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Simultaneous Spectrophotometric Estimation of Amlodipine Besylate and Telmisartan in Tablet Dosage Form

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ABSTRACT: Three simple, accurate and reproducible spectrophotometric methods have been developed for the simultaneous estimation of Amlodipine Besylate (Amlo) and Telmisartan (Tel) in combined tablet dosage forms. The first method involves determination using the simultaneous equation method, the sampling wavelengths selected are 364.5 nm and 254.5 nm over the concentration ranges of 1-50 mcg ml^{-1} and 10-80 mcg ml^{-1} for Amlo and Tel respectively. The second method is the Area Under Curve method (AUC), the sampling wavelength ranges selected are 366.5-362.5nm and 256.5-252.5nm with linearity in the concentration ranges of 1-50 mcg ml^{-1} and 10-80 mcg ml^{-1} for Amlo and Tel respectively. The third method involves determination using the Multicomponent Mode method, the sampling wavelengths selected are 364.5 nm and 254.5 nm over the concentration ranges of 1-50 mcg ml^{-1} and 10-80 mcg ml^{-1} for Amlo and Tel respectively. The results of the analysis were validated statistically and recovery studies were carried out as per ICH guidelines.

KEY WORDS: Amlodipine Besylate (Amlo) and Telmisartan (Tel), Simultaneous equation method, Area Under Curve method (AUC), Multicomponent Mode Method.

INTRODUCTION

Amlodipine besylate (Amlo), is a calcium channel blocker, chemically it is [3-ethyl-5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-methyl-1-dihydropyridine-3,5-dicarboxylate benzenesulfonate [1]. Literature survey reveals several spectroscopic [2-13], HPLC [14-23] and HPTLC [24-27] methods for the estimation of Amlodipine Besylate individually as well as in combination with other drugs.

Telmisartan (Tel), is an angiotensin receptor blocker, chemically it is 4'-[(1,4'- dimethyl – 2'-propyl [2,6' –bi-1H- benzimidazol] - 1'-yl) methyl] [1,1'-biphenyl] - 2- carboxylic acid[28]. Literature survey reveals UV spectroscopic [29-30], HPLC [31-34] and HPTLC [35-36] methods for the estimation of Telmisartan individually as well as in combination with other drugs. A combination of Telmisartan and Amlodipine besylate has been reported to show substantial and sustained 24-hour blood pressure (BP) reduction and is well-tolerated in a range of patients with hypertension and at risk of cardiovascular (CV) events. Amlo and Tel are available in combined tablet dosage form for the treatment of hypertension. Not a single UV or HPLC method is reported so far for the simultaneous analysis of Amlo and Tel in their combined dosage form. So a need was felt to develop new methods to analyze the drugs simultaneously. A successful attempt has been made to estimate the two drugs simultaneously by UV spectrophotometric analysis. This paper describes three simple, rapid, accurate, reproducible and economical methods for the simultaneous determination of Amlo and Tel in tablet formulations using simultaneous equation method, Area under Curve method (AUC) and Multicomponent Mode Method.

EXPERIMENTAL

INSTRUMENTATION:

A Shimadzu UV/Visible spectrophotometer, model 1700 (Japan), spectral bandwidth of 2 nm and wavelength accuracy of ± 0.5 nm, with automatic wavelength correction was employed. A Shimadzu electronic

analytical balance (AX-200) was used for weighing the sample. An ultrasonic cleaner (Art No.400014CL) was used for sonicating the tablet sample solution.

REAGENTS AND CHEMICALS:

Analytical pure samples of Amlodipine besylate (Micro labs ltd. India), and Telmisartan (Glenmark Pharmaceuticals Ltd., India) were used in the study. The pharmaceutical dosage form used in this study was Telma-AM (Glenmark Pharmaceuticals Ltd., Solan, India) labeled to contain 5 mg Amlo and 40 mg of Tel per tablet.

PREPARATION OF STANDARD STOCK SOLUTION:

Standard stock solutions (100 mcg ml^{-1}) of Amlo and Tel were prepared by dissolving separately 10 mg of drug each in 100 ml methanol. The working standard solutions of these drugs were obtained by dilution of the respective stock solution with distilled water.

PREPARATION OF SAMPLE STOCK SOLUTIONS:

Twenty tablets were weighed and crushed to fine powder. An accurately weighed powder sample equivalent to 5 mg of Amlodipine besylate was transferred to a 100 ml volumetric flask and dissolved in 50 ml of methanol. After the immediate dissolution, the volume was made up to the mark with the same solvent. The solution was sonicated for about 30 mins and was then filtered through Whatmann filter paper No.41. The solution was suitably diluted with distilled water to obtain sample solutions containing Amlo and Tel in the concentrations ratio of 1:8 mcg ml^{-1} respectively as in the tablet formulation.

METHOD I : SIMULTANEOUS EQUATION METHOD

Construction of calibration curve and formation of simultaneous equations

For the simultaneous equation method, 364.5nm, and 254.5 nm were selected as the two sampling wavelengths for Amlodipine besylate and Telmisartan respectively. Fig.1 represents the overlain UV spectra of Amlo and Tel. Amlo and Tel exhibited linearity with absorbances in the range of 1-50 mcg ml^{-1} and 10-80 mcg ml^{-1} at their respective selected wavelengths. Coefficients of correlation were found to be 0.9997 and 0.9996 for Amlo and Tel respectively. The optical characteristics and regression values for the calibration curves are presented in Table 1. For simultaneous estimation of Amlo and Tel, mixed standards containing Amlo and Tel in a concentration ratio of 1:8 mcg ml^{-1} each were prepared by appropriate dilution of the standard stock solutions with distilled water. The absorbances of the mixed standard solutions were measured at the selected wavelengths. A set of two simultaneous equations were established using the mean absorptivity coefficients of Amlo and Tel at the selected λ's.

$A1 = 24.2\ C_{Amlo} + 42.1 C_{Tel}$ ..... (I) at 364.5.5nm (λ_1)

$A2 = 0.1125 C_{Amlo} + 20.6125 C_{Tel}$ ..... (II) at 254.5 nm (λ_2)

Where- –24.2 and 42.1 are absorbtivity values of Amlo at λ_1 and λ_2 respectively.

0.1125 and 20.6125 are absorbtivity values of Tel at λ1, and λ2 respectively.

A1 and A2 are the absorbance of mixed standard and sample solutions at λ1, and λ2 respectively.

C_{Amlo}, and C_{Tel} are concentrations in g L^{-1}.

The concentration of C_{Amlo}, and C_{Tel} in mixed standard and tablet formulations can be obtained by solving equations (I) and (II).

METHOD II: AREA UNDER CURVE METHOD

For the Area under curve method (AUC), 362.5-366.5nm, and 252.5-256.5 nm were selected as the two sampling wavelength intervals for Amlodipine besylate and Telmisartan respectively. Fig.2 represents the overlain UV spectra of Amlo and Tel with AUC ranges. Amlo and Tel exhibited linearity in the concentration range of 1-50 mcg ml^{-1} and 10-80 mcg ml^{-1} at their respective selected wavelength intervals. Coefficients of correlation were found to be 0.9992 and 0.9985 for Amlo and Tel respectively. The optical characteristics and regression values for the calibration curves are presented in Table 1. For the simultaneous estimation, mixed standards containing Amlo and Tel in the ratio of 1:8 were prepared by appropriate dilution of the standard stock solutions. The AUC of the mixed standard solutions were measured at the selected wavelength intervals. A set of two simultaneous equations were established using the mean absorptivity coefficients of Amlo and Tel at the selected wavelength intervals.

A1 = 82.3CAmlo+1.1375CTel ..... (III) at 366.5-362.5nm (λ1- λ2)

A2 = 145.7CAmlo+156.1375CTel ..... (IV) at 256.5-252.5 nm (λ3- λ4)

Where – 82.3and 145.7 are mean absorbtivity values of Amlo at (λ1- λ2) and (λ3- λ4) respectively.

1.1375 and 156.1375 are mean absorbtivity values of Tel at (λ1- λ2) and (λ3- λ4) respectively.

A1 and A2 are the AUC of mixed standard and sample solutions at (λ1- λ2) and (λ3- λ4) respectively.

C_{Amlo}, and C_{Tel} are concentrations in g L^{-1}.

The concentration of C_{Amlo}, and C_{Tel} in mixed standard and tablet formulation can be obtained by solving equation (III) and (IV).

METHOD III: MULTICOMPONENT MODE METHOD

For the analysis of Amlo and Tel by multicomponent method of analysis, the multicomponent mode of the UV visible spectrophotometer was used. For multicomponent method of analysis, 364.5 nm and 254.5 nm were selected as the two sampling wavelengths for Amlo and Tel respectively. The drugs showed linearity in the concentration ranges of 1-50 mcg ml^{-1}, 10-80 mcg ml^{-1} with regression coefficient (r^2) values of 0.9997, 0.9995 for Amlo and Tel respectively.Six mixed standards in the ratio of 1:8 mcg ml^{-1} within the Beer's concentration range of Amlo and Tel were prepared by appropriate dilution of standard stock solutions (100 mcg ml^{-1}). The mixed standards were scanned in the multicomponent mode of the instrument, over the range of 190-400 nm at the selected sampling wavelengths. The overlain spectra of the six mixed standards were then employed to determine the concentration of the drugs in sample solutions by analysis of the spectral data of sample solution with reference to that of mixed standards.

ASSAY OF TABLET FORMULATION:

Twenty tablets were accurately weighed and a quantity of tablet powder equivalent to 5 mg of Amlodipine Besylate and 40 mg of Telmisartan was weighed and dissolved in 100 mL methanol with the aid of ultrasonication for 30 min. The solution was then filtered through Whatmann filter paper No.41 and diluted further to obtain final concentration of 5 mcg ml^{-1} of Amlo and 40 mcg ml^{-1} of Tel. The sample solutions were analyzed as per the procedure for mixed standards. The concentrations of each drug in sample solutions were calculated using equations (I) and (II) for the simultaneous equation method, equations (III) and (IV) for the Area under curve method and using the multicomponent mode of the instrument for the Multicomponent method of analysis. The proposed methods were validated as per ICH guidelines [37].The accuracy of the proposed methods were determined by performing recovery studies at 80%, 100% and 120% of the test concentration. The results of the analysis and statistical validation data of the tablet formulation are given in table 1. The statistical validation data of recovery study are given in table 2.

RESULTS AND DISCUSSION

Under the experimental conditions described, calibration curve, assay of tablets and recovery studies were performed. The developed methods were validated as per ICH guidelines for linearity, repeatability, intermediate precision (inter-day and intra-day precision studies), LOD, LOQ as shown in Table 1. The mean % content of Amlo and Tel in tablet formulation by the developed methods methods were 99.193% and 99.74% respectively (Table 2). The mean % recoveries of Amlo and Tel were found to be 99.162 % and 100.88 % respectively (Table 3). The ruggedness of the developed methods was determined by evaluating the effect of change in instruments and analysts on the % mean content of drugs. The statistical validation data of ruggedness study given in table 4. Also the results of the proposed methods were evaluated using F test to determine if there exist any significant difference between these methods for the analysis of Amlo and Tel, the results of which are given in Table 5.

Table 1: Optical Characteristics and Validation Data of Amlodipine Besylate (Amlo) and Telmisartan (Tel)

Parameters	Amlodipine besylate			Telmisartan		
	Method-I	**Method-II**	**Method-III**	**Method-I**	**Method-II**	**Method-III**
Working wavelengths	364.5nm	366.5nm-362.5nm	364.5nm	254.5nm	256.5nm-252.5 nm	254.5 nm
Beer-Lamberts Law range (mcg mL^{-1})	1-50	1-50	1-50	10-80	10-80	10-80
Precision*						
Interday (%RSD)	0.2779	0.5225	0.7521	0.1882	0.0639	0.0105
Intraday (%RSD)	0.2760	0.4855	0.8149	0.2103	0.0639	0.0585
LOD (mcg mL^{-1})*	0.1597	0.2069	0.1845	0.2177	0.1000	0.0785
LOQ (mcg mL^{-1})*	0.4840	0.6269	0.5590	0.6596	0.2814	0.2379
Regression Values:						
I. Slope*	0.016	0.0713	0.016	0.0376	0.1759	0.0376
II. Intercept*	0.00512	0.0082	0.0049	0.0159	0.2123	0.016
III. Regression Coefficient (r^2)*	0.9996	0.9992	0.9995	0.9996	0.9985	0.9995

*Denotes average of six estimations

Table 2: Statistical Validation Data of Tablet Formulation

Component	Amount present(mg)	Method	% Amount Found	S.D.*	% R.S.D.*
Amlo	1	I	99.30	0.0026832	0.2700
	1	II	98.33	0.0071274	0.72506
	1	III	99.95	0.0067156	0.67189
Tel	8	I	98.00	0.0118869	0.15163
	8	II	101.25	0.0030983	0.03817
	8	III	99.97	0.0075828	0.09479

*Denotes average of six estimations

Tablet Formulation, Telma-AM manufactured by Glenmark Pharmaceuticals Ltd., Solan, India.

Where,

Method-I – Simultaneous equation method

Method-II – Area Under Curve method (AUC)

Method-III – Multicomponent Mode Method

Table 3: Statistical Validation of Recovery Studies

Level of % recovery	Methods	% Recovery*		% R.S.D.*	
		Amlo	Tel	Amlo	Tel
80	I	98.500	101.50	0.28284	0.05466
	II	99.062	100.98	0.1995	0.02446
	III	100.32	99.810	0.5911	0.37130
100	I	98.500	101.08	0.3598	0.04371
	II	99.250	100.97	0.1593	0.15930
	III	99.130	100.78	0.0781	0.09805
120	I	98.330	101.54	0.3002	0.36542
	II	99.375	101.01	0.1330	0.01630
	III	99.990	101.21	0.5270	0.13148

*Denotes average of three estimations at each level of recovery.

Table 4 : Ruggedness Study

Method	Parameter	% Mean		S.D.*		% R.S.D.*	
		Amlo	Tel	Amlo	Tel	Amlo	Tel
Simultaneous Equation method	Instrument	99.42	98.16	0.0018439	0.0359833	0.18548	0.45827
	Analyst	99.36	98.46	0.0016733	0.0353199	0.16844	0.44847
Area Under Curve (AUC) Method	Instrument	98.73	101.26	0.0041109	0.0040987	0.41637	0.05058
	Analyst	98.75	101.29	0.0043817	0.0051478	0.44440	0.06352
Multicomponet Method	Instrument	100.08	99.98	0.0091268	0.0044609	0.91423	0.05577
	Analyst	100.41	99.94	0.0051478	0.0053572	0.51308	0.06700

*Denotes average of three estimations at each level of recovery.

Table 5 : Statistical Significance of Difference between Three Methods (F Test)

Comparison	Rank Sum Difference	P value
Method-I vs. II	-1.000	ns P>0.05
Method-I vs. III	-2.000	ns P>0.05
Method-II vs. III	-1.000	ns P>0.05

The P value is 0.8333, considered not significant. Variation among column medians is not significantly greater than expected by chance

Where,
Method-I – Simultaneous equation method
Method-II – Area Under Curve method (AUC)
Method-III – Multicomponent Mode Method

Fig.1: Overlain Spectra of Amlo and Tel in Simultaneous Equation and Multicomponent Mode Method

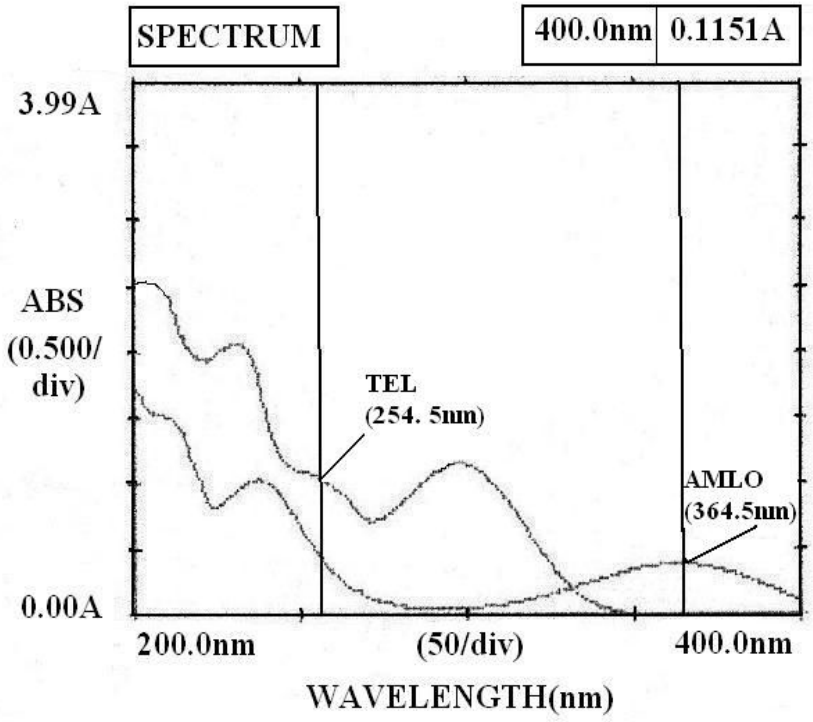
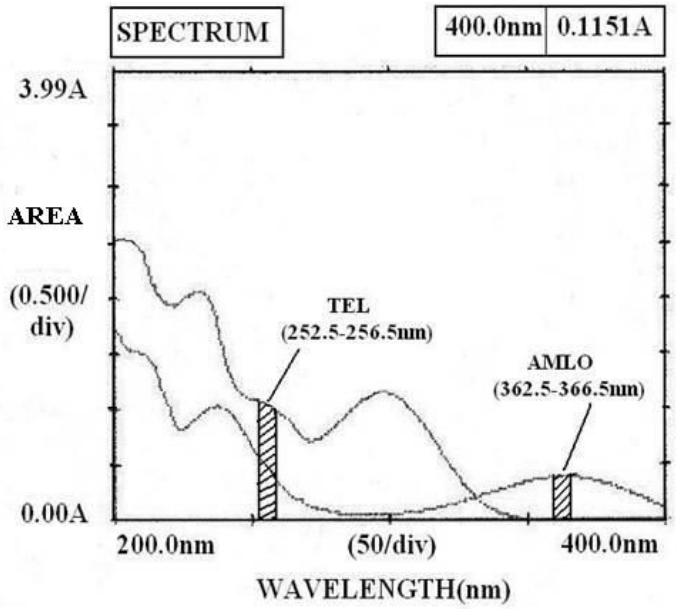


Fig. 2: Overlain spectra of Amlo and Tel in Area Under Curve (AUC) method



CONCLUSIONS

Amlodipine besylate (Amlo) and Telmisartan (Tel) are available in combined tablet dosage form for the treatment of hypertension. No single UV spectrophotometric method has been reported so far for the estimation of both the drugs in combination. Here three simple UV spectrophotometric methods (Simultaneous equation method, Area Under Curve method (AUC), Multicomponent Mode Method) were developed for their simultaneous analysis. The standard deviation, RSD and standard error calculated for the methods are low, indicating high degree of precision of the methods. The RSD is also less than 2% as required by ICH guidelines. The % recovery was between 98-102% indicating high degree of accuracy of the proposed methods. The results of the F test also indicated that there exists no significant difference between the developed methods for the analysis of Amlo and Tel in bulk and formulation. The developed methods are simple, rapid, precise, accurate and can be employed for the routine estimation of Amlo and Tel in both bulk and tablet dosage form.

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