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Eco Friendly Analytical Method Development And Validation Of Clevidipine By Using Reverse Phase Ultra Performance Liquid Chromatography

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Abstract: *A simple, Accurate, precise, Ecofriendly analytical method was developed for the estimation of the Clevidipine in Api. Chromatogram was run through ACQUITY UPLC CHS C18 Column, 100x 2.1mm 1.8µm. Mobile phase containing Buffer KH2PO4: Acetonitrile taken in the ratio 60:40 was pumped through column at a flow rate of 0.3 ml/min.. Temperature was maintained at 30°C. Optimized wavelength selected was 240.0 nm. Retention time of Clevidipine was 1.146. Standard %RSD of Clevidipine were and found to be 0.7. %Recovery was obtained as 99.60%. LOD, LOQ values obtained from regression equations were 0.01, 0.03. Regression equation of Clevidipine is y = 51673x + 2873.4. Retention times were decreased and that run time was decreased, so the method developed was simple and economical that can be adopted in regular Quality control test in Industries.*

Key Words: *Clevidipine, RP-UPLC, Eco Friendly, Analytical Method development and Validation*

INTRODUCTION

UPLC:

UPLC is an emerging area of analytical separation science which retains the practicality and principles of HPLC while increasing the overall interlaced attributes of speed, sensitivity and resolution. Speed and peak capacity can be extended to new limits, termed Ultra Performance Liquid Chromatography, or UPLC by using fine particles. UPLC takes full advantage of chromatographic principles to run separations using columns packed with smaller particles and/or higher flow rates for increased speed, sensitivity and superior resolution.

In this article we explored the potential of UPLC to improve the analysis of the samples that are encountered during pharmaceutical development and manufacturing. Particular emphasis has been placed on determining whether UPLC can reduce analysis times without compromising the quantity and quality of the analytical data generated compared to HPLC.

Here particular emphasis is given on principle involved, instrumentation encountering different UPLC columns, different particle chemistries, detectors and various applications. UPLC generated higher separating efficiencies through the use of a smaller diameter particle packing and higher operating pressures. A commercial system capable of generating much higher pressures (1000 bar) than used in standard HPLC has been evaluated to determine its potential in routine analysis. UPLC has been shown to generate high peak capacities in short times and this is found to be quite beneficial in analyzing the complex mixtures that constitute metabolism samples. The application of UPLC resulted in the detection of additional drug metabolites, improved the spectrum quality and separation efficiency[1,2].

PRINCIPLE

The UPLC is based on the principal of use of stationary phase consisting of particles less than 2µm, while HPLC columns are typically filled with particles of 3 to 5µm. The underlying principles of this evolution are governed by the van Deemter equation, which is an empirical formula that describes the relationship between linear velocity (flow rate) and plate height (HETP or column efficiency) [3]. The Van Deemter curve, governed by an equation with three components shows that the usable flow range for a good efficiency with a small diameter particles is much greater than for larger diameters[4,5].

$$H = A + \frac{B}{\mathrm{v}} + C\mathrm{v}$$

Where A, B and C are constants and v is the linear velocity, the carrier gas flow rate. The A term is independent of velocity and represents "eddy" mixing. It is smallest when the packed column particles are small and uniform. The B term represents axial diffusion or the natural diffusion tendency of molecules. This effect is diminished at high flow rates and so this term is divided by v. The C term is due to kinetic resistance to equilibrium in the separation process. The kinetic resistance is the time lag involved in moving from the gas phase to the packing stationary phase and back again. The greater the flow of gas, the more a molecule on the packing tends to lag behind molecules in the mobile phase. Thus this term is proportional to v

Clevidipine belongs to a well-known class of drugs called dihydropyridine calcium channel antagonists. Clevidpine is the first third generation intravenous dihydropyridine calcium channel blocker. In vitro studies demonstrated that clevidipine acts by selectively relaxing the smooth muscle cells that line small arteries, resulting in arterial dilation, widening of the artery opening, and without reducing central venous pressure or reducing cardiac output. Th Chemically called as methyl 5-{[(butanoyloxy)methoxy]carbonyl}-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate.

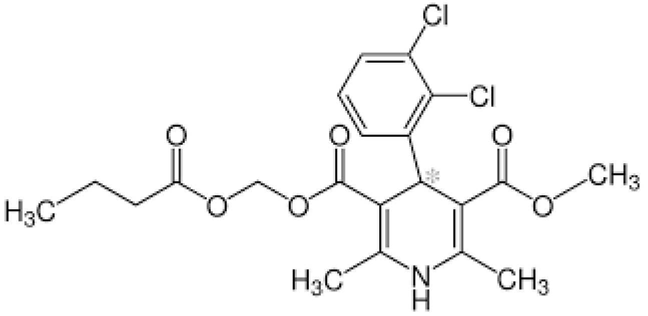

Figure 1: Chemical structure of Clevidipine

Experimental Work:

MATERIAL AND METHOD

Clevidipine were gift Sample Collected Akirvis Pvt Ltd, Hyderabad, Chemicals were used in the project were AR grade and Instruments used in the Project were calibrated.

Methods:

Preparation of Standard stock solutions: Accurately weighed 5mg of Clevidipine transferred 50ml and volumetric flasks, 3/4 th of diluents was added and sonicated for 10 minutes. Flasks were made up with diluents and labeled as Standard stock solution (100µg/ml of Clevidipine)

Preparation of Standard working solutions (100% solution): 1ml of Clevidipine from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (10µg/ml of Clevidipine)

Preparation of Sample stock solutions: 1ml of vial of injection was taken that is equivalent to 0.5mg/1ml of dosage form was transferred into a 100 ml volumetric flask, 100ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters. (100 µg/ml of Clevidipine)

Preparation of Sample working solutions (100% solution): 2ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent. (10µg/ml of Clevidipine)

Validation:

System suitability parameters:

The system suitability parameters were determined by preparing standard solutions of Clevidipine (10ppm) and the solutions were injected six times and the parameters like peak tailing, resolution and USP plate count were determined.

The % RSD for the area of six standard injections results should not be more than 2%.

Specificity: Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. So this method was said to be specific.

Precision:

Preparation of Standard stock solutions: Accurately weighed 5mg of Clevidipine transferred 50ml and volumetric flasks, 3/4 th of diluents was added and sonicated for 10 minutes. Flasks were made up with diluents and labeled as Standard stock solution (100µg/ml of Clevidipine)

Preparation of Standard working solutions (100% solution): 1ml of Clevidipine from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (10µg/ml of Clevidipine)

Preparation of Sample stock solutions: 1ml of vial of injection was taken that is equivalent to 0.5mg/1ml of dosage form was transferred into a 100 ml volumetric flask, 100ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters. (100 µg/ml of Clevidipine)

Preparation of Sample working solutions (100% solution): 2ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent. (10µg/ml of Clevidipine)

Linearity:

Preparation of Standard stock solutions: Accurately weighed 5mg of Clevidipine transferred 50ml and volumetric flasks, 3/4 th of diluents was added and sonicated for 10 minutes. Flasks were made up with diluents and labeled as Standard stock solution (100µg/ml of Clevidipine)

25% Standard solution: 0.25ml each from two standard stock solutions was pipette out and made up to 10ml. (2.5µg/ml of Clevidipine)

50% Standard solution: 0.5ml each from two standard stock solutions was pipetted out and made up to 10ml. (5µg/ml of Clevidipine)

75% Standard solution: 0.75ml each from two standard stock solutions was pipetted out and made up to 10ml. (7.5µg/ml of Clevidipine,)

100% Standard solution: 1.0ml each from two standard stock solutions was pipetted out and made up to 10ml. (10µg/ml of Clevidipine)

125% Standard solution: 1.25ml each from two standard stock solutions was pipetted out and made up to 10ml. (12.5µg/ml of Clevidipine)

150% Standard solution: 1.5ml each from two standard stock solutions was pipettede out and made up to 10ml. (15µg/ml of Clevidipine)

Accuracy:

Preparation of Sample stock solutions: 1ml of vial of injection was taken that is equivalent to 0.5mg/1ml of dosage form was transferred into a 100 ml volumetric flask, 100ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters. (100 µg/ml of Clevidipine)

Preparation of Sample working solutions (100% solution): 1.5 ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent. (10µg/ml of Clevidipine)

Preparation of 50% Spiked Solution: 2ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Preparation of 100% Spiked Solution: 2.0ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Preparation of 150% Spiked Solution: 1.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Acceptance Criteria:

The % Recovery for each level should be between 98.0 to 102

Robustness: Small deliberate changes in method like Flow rate, mobile phase ratio, and temperature are made but there were no recognized change in the result and are within range as per ICH Guide lines.

Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.1ml/min), mobile phase minus, mobile phase plus, temperature minus (25°C) and temperature plus (35°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much effected and all the parameters were passed. %RSD was within the limit.

Sensitivity: 0.3ml Standard stock solutions was pipetted out and transferred to 10ml volumetric flasks and made up with diluents.

LOD sample Preparation: From the above solutions 0.1ml Clevidipine, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluents

LOQ sample Preparation: From the above solutions 0.3ml Clevidipine of, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluent.

Degradation studies:

Oxidation:

To 1 ml of stock solution of Clevidipine, 1 ml of 20% hydrogen peroxide (H2O2) was added separately. The solutions were kept for 30 min at 60^0c. For HPLC study, the resultant solution was diluted to obtain 10μg/ml solution and 10 μl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Acid Degradation Studies:

To 1 ml of stock ssolution Clevidipine, 1 ml of 2N Hydrochloric acid was added and refluxed for 30mins at 60^0c .The resultant solution was diluted to obtain 10μg/ml solution and 10 μl solutions were injected into the system and the chromatograms were recorded to assess the stability of sample.

Alkali Degradation Studies:

To 1 ml of stock solution Clevidipine, 1 ml of 2N sodium hydroxide was added and refluxed for 30mins at 60^0c. The resultant solution was diluted to obtain 10μg/ml solution and 10 μl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Dry Heat Degradation Studies:

The standard drug solution was placed in oven at 105°C for 1 h to study dry heat degradation. For HPLC study, the resultant solution was diluted to 10μg/ml solution and10μl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

Photo Stability studies:

The photochemical stability of the drug was also studied by exposing the 250μg/ml solution to UV Light by keeping the beaker in UV Chamber for 1days or 200 Watt hours/m^2 in photo stability chamber. For HPLC study, the resultant solution was diluted to obtain 10μg/ml solutions and 10 μl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Neutral Degradation Studies:

Stress testing under neutral conditions was studied by refluxing the drug in water for 6hrs at a temperature of 60°. For HPLC study, the resultant solution was diluted to 10μg/ml solution and 10 μl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

RESULTS AND DISCUSSION

Based on drug solubility and P^{ka} Value following conditions has been used to develop the method estimation of Clevidipine.

Trial 1

Chromatographic Conditions

Mobile phase: **Water**: Methanol (40:60 v/v)
Flow rate: 0.3 ml/min
Column: HSS C18 (2.1 x 100mm, 1.8μm)
Detector wave length: 240nm
Column temperature: 30°C
Injection volume: 1.00μL
Run time: 10.0 min

Results: In this Trail peak were eluted but baseline disturbance is seen, so further trail was carried out.

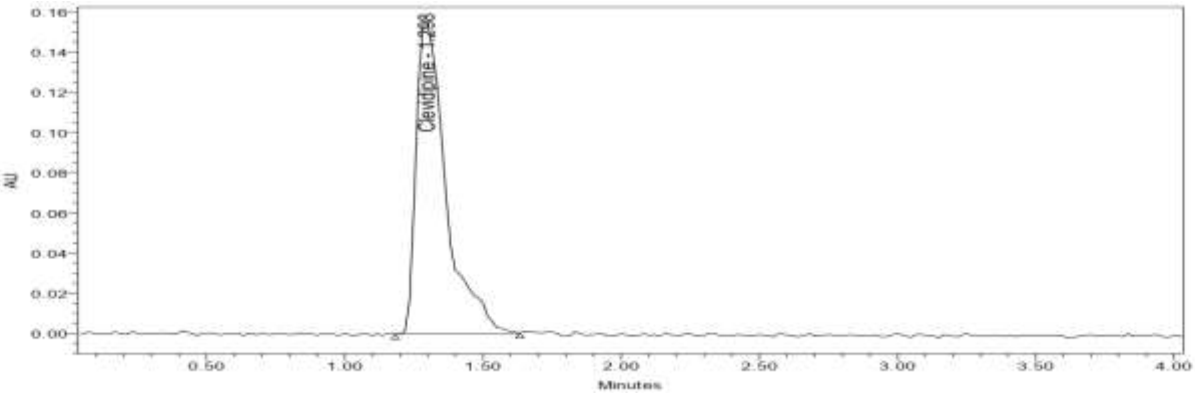

Figure 2 trial chromatogram -1

Trial 2

Chromatographic Conditions

Mobile phase: **Water**: Methanol (70:30 v/v)
Flow rate: 0.3 ml/min
Column: HSS C18 (2.1 x 100mm, 1.8µm)
Detector wave length: 240nm
Column temperature: 30°C
Injection volume: 1.00µL
Run time: 10.0 min

Results: In this Trail peak were eluted but peak split is seen, so further trail was carried out.

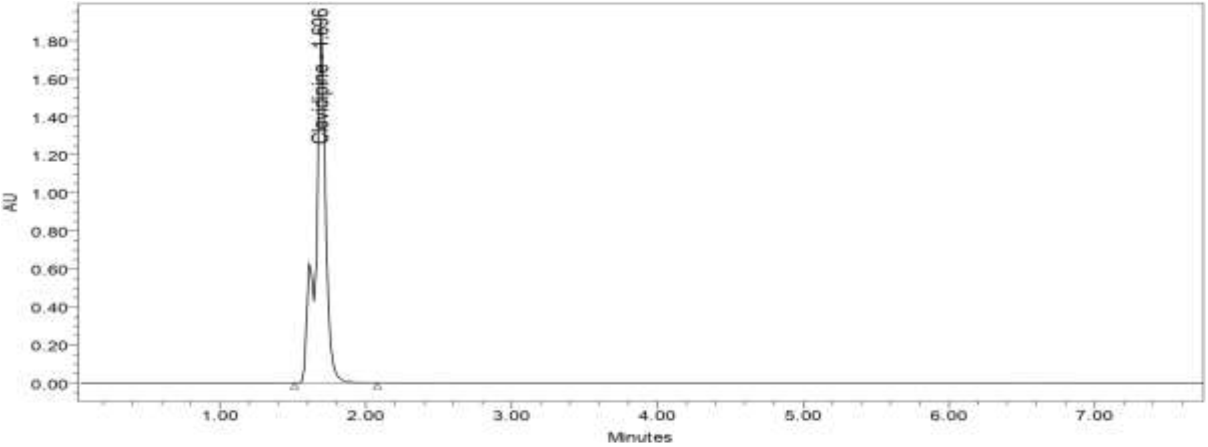

Figure 3 trial chromatogram -2

Trial 3

Chromatographic Conditions

Mobile phase: **OPA**: Methanol (60:40 v/v)
Flow rate: 0.3 ml/min
Column: HSS C18 (2.1 x 100mm, 1.8µm)
Detector wave length: 240nm
Column temperature: 30°C
Injection volume: 1.00µL
Run time: 10.0 min

Results: In this Trail peak were eluted but baseline disturbance is seen, so further trail was carried out.

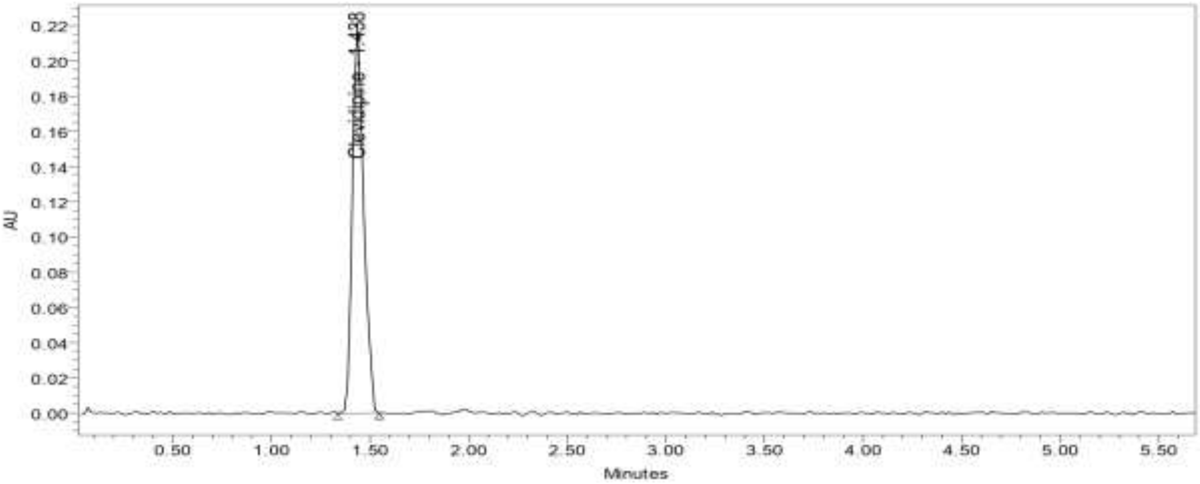

Figure 4 trial chromatogram -3

Trial 4
Chromatographic Conditions
Mobile phase: **ammonium formate**: methanol (90:10 v/v)
Flow rate: 0.3 ml/min
Column: HSS C18 (2.1 x 100mm, 1.8µm)
Detector wave length: 240nm
Column temperature: 30°C
Injection volume: 1.00µL
Run time: 10.0 min
Results: In this Trail peak were eluted but baseline disturbance is seen, so further trail was carried out.

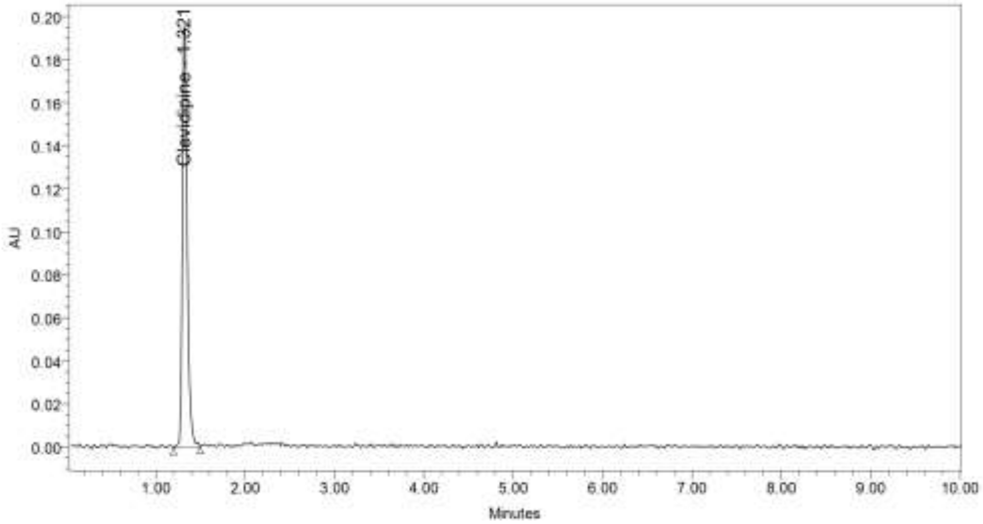

Figure 5 trial chromatogram -4
Optimized Chromatogram
Chromatographic Conditions
Mobile phase: KH_2PO_4: Acetonitrile (60:40 v/v)
Flow rate: 0.3 ml/min
Column: CHS C_{18} (2.1 x 100mm, 1.8µm)
Detector wave length: 240nm
Column temperature: 30°C
Injection volume: 1.00µL
Run time: 2.5 min
Results: all parameters are passed hence this method is optimized

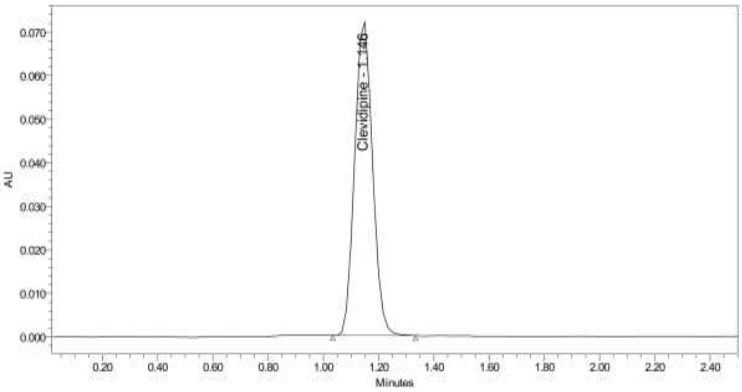

Figure 6 optimized Chromatogram

SYSTEM SUITABILITY

A Standard solution of Clevidipine working standard was prepared as per procedure and was injected five times into the HPLC system. The system suitability parameters were evaluated from standard Chromatograms obtained by calculating the % RSD of retention time, tailing factor, theoretical plates and peak areas from five replicate injections are within range and Results were shown in table 1

Table 1: System Suitability of Clevidipine

S no	**Clevidipine**			
Inj	RT(min)	area	USP Plate Count	Tailing
1	1.135	517399	3405	1.09
2	1.135	524388	3401	1.09
3	1.138	524846	3433	1.08
4	1.144	519935	3454	1.06
5	1.145	524384	3450	1.06
6	1.146	526588	3427	1.07
area		522923		
stdev		3488.7		
RSD		0.7		

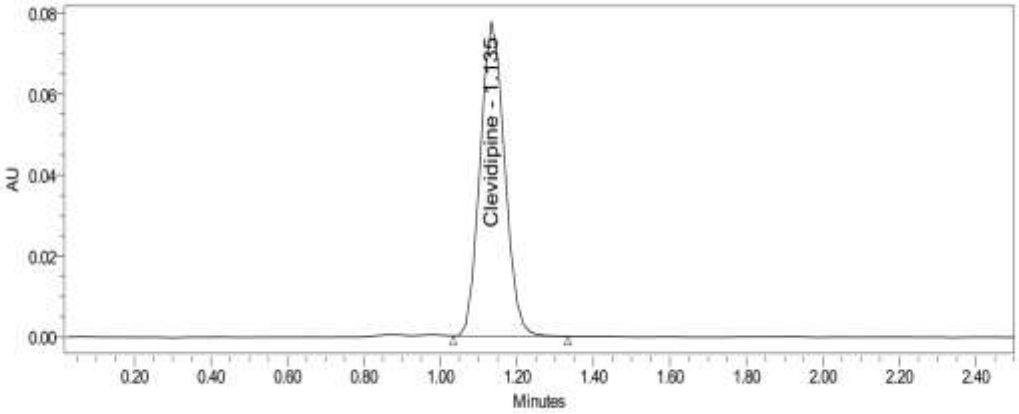

Figure7 System suitability Chromatogram

Discussion: According to ICH guidelines plate count should be more than 2000, tailing factor should be less than 2 and resolution must be more than 2. All the system suitable parameters were passed and were within the limits.

Specificity:

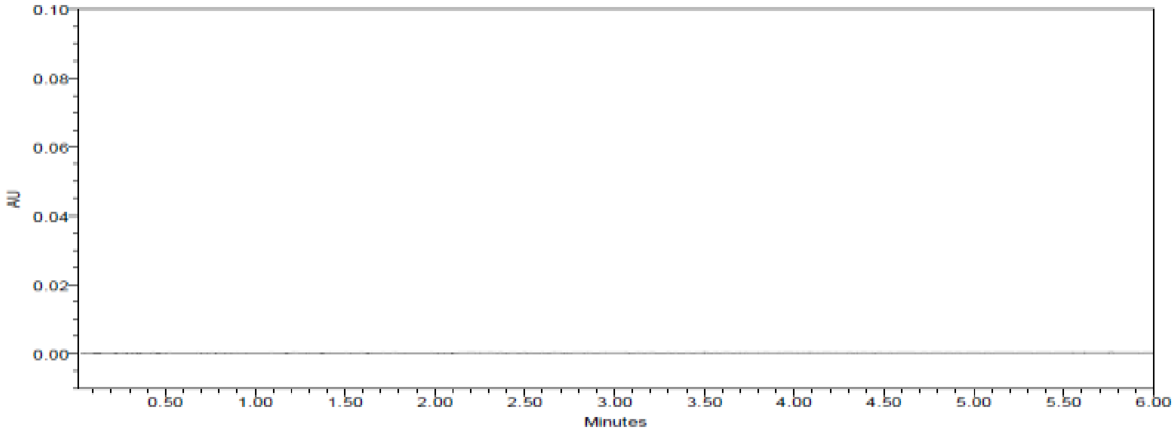

Figure8 blank Chromatogram

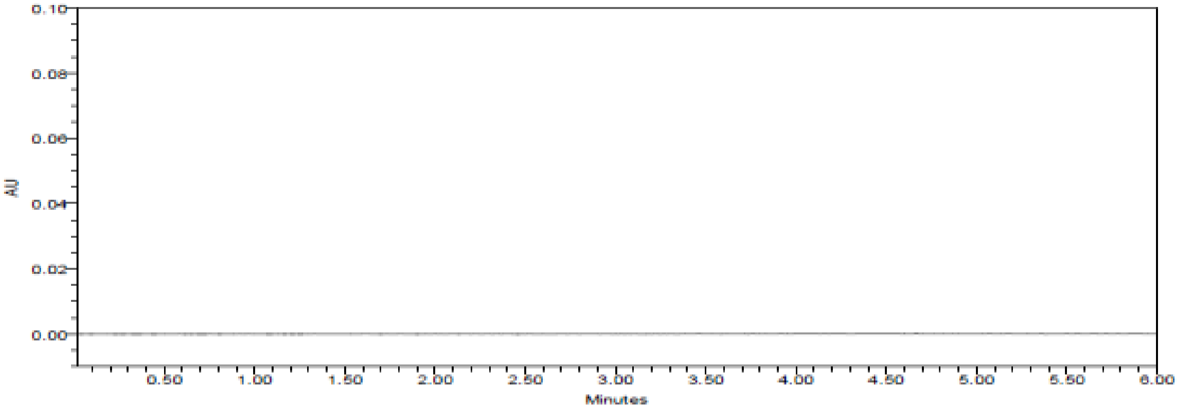

Figure 9 Placebo Chromatogram

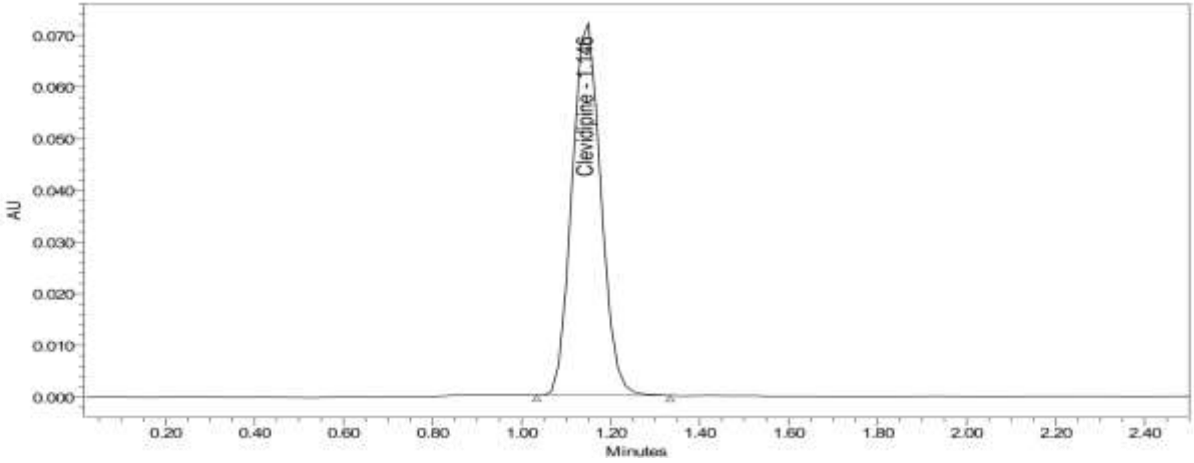

Figure10 Typical Chromatogram

Discussion: Retention times of Clevidipine was1.146 min. respectively. We did not find and interfering peaks in blank and placebo at retention times of these drugs in this method. So, this method was said to be specific.

Precision:

Repeatability: Six working sample solutions of 25ppm are injected and the % Amount found was calculated and %RSD was found to be 0.4 and chromatogram was shown in fig 6.2.

Table 2 Repeatability data

S.No	Peak Area
1	521327

2	522183
3	525720
4	523308
5	523752
6	525618
AVG	523651
STDEV	1779.5
%RSD	0.3

Discussion: Multiple sampling from a sample stock solution was done and six working sample solutions of same concentrations were prepared, each injection from each working sample solution was given and obtained areas were mentioned in the above table Average area, standard deviation and % RSD were calculated for two drugs. % RSD obtained as 0.3% respectively for Clevidipine. As the limit of Precision was less than "2" the system precision was passed in this method.

Intermediate precision: Six working sample solutions of 25ppm are injected on the next day of the preparation of samples and the % Amount found was calculated and %RSD was found to be 0.3 and chromatogram was shown in fig 6.3.

Table 3 Intermediate precision data

S.No	Peak Area
1	520881
2	517807
3	515820
4	512919
5	520100
6	518203
AVG	517622
STDEV	2915.4
%RSD	0.6

Discussion: Multiple sampling from a sample stock solution was done and six working sample solutions of same concentrations were prepared, each injection from each working sample solution was given on the next day of the sample preparation and obtained areas were mentioned in the above table. Average area, standard deviation and % RSD were calculated for two drugs and obtained as 0.6% respectively for Clevidipine. As the limit of Precision was less than "2" the system precision was passed in this method.

6.3 LINEARITY:

To demonstrate the linearity of assay method, inject 6 standard solutions with concentrations of about 2.5ppm to 15ppm of Clevidipine. Plot a graph to concentration versus peak area. Slope obtained & Y-Intercept was = 51673x + 2873.4and Correlation Co-efficient was found to be 0.999 and Linearity plot was shown in Fig 6.10.

Table 4 Linearity Concentration and Response

Linearity Level (%)	**Concentration (ppm)**
6.25	216762
12.5	434287
18.75	647026
25	867261
31.25	1069109
37.5	1255650

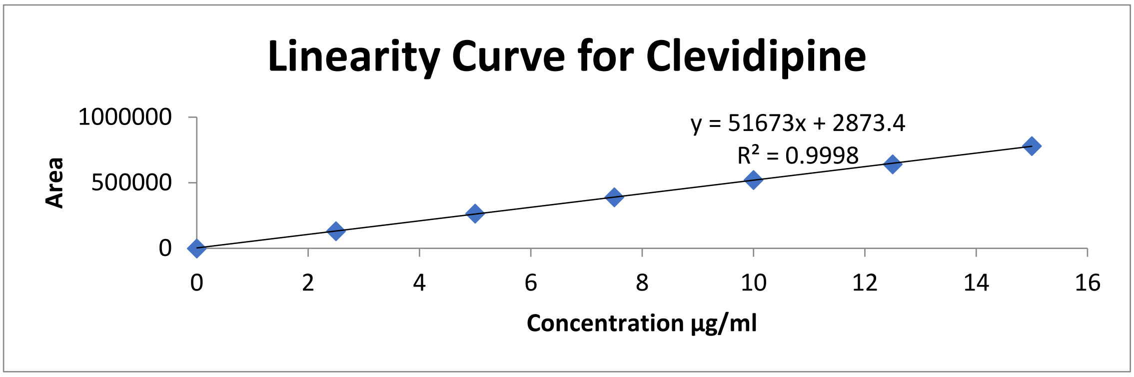

Figure 11 Linearity curve fir Clevidipine

6.4 Accuracy: Three Concentrations of 50%, 100%, 150% are Injected in a triplicate manner and %Recover was calculated as 99.60% and %RSD was found to be 1.00 and chromatograms were shown in fig 6.11-6.13.

Table 5 Accuracy data

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	5	4.972	99.44	99.60%
	5	4.970	99.40	
	5	4.975	99.50	
100%	10	9.920	99.20	
	10	9.906	99.06	
	10	10.069	100.69	
150%	15	14.89	99.30	
	15	14.99	99.96	
	15	14.98	99.88	

Sensitivity:

Table 6 Sensitivity table of Clevidipine

Molecule	LOD	LOQ
Clevidipine	0.01	0.03

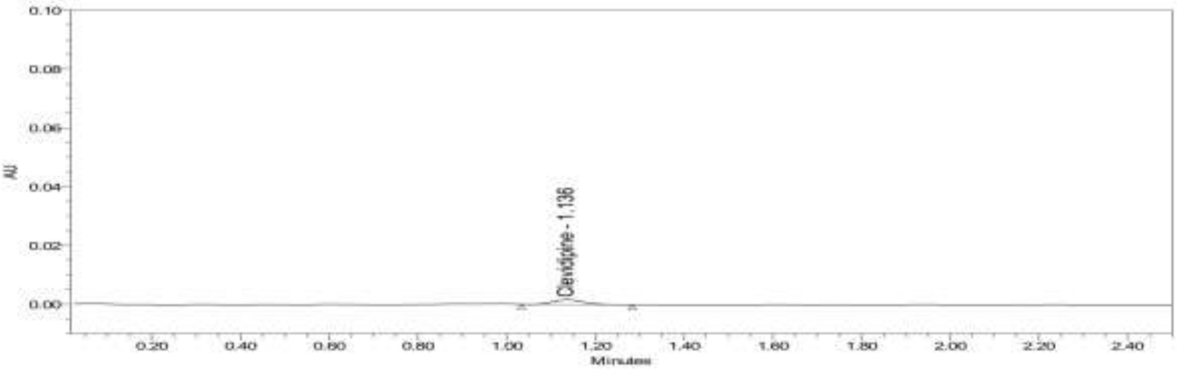

Figure 12. LOD Chromatogram of Clevidipine

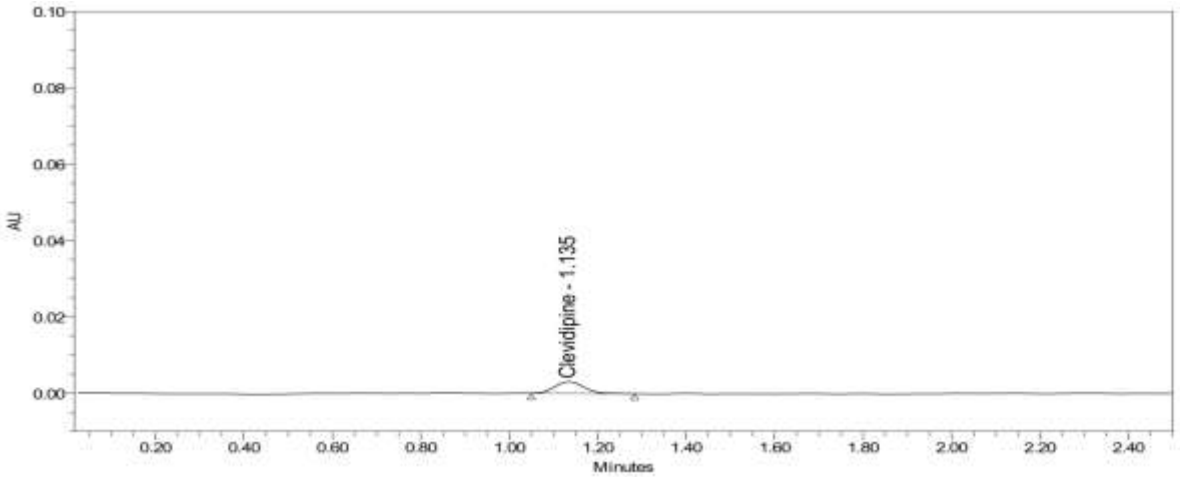

Figure 13 . LOQ Chromatogram of Clevidipine

Robustness: Small Deliberate change in the method is made like Flow minus, flow plus, Mobile phase minus, Mobile phase plus, Temperature minus, Temperature Plus. %RSD of the above conditions are calculated.

Table 7 Robustness Data

Condition	**% RSD of Clevidipine**
Flow rate (-) 0.9ml/min	1.6
Flow rate (+) 1.1ml/min	1.8
Mobile phase (-) 55B:45A	1.4
Mobile phase (+) 65B:45A	0.2
Temperature (-) 25°C	1.8
Temperature (+) 35°C	1.2

ASSAY OF MARKETED FORMULATION

The label claim 0.5 mg /ml (Celviprex) used for assay for the Marketed Sample. The Standard solution and sample solution were injected separately into the system and chromatograms were recorded and drug present in sample was calculated and was found to be 99.94%.

Table 8 Assay of Formulation

Sample No	**Sample Area**	**Standard Area**	**%Assay**
1	521327	517399	99.50
2	522183	524388	99.66
3.	525720	524846	100.33
4.	523308	519935	99.87
5.	523752	524384	99.96
6.	525618	526588	100.31

AVG	523651	522923	99.94
STDEV	1779.5	3488.7	0.34
%RSD	0.3	0.7	0.3

Degradation Studies:

Degradation studies were performed with the formulation and the degraded samples were injected. Assay of the injected samples was calculated and all the samples passed the limits of degradation

Table9 Degradation Data of Clevidipine

S.NO	Degradation Condition	% Un Drug Degraded	% Drug Degraded
1	Acid degradation	93.66	6.34
2	Alkali degradation	94.27	5.73
3	Oxidation	94.62	5.38
4	Thermal	96.58	3.42
5	UV	97.55	2.45
6	Water	99.18	0.82

Summary

Table 10 Summary Table for Clevidipine

Parameters		Clevidipine	Limit
Linearity Range (µg/ml)		2.5-15µg/ml	R< 1
Regression coefficient		0.999	
Slope(m)		51673	
Intercept(c)		2873.4	
Regression equation (Y=mx+c)		y = 51673x + 2873.4	
Assay (% mean assay)		99.94%	90-110%
Specificity		Specific	No interference of any peak
System precision %RSD		0.7	NMT 2.0%
Method precision %RSD		0.3	NMT 2.0%
Accuracy %recovery		99.60%	98-102%
LOD		0.01	NMT 3
LOQ		0.03	NMT 10
Robustness	FM	1.6	%RSD NMT 2.0
	FP	1.8	
	MM	1.4	
	MP	0.2	
	TM	1.8	
	TP	1.2	

CONCLUSION

A simple, Accurate, precise method was developed for the estimation of the Clevidipine in pharmaceutical dosage form. Retention time of Clevidipine was 1.146. Standard %RSD of Clevidipine were and found to be 0.7. %Recovery was obtained as 99.60%. LOD, LOQ values obtained from regression equations were 0.01, 0.03. Regression equation of Clevidipine is y = 51673x + 2873.4. Retention times were decreased and that run time was decreased, so the method developed was simple and economical that can be adopted in regular Quality control test in Industries.

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