

Original Article

QbD Approach and Chemo metric Method Development for the estimation of Metoprolol succinate and Cilnidipine in combined solid dosage form

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ABSTRACT

Background: Development of several pharmaceutical processes including analytical methods by applying Quality by design assists in ensuring the robustness of the method. USFDA and other regulatory agencies have recommended implementation of Quality by design (QbD) a systematic process for pharmaceutical development along with its significance. **Objective:** Chemo metric assisted UV-VIS spectrophotometric analytical method based on QbD was developed for the estimation of metoprolol succinate (MET) and cilnidipine (CIL) from the combined dosage forms. **Method:** Nature of spectra focused applicability of absorbance correction and amplitude modulation methods for estimation of both drugs from the formulations; and 50 % alcohol was being the common solvent. For both this method 221 nm and 242 nm was the wavelength for measurement of absorbance of metoprolol and cilnidipine respectively. Effect of input variables on spectrum characteristics were studied for selection of critical parameters and developed method was validated as per ICH Q 2 R1 regulatory guidelines. **Result and conclusion:** Linearity of the drugs was ascertained over the conc range 1-36 µg/ml (microgram/ml) for MET and 1-16 µg/ml for CIL. The percentage purity of assay in method II was found 103.773 % for MET and 96.825 % for CIL; and the accuracy study data of method I were varied 2.04859 for MET and 1.26321 for CIL. Precision study was shown acceptable data as % RSD in method I data varied 0.58894 for MET and 1.15116 for CIL. The developed method is rigid, robust and efficient for the estimation of MET and CIL from the composition of dosage form.

Keywords: Metoprolol succinate, Cilnidipine, QbD, ICH, Absorbance correction method, Amplitude modulation method

Cilnidipine (CIL) chemically 1, 4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylic acid 2-methoxyethyl (2E)-3-phenyl-2-propenyl ester [1] is a dihydropyridine calcium channel blocker given orally in the management of hypertension [2] Reported analytical methods for estimation of cilnidipine were includes alone by UV spectrophotometric method [3], UV spectrometric methods with metoprolol [4, 5] alone UV-HPLC method [6], Stability indicating HPLC [7] QbD based HPLC [8] chromatographic methods [9-12] and have been found in the literature. Metoprolol succinate (MET) is a beta blocker; used in the treatment of hypertension, angina and to reduce myocardial infarction [2]. Chemically it is (RS)-1-(Isopropylamino)-3-[p-(2- Methoxyethyl) phenoxy]-2-propan-2-ol succinate [1].

Literature survey revealed that various analytical methods have been reported for estimation of MET such as alone UV spectrophotometric method [13-16], with other drugs UV spectrophotometric method [17-22], bio analytical method [23], MET alone by RP-HPLC [24], with other drug by RP-HPLC [25-30], stability indicating HPLC [31, 32], designed and eco-friendly TLC densitometry [33] and HPTLC [34] in combination with other drug. Cilnidipine and Metoprolol succinate are official in Indian Pharmacopoeia [35], whereas Metoprolol is official in BP [36]. Chemical structures of both drugs are shown in (Fig 1). Quality by design concept is applied for the development of pharmaceutical processes to assure a predefined product quality.

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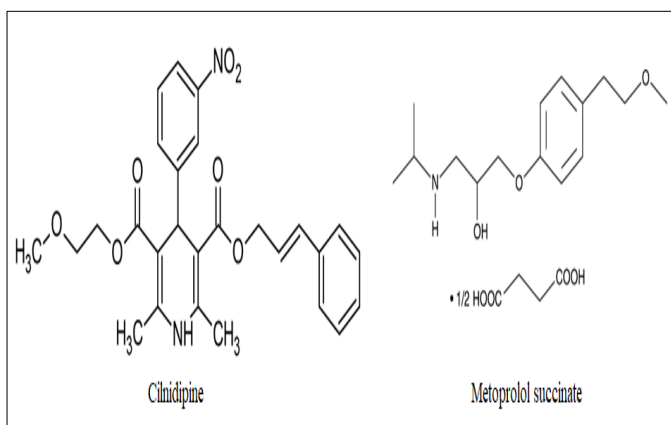


Fig 1: Chemical structure of Drug molecule

QbD concepts are mentioned in ICH guidelines Q 8(R2) (Pharmaceutical development), Q9 (Quality risk management), and Q10 (Pharmaceutical quality system) [37-39] shown in Fig 2. ICH guidelines Q8 (R2) [40] defines QbD as a “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management”. QbD approach in analytical method summarizes a complete understanding of how the analytical technique attributes and operating conditions affect the analytical performance. Factors to study in analytical quality by design (AQbD) approach may include the type of analytical technique chosen, reagents used and instrument parameters. QbD was applied to build rigid robust method through risk assessment at early stage and defining the design space at the later stage.

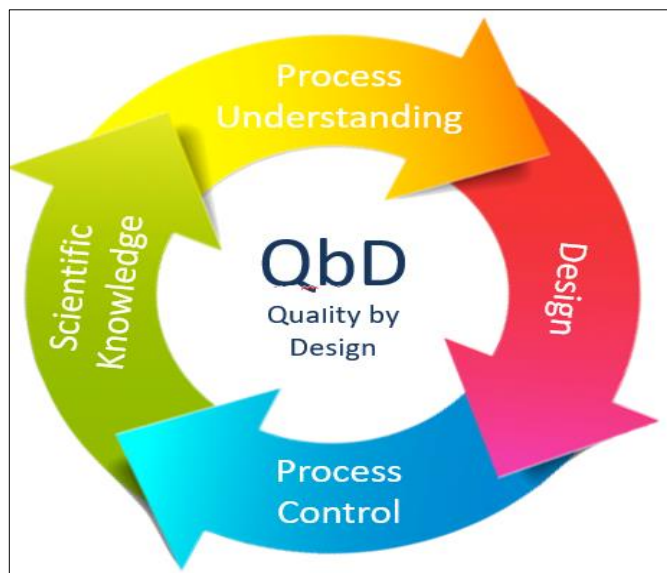


Fig 2: Analytical QbD approach

There are similar advantages of applying QbD principles to analytical methods as to manufacturing processes and product [41]. A QbD approach can be beneficial in the development of suitable, robust, low cost and eco-friendly (eco-friendly

solvent, chemicals) method which is applicable at any stage of the lifecycle of the product. Also some regulatory guidelines have mentioned flexibility of changing analytical method without revalidation if the AQbD approach has been implemented during analytical method development. The first stage of AQbD approach is to fix an analytical target profile (ATP) for the method. ATP defines the goal of the analytical method development process and it is the sign of method performance [42, 43]. For analytical method validation ICH Q2 (R1) has given various method performance characteristics for an analytical method. Thus a QbD based UV spectrophotometric was developed, QbD approach was implemented with the study of the effect of method input variables on spectral shape, intensity of absorbance, and absorbance maxima $\lambda_{\max}$ and critical parameters were selected for the proposed method and method was validated as per ICH guidelines Q2 (R1).

MATERIALS AND METHODS

Instrumentation: Analysis was performed with a Shimadzu Double beam UV-Visible spectrophotometer 1900i and 1700 (Shimadzu, Kyoto, Japan) with spectral bandwidth of 2 nm and wavelength accuracy of ± 1 nm with 10 mm matched Quartz cells was used. Electronic balance Afcoset balance (The Bombay Burmah Trading corpo Ltd) with accuracy ± 0.1 mg Model No. ER 200A was utilised for weighing and for degassing the solution Digital Ultrasonic cleaner 1.8 Ltr (Labman scientific Instruments Chennai) was used.

Reagents and Chemicals: Pharmaceutically pure sample of MET was procured from Macleods Pharmaceuticals Ltd. Mumbai and CIL from Swapnroop drugs and pharmaceuticals, Aurangabad, Maharashtra, India procured as a gift samples and the commercial formulation Cilacar-M manufactured by J B Chemicals and Pharmaceuticals containing cilnidipine 10 and metoprolol 50 mg was procured from the local market.

AQbD approach application in method development: AQbD approach was applied to study the influence of input variable parameters on spectrophotometric analytical method performance shown in (Fig 3).

Solvent selection: CIL is very soluble in N, N-Dimethyl acetamide, freely soluble in acetone, soluble in methanol and practically insoluble in water, whereas MET is freely soluble in water, ethanol, methanol and ethyl acetate;. Although the solubility of the procured drugs were studied in alcohol 90%, 0.1 N HCl and 0.1 N NaOH separately; and found that CIL is insoluble in both these solvents however MET is soluble in 0.1 N NaOH. Alcohol 90% was selected as common solvent as both drugs have solubility. Each solution with known conc of analyte was scanned in UV range of 400 nm to 200 nm. It was found that suitable solvent is alcohol 90% with respect to stable, robust and precise in producing result.

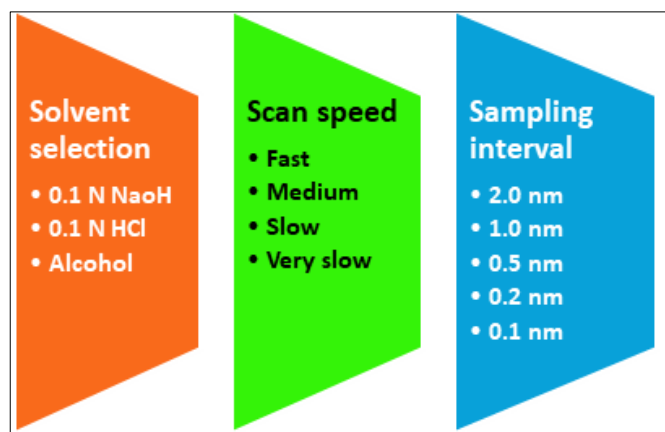


Fig 3: Diagram showing the relationship between input variable parameters and the spectrophotometric method performance characteristics

Preparation of stock solutions and standard solutions: 10 mg each of drug CIL and MET were separately and accurately weighed; and transferred into separate 25 ml volumetric flask. Dissolved into alcohol 90% solvent and volume was made to 25 ml with solvent. Subsequent standard solution of drug MET with conc 16 µg/ml and CIL with conc 8 µg/ml were prepared by diluting aliquot of stock solution to 10 ml with 50% alcohol into 10 ml capacity volumetric flask.

Selection of method, wavelength and conc range: From UV spectra it was found that CIL has measurable absorbance at 242 nm (Fig 4) and less interference was observed by MET; similarly MET has maximum absorbance at 221 nm (Fig 4) and measurable interference having constant absorptivity by CIL was accounted. Chemo metric method i.e. absorbance correction method was applied and which was reasonable remedy to overcome interference at each other's absorbance, and other method was amplitude modulation method. From the nature of spectra to study linearity, working conc range 1 to 16 µg/ml for CIL and 1 to 36 µg/ml for MET was selected. Also combined drug solution was prepared simulated to marketed formulation. Selected critical parameters based upon above discussion, observations are listed in and by using these; method was validated as per ICH guidelines and by analysing marketed preparations.

Experimental Method for estimation: From the overlain spectra absorbance correction method was applicable for estimation of both the analytes from the combined dosage form.

Method-I: Absorbance correction method for estimation of MET and CIL:

MET was shown maximum absorbance i.e. $\lambda_{\max}$ at 221 nm where measurable interference with constant absorptivity by CIL found and CIL has maximum absorbance i.e. $\lambda_{\max}$ at 242 nm where negligible interference observed by MET. At 242 nm the $\lambda_{\max}$ of CIL, MET was shown consistency in the

absorptivity; hence two wavelengths 221 and 242 nm were considered as 1 and 2 respectively for the said method to estimate MET and CIL. The equation $A = abc$ was applied for x (MET) and y (CIL) determination. Conc of working standard solutions of MET and CIL containing 28 mcg/ml and 8 mcg/ml conc respectively were separately prepared and used for the method.

$$C_x = \frac{A_2 \cdot a_{y1} - A_1 \cdot a_{y2}}{a_{x2} \cdot a_{y1} - a_{x1} \cdot a_{y2}}$$

$$C_y = \frac{A_s - a_{x2} \cdot C_x}{a_{y2}}$$

Where C_x = Conc of MPS in sample solution

A_1 and A_2 = absorbance of sample solution at 1 and 2 wavelength

a_{y1} and a_{y2} = absorptivity of CIL at 1 and 2 wavelength of standard solution

a_{x1} and a_{x2} = absorptivity of MET at 1 and 2 wavelength of standard solution

C_y = Conc of CIL in sample solution

A_s = Absorbance of Sample solution at 2 wavelength

Method-II: Amplitude Modulation method: This method comprises the conversion of zero order/normal spectra to its first, second or higher derivative spectrum. The amplitude is directly proportional to the conc of solution provided Beer's law is obeyed by spectrum. In derivative method zero crossing wave length for both drugs is found such that at the zero crossing of one drug the other drug should show substantial absorbance Here standard solutions 16 µg/ml each of metoprolol and cilnidipine were prepared in 10 ml volumetric flask and scanned from 400 to 200 nm wavelength range against ethanol 50% as blank. Absorption spectra of both drugs were recorded and the found $\lambda_{\max}$ of MET and CIL were stated in earlier discussed method. From overlain spectra CIL has substantial interference due to absorption at wavelength 221 nm and MET shows negligible absorption at 242 nm, hence it was decided to apply derivative method. Zero order spectra of both drug was modulated and converted to first order derivative spectra. From overlain spectra, it clearly shows that no interference or zero absorbance of MET was found at 263 nm hence it was selected $\lambda_{\max}$ of CIL and 229.5 nm was zero crossing of CIL, so it was selected as $\lambda_{\max}$ of MET. Both drugs were obeying Beer's law in first order derivative mode at the respective wavelength.

Validation of the Method: Selected critical parameters should meet the performance characteristics of the analytical method so as to attain analytical target profile of the method. An ICH guideline Q2 R1 was applied to study methods

performance with critical parameters in order to implement AQbD approach. The method was validated as per ICH guidelines.

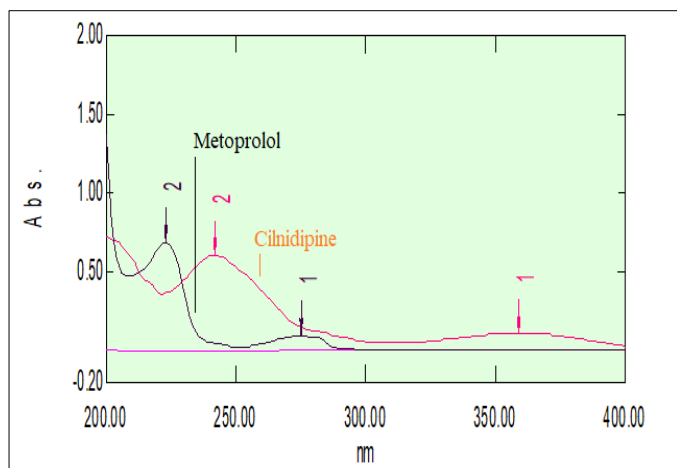


Fig 4: UV spectra of Cilnidipine and Metoprolol succinate in ethanol

System suitability: System suitability is studied to demonstrate the suitability of the developed procedure under consideration for the analytical method. Six replicates of working standard solutions with conc 16 $\mu\text{g/ml}$ and 8 $\mu\text{g/ml}$ each of MET and CIL respectively were prepared separately and absorbance was recorded, SD and % RSD of the response was calculated.

Linearity: The linearity of an analytical method is its ability to obtain response i.e. absorbance which is directly proportional to the conc of analyte. Series of working standard solutions were prepared in conc. range of 1-36 $\mu\text{g/ml}$ for MET and 1-16 $\mu\text{g/ml}$ for CIL and scanned in 400 to 200 nm range in spectrum mode of the spectrophotometer, absorbance of the standard solutions were recorded at their respective wavelength; i.e. 221 for MET and 242 nm for CIL in spectrum order. Microsoft office excel software tool was used to obtain the standard regression curve and its analysis as slope, intercept, and correlation coefficient.

Assay of formulation: Assay was carried out by proposed methods and assay was validated by statistical parameters.

Estimation of formulations by absorbance correction and amplitude modulation method: Tablet powder equivalent to 12.5 mg MET and 2.5 mg CIL was weighed and transferred into 25 ml volumetric flask. Dissolved into 90% alcohol, mixed well for 10 mins and volume was made to 25 ml with the solvent. Solution was filtered through what man filter paper and aliquots of solution were further diluted with the 50% alcohol to obtain tablet sample solution. Solution was scanned in the range of 400 to 200 nm to obtain absorbance of tablet solution at 221 nm and 242 nm in spectrum order. Also spectrum converted to first order derivative and absorbance

was recorded at 229.5 and 263 nm. Obtained absorbance were utilised to estimate unknown conc of formulation; and results were statistically validated to obtain % of nominal conc, standard deviation and % of RSD.

Accuracy and Precision: The accuracy of an analytical method expresses the closeness of an agreement between test result and true result. Accuracy study was performed by recovery study i.e. standard addition method; diluted standard solutions of MET and CIL were prepared and standard solutions added in 100 % proportionate to the tablet solution. Three replicates at this level was prepared, absorbance measured and % of conc, SD and RSD were calculated. The precision study was carried out by performing assay of tablet six times; also the reproducibility in result was studied by inter day and intraday precision.

Limit of Detection (LOD) and Limit of Quantitation (LOQ): The LOD and LOQ of MET and CIL by the proposed method were determined using calibration graph method and calculated as $3.3\sigma/s$ and $10\sigma/s$ for LOD and LOQ respectively; σ is the standard deviation of calibration curve and s is the slope of regression line.

Robustness and Ruggedness: It is measure of capacity of analytical procedure to remain unaffected by small but deliberate variations in method parameter.

RESULTS

Method development comprises numerous steps, and of which solvent selection, selection of method for measurement are significant one. Uses of aqueous solvents, eco-friendly solvents like hydrotropic have got remarkable weightage due to low cost, readily available and environmentally sound. Drugs underlying analysis must have appreciable solubility in the selected solvent. Chemical structure of the drug and physico-chemical properties available in the literature guides about use of appropriate solvent in the method.

From UV spectra two wavelengths were selected as 221nm (λ_{max} of MET) and 242 nm (λ_{max} of CIL) shown in Fig 5 for calculation of both drugs in combined solution shown.

System Suitability: The absorbances of six replicates of standard solutions of tabulated respective conc are reported in Table No 1. The SD and % RSD was found for MET and CIL and meets the system suitability requirements indicates method was suitable for analysis.

Linearity: The calibration curve of both drugs was found to be linear in the conc range of 1-36 $\mu\text{g/ml}$ for MET and 1-16 $\mu\text{g/ml}$ for CIL in normal spectrum as shown in Fig 6 and in first order derivative mode Fig 7. The regression equation of line and its parameters slope, r^2 value and intercept are tabulated in Table No 2, which proved the linear relationship between conc and obtained response.

Assay: The assay was carried out by the proposed method. The overlaid spectra obtained in amplitude modulation method are shown in Fig 8. The assay of formulation was carried out by proposed method and calculated % of nominal conc and RSD was found within acceptable limits are summarized in Table No 3. The results indicated applicability of the method for estimation of formulation.

Accuracy and Precision: The results of accuracy are summarised in Table No 4, the obtained results were within acceptable limit; and methods accuracy was justified by calculating % drug content. The precision study was carried out by performing assay of solutions; further the

reproducibility in result was studied by interday and intraday precision. The values obtained SD and % RSD was shown methods precision and are summarised in Table No 4.

Limit of Detection (LOD) and Limit of Quantitation (LOQ) and Robustness and Ruggedness: The LOD and LOQ of CIL and MET were found in acceptable limits by the proposed method. Robustness was studied and capacity of analytical procedure to measure analyte was remain unaffected by small but deliberate variations in method parameter. The analytical method was found rugged during development; similarity the result was produced by performing the analysis by different analyst.

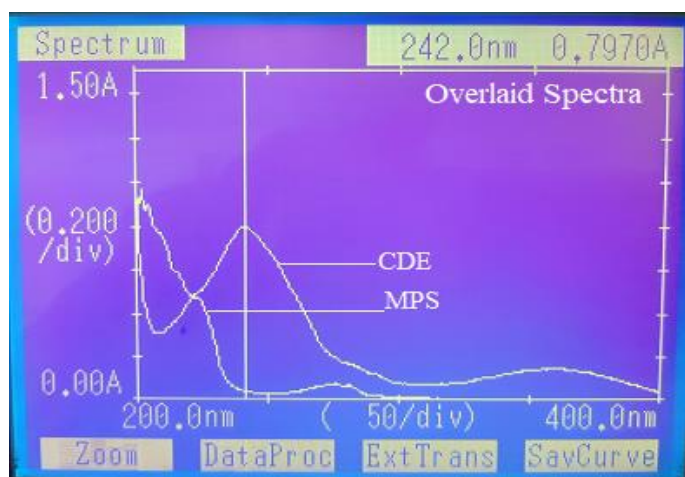


Fig 5: Overlaid spectra of MET and CIL

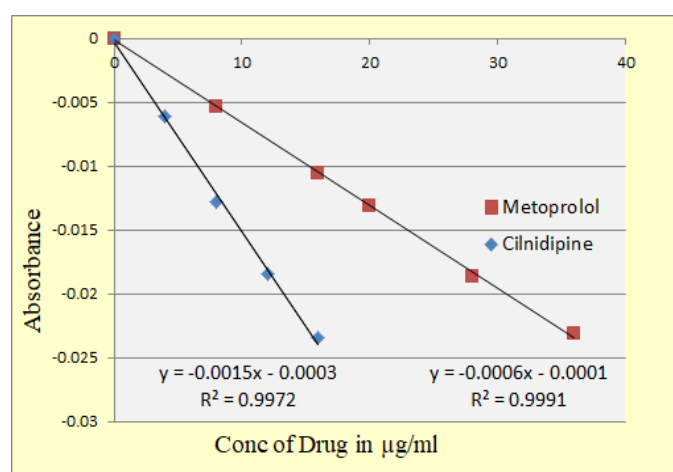


Fig 7: Calibration curve of MET and CIL in First order derivative

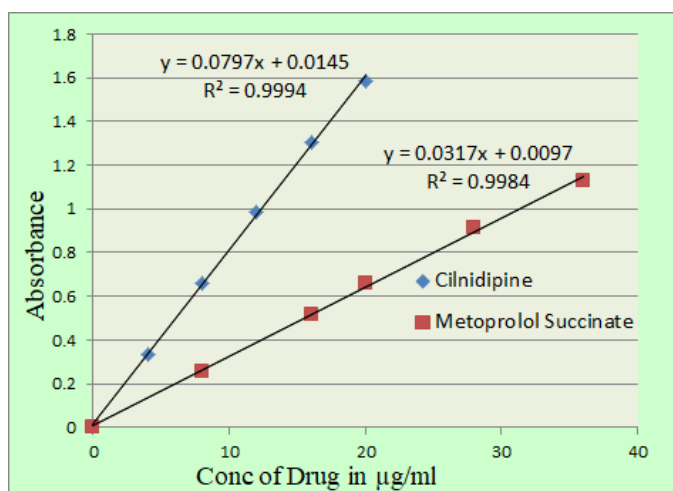


Fig 6: Normal spectrum kind Calibration curve of MET and CIL

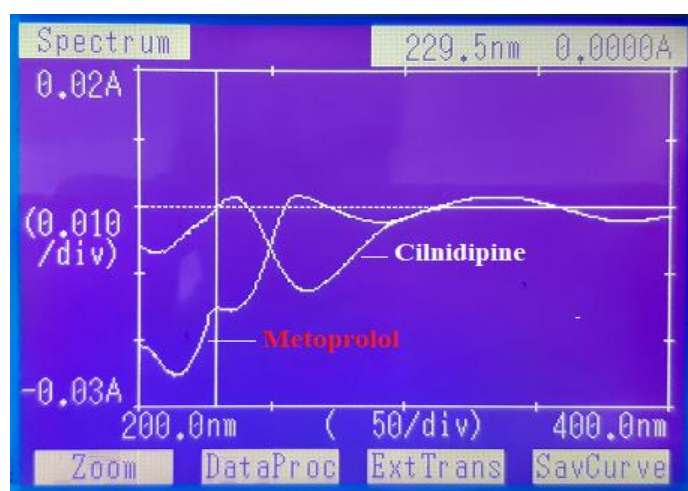


Fig 8: Overlaid spectra obtained in amplitude modulation method

Table No 1: System suitability study of MET and CIL

Sr No	Conc in µg /ml	Absorbance of MET*	Conc in µg /ml	Absorbance of CIL*
1	16µg/ml	0.5157	8 µg /ml	0.6519
2	SD	0.004676	SD	0.004809
	RSD %	0.9060	RSD	0.73774

*Mean of six determinations

Table No 2: Parameters of regression equation obtained in Microsoft excel

Parameters	MET	CIL	MET	CIL
	Linearity study in Normal		Linearity in derivative	
Detection wavelength	221	242	229.5	263
Beer’s law limit (µg/ml)	1–36 µg/ml	1–16 µg/ml	1–36 µg/ml	1–16 µg/ml
Correlation coefficient (r²)	0.9984	0.9994	0.9991	0.9972
Regression equation (y = mx + c)	Y = 0.0317X + 0.0097	Y = 0.0797X + 0.0145	Y=-0.0006X- 0.0001	Y=-0.0015X-0.0003

Table No 3: Results of assay of formulation by proposed method

Formulation	Drug	Label Claim (mg/Tablet; n=6)	Amount found/mg	Drug Content %	Std Deviation	% RSD
Method-I	MET	50	47.084	94.167	4.16146	4.4192
	CIL	10	9.681	96.787	1.76063	1.80967
Method-II	MET	50	51.886	103.773	1.88651	1.81791
	CIL	10	9.682	96.825	2.74934	2.83949

Table No 4: Results of accuracy and precision

Sr. No.	Parameter	Level of study	Drug Name	% Mean	S.D.	% RSD
Method - I	Precision	Intraday precision	MET	94.877%	0.58894	0.62074
			CIL	97.744%	1.15116	1.17712
	Accuracy	100%	MET	96.308%	2.04859	2.12712
			CIL	94.845%	1.26321	1.33188
Method - II	Precision	Intraday precision	MET	102.066%	1.66533	1.62208
			CIL	99.476%	2.26024	2.27215
	Accuracy	100%	MET	97.646%	1.17675	1.20511
			CIL	96.667%	1.15971	1.19452

DISCUSSION

Both the drugs were estimated from the combined formulation by absorbance correction and amplitude modulation method. Results were found within acceptable limits, statistical data obtained were shown rigidity of the method. The validated method was employed alcohol as solvent thus become towards eco-friendly.

CONCLUSION

The proposed methods are precise, accurate, robust and reproducible hence can be routinely used for simultaneous estimation of cilnidipine and metoprolol succinate from combined dosage form.

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