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Novel UV Spectrophotometer Methods for Quantitative Estimation of Concensi (Amlodipine 10mg and Celecoxib 200mg) Using Hydrotropic Solubilizing Agents

Durga Kushwaha*, Sunil Diwakar[1], R. K. Roy[1], Sarita Karole[1], Hemant Kushwaha[1], Prabhat Jain[2]

[1]Oriental College of Pharmacy, Raisen Rd, Patel Nagar, Bhopal, (MP) 462022

[2]Scan Research Laboratories, Sector A H No. 109, J K Road, Indrapuri, Bhopal, MP 462023

ABSTRACT

Two simple, accurate, novel, safe and precise methods were developed for the simultaneous estimation of poorly water-soluble drugs Amlodipine besylate (AMD) and Celecoxib (CLX) in a in-house formulation using 2M sodium benzoate as a hydrotropic solution. AMD and CLX show maximum absorbances at 243 and 255 nm, respectively. Sodium benzoate did not show any absorbance above 225 nm and thus no interference in the estimation of drugs was seen. AMD and CLX follow Beer's law in the concentration range of 2-10μg/ml and 10-50μg/ml (r^2 = 0.9992 and 0.9995). Method-A employs the simultaneous equation method using 243 and 255 nm as two analytical wavelengths; method-B employs the absorption ratio method, which uses 243 and 250nm as two analytical wavelengths for estimation of AMD and CLX. The mean percent label claims of in-house formulation were found to be 98.74± 0.912and 99.22± 1.012in method-1, 97.89± 0.872and 99.49± 0.903 in method 2 for AMD and CLX, respectively. The developed methods were validated according to ICH guidelines and values of accuracy, precision and other statistical analysis were found to be in good accordance with the prescribed values therefore both methods can be used for routine monitoring of AMD and CLX in industry in the assay of bulk drug and pharmaceutical formulation.

Keywords: Amlodipine besylate, Celecoxib, Simultaneous equation method; Absorption ratio method, Hydrotropic solubilizing agents

INTRODUCTION

Amlodipine besylate (AMD) chemically [3-ethyl5-methyl(4RS)-2-[(2-aminoethoxy) methyl]-4- (2-chlorophenyl)-methyl-1-dihydropyridine-3,5-dicarboxylatebenzenesulfonate (Figure 1a) is a dihydropyridine long acting calcium-channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscles and cardiac muscles, which in turn affects their contractile process and results in reduced blood pressure. It is used in the treatment of hypertension and angina.

Amlodipine besylate have an absolute bioavailability of 64 to90% and half-life of about 30-50 hours[1-4]. Celecoxib (CLX) is chemically designated as 4-[5-(4- methylphenyl)-3-7(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (Figure 1b) and is a diaryl substituted pyrazole [5, 6]. The mechanism of action of CLX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of Cyclooxygenase-2 (Cox-2). It is supplied only in tablets and capsules for oral administration. CLX is practically insoluble in water which precludes its use in parenteral and oral solutions dosage forms[7]. Formulation of lipophilic drugs is frequently hampered by their poor aqueous solubility which again can limit their therapeutic applications.
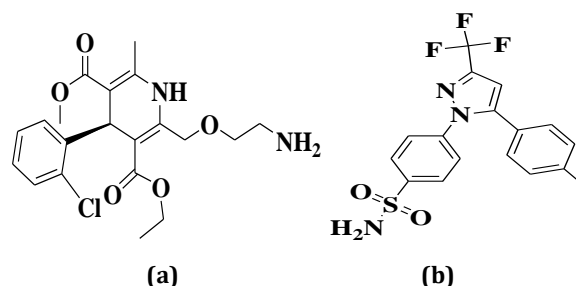
Figure 1. Chemical structure of (a) Amlodipine besylate (b) Celecoxib

AMD is official in IP[8], BP[9]. Several analytical methods that have been reported for the estimation of amlodipine besylate in biological fluids and/or pharmaceutical formulations include spectrophotometric[10-14], HPLC[15-17]and HPTLC[18]. A survey of literature showed HPLC methods for the estimation of CLX in pharmaceutical preparations[19-23] and in biological fluids[24-26]. It was also estimated by HPTLC[27], spectroflurometric[28] and densitometric[29], spectrophotometric[30,31] methods. Hydrotropic solubilization is the phenomenon by which aqueous solubility of poorly water soluble drugs and insoluble drugs increases. Various techniques have been employed to enhance the aqueous solubility and hydrotropy is one of them. Sodium salicylate, sodium benzoate, urea, nicotinamide, sodium citrate and sodium acetate are the most common examples of hydrotropic agents utilized to increase the water solubility of the drug. Maheshwari[32,33] and Jain et al[34-43] have analyzed various poorly water-soluble drugs using hydrotropic solubilization phenomenon for single drug or in combination viz. Frusemide, ketoprofen, amlodipine besylate, pramipexole dihyrochloride, olmesartan maedoxamil, lomefloxacin, furazolidone, entacapone, metronidazole & Ofloxacin, Ornidazole, Tinidazole, Metronidazole & Furazolidone. Various organic solvents such as methanol, chloroform, dimethyl formamide and acetonitrile have been employed for solubilization of poorly water-soluble drugs to carry out spectrophotometric analysis. Drawbacks of organic solvents include their higher cost, toxicity and pollution. Hydrotropic solution may be a proper choice to preclude the use of organic solvents. UV/VIS spectroscopy is an instrumental technique of choice for the mentioned purpose in industrial laboratories due to its simplicity and ease of operation. Kitov Pharma announced that the Food and Drug Administration (FDA) has approved Consensi (amlodipine and celecoxib) for patients with osteoarthritis pain and hypertension. He trial used celecoxib capsules and amlodipine tablets that were individually over-encapsulated and then taken together or with matching placebos. Patients were randomized to 1 of 4 treatment arms: celecoxib 200mg + amlodipine 10mg, amlodipine 10mg, celecoxib 200mg or placebo; all treatments were given once a day for 14 days. Results showed that the combination of celecoxib and amlodipine provided similar blood pressure reduction to an equal dose of amlodipine. We suppose that Consensi, as a single pill combination treatment for osteoarthritis and hypertension, presents a unique value proposition of potentially increasing treatment adherence[44]. Therefore, it was thought worthwhile to employ hydrotropic solution to extract out the drug from fine powder of marketed formulation to carry out spectrophotometric estimation. There are no reports yet for the determination of this combination by proposed methods. The present work emphasizes on the quantitative estimation of AMD and CLX in their combined dosage form by UV Spectroscopic methods.

MATERIALS AND METHODS

Pure sample of AMD and CLX was obtained as a gift sample from Matrix Laboratories, Mumbai and Reddy's Labs, Hyderabad, India respectively. Sodium benzoate was obtained from Merck Chemical Division, Mumbai. All other chemicals used were of analytical grade. Reverse osmosis water was used throughout the study. In House synthetic mixture of AMD and CLX were prepared in the ratio of (10:200mg). Label claim of AMD and CLX in tablet is 10 and 200mg respectively. A Labindia 3000+ UV/VIS spectrophotometer with 1 cm matched quartz cells was used for the estimation.

Preliminary solubility studies of drugs

Solubility of both drugs was determined at 25±1°C. An excess amount of drug was added to two screw capped 25 ml of volumetric flasks containing different aqueous systems viz. distilled water and different combination of hydrotropic agent. The volumetric flasks were shaken mechanically for 12 h at 25±1°C in a mechanical shaker. These solutions were allowed to equilibrate for next 24 hr and then centrifuged for 5 min at 2000 rpm. The supernatant liquid was taken for appropriate dilution after filtering through Whatman filter paper #41 and analyzed spectrophotometrically against water as blank. After analysis, it was found that the enhancement in the solubility of AMD and CLX was found to be more than 32 and 26 folds, respectively in a 2M sodium benzoate as compared to solubility studies in other solvents

Selection of hydrotropic agent

AMD and CLX were scanned in hydrotropic agent in the spectrum mode over the UV range 200-400 and 2M sodium benzoate solution was found to be most appropriate because:

AMD and CLX are soluble in it (32 and 26 fold enhancement of solubility).

AMD and CLX are stable in hydrotropic agent.

AMD and CLX, both exhibit good spectral characteristics in it.

Sodium benzoate has no interference with the λ_{max} of AMD and CLX, 243and 255nm, respectively (Figure 2).
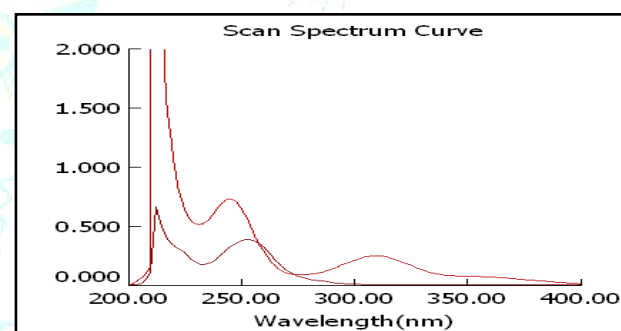

Figure 2. **Overlay spectra of AMD 8μg/ml and CLX 30 μg/ml**

Establishment of stability profile

Stability of AMD and CLX was observed by dissolving in a 2M sodium benzoate solution used as hydrotropic agent. Solution of AMD and CLX was scanned under time scan for 30 min. Spectra of the drug under time scan shows that drug is stable in hydrotropic solution.

Linearity range and calibration graph

Preparation of standard stock solutions of AMD and CLX

Standard stock solutions of 1000 μg/ml were prepared by dissolving separately 100 mg of each drug in hydrotropic solution and the flask was sonicated for about 10 min to solubilized the drug (Stock-A).

Preparation of working standard solution for calibration curve

The standard solution (1000μg/ml) was further diluted in different dilutions and prepared ranging from 2-10μg/ml for AMD and 10-50μg/ml for CLX. The calibration curve was plotted between concentrations and absorbances. Linearity data and result of their optical characteristics are shown in Table 1

Table 1 Optical characteristics and linearity data of AMD and CLX

S. N.	Parameters	AMD	CLX
1	Working λ	243	255
2	Beer's law limit (μg/ml)	2-10	10-50
3	Correlation coefficient (r^2)*	0.9992	0.9995
4	Slope (m)*	0.075	0.010
5	Intercept (c)*	0.002	0.002
6	LOD (μg/ml)	0.298	0.343
7	LOQ (μg/ml)	0.081	0.734

* Average of five determinations

Study of overlay spectra of drugs and selection of method

The spectra exhibit major absorbance maxima at 243 nm and 255 nm for AMD and CLX, respectively and isosbestic point at 250 nm Figure 2. Due to difference in absorbance maxima and having no interference with each other both drugs can be simultaneously estimated by the simultaneous equation method (Method A) and the Q-analysis method (Method B).

Vierordt's simultaneous equation method (Method 1)

The wavelength 243 nm (λ_{max} of AMD) and 255 nm (λ_{max} of CLX) was selected. The absorbencies of AMD and CLX were measured at 243 nm and 255 nm. This method of analysis is based on the absorption of drugs X and Y at the wavelength maxima of the other. The quantification analysis of AMDand CLX in a binary mixture was performed by using Eqs (1) and (2). Where C_X and C_Y are the concentrations of AMD and CLX, respectively in the diluted sample, ax_1 and ax_2 are

absorptivities of AMD at λ_1 and λ_2, ay_1 and ay_2 are absorptivities of CLX at λ_1 and λ_2, respectively (Table 2). A_1 and A_2 are the absorbances of samples at the 243 and 255 nm, respectively[45].

$$C_X = A_2 ay_1 - A_1 ay_2 / ax_2 ay_1 - ax_1 ay_2 \quad (1)$$

$$C_Y = A_1 ax_2 - A_2 ax_1 / ax_2 ay_1 - ax_1 ay_2 \quad (2)$$

Q-analysis method (Method 2)

In this method absorbances of both the drugs were calculated at two selected wavelengths; among which λ_1 is the wavelength of isoabsorptive point of both drugs and λ_2 is the λmax of either drug among both drugs. From the overlain spectra wavelength 250 nm (isoabsorption point) and 243 (λmax of AMD) were selected for the study. The absorbencies at 250 nm and 243 nm for CLX were obtained and similarly for AMD absorbencies are measured at 250 nm and 243 nm. The concentrations of the individual components were calculated by using the following equations;

$$C_X = Q_m - Q_y / Q_x - Q_y \times A_1 / ax_1 \quad (3)$$

$$C_Y = Q_m - Q_y / Q_y - Q_x \times A_1 / ax_1 \quad (4)$$

Where $Q_m = A_2 / A_1$, A_1 is absorbance of sample at isoabsorptive point, A_2 is absorbance of sample at λmax of one of the two components. ax_1 and ax_2 represent absorptivities of AMD at λ_1 and λ_2 and ay_1 and ay_2 denote absorptivities of CLX at λ_1 and λ_2, respectively (Table 2); C_X and C_Y are the concentrations of AMD and CLX, respectively[45, 46].

Table 2 Absorptivities of AMD (x) and CLX (y) at λ_1 and λ_2

Drug	Method-1				Method-2			
	243nm (λ_1)		255nm (λ_2)		250 nm (λ_1)		243nm (λ_2)	
AMD	ax_1	0.0248	ax_2	0.0053	ax_1	0.0179	ax_2	0.0064
CLX	ay_1	0.0229	ay_2	0.0514	ay_1	0.0434	ay_2	0.0514
					Q_X	0.2900	Q_Y	1.4015

N=5

Analysis of in-house formulation

Twenty in-house tablets of AMD and CLX were weighed and ground to a fine powder; amount equal to 10 mg of AMD was taken in a 100 ml volumetric flask. The CLX present in this amount of tablet powder was 200 mg. Then 80 ml of sodium benzoate solution was added and the flask was sonicated for about 10 min to solubilize the drug present in tablet powder and the volume was made up to the mark with hydrotropic

solution. After sonication filtration was done through Whatman filter paper No. 41. Filtrate was collected and further diluted with RO water to get the final concentrations of both drugs in the working range. The absorbances of final dilutions were observed at selected wavelengths and the concentrations were obtained from the simultaneous equation method and the absorbance ratio method. The result of statistical evaluation of tablet analysis is reported in Table 3.

Table 3 Results and statistical parameters for tablet analysis: In-house (AMD10/CLX-200)

S. No.	Drug	Label claim	Amount found	Recovery%*	S.D.*	%COV*	%COV*
Method-1	AMD	10	9.874	98.74	0.912	0.923	0.168
	CLX	200	198.43	99.22	1.012	1.019	0.187
Method-2	AMD	10	9.789	97.89	0.872	0.890	0.169
	CLX	200	198.98	99.49	0.903	0.453	0.161

* Average of five determinations

Validation of method

The developed methods for simultaneous estimation of AMD and CLX were validated as per ICH guidelines (Linearity, Accuracy, Precision and Robustness) [47].

Linearity

Linearity of AMD and CLX was established by response ratios of drugs. Response ratio of both drugs was calculated

by dividing the absorbance with respective concentration and then a graph was plotted between concentration and response ratio.

Limit of detection (LOD) and limit of quantification (LOQ)

The LOD and LOQ of AMD and CLX were determined by using standard deviation of the response and slope approach as defined in International Conference on Harmonization (ICH) guidelines. The limit of detection (LOD) and limit of

quantification (LOQ) for AMD and CLX were found to be 0.298μg/ml, 0.081μg/ml and 0.343μg/ml, 0.734μg/ml, respectively (Table 1) indicating that the proposed UV method is highly sensitive.

Accuracy

The accuracy of the proposed methods was assessed by recovery studies at three different levels i.e., 80%, 100% and

120%. The recovery studies were carried out by adding a known amount of standard solution of AMD and CLX to preanalyzed tablet solutions. The resulting solutions were then re-analyzed by proposed methods. Total amount of drug found and percentage recovery were calculated. Results of recovery studies are reported in Table 4.

Table 4 **Results of recovery studies on marketed formulations**

Recovery level%	% Recovery (Mean ± SD)*			
	Method-1		Method-2	
	AMD	CLX	AMD	CLX
80	99.05±0.284	95.20±0.101	99.42±0.475	98.39±1.023
100	99.06±0.400	96.62±0.093	98.44±0.672	99.64±0.172
120	99.83±0.308	95.08±0.086	97.74±0.451	98.54±0.673
Mean	99.31±0.331	95.64±0.094	98.54±0.532	98.86±0.622

* Average of five determination

Precision

Precision of the methods was studied at three levels as repeatability, intermediate precision (Day to Day and analyst to analyst) and reproducibility (Table 5 & 6).

Table 5 **Results of validation (Mean ± SD)**

Parameter	Method-1			
Precision (Mean ± SD)*	AMD	% RSD	CLX	% RSD
Repeatability	99.21±0.033	0.571	99.72±0.043	0.189
Day to day	98.71±0.050	1.071	99.54±0.038	0.171
Analyst to analyst	99.12±0.033	0.656	99.46±0.150	0.475
Reproducibility	98.94±0.071	0.984	99.67±0.039	0.196

* Average of five determinations

Table 6 **Results of validation (Mean ± SD)**

Parameter	Method-2			
Precision (Mean ± SD)*	AMD	% RSD	CLX	% RSD
Repeatability	98.74 ± 0.61	0.618	98.84 ± 1.04	1.052
Day to day	98.84 ± 1.04	1.052	99.51 ± 0.81	0.814
Analyst to analyst	99.55 ± 0.93	0.934	98.55 ± 0.28	0.284
Reproducibility	98.43 ± 0.88	0.894	98.78 ± 0.27	0.273

* Average of five determinations

RESULTS AND DISCUSSIONS

Based on the solubility and stability and spectral characteristics of the drugs, 2M sodium benzoate was used as a hydrotropic solution. It was found that solubility enhancement of AMD and CLX was more than 32 and 26-fold, respectively in hydrotropic solution as compared with distilled water. AMD and CLX show maximum absorbances at 243 and 255 nm, respectively. Sodium benzoate solution did not show any absorbance above 225nm and thus no interference in the estimation of drugs was seen. AMD and CLX follow Beer's law in the concentration range of 2-10μg/ml and 10-50μg/ml (r^2=0.9992 and 0.9995). Method-1 employs the simultaneous equation method using 243 and 255nm as two analytical wavelengths; method-2 employs the absorption ratio method, which uses 255 and 243nm as two analytical wavelengths for estimation of AMD and CLX. The optimized methods showed good reproducibility and mean recovery with 99.31±0.331and 95.64±0.094in method-1 and 98.54±0.532and 98.86±0.622in method-2 for AMD and CLX respectively. The mean percent label claims of in-house tablet dosage were found to be 98.74± 0.912and 99.22± 1.012in method-1, 97.89± 0.872and 99.49± 0.903 in method-2 for AMD and CLX, respectively. The standard deviation, coefficient of variance and standard error were obtained for AMD and CLX were satisfactorily low. Result of

precision at different levels was found to be within acceptable limits (RSD < 2).

CONCLUSION

There was no interference of 2M sodium benzoate solution in the estimation and hence the two UV spectrophotometric methods were found to be simple, accurate, economic and rapid for simultaneous estimation of AMD and CLX in bulk and in-house tablet dosage forms. The proposed method can be successfully employed for the routine analysis of AMD and CLX containing dosage forms.

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