , 5 µm). **Mobile phase :** ACN and 0.01mol/L sodium Acetate buffer (7:3 v/v) **Wavelength :** 240nm **Flow Rate :** 1ml/min. **Injection volume :** 20µL.
2)	Japanese pharmacopeia (JP-2018)	Liquid chromatography	**Column :** stainless steel column C18 (25cm × 4.6mm , 5 µ). **Mobile phase :** Mixture of methanol and 0.01mol/L Sodium Acetate **Wavelength :** 240nm **Flow Rate :** 1ml/min **Injection volume :** 10µL.

4.2. OFFICIAL METHODS FOR TELMISARTAN :

S.no	Official in	Methods	Description
1)	Indian pharmacopoeia (IP-2018)	Liquid chromatography	**Column :** stainless steel column packed with C18 (125 ×4.6 , 5 µm). **Mobile phase :** mixture of methanol and acetonitrile (20:80 v/v). **Wavelength :** 298nm. **Flow Rate :** 1.0 ml/min **Injection volume :** 20 µL.
2)	United state pharmacopoeia (USP-2015)	Liquid chromatography	**Column :** stainless steel column packed with C18 (12.5 cm×4mm, 5µ). **Mobile phase :** Mixture consisting of Acetonitrile and Methanol **Wavelength :** 298nm. **Flow Rate :** 1 ml/min **Injection volume :** 20 µL.
3)	British pharmacopoeia (BP- 2009)	Liquid chromatography	**Column :** octadecyl (C18) silica gel column (12.5 cm × 4.0 mm (ID), 5 µ). **Mobile phase :** Mixture of Acetonitrile and Methanol (2:8,v/v). **Wavelength :** 298nm. **Flow Rate :** 1ml/min **Injection volume :** 10 µL

4.3. REPORTED UV METHOD FOR CILNIDIPINE AND TELMISARTAN :

This review article discusses about the various UV spectroscopy methods, such as multi-component method, Absorbance ratio method (Q-analysis), Derivative spectroscopy, Area Under Curve (AUC), Dual wavelength method, and multivariate UV spectroscopic method of concurrent determination of cilnidipine and telmisartan and individually both . These analytical approaches provide simple, accurate, robust, and cost economical techniques for concurrent determination in APIs and tablet forms.

<table>
<tr><th>S.no</th><th>Method</th><th>Solvent</th><th>Description</th><th>Ref.no</th></tr>
<tr><td>1)</td><td>Simultaneous Equation and Absorbance Ratio Method - Cilnidipine and Telmisartan in tablets.</td><td>Methanol</td><td>Method I :
<table><tr><th>PARAMETER</th><th>CIL</th><th>TEL</th></tr><tr><td>Linearity (µg/ml)</td><td>4-10</td><td>6-18</td></tr><tr><td>Correlation Coefficient(r^2)</td><td>0.9998</td><td>0.9991</td></tr><tr><td>% Recovery</td><td>99.72</td><td>100.10</td></tr></table></td><td>[9]</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td>Method II :
<table><tr><td>PARAMETER</td><td>CIL</td><td>TEL</td></tr><tr><td>Linearity (µg/ml)</td><td>4-10</td><td>6-18</td></tr><tr><td>Correlation Coefficient(r^2)</td><td>0.9998</td><td>0.999</td></tr><tr><td>% Recovery</td><td>98.94</td><td>98.95</td></tr></table>Wavelength : CIL - 240nm;TEL - 297nm
Isoabsorbtive point - 270nm</td><td></td></tr>
<tr><td>2)</td><td>UV -Visible Spectro Photometric Method - Cilnidipine and Telmisartan in Bulk and Dosage Form.</td><td>ACN : Phosphate buffer (70:30% v/v)</td><td><table><tr><td>PARAMETER</td><td>CIL</td><td>TEL</td></tr><tr><td>Linearity (µg/ml,)</td><td>0.5 -2.50</td><td>2-10</td></tr><tr><td>Correlation Coefficient(r^2)</td><td>0.9998</td><td>0.9996</td></tr><tr><td>% Recovery</td><td>100.9</td><td>101</td></tr></table>Wavelength : CIL - 203nm; TEL - 241nm
Isoabsorbtive point - 237nm</td><td>[10]</td></tr>
<tr><td>3)</td><td>UV spectrophotometric method - Cilnidipine and Telmisartan</td><td>Methanol : 0.001M ammonium acetate</td><td><table><tr><td>PARAMETERS</td><td>CIL</td><td>TEL</td></tr><tr><td>Linearity (µg/ml)</td><td>1-30</td><td>1-80</td></tr><tr><td>Correlation Coefficient(r^2)</td><td>0.999</td><td>0.9992</td></tr><tr><td>% Recovery</td><td>98.50</td><td>99.57</td></tr></table>Wavelength : CIL - 357nm;TEL - 297nm</td><td>[11]</td></tr>
<tr><td>4)</td><td>Dual wavelength method - Cilnidipine and Telmisartan</td><td>Methanol</td><td><table><tr><td>PARAMETER</td><td>CIL</td><td>TEL</td></tr><tr><td>Linearity (µg/ml)</td><td>2-6</td><td>3-15</td></tr><tr><td>Correlation Coefficient(r^2)</td><td>0.999</td><td>0.997</td></tr><tr><td>% Recovery</td><td>97.87</td><td>100.63</td></tr></table>Wavelength : CIL-264nm;TEL-229nm
CIL-297nm;TEL-246nm</td><td>[12]</td></tr>
<tr><td>5)</td><td>UV and RP-HPLC methods - Cilnidipine</td><td>Mixture of ACN and Methanol (50:50% v/v)</td><td>Linearity,(µg/ml) : 2.0 -10.0µg/ml

Correlation coefficient (r^2) : 0.9999

% Recovery : 99.91-99.98%
Wavelength : CIL-242nm</td><td>[13]</td></tr>
</table>

<table>
<tr><td>6)</td><td>Spectrophotometric estimation - Cilnidipine using N-(1-Naphthyl) ethylene diamine dihydrochloride</td><td>Water : Methanol (1:3% v/v)</td><td>Linearity(µg/ml) : 16.0-24.0 µg/ml
Correlation coefficient (r^2) : 0.9991
% Recovery : 100.43%
Wavelength : CIL - 554nm</td><td>[14]</td></tr>
<tr><td>7)</td><td>UV Spectroscopic Method - Telmisartan</td><td>Solvent A
ACN & Buffer (50:50%v/v)

Solvent B
0.1N HCL : methanol (3:1% v/v)</td><td><table><tr><th>PARAMETER</th><th>Solvent A</th><th>Solvent B</th></tr><tr><td>Linearity (µg/ml)</td><td>2-20</td><td>1-22</td></tr><tr><td>Correlation Coefficient(r^2)</td><td>0.999</td><td>0.998</td></tr><tr><td>% Recovery</td><td>98.7-101</td><td>98.7-101</td></tr></table>Wavelength : A - TEL - 297nm and B - TEL - 291nm</td><td>[15]</td></tr>
<tr><td>8)</td><td>UV Spectrophotometric Method - Telmisartan in Pure API</td><td>Ethanol (95%) : 0.1 N Sodium bicarbonate (6:4%,v/v)</td><td>Linearity,(µg/ml) : 2-14µg/ml
Correlation coefficient (r^2) : 0.9995
% Recovery : 99.65%
Wavelength : TEL - 240nm</td><td>[16]</td></tr>
<tr><td>9)</td><td>UV-Spectrophotometric Method - Telmisartan</td><td>0.1N NaOH</td><td>Linearity (µg/ml) : 4.0-24µg/ml
Correlation Coefficient (r^2) : 0.9992
%Recovery : 98.54%
Wavelength : TEL - 234nm</td><td>[17]</td></tr>
<tr><td>10)</td><td>UV Spectroscopic Method - Telmisartan</td><td>Triethyl amine : distilled water : Methanol (5:85:10%,v/v/v)</td><td>Linearity,(µg/ml) : 10-50µg/ml
Correlation coefficient(r^2) : 0.999
% Recovery : 99.84%
Wavelength : TEL - 297nm</td><td>[18]</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>

11)	**Visible Spectrophotometric** Determination of **Telmisartan** from Urine	Methanol	**Linearity (µg/ml) :** 10-60µg/ml **Correlation coefficient (r^2):** 0.999 **% Recovery :** 99.84% **Wavelength :** TEL - 427nm	[19]
12)	**UV spectrophotometric method - Cilnidipine** and **Olmesartan**	Water : Methanol (1:1 % v/v)	**Linearity (µg/ml) :** 10-100 µg/ml **Correlation coefficient (r^2) :** 0.999 **% Recovery :** 100.75% **Wavelength :** CIL - 257nm	[20]
13)	**UV spectrophotometric method - Absorbance ratio method Cilnidipine** and Metoprolol succinate	Methanol	**Absorbance Ratio Method :** **Linearity,(µg/ml) :** 2.0-10µg/ml **Correlation coefficient(r^2) :** 0.9986 **% Recovery :** 100.77 ± 0.58 **Wavelength :** CIL - 223nm and 230.4nm	[21]
14)	**UV spectrophotometric method - Cilnidipine** and **Chlorthalidone**	Methanol	**Dual wavelength method :** **Linearity (µg/ml) :** 2.0-10.0 µg/ml **Correlation coefficient (r^2) :** 0.999 **% Recovery :** 100-104% **Wavelength :** CIL - 271nm and 278.3nm	[22]
15)	**Dual wavelength method - Azilsartan medoxomil and Cilnidipine**	Ethanol	**Linearity (µg/ml) :** 1-5 µg/ml **Correlation coefficient (r^2) :** 0.999 **% Recovery :** 100.15±0.035% **Wavelength :** CIL - 238nm and 258nm	[23]
16)	**UV Spectro photometric method -**		**Linearity (µg/ml) :** 4.0-20.0 µg/ml	

	Telmisartan and Ramipril	0.1N NaOH	**Correlation coefficient,(r^2) :** 0.996 **% Recovery :** 96.1-105% **Wavelength :** TEL - 232nm	[24]
17)	**UV-Spectro photometric method - Telmisartan** and Amlodipine besylate	Methanol	**Linearity (µg/ml) :** 2.0-25 µg/ml **Correlation Coefficient,(r^2) :** 0.9994 **% Recovery :** 98.40% **Wavelength :** TEL - 295nm	[25]
18)	**UV Spectrophotometric methods - Telmisartan** and cilostazol in synthetic mixture	Methanol	**Linearity (µg/ml) :** 5-30 µg/ml **Correlation coefficient,(r^2) :** 0.999 **% Recovery :** 98.40% **Wavelength :** TEL - 296nm	[26]

5. CHROMATOGRAPHIC METHODS FOR CILNIDIPINE AND TELMISARTAN :

Chromatographic methods are extensively used for precise and reliable drug determination in APIs and solid oral formulations. A wide variety - chromatographic techniques has documented for concurrent determination of Cilnidipine and Telmisartan. Because of its great sensitivity, selectivity, and repeatability. Liquid chromatographic methods - HPLC, HPTLC and Stability Indicating Method under Forced degradation study for both drugs are frequently utilised. Their widespread utilisation in a variety of analytical applications testifies to their vital role in assuring product quality and safety in the production and analysis of pharmaceuticals.

S.no	Method	Description	Ref.no
1)	**RP-HPLC method - Telmisartan and Cilnidipine**	**Column :** Intersil ODS C18 (25cm× 4.6mm, 5µ). **Mobile phase :** Mixture of Buffer pH4 (KH_2PO_4), Methanol and Acetonitrile (30:40:30 v/v/v). **Linearity (µg/ml) : CIL :** 12-28 µg/ml, **TEL :** 48-112 µg/ml. **Flow Rate :** 1 ml/min **Injection Volume :** 20 µl. **Retention Time (RT) : CIL :** 4.95 mins, **TEL :** 2.73 mins. **Recovery % : CIL :** 99.5-100.13% **TEL :** 99.58-100.12%. **Wavelength :** 232nm.	[27]

2)	**RP-HPLC Estimation - Cilnidipine** and **Telmisartan**	**Column :** HiQ sil C18 (250 × 4.6, 5µ). **Mobile phase :** Mixture of methanol and KH_2PO_4 Buffer pH 3 (90:10,v/v). **Linearity,(µg/ml) : CIL :** 1.0-10.0 µg/ml **TEL :** 5-30 µg/ml. **Flow Rate :** 1.0ml/min. **Injection Volume :** 50 µl **Retention Time (RT) : CIL :** 5.72mins, **TEL :** 2.58mins. **Recovery % : CIL :** 99.40-100.39% **TEL :** 99.60-99.83%. **Wavelength :** 245nm.	[28]
3)	**RP-HPLC Method -Telmisartan** and **Cilnidipine**	**Column :** Zodiac ODS (250mm × 4.6mm, 5µ). **Mobile phase :** Mixture of KH_2PO_4 Methanol and Tetra hydro furan (45:45:10,v/v/v) **Linearity(µg/ml) : CIL :**12.0-28.0µg/ml **TEL :** 48.0 -112. 0µg/ml **Flow Rate :** 1ml/ min **Injection Volume :** 20 µl **Retention time (RT) : CIL :** 4.96mins, **TEL :** 2.78mins. **Recovery % : CIL :** 99.85 % **TEL :** 98.05 % **Wavelength :** 232nm.	[29]
4)	**RP-HPLC Method - Telmisartan** and **Cilnidipine.**	**Column :** Water's Supleco C18 (15cm ×4.60 mm I.D). **Mobile phase :** Methanol: NaH_2PO_4 buffer (7:3, v/v, pH 7) **Linearity,(µg/ml) : CIL :** 50-150 µg/ml, **TEL :** 50-150µg/ml **Flow Rate :** 1ml/min. **Injection Volume :** 10 µL. **Retention Time (RT) : CIL :** 4.15mins, **TEL :** 2.89mins. **Recovery % : CIL :** 98% , **TEL :** 99% **Wavelength :** 273nm.	[30]
5)	**RP-HPLC Method - Cilnidipine** and **Telmisartan**	**Column :** Youglin ODS (25cm × 4.6mm 5 µ). **Mobile phase :** ACN : .05 % Ortho phosphoric Acid (60:40,v/v) **Linearity (µg/ml) : CIL :** 1-10 µg/ml,	

		TEL : 10-40 µg/ml **Flow Rate :** 0.7 ml/min. **Injection Volume :** 10 µl. **Retention Time (RT) : CIL :** 4.70mins, **TEL :** 8.01mins. **Recovery % : CIL :** 99.86 % **TEL :** 99.6 % **Wavelength :** 236nm.	[31]
6)	**RP-HPLC Method - Cilnidipine** and **Telmisartan**	**Column :** Symmetry Octadecylsilane (15cm × 4.6mm I.D, 5µm). **Mobile phase :** mixture of methanol and 0.1% ortho phosphoric Acid (64:36,v/v) **Linearity(µg/ml) : CIL :** 20.0-100 µg/ml, **TEL :** 60.0 -140µg/ml. **Flow Rate :** 1 ml/min. **Injection Volume :** 20µl **Retention Time (RT) : CIL :** 2.80mins, **TEL :** 3.88mins. **Recovery % : CIL :** 100.30 % **TEL :** 100.21 % **Wavelength :** 224nm.	[32]
7)	**RP-HPLC Method - Telmisartan** and **Cilnidipine**	**Column :** Agilent octadecyl-bonded silica (15cm × 4.6mm, 5 µ). **Mobile phase :** ACN : Buffer - phosphate pH 3 (90:10,v/v) **Linearity,(µg/ml) : CIL :** 10-60µg/ml, **TEL :** 40-240µg/ml **Flow Rate :** 1 ml/min. **Injection Volume :** 20 µL. **Retention Time (RT) : CIL :** 7.59mins, **TEL :** 4.75mins. **Recovery % : CIL :** 108.32-111.47% **TEL :** 98.27-99.81 % **Wavelength :** 254nm.	[33]
8)	**Stability-Indicating RP-HPLC Method - Cilnidipine** and **Telmisartan**	**Column :** Agilent RP -18 (100mm x 4.6mm, 2.5µm). **Mobile phase :** Mixture of methanol and 0.1% triethylamine (pH 6.0 - Ortho phosphoric acid ,6:4 v/v) **Linearity (µg/ml) : CIL :** 2.0-10.0 µg/ml, **TEL :** 1.50 -7.50 µg/ml **Flow Rate :** 0.9ml/min **Injection Volume :** 20 µL.	[34]

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Retention time : CIL : 2.38mins,
TEL : 3.31mins.
Recovery % : CIL : 99.72-100.51%
TEL : 99.3-101%
Wavelength : 251nm.

Degradation study results :

<table>
<tr><th>Stress Condition</th><th>CIL % D</th><th>TEL % D</th></tr>
<tr><td>Acid (0.1N HCL)</td><td>1.60</td><td>2.07</td></tr>
<tr><td>Base (0.1N NaOH)</td><td>3.15</td><td>5.37</td></tr>
<tr><td>Oxidative 3% H_2O_2)</td><td>6.02</td><td>21.15</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>9)</td>
<td>Stability-Indicating Method and Dissolution Study By RP-HPLC - Cilnidipine and Telmisartan

.</td>
<td>
Column : Sunfire octadecyl-bonded silica (25cm × 4.6 mm, 5µm)
Mobile phase : Mixture of methanol, ACN and 0.02M KH_2PO_4 Buffer (70:10:20, pH 3.0 - 1% Orthophosphoric acid)
Linearity,(µg/ml) : CIL : 0.50-10.0 µg/ml,
TEL : 2.0-40.0 µg/ml
Flow Rate : 1ml/min
Injection Volume : 20µl
Retention Time (RT) : CIL : 7.2mins,
TEL : 3.1mins
Recovery % : CIL 98.4-104.5%
TEL : 100.3-101.8%
Wavelength : 254nm

Degradation study results :

<table>
<tr><th>Stress Condition</th><th>CIL % D</th><th>TEL % D</th></tr>
<tr><td>Acid (0.5N HCL,1hr)</td><td>32.7</td><td>34.4</td></tr>
<tr><td>Base (0.1N NaOH,1hr)</td><td>34.2</td><td>23.1</td></tr>
<tr><td>Oxidative 12% H_2O_2,1hr)</td><td>40.8</td><td>30.15</td></tr>
<tr><td>UV (1day)</td><td>38.5</td><td>17.79</td></tr>
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<td>[35]</td>
</tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>

10)	**Stability-Indicating method by RP-HPLC Method - Telmisartan** and **Cilnidipine**	**Column :** Water's C18 (25cm × 4.6mm, 5µm). **Mobile phase :** ACN : Phosphate Buffer pH 3 (68:32,v/v) **Linearity(µg/ml) : CIL :**10.0-40.0 µg/ml, **TEL :** 40.0-160 µg/ml **Flow Rate :** 1 ml/ min **Injection Volume :** 20µl **Retention Time (RT) : CIL :** 2.38mins, **TEL :** 3.31mins **Recovery % : CIL :** 99.68-99.52% **TEL :** 98.37-99.52% **Wavelength :** 245nm **Degradation study results :** **Alkali condition : CIL :** 32.99% and **TEL :** 5.74% No degradation was detected in Acidic, oxidative and photolytic degradation.	[36]
11)	**UV And RP-HPLC Methods - Cilnidipine**	**Column :** Thermo scientific stainless steel C18 (25cm × 4.6 mm, 5 µm) Mobile phase : mixture of acetonitrile and methanol (50:50,v/v) **Linearity,(µg/ml) : CIL :** 2.0-10µg/ml **Flow Rate :** 1.0 ml/min. **Injection Volume :** 20µl **Retention Time (RT) : CIL :** 3.06mins **Recovery % : CIL :** 99% **Wavelength :** 242nm	[37]
12)	**Stability indicating RP-HPLC method** for estimation of **cilnidipine**	**Column :** Cosmosil (25cm × 4.6mm, 5µm). **Mobile phase :** Monobasic potassium phosphate buffer : Methanol (50:50,v/v) **Linearity (µg/ml) : CIL :**100-500 µg / ml **Flow Rate :** 1.0 ml per min **Injection Volume :** 20 µL **Retention Time (RT) : CIL :** 4.81mins **Recovery % : CIL :** 98-100% **Wavelength :** 241nm.	[38]
13)	**RP-HPLC method - Cilnidipine** in Pure Form and Marketed Formulation	**Column :** Symmetry ODS C18 (25cm × 4.6mm, 5µm). **Mobile phase :** Methanol : Acetonitrile : 0.1% Ortho phosphoric acid (3:6:1,v/v/v) **Linearity (µg/ml) : CIL :** 6-14 µg/ml **Flow Rate :** 1 ml/ min **Injection Volume :** 20 µl	[39]

		Retention Time (RT) : CIL : 2.57 mins **Recovery % : CIL :** 98-120% **Wavelength :** 235nm	
14)	**Stability-Indicating Reversed-Phase HPLC Method - Cilnidipine**	**Column :** X-Terra C18 (25cm × 4.6 mm,5 µm) **Mobile phase :** Buffer : Methanol (1:9 v/v, pH 5.8) **Linearity (µg/ml) : CIL :** 2-12 µg/ml **Flow Rate :** 1.0 ml/ min **Injection Volume :** 20 µl **Retention Time (RT) : CIL :** 7.2mins **Recovery % : CIL :** 98% **Wavelength :** 229nm **Degradation study results :** **Acid condition :** 5.34% **Alkali condition :** 6.22% **Oxidative condition :** 4.9% **Thermal condition :** 4.31% No significant degradation in photolytic condition for Cilnidipine	[40]
15)	**Stability Indicating RP-HPLC method - Cilnidipine**	**Column :** Water's Xterra (100mm × 4.6mm, 3.5µ). **Mobile phase :** ACN :10mM Phosphate Buffer pH - 2.6 (30:70,v/v) **Linearity (µg/ml) : CIL :** 40-120 µg/ml **Flow Rate :** 1 ml/min . **Injection volume :** 20 µL **Retention time : CIL :** 3 mins **Recovery % : CIL :** 98.23-99.60% **Wavelength :** 240nm **Degradation study result for CIL:** **Acid condition (2N HCL for 3hr) :** Drug substance and product – 1.15% and 0.29%. **Alkali condition (2N NaOH for 3hr) :** Drug substance and product – 0.90% and 26.25%.	[41]

		Photolytic condition (UV light for 24hr) : drug product – 1.21% No degradation in 6% H_2O_2 and Thermal degradation for Cilnidipine.	
16)	**RP-HPLC Method - Telmisartan**	**Column :** Water's Zorbax-SB-18 ODS (15cm ×4.6mm , 3.5µm). **Mobile Phase :** Mixture of Buffer and Methanol (4:6,v /v) **Linearity(µg/ml) : TEL :** 4-20 µg/ml. **Flow Rate :** 1 ml min^{-1} **Injection Volume :** 10µl **Retention time : TEL :** 6.2mins. **Recovery % : TEL :** 99.55% **Wavelength :** 230nm.	[42]
17)	**RP-HPLC method - Telmisartan**	**Column :** Water's RP 18 (250cm x 4.6mm, 3.5µm). **Mobile phase :** MeOH : 0.025M PDP : ACN (5:45:50,v/v/v) **Linearity (µg/ml) : TEL:**100-200µg/ml. **Flow Rate :** 1 ml/ min **Injection Volume :** 20 µL **Retention Time (RT) : TEL :** 3.6mins. **Recovery % : TEL :** 99.7-101.31% **Wavelength :** 216nm.	[43]
18)	**RP-HPLC method** of **Telmisartan** in **Human plasma**	**Column :** Hibar (25cm x 4.6mm , 5µm). **Mobile phase :** NH_4HCOO (pH4) : Methanol (7:3,v/v) **Linearity (µg/ml) : TEL:** 0.1-1.5 µg/ml **Flow Rate :** 1ml/min **Injection Volume :** 20µl **Retention Time (RT) : TEL :** 3.7mins **Recovery % : TEL :** 94.0-99.2% **Wavelength :** 275nm	[44]
19)	**High Performance Thin Layer Chromatography Method - Telmisartan** and **Cilnidipine**	**Stationary medium :** Pre-coated aluminium TLC plates of silica gel 60 **Solvent :** toluene : dichloromethane : methanol (2:1:7) **Linearity (ng/spot) :** **CIL :** 100-300, **TEL :** 200-600. **RF Values : CIL :** 0.55, **TEL :** 0.43	[45]

<table>
<tr><td></td><td></td><td>% Recovery : CIL : 99.15- 99.6%,
TEL : 99.43-100.07%
Wavelength : 265nm</td><td></td></tr>
<tr><td>20)</td><td>High Performance Thin Layer Chromatography with Ultraviolet Detection- Cilnidipine and Telmisartan</td><td>Stationary medium : Silica sorbent layer 60 F245
Solvent : Toluene : DMF : Ester solvent (6.5:0.5:3 ,v/v/v)
Linearity (ng/spot) :
CIL : 100-600, TEL : 100-600
RF Values : CIL : 0.46 , TEL : 0.18
% Recovery : CIL : 98.12%,
TEL : 97.24%
Wavelength : 260nm</td><td>[46]</td></tr>
<tr><td>21)</td><td>Stability Indicating HPTLC Method - Cilnidipine and Telmisartan</td><td>Stationary medium : Pre-coated aluminium TLC plates of silica gel 60
Solvent : Methanol : Toluene : chloroform (0.7:2:6%,v/v/v)
Linearity range (ng/spot) :
CIL : 100-600, TEL : 400-2400
RF Values : CIL : 0.59, TEL : 0.30
Recovery % : CIL : 99.4 -100%,
TEL : 100.7-101.1%
Wavelength : 254nm

Degradation study results :
<table><tr><th>Stress Condition</th><th>CIL % D</th><th>TEL % D</th></tr><tr><td>Acid (0.5N HCL)</td><td>25.4</td><td>38.9</td></tr><tr><td>Base (0.5N NaOH)</td><td>13.1</td><td>63.11</td></tr><tr><td>Oxidative 12% H_2O_2)</td><td>15.7</td><td>39.54</td></tr></table></td><td>[47]</td></tr>
<tr><td>22)</td><td>Stability-Indicating HPTLC Method - Telmisartan and Cilnidipine</td><td>Stationary medium : silica gel 60 F254 aluminium coated plate (250µm x 10 x 10)
Solvent : Mixture of glacial acetic acid, toluene and methanol (1:8:2)
Linearity range (ng/Band) :
CIL : 200 -1400, TEL : 50-600
RF Values : CIL : 0.62, TEL : 0.38
Recovery % : CIL : 99.55 ± 1.38%,
TEL : 100.79 ± 1.38%
Wavelength : 260nm</td><td>[48]</td></tr>
</table>

Degradation study results :

Stress Condition	CIL % D	TEL % D
Acid (0.1N HCL,1hr)	13.30	12.06
Base (0.1N NaOH,1hr)	10.93	13.97
Oxidative (3% H_2O_2)	14.27	18.04
Dry heat (60ºC,24hr)	10.70	10.41

6. CONCLUSION :

Multiple analytical approaches has been published for concurrent analysis of Cilnidipine and Telmisartan in APIs , oral solid preparations and body fluids , Techniques such as Ultraviolet spectrophotometry, Liquid Chromatographic methods and forced degradation studies for these drugs. Among these techniques, many research articles have focused on RP-HPLC analytical method, whereas only a few studies have reported HPTLC method and analytical methods for biological matrices. Future research may focus on the development of more rapid, eco-friendly, and highly sensitive analytical techniques for the analysis of cilnidipine and telmisartan in complex matrices.

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