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Sensitive spectrophotometric determination of amlodipine and felodipine using iron(III) and ferricyanide

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Abstract

A simple, accurate, sensitive and economical procedure for the estimation of amlodipine besylate and felodipine, both in pure form and in formulations has been developed. The method is based on the reduction of iron(III) by the studied drugs in acid medium and subsequent interaction of iron(II) with ferricyanide to form Prussian blue. The product exhibits absorption maximum at 760 nm in both cases. Beer's law is obeyed in the concentration ranges 5.0–15.0 and 1.5–5.0 μg/ml, for amlodipine and felodipine, respectively. The molar absorptivities are 1.76×10^4 and 4.24×10^4 l/mol cm. The corresponding Sandell sensitivities are 23.18 and 9.06 ng/cm^2. The limits of detection as well as quantification are reported. Seven replicate analyses of solutions containing three different concentrations of each drug were carried out and the percent error and the RSD values have been reported. The proposed method was applied to the determination of these drugs in pharmaceutical formulations and the results demonstrate that the method is equally accurate and precise as the official methods as found from the *t*- and *F*-values. The reliability of the method was established by recovery studies using standard-addition technique.

Keywords: Felodipine; Amlodipine; Determination; Spectrophotometry; Iron(III) chloride; Ferricyanide

1. Introduction

Amlodipine besylate (ADB) is 2-[(2-amino-ethoxy)-methyl]-4-2-chlorophenyl), 1,4-dihydro-6-methyl-3,5-pyridine dicarboxylic acid, 3-ethyl-5-methyl ester [1]. ADB, a calcium channel blocker with vasodilatory activity similar to those of nifedipine, is mainly used in antianginal, anthihypertensive and antiarrythmic activity. ADB is not official in any pharmacopoeia. Hence, no official method is available for its assay. Literature survey revealed that ADB has been estimated by high-performance liquid chromatographic (HPLC) [2–4], gas chromatographic [5,6] and liquid chromatographic (LC) [7] techniques in biological fluids. Assay of ADB has also been achieved by UV [8,9] and derivative [10] spectrophotometric techniques, but the methods lack the desired sensitivity, the linear ranges being 10–80 [8] and 5–30 μg/ml [9,10], respectively. Not many visible spectrophotometric methods are found in the literature. Anu et al. [11] have recently reported two procedures based on the use of sodium salt of 1,2-naphthaquinone sulphonic acid and chloranil as chromogenic agents, but the procedures are poorly sensitive with molar absorptivity (ε) values of 4.4×10^2 and 1.3×10^3 l/mol cm, respectively. Very recently [12], two extractive spectrophotometric methods involving ion pair formation between the drug and acid dyes, fast green FCF[1] and orange II have been reported. Though the procedures are sensitive ($\varepsilon = 2.1 \times 10^4$) enough for micro scale analysis, they involve tedious extraction step and use of organic solvent.

Felodipine (FLD), ethyl methyl-4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid-3-ethyl-5-methyl ester, is a calcium antagonist useful in the treatment of hypertension, heart failure and angina pectoris [13].

Various techniques have been used for the assay of felodipine in pure form, different dosage forms and body fluids. However, majority of the techniques are devoted to the determination of FLD and its metabo-

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lites in blood serum and urine. They include GC [14,15], capillary GC [16,17], high selectivity GC [18], HPLC [19,20] and LC [21]. FLD in its formulations has been determined using such diverse techniques as LC [22,23], GC [24], HPLC [25,26], reversed phase HPLC [27], cyclic voltammetry [28] and nuclear magnetic resonance spectroscopy (NMR) [29]. Most of these techniques involve expensive instrumental set up, lengthy treatments and hence lack the simplicity needed for routine analysis, besides being poorly sensitive [22,24,27]. However, there appears to be only one spectrophotometric method [30] for the assay of FLD in pure drug as well as in dosage forms based on the colour reaction of drug with sodium hydroxide in dimethyl formamide medium. Even this method lacks the required sensitivity, the linear concentration range being 10–50 μg/ml.

The purpose of this work is to describe a simple, precise, accurate and sensitive spectrophotometric method for the determination of ADB and FLD in bulk drugs and in pharmaceutical formulations by use of iron(III) and ferricyanide. The structures of ADB and FLD are given in Fig. 1.

2. Experimental

2.1. Apparatus

A Systronics model 106 digital spectrophotometer (Systronics, Noida Ahmedabad, Gujarat, India) with 1-cm matched glass cells was used for absorbance measurements.

2.2. Reagents and solutions

All reagents used were of analytical reagent grade and double distilled water was used to prepare all solutions unless specified otherwise. A 0.2% (w/v) solution each of anhydrous $FeCl_3$ (NICE, Kochi, Kerala, India) and $K_3Fe(CN)_6$ (BDH Lab. Chemicals, Poole, England) was prepared in water. Sulphuric acid (10 M) was prepared by adding 555 ml of concentrated acid (s.d. Fine Chem., Mumbai, Maharashtra, India), Sp. Gr. 1.83, to 445 ml of water with cooling.

2.2.1. Standard drug solutions

Pure ADB and FLD were provided by Cipla India Ltd., Mumbai, Maharashtra, India and were used as received. Stock standard solutions of ADB and FLD (200 μg/ml) were prepared by dissolving separately 20 mg of ADB and FLD in EtOH (95%) and diluting to 100 ml with water in a volumetric flask. The stock solutions were diluted to get working standards of 50 (ADB) and 20 μg/ml (FLD) with water.

2.2.2. Dosage forms

The following commercial formulations containing ADB or FLD were subjected to analysis by the proposed procedure: (1) Amlocor (2.5 mg)—contains amlodipine (2.5 mg), magnesium stearate (40 mg), sodium alginate (20 mg), talc (10 mg). (2) Amlocor (5.0 mg)—contains amlodipine (5.0 mg), magnesium stearate (20 mg), sodium alginate (30 mg), talc (50 mg). (3) Amlocor (10.0 mg)—contains amlodipine (10.0 mg), magnesium stearate (40 mg), sodium alginate (50 mg), talc (35 mg). (4) Amlopres (2.5 mg)—contains amlodipine (2.5 mg), magnesium stearate (40 mg), sodium alginate (25 mg), talc (10 mg). (5) Amlopres (5.0 mg)—contains amlodipine (5.0 mg), magnesium stearate (50 mg), sodium alginate (40 mg), talc (25 mg). (6) Amlopres (10.0 mg)—contains amlodipine (10.0 mg), magnesium stearate (60 mg), sodium alginate (50 mg), talc (30 mg). (7) Felogard ER (2.5 mg)—contains felodipine (2.5 mg), magnesium stearate (35 mg), sodium alginate (45 mg), talc (20 mg). (8) Felogard ER (5.0 mg)—contains felodipine (5.0 mg), magnesium stearate (40 mg), sodium alginate (60 mg), talc (40 mg). (9) Felogard ER (10 mg)—contains felodipine (10 mg), magnesium stearate (40 mg), sodium alginate (65 mg), talc (30 mg). (10) Plendil (2.5 mg)—contains felodipine (2.5 mg), magnesium stearate (25 mg), sodium alginate (30 mg), talc (20 mg). (11) Plendil (5.0 mg)—contains felodipine (5.0 mg), magnesium stearate (35 mg), sodium alginate (50 mg), talc (30 mg). (12) Plendil (10 mg)—contains felodipine

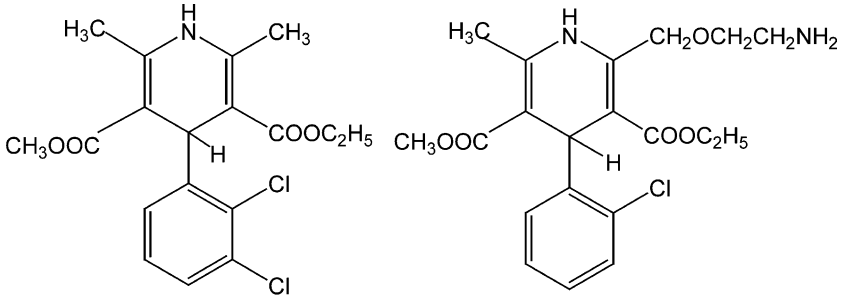

Fig. 1. Structures of ADB and FLD.

(10 mg), magnesium stearate (50 mg), sodium alginate (20 mg), talc (40 mg).

2.3. General procedure

Into a series of 10 ml volumetric flasks, different aliquots (1.0–3.0 ml) of standard ADB solution (50 μg/ml) or 0.75–2.5 ml aliquots of 20 μg/ml of FLD solution were transferred using a microburette and the total volume was adjusted to 3.0 ml by adding water. Then, 2 ml each of $FeCl_3$ (0.2%) and ferricyanide (0.2%) were added to each flask, mixed well and let stand for 10 min. Finally, 1.0 ml of 10 M H_2SO_4 was added to each flask and diluted to mark with water and mixed well. The absorbance of the resulting solution was measured at 760 nm against reagent blank prepared similarly. Calibration graph in each case was constructed by plotting the absorbance against the concentration of drug. The concentration of the unknown was read from the respective calibration graph or calculated using the regression equation.

2.4. Pharmaceutical preparations

Twenty tablets were weighed accurately and ground into a fine powder. An amount of the powder equivalent to 20 mg of ADB or FLD was weighed into a 100 ml volumetric flask. About 40 ml water containing 10 ml of EtOH (95%) were added and shaken thoroughly for about 20 min. Then, the volume was made upto the mark with water, mixed well and filtered using quantitative filter paper. First 10 ml portion of the filtrate was rejected. The filtrate (200 μg/ml) was diluted to get 50 μg/ml of ADB or 20 μg/ml of FLD, with water.

3. Results and discussion

ADB and FLD being amines reduce iron(III) to iron(II), the latter reacting with ferricyanide to form intense blue [31] coloured Prussian blue having an absorption maximum at 760 nm. The optimum conditions were established by variation of such parameters as iron(III), ferricyanide and acid concentrations, reaction time and order of addition of reactants.

3.1. Absorption spectra

Fig. 2 shows the absorption spectra of the reaction products of ADB and FLD with iron(III) ferricyanide and the reagent blank. The greenish–blue product from the studied antihypertensive drugs exhibits an absorption maximum at 760 nm, and the respective blanks display only slight absorption at this wavelength. Further, neither iron(III) nor ferricyanide solution absorbs at this wavelength. Hence, the use of measured volumes of the reagent solutions and measurement against corresponding reagent blanks give a linear calibration graph for the drugs. The similarity of $\lambda_{max(s)}$ for reaction products of both drugs suggest that the products formed have similar composition.

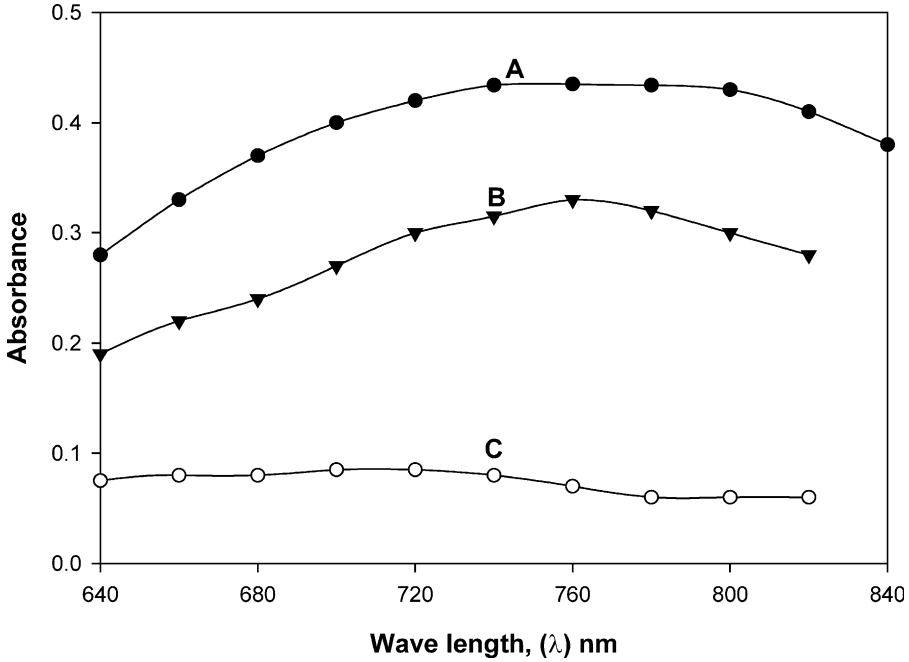

Fig. 2. Absorption spectra of: (A) reaction product of ADB (100 μg) with iron(III) and ferricyanide; (B) reaction product of FLD (30 μg) with iron(III)–ferricyanide; (C) reagent blank.

3.2. Optimum iron(III) and ferricyanide concentrations

When a study on the effect of iron(III) chloride concentration on the colour development was performed, it was observed that in both cases the absorbance increased with increase in the volume of 0.2% iron(III) solution and reached maximum when 1.5 ml of the reagent solution were added to 100 μg of ADB or 30 μg of FLD, and 2 ml of 0.2% ferricyanide solution in a total volume of 10 ml. These results indicate that a maximum absorbance is obtained when the final iron(III) chloride concentration is 0.03%. Larger volumes of iron(III) chloride upto 2.5 ml had no effect on the sensitivity of the reaction (Fig. 3).

Similar observations were made when varying volumes of 0.2% ferricyanide solution were added to fixed amounts of drug (100 μg of ADB or 30 μg FLD) and iron(III) chloride (2 ml; 0.2%) and diluted to 10 ml after full colour development (Fig. 4). The results of this study reveal that the concentrations of iron(III) and ferricyanide reagents are not critical. However, 2 ml each of 0.2% reagent solutions in a total volume of 10 ml were used to ensure adequate reagent concentrations for higher drug concentrations.

3.3. Effect of nature of acid, and its concentration

The reaction product Prussian blue was found to flocculate within 20–30 min of colour development. To delay the flocculation, addition of acid after full colour development and before diluting to the mark was found necessary. Sulphuric acid was found to give more stable colour and reproducible results compared to hydrochloric acid. A 1 ml volume of 10 M sulphuric acid in a total volume of 10 ml was found adequate for the purpose.

3.4. Effect of reaction time and stability of coloured species

The reaction is slow at 32 ± 2 °C but the absorbance increases with time and reaches a maximum in 10 min in both instances. The developed colour remained stable for atleast 4 and 3 h in respect of ADB and FLD, respectively.

3.5. Analytical appraisal

Under the experimental conditions described, Beer's law is obeyed over the concentration ranges, 5.00–15.00 and 1.50–5.00 μg/ml, respectively, for ADB and FLD. The molar absorptivities at 760 nm are 1.76×10^4 and 4.24×10^4 l/mol cm and Sandell sensitivities are 23.18 and 9.06 ng/cm^2 for ADB and FLD, respectively. The limits of detection and quantification for ADB are 0.13 and 0.43 μg/ml, respectively. Similar parameters for FLD are 0.05 and 0.17 μg/ml. The equations relating absorbance to concentration are:

$$A = -0.024 + 0.046C \quad \text{for ADB}$$

and

$$A = -0.003 + 0.112C \quad \text{for FLD},$$

where C is concentration in μg/ml.

3.6. Effect of order of addition of reactants

After fixing all other parameters, a few other experiments were performed to ascertain the influence of the

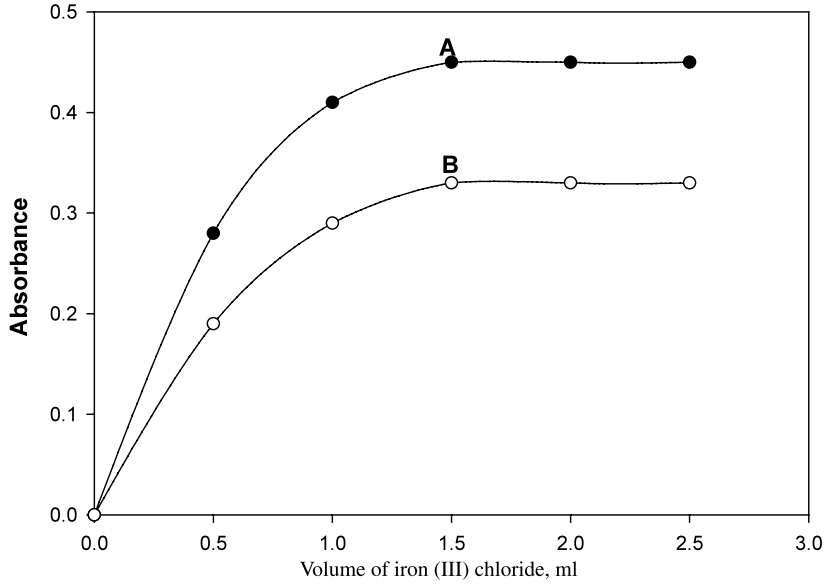

Fig. 3. Effect of iron(III) chloride concentration (0.2%). (A) ADB (100 μg) + 2.0 ml of 0.2% ferricyanide + 1.0 ml of 10 M sulphuric acid per 10.0 ml. (B) FLD (30 μg) + 2.0 ml of 2% ferricyanide + 1.0 ml of 10 M sulphuric acid per 10.0 ml.

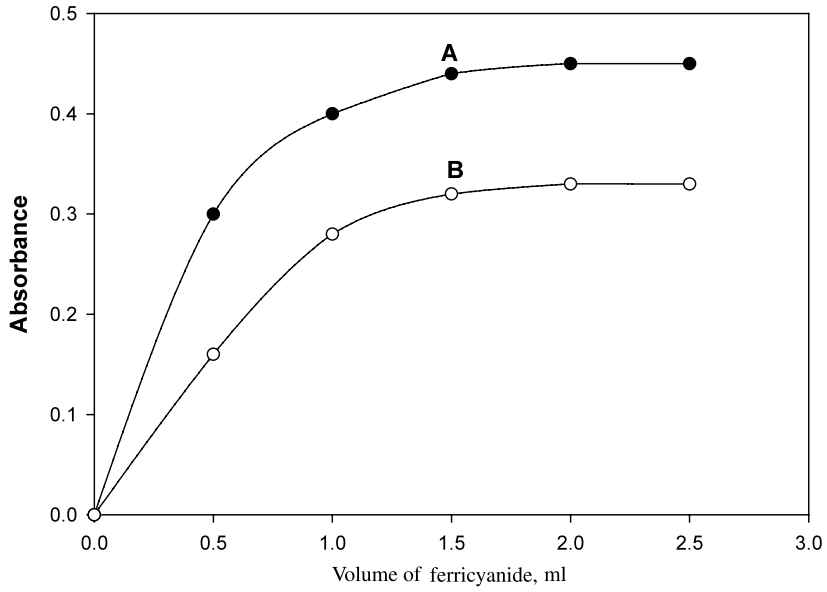

Fig. 4. Effect of ferricyanide concentration (0.2%). (A) ADB (100 μg)+2.0 ml of 0.2% iron(III) chloride+1.0 ml of 10 M sulphuric acid per 10.0 ml. (B) FLD (30 μg)+2.0 ml of 0.2% iron(III) chloride+1.0 ml of 10 M sulphuric acid per 10.0 ml.

order of addition of reactants. The order: drug, ferricyanide and iron(III) followed by sulphuric acid after full development of colour gave maximum absorbance and stability, and hence the same order of addition was followed throughout the investigation.

3.7. Accuracy and precision

Accuracy and precision were established by performing seven replicate determinations containing different amounts within Beer's law limits. The range, percentage error, standard deviation, relative standard deviation (RSD) (%) for seven determinations at each level are given in Table 1. The accuracy of the method is evident from the percent error lying between 0.68 and 0.17% for ADB, and 0.53 and 0.30% for FLD. The RSD values which are less than 3% (except ADB, 50 μg level) for three different levels studied for both drugs indicate the high reproducibility of the method. To evaluate the significance of the results obtained for bulk drug using the proposed procedure, a comparison of the experimental mean values ($\bar{x}$) was made with the true values (μ) using n- and t-values. The actual difference between the mean and the true value ($\bar{x}-\mu$) was compared with the largest difference that could be expected as a result of indeterminate error ($\pm ts/\sqrt{n}$) given in the last column of Table 1. It is clear from the results that the values of ($\bar{x}-\mu$) are less than $\pm ts/\sqrt{n}$ indicating no significant difference between the mean and the true values.

3.8. Application

The method was applied to the determination of ADB and FLD in proprietary drugs purchased from local stores and containing other inactive ingredients. The results in Table 2 show that the method is successful for the determination of ADB and FLD and that the excipients in the dosage forms do not interfere. A statistical comparison of results of determination ADB and FLD by the proposed method and reference methods [12,30] for the same batch of material is presented in Table 3. The Student's t- and F-values

Table 1
Accuracy and precision of the method

Drug studied	Amount taken (μg)	Amount found [a] (μg)	Range (μg)	Error (%)	SD (μg)	RSD (%)	$\bar{x}-\mu$	$\pm ts/\sqrt{n}$ [b]
ADB	50.0	49.66	1.48	0.68	2.45	4.90	0.34	2.26
	80.0	80.16	0.80	0.20	0.32	0.40	0.16	0.30
	120.0	120.20	1.20	0.17	0.42	0.35	0.20	0.39
FLD	15.0	15.08	1.02	0.53	0.43	2.84	0.08	0.40
	30.0	30.13	1.71	0.43	0.18	0.59	0.13	0.17
	40.0	40.12	0.81	0.30	0.32	0.81	0.12	0.30

[a] Average of seven determinations.
[b] t is tabulated value (2.447) at 95% confidence level, $n=7$ and s is standard deviation.

Table 2
Results of determination of ADB and FLD in dosage forms

Drug *	Nominal amount (mg)	Drug found ** (mg)	Error (%)
ADB			
Amlocor [a]	2.5	2.52	0.80
	5.0	5.06	1.20
	10.0	10.15	1.50
Amlopres [b]	2.5	2.48	0.80
	5.0	4.95	1.00
	10.0	9.89	1.10
FLD			
Felogard ER-10 [b]	2.5	2.54	1.60
	5.0	4.95	1.20
	10.0	9.89	1.50
Plendil [c]	2.5	2.48	0.80
	5.0	5.04	0.80
	10.0	10.10	1.00

** Average of five determinations.
* Marketed by.
[a] Torrent India, Ltd.
[b] Cipla India, Ltd.
[c] Astra-IDH, India, Ltd.

indicate that there is no significant difference between the methods in respect of accuracy and precision.

To study the reliability and reproducibility of the proposed method, a standard addition technique was followed. A fixed amount of each drug from preparations was taken and pure (standard) drug at three different concentrations was added. The total concentration was found by the proposed method. The determination with each concentration was repeated three times and the percent recovery of the added standard was calculated from:

$$\% \text{ Recovery} = [C_v - C_u)/C_a] \times 100$$

where C_v is the total concentration of the analyte measured; C_u, concentration of the analyte present in the formulation; C_a, concentration of analyte (pure drug) added to formulation.

Results of this study presented in Table 4 reveal that the method was unaffected by the various excipients present in the formulations.

The method is simple and economical for the estimation of ADB and FLD both in pure form and in

Table 3
Comparison of results of ADB and FLD determination by the proposed method with those of reference method

Preparation	% Recovery ± SD		t-value [a] (2.776)	F-value [a] (6.39)
	Proposed method	Reference method		
Amoclor (mg)				
2.5	100.80 ± 0.20	100.40 ± 0.40	2.11	4.00
5.0	101.20 ± 0.21	101.00 ± 0.46	0.94	4.80
10.0	101.50 ± 0.09	101.60 ± 0.10	1.66	1.23
Amlopress (mg)				
2.5	99.20 ± 0.42	99.80 ± 0.35	2.46	1.44
5.0	99.00 ± 0.35	99.80 ± 0.63	2.63	3.24
10.0	99.80 ± 0.12	100.00 ± 0.21	1.92	3.06
Felogard EF (mg)				
2.5	100.60 ± 0.91	99.50 ± 0.45	2.56	4.09
5.0	99.60 ± 0.35	99.80 ± 0.15	0.45	5.44
10.0	99.50 ± 1.00	100.50 ± 0.85	1.71	1.38
Plendil (mg)				
2.5	99.40 ± 0.51	100.20 ± 0.49	2.53	1.08
5.0	100.80 ± 0.40	101.00 ± 0.42	0.77	1.05
10.0	100.20 ± 1.20	98.80 ± 0.89	2.31	1.82

[a] Figures in the parentheses are the tabulated values at 95% confidence level.

Table 4
Results of recovery study by standard-addition method

Formulation	Amount of drug in formulation (μg)	Amount of pure drug added (μg)	Total found (μg)	% Recovery of pure drug added
Amoclor (10 mg)	30.24	40.00	69.71	98.68
	30.24	60.00	89.71	99.12
	30.24	90.00	118.31	97.85
Plendil (10 mg)	10.10	20.00	30.23	100.63
	10.10	25.00	35.42	101.28
	10.10	30.00	39.96	99.54

formulations. The species formed is fairly stable. The results indicate that the procedure is sensitive with reasonable accuracy and precision.

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